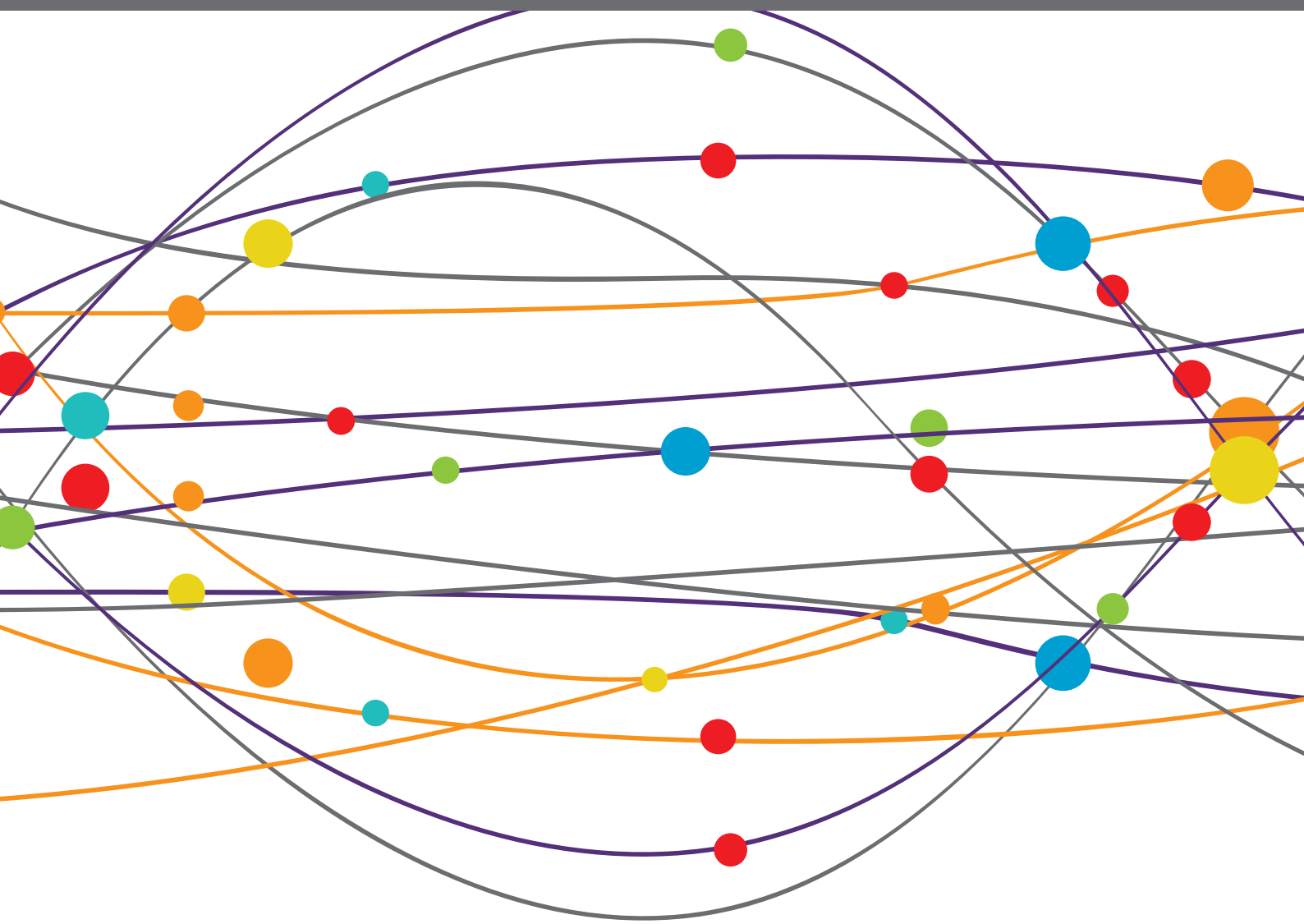
CONSEQUENCES OF THE COVID-19 PANDEMIC ON CARE FOR NEUROLOGICAL CONDITIONS

EDITED BY: Cheng-Yang Hsieh, Jordi A. Matias-Guiu, Jesús Porta-Etessam, Sheng-Feng Sung, Tomohisa Nezu, Ricardo F. Allegri, Shen-Yang Lim and Giovanni Assenza

PUBLISHED IN: Frontiers in Neurology



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88971-997-6
DOI 10.3389/978-2-88971-997-6

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

CONSEQUENCES OF THE COVID-19 PANDEMIC ON CARE FOR NEUROLOGICAL CONDITIONS

Topic Editors:
Cheng-Yang Hsieh, Sin-Lau Christian Hospital, Taiwan
Jordi A. Matias-Guiu, Servicio de Neurología, Hospital Clínico San Carlos, Spain
Jesús Porta-Etessam, Servicio de Neurología, Hospital Clínico San Carlos, Spain
Sheng-Feng Sung, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Taiwan
Tomohisa Nezu, Hiroshima University, Japan
Ricardo F. Allegri, Instituto de Investigaciones Neurológicas Fleni, Argentina
Shen-Yang Lim, University of Malaya, Malaysia
Giovanni Assenza, Campus Bio-Medico University, Italy

Citation: Hsieh, C.-Y., Matias-Guiu, J. A., Porta-Etessam, J., Sung, S.-F., Nezu, T., Allegri, R. F., Lim, S.-Y., Assenza, G., eds. (2021). Consequences of the COVID-19 Pandemic on Care for Neurological Conditions.
Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88971-997-6

Table of Contents

frontiers in Neurology

EDITORIAL
published: 15 November 2021
doi: 10.3389/fneur.2021.788912

Editorial: Consequences of the COVID-19 Pandemic on Care for Neurological Conditions

Jordi A. Matias-Guiu[1], Sheng-Feng Sung[2], Cheng-Yang Hsieh[3], Tomohisa Nezu[4], Jesús Porta-Etessam[1] and Ricardo F. Allegri[5]*

[1] Department of Neurology, Hospital Clínico San Carlos, Health Research Institute "San Carlos" (IdISCC), Universidad Complutense de Madrid, Madrid, Spain, [2] Division of Neurology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi City, Taiwan, [3] Department of Neurology, Tainan Sin Lau Hospital, Tainan, Taiwan, [4] Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan, [5] Department of Cognitive Neurology, Neuropsychiatry and Neuropsychology, Instituto Neurológico Fleni, Buenos Aires, Argentina

Keywords: COVID-19, SARS-CoV-2, neurological care, coronavirus, healthcare

OPEN ACCESS

Edited and reviewed by:
Jean-Claude Baron, University of Cambridge, United Kingdom

****Correspondence:***
Jordi A. Matias-Guiu
jordimatiasguiu@hotmail.com; jordi.matias-guiu@salud.madrid.org

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *03 October 2021*
Accepted: *18 October 2021*
Published: *15 November 2021*

Citation:
Matias-Guiu JA, Sung S-F, Hsieh C-Y, Nezu T, Porta-Etessam J and Allegri RF (2021) Editorial: Consequences of the COVID-19 Pandemic on Care for Neurological Conditions. Front. Neurol. 12:788912. doi: 10.3389/fneur.2021.788912

Editorial on the Research Topic

Consequences of the COVID-19 Pandemic on Care for Neurological Conditions

The coronavirus disease 2019 (COVID-19) pandemic has caused a wide range of unprecedented consequences, including social, economic, and health disruptions. From the point of view of healthcare assistance, COVID-19 has deeply impacted usual practice at all levels since the beginning of 2020. In this setting, neurological assistance has adapted to the circumstances of the pandemic. In fact, because COVID-19 involves neurological symptoms, affected patients require the attention of neurologists, and the high demand for clinical care entailed the recruitment of many neurologists to frontline assistance (1). In addition, the pandemic has impacted the management of patients with neurological disorders, with changes in the management of relapses, usual follow-up, diagnostic procedures, implementation or generalization of telemedicine, etc. Lockdown and social isolation were also very harmful in patients with neurological disorders (2). Furthermore, the treatment of neurological emergencies, such as stroke, was also compromised because of resource re-allocation during the emergency, and the fear of patients to attend the hospital.

The neurological community needed to share experiences about how to face this global challenge. Accordingly, this Research Topic was launched in April 2020 to address these issues. Over 117 manuscripts were submitted, and 76 papers have been published, including originals, reviews, and case reports. Studies have covered the main areas of neurological care, including general neurological care, stroke, epilepsy, multiple sclerosis, movement disorders, cognitive neurology, neuromuscular disorders, headache, and neuropediatrics.

STUDIES ON GENERAL NEUROLOGICAL CARE

Healthcare systems were challenged by the COVID-19 pandemic. In a study by Calandri et al., emergency department and outpatient consultations to a tertiary neurological center during the first wave in Argentina were significantly correlated with social mobility estimated by the Google Mobility Index as a result of the long lockdown. Besides, telemedicine was successfully implemented, with increased access to distant zones, which may be important for better access to specialized neurological care.

Protocols of changes in neurological care were proposed in two studies conducted by the Pandemic Health System Resilience Program Consortium (REPROGRAM) Pathway in both

the acute and chronic settings (Bhaskar, Sharma et al.; Bhaskar, Bradley et al.). These changes were considered appropriate to ensure healthcare professionals' and patients' safety and minimize the impact of the pandemic in neurological care.

STUDIES ON STROKE AND NEUROCRITICAL CARE

Stroke was one of the main subjects addressed in this Research Topic, with a large number of articles. Many regions reported a decline in stroke admissions during the early months of the pandemic. This reduction was mainly observed in the most severe and disabling strokes (Yao et al.), and was reported in several countries and settings, and for ischemic and hemorrhagic stroke, especially during the lockdowns (Abdulazim et al.; Ota et al.; Uphaus et al.; Erdur et al.). Conversely, the impact on the reperfusion procedures was variable, although it was also affected in the peak of the pandemic as suggested by several studies (D'Anna et al.; Koge et al.).

Some papers proposed modifications in the protocols for stroke care, from the acute phase to the rehabilitation therapies, suggesting a complete reorganization of the assistance to avoid the worsening of outcomes of stroke patients [Venketasubramanian; Candeloro et al.; Al-Jehani et al.; (3)].

Other studies focused on the relationship between COVID-19 and stroke, contributing to the knowledge about stroke subtypes, severity, management, and outcomes (Fraiman et al.; Grewal et al.; Tiwari et al.; Yang et al.; Wang et al.).

STUDIES ON EPILEPSY

The treatment of patients with epilepsy is another of the topics examined in the Research Topic. Mostacci et al. reviewed the literature regarding the impact of the pandemic on the health of patients with epilepsy, and conducted a survey regarding this topic. Although most patients did not report a significant change, clinical worsening was detected in a proportion of changes and was associated with sleep disorders or limited access to healthcare, among other factors. Lanzone et al. conducted a study evaluating the impact of lockdown in patients with epilepsy. In this case, the survey was analyzed with a text mining approach. Patients with epilepsy used different kinds of words, suggesting a different reaction to the lockdown compared with controls, which may be important in the follow-up and treatment of these patients during traumatic or stressful events.

Telemedicine has become very widespread in epilepsy care since the pandemic. Accordingly, a decision-making tree to manage patients with epilepsy was proposed (Kuroda).

STUDIES ON MULTIPLE SCLEROSIS

Patients with multiple sclerosis (MS) were regarded as a high-risk population due to the potential immunosuppressive effect of several treatments used in the disease. In a study by the Portuguese Multiple Sclerosis Study Group a consensus was obtained using a Delphi methodology about the implementation of several changes in the management in the context of the pandemic (Cerqueira et al.).

STUDIES ON PARKINSON'S DISEASE

Several studies evaluated the impact in patients with Parkinson's disease and other movement disorders of the pandemic. Hanff et al., used a semi-structured interview to examine unmet needs during the lockdown, and Piano et al., examined the impact of lockdown in patients treated with deep brain stimulation. Motolese et al., reported the experience of a remote monitoring program during the lockdown, with adequate degrees of satisfaction. Similarly, Shalash et al., presented their experience of virtual visits in patients with Parkinson's disease in Egypt.

STUDIES ON COGNITIVE NEUROLOGY

Patients with dementia were among the most affected by both the quarantine and COVID-19 (LaHue et al.). The effects of lockdown resulted in a clinical worsening in patients with mild cognitive impairment and dementia (Barguilla et al.; Pelicioni et al.). In addition, cognitive training and rehabilitation were adapted to telehealth. In this regard, Bernini et al. implemented HomeCoRe, an innovative approach to offer remote cognitive training.

STUDIES ON NEUROMUSCULAR DISORDERS

Patients with neuromuscular disorders were at higher risk of COVID-19 due to the frequent respiratory involvement and some immunosuppressive therapies. In this regard, several studies evaluated the impact of the pandemic and the SARS-CoV-2 infection in patients with neuromuscular disorders. Katyal et al., reviewed the potential neuromuscular complications of COVID-19, such as Guillain-Barre syndrome. In two studies by Bertran Recasens and Rubio and Tseng and Chen, the authors proposed recommendations for the management of patients with neuromuscular disorders during the pandemic or during COVID-19, and evaluated the impact of the pandemic on these patients.

STUDIES ON HEADACHE

Headache is one of the most frequent symptoms during COVID-19. However, primary headaches are also influenced by environmental factors. This topic was examined by Delussi et al., in a cross-sectional study from the Italian National Headache Registry, in which changes in migraine during the quarantine were investigated. According to the study by Dallavale et al., in children and adolescents, there was a mild improvement of migraine symptoms. Furthermore, Planchuelo-Gómez et al., tried to characterize the headache phenotypes in COVID-19 and link these features with inflammatory biomarkers.

STUDIES ON NEUROPEDIATRICS

SARS-CoV-2 also affects children, although to a lesser extent than adults. In the article by Boronat, the evidence about neurological symptoms and complications in children was reviewed. Compared with adults, neurological complications were less frequent. However, a multisystem inflammatory syndrome can occur, with the development of encephalopathy as the most frequent clinical manifestation. Furthermore, in this article, a review of the changes in the care of children with neurological disorders (e.g., cerebral palsy, epilepsy, attention deficit and hyperactivity disorder, etc.) was presented. Other collateral problems in children have been the closure of schools, lack of free time outdoors, and financial insecurity.

STUDIES ON DIAGNOSTIC PROCEDURES

Another important challenge during the pandemic concerns the use of diagnostic tools. Postponed examinations are associated with diagnostic delays and worse outcomes. Currently, these techniques are key for adequate neurological care, but they may entail a risk of COVID-19 infection. In this regard, González-Ortiz et al., Chen et al., and Valsamis et al. proposed process modifications for neuroimaging, cerebrospinal fluid samples, and electroencephalography.

CONCLUSIONS

In this Research Topic, the authors have presented important experiences and solutions to the changes generated by the COVID-19 pandemic in neurological care. Most of the studies were conducted during the first stages of the COVID-19 to face many of the challenges that had arisen, including the lockdown and quarantines, safety concerns because of high transmissibility, and risks of COVID-19 in patients with neurological disorders. As in other crises, the lessons learned should be applied for the future benefit of patients and the healthcare system during the COVID-19 pandemic, and probably afterward. Some changes in neurological care, such as safety protocols or implementation of teletherapy, may be helpful and relevant in daily practice (4, 5). How the current pandemic will give rise to long-term changes in neurological assistance, and the convenience of these changes, should be evaluated in the future.

AUTHOR CONTRIBUTIONS

JM-G wrote the first draft of the manuscript. RA wrote parts of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

1. Manji H, Carr AS, Brownlee WJ, Lunn MP. Neurology in the time of COVID-19. *J Neurol Neurosurg Psychiatry.* (2020) 91:568–70. doi: 10.1136/jnnp-2020-323414
2. Azevedo LVDS, Calandri IL, Slachevsky A, Graviotto HG, Vieira MCS, Andrade CB, et al. Impact of social isolation on people with dementia and their family caregivers. *J Alzheimers Dis.* (2021) 81:607–17. doi: 10.3233/JAD-201580
3. Tan Q, Liu Q-J, Fan W-H, Du X-Y, Wu L, Gong H-M, et al. Impact of COVID-19 on acute stroke presentation in a designated COVID-19 Hospital. *Front Neurol.* (2021) 12:673703. doi: 10.3389/fneur.2021.673703
4. Matias-Guiu J, Porta-Etessam J, López-Valdés E, García-Morales I, Guerrero-Solá A, Matías-Guiu JA. Management of neurological care during the COVID-19 pandemic. *Neurologia.* (2020) 35:233–7. doi: 10.1016/j.nrleng.2020.04.001
5. Matias-Guiu J, Matias-Guiu JA, Álvarez-Sabín J, Ramón Ara J, Arenillas J, Casado-Naranjo I, et al. Will neurological care change over the next 5 years due to COVID-19 pandemic? Key informant consensus survey. *Neurologia.* (2020) 35:252–7. doi: 10.1016/j.nrleng.2020.04.010

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 21 April 2020
doi: 10.3389/fneur.2020.00353

Triage of Acute Ischemic Stroke in Confirmed COVID-19: Large Vessel Occlusion Associated With Coronavirus Infection

*Pouria Moshayedi[1], Timothy E. Ryan[1], Lucido Luciano Ponce Mejia[2], May Nour[1,2] and David S. Liebeskind[1]**

[1] Department of Neurology, University of California, Los Angeles, Los Angeles, CA, United States, [2] Department of Interventional Neuroradiology, University of California, Los Angeles, Los Angeles, CA, United States

The outbreak of COVID-19 has posed a significant challenge to global healthcare. Acute stroke care requires rapid bedside attendance, imaging, and intervention. However, for acute stroke patients who have a diagnosis of or are under investigation for COVID-19, the concern for nosocomial transmission moderates operational procedures for acute stroke care. We present our experience with an in-hospital stroke code called on a COVID-19-positive patient with a left middle cerebral artery syndrome and the challenges faced for timely examination, imaging, and decision to intervene. The outlook for the ongoing COVID-19 pandemic necessitates the development of protocols to sustain timely and effective acute stroke care while mitigating healthcare-associated transmission.

Keywords: COVID-19, stroke—diagnosis, therapy, large vessel occlusion (LVO), disease transmission, triage

OPEN ACCESS

Edited by:
Jean-Claude Baron, University of Cambridge, United Kingdom

Reviewed by:
Michael V. Mazya, Karolinska University Hospital, Sweden
Anthony Rudd, King's College London, United Kingdom

***Correspondence:**
David S. Liebeskind
dliebeskind@mednet.ucla.edu

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *02 April 2020*
Accepted: *09 April 2020*
Published: *21 April 2020*

Citation:
Moshayedi P, Ryan TE, Mejia LLP, Nour M and Liebeskind DS (2020) Triage of Acute Ischemic Stroke in Confirmed COVID-19: Large Vessel Occlusion Associated With Coronavirus Infection. Front. Neurol. 11:353. doi: 10.3389/fneur.2020.00353

INTRODUCTION

Rapid attendance at the patient bedside, clinical exam, and timely imaging studies have been emphasized in the care of acute ischemic stroke patients, but the global pandemic outbreak of COVID-19 (1) has created novel and significant challenges to acute stroke care. Protocols to sustain acute stroke care for COVID-19 patients while mitigating nosocomial transmission are needed. In this report, we share unique challenges in treating a COVID-19-positive patient with acute ischemic stroke due to occlusion of the left middle cerebral artery. We also discuss the current evidence and recommendations to decrease healthcare-associated transmission in acute clinical examination, imaging, and interventional procedures in acute stroke patients with a diagnosis of COVID-19.

CASE PRESENTATION

A patient in his 8th decade of life was admitted to our facility with acute chest pain, diaphoresis, and hypotension with ST-elevation myocardial infarction (STEMI). He underwent coronary angioplasty followed by stent deployment and was admitted to the coronary care unit (CCU). Transthoracic echocardiogram revealed left ventricle (LV) ejection fraction of 10–15% and LV thrombosis measuring 2.8 cm × 1.1 cm, prompting initiation of IV heparin. He also had bilateral lower limb paresthesia and loss of temperature and arterial pulses, raising concern of ischemic limbs, with lower extremity arterial Doppler confirming occlusion in multiple arterial segments.

Due to his presentation with shortness of breath, he was designated as a Patient Under Investigation (PUI) for COVID-19, and, the day following admission, his PCR testing of respiratory

secretions showed evidence of 2019-nCOV RNA. He was intubated due to hypoxemic respiratory failure. Standard facility protocols for droplet isolation in a negative pressure room were implemented. The patient was extubated on day 4.

On day 5, an in-hospital stroke code was called after the bedside nurse found him to have an inability to speak, right-sided weakness, and right-sided facial droop, with last known well time the night before. The stroke team arrived, and one team member wore personal protection equipment including an N95 respirator mask, goggle, gown, and gloves and entered the patient's room to perform an examination, which revealed an inability to speak or comprehend, a conjugate gaze preference toward the left side, no blink to threat on the right side, and no movement in the right arm and leg. Since the patient presented with a large vessel occlusion stroke syndrome within an extended time window, advanced multimodal imaging was indicated to measure infarct volume as well as salvageable tissue. According to the institutional policy for acute stroke codes, as well as the patient's renal failure prohibiting the use of iodine contrast for CT perfusion studies, he was transported to MRI. The institutional protocol for transferring patients in aerosol isolation was applied by having the patient wear a surgical face mask. Laboratory results were notable for renal failure, normal platelet count, and activated partial thromboplastin time (PTT) >85.5 while on heparin.

Brain MRI, obtained without contrast administration (due to severe renal failure) and reviewed during image acquisition, revealed a 60-cc acute infarct in the left insular, temporal, parietal, and frontal lobes, as well as smaller acute infarcts in the right caudate and left cerebellar hemisphere. MRI also showed evidence of hemorrhagic conversion in the left fronto-temporal territory. MR angiogram showed occlusion of the left middle cerebral artery proximal M1 segment.

The patient was not a candidate for thrombolysis as he had elevated activated PTT on heparin, in addition to an unknown time of stroke onset and evidence of large and established infarction with a small region of hemorrhagic transformation. Endovascular thrombectomy was considered but not pursued given the large infarct size and evidence of hemorrhagic transformation since reperfusion could have led to a much larger intracranial hemorrhage with no meaningful clinical benefit. Following this ischemic stroke, and given other comorbidities including heart failure, cardiovascular shock, and ischemic bilateral lower limbs, discussions on goals of care were held with the family, and his care was focused on comfort according to the patient's wishes.

Following the completion of his MRI, the MRI suite was out of commission for about 3 h to complete disinfection.

DISCUSSION

Early reports from the COVID-19 pandemic have noted a 41% nosocomial infection rate (2), which highlights the importance of developing protocols for transfer, imaging, intubation, and surgical or endovascular procedures on COVID-19 patients presenting with acute stroke. The novelty of the COVID-19 pandemic outbreak means that there are few evidence-based and informed protocols. The current recommendations have centered on the airborne and direct contact methods of transmission (3).

To perform MRI or other imaging modalities, it is recommended to switch a patient's bed and accessories to MRI-compatible equipment in the patient room with enhanced airborne precautions rather than in the MRI suite. Designation of a single entry point to imaging facilities and limiting other traffic through the healthcare facility is preferred (4). Installment of physical barriers and the donning of N95 masks, face protection, and gloves for physicians or ancillary staff en-route are recommended.

Discussions on safe pre-operative procedures are underway (5). Studies published before the COVID-19 outbreak noted that a high-flow nasal cannula, non-invasive ventilation by masks with optimized vent holes, or a helmet connected to a double-limb circuit may lower airborne transmission (6), but closed-circuit ventilation with use of filters is regarded as a safer option. Given the relatively low risk of operative site infection, endovascular suites capable of conversion to negative pressure facilities appear to be ideal solutions.

The COVID-19 pandemic outbreak has exhausted and overburdened healthcare systems. In a situation of extreme facility shortages, triaging COVID-19-positive patients with acute stroke based on severity and extent of their pre-morbidities is a grim but unavoidable necessity. In acute stroke patients presenting with symptoms of large vessel occlusion in an extended time window, and therefore requiring advanced imaging, CT perfusion has been shown to be equally capable of selecting patients for endovascular thrombectomy when compared with MRI (7). The time required for disinfection protocols to be conducted may require judicious use of MRI for acute stroke patients. In the face of the current pandemic, our institutional policy for acute stroke care has changed and now prioritizes CT perfusion over MRI.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UCLA IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PM and DL: conception and design and administrative/technical/material support. PM: acquisition of data and drafting the article. All authors: analysis and interpretation of data, critically revising the article, and reviewed submitted version of manuscript. DL: approved the final version of the manuscript on behalf of all authors and study supervision.

REFERENCES

1. Gates B. Responding to Covid-19 - a once-in-a-century pandemic? *N Engl J Med.* (2020). doi: 10.1056/NEJMp2003762. [Epub ahead of print].
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. (2020). 323:1061–9. doi: 10.1001/jama.2020.1585
3. Guan L, Zhou L, Zhang J, Peng W, Chen R. More awareness is needed for severe acute respiratory syndrome coronavirus 2019 transmission through exhaled air during non-invasive respiratory support: experience from China. *Eur Respir J.* (2020) 55:2000352. doi: 10.1183/13993003.00352-2020
4. Mirza SK, Tragon TR, Fukui MB, Hartman MS, Hartman AL. Microbiology for radiologists: how to minimize infection transmission in the radiology department. *Radiographics.* (2015) 35:1231–44. doi: 10.1148/rg.20151 40034
5. Meng L, Qiu H, Wan L, Ai Y, Xue Z, Guo Q, et al. Intubation and ventilation amid the COVID-19 outbreak: Wuhan's experience. *Anesthesiology.* (2020). doi: 10.1097/ALN.0000000000003296. [Epub ahead of print].
6. Hui DS, Chow BK, Lo T, Ng SS, Ko FW, Gin T, et al. Exhaled air dispersion during noninvasive ventilation via helmets and a total facemask. *Chest*. (2015) 147:1336–43. doi: 10.1378/chest. 14-1934
7. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973

Conflict of Interest: DL is consultant to Cerenovus, Genentech, Stryker and Medtronic as Imaging Core Lab.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 22 May 2020
doi: 10.3389/fneur.2020.00516

Medical and Paramedical Care of Patients With Cerebellar Ataxia During the COVID-19 Outbreak: Seven Practical Recommendations of the COVID 19 Cerebellum Task Force

Mario Manto[1], Nicolas Dupre[2], Marios Hadjivassiliou[3], Elan D. Louis[4], Hiroshi Mitoma[5], Marco Molinari[6], Aasef G. Shaikh[7], Bing-Wen Soong[8,9,10], Michael Strupp[11], Frank Van Overwalle[12] and Jeremy D. Schmahmann[13]*

[1] CHU-Charleroi and Service des Neurosciences, University of Mons, Mons, Belgium, [2] Department of Medicine, Faculty of Medicine, Université Laval & Neuroscience Axis, CHU de Québec-Université Laval, Quebec City, QC, Canada, [3] Academic Department of Neurosciences, Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom, [4] Department of Neurology and Neurotherapeutics, University of Texas Southwestern, Dallas, TX, United States, [5] Department of Medical Education, Tokyo Medical University, Tokyo, Japan, [6] IRCCS Fondazione S. Lucia, Rome, Italy, [7] Department of Neurology, Case Western Reserve University, University Hospitals Cleveland Medical Center, Cleveland VA Medical Center, Cleveland, OH, United States, [8] Taipei Neuroscience Institute, Taipei Medical University, Taipei, Taiwan, [9] Department of Neurology, Taipei Medical University-Shuang Ho Hospital, New Taipei City, Taiwan, [10] Department of Neurology, Taipei Veterans General Hospital, and Brain Research Center, National Yang-Ming University, Taipei, Taiwan, [11] Department of Neurology, Ludwig Maximilians University, Munich, Germany, [12] Brain, Body and Cognition Lab, Faculty of Psychology, Vrije Universiteit Brussel, Brussels, Belgium, [13] Ataxia Center, Cognitive Behavioral Neurology Unit, Laboratory for Neuroanatomy and Cerebellar Neurobiology, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh, Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Tsang-Shan Chen, Sin-Lau Christian Hospital, Taiwan
Rizaldy Taslim Pinzon, Duta Wacana Christian University, Indonesia

***Correspondence:**
Mario Manto
mmanto@ulb.ac.be

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *28 April 2020*
Accepted: *11 May 2020*
Published: *22 May 2020*

Citation:
Manto M, Dupre N, Hadjivassiliou M, Louis ED, Mitoma H, Molinari M, Shaikh AG, Soong B-W, Strupp M, Van Overwalle F and Schmahmann JD (2020) Medical and Paramedical Care of Patients With Cerebellar Ataxia During the COVID-19 Outbreak: Seven Practical Recommendations of the COVID 19 Cerebellum Task Force. Front. Neurol. 11:516. doi: 10.3389/fneur.2020.00516

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), the cause of the current pandemic coronavirus disease 2019 (COVID-19), primarily targets the respiratory system. Some patients also experience neurological signs and symptoms ranging from anosmia, ageusia, headache, nausea, and vomiting to confusion, encephalitis, and stroke. Approximately 36% of those with severe COVID-19 experience neurological complications. The virus may enter the central nervous system through the olfactory nerve in the nasal cavity and damage neurons in the brainstem nuclei involved in the regulation of respiration. Patients with cerebellar ataxia (CA) are particularly vulnerable to severe outcome if they contract COVID-19 because of the complexity of their disease, the presence of comorbidities, and their use of immunosuppressive therapies. Most CA patients burdened by progressive neurologic deficits have substantially impaired mobility and other essential functions, for which they rely heavily on ambulatory services, including rehabilitation and psychosocial care. Cessation of these interventions because of isolation restrictions places the CA patient population at risk of further deterioration. This international panel of ataxia experts provides recommendations for neurologists caring for patients with CA, emphasizing a pro-active approach designed to maintain their autonomy and well-being: continue long-term medications, promote rehabilitation efforts, utilize the technology of virtual visits for regular contact with healthcare providers,

and pay attention to emotional and psychosocial health. Neurologists should play an active role in decision-making in those CA cases requiring escalation to intensive care and resuscitation. Multi-disciplinary collaboration between care teams is always important, and never more so than in the context of the current pandemic.

Keywords: SARS-CoV-2, COVID-19, cerebellum, therapies, ataxia

The novel zoonotic corona virus (severe acute respiratory syndrome coronavirus 2: SARS-CoV2) has caused a global pandemic, coronavirus disease-2019 (COVID-19), which presents primarily with severe pulmonary disease, acute respiratory collapse, and multisystem failure (1). As many as 36% of hospitalized patients in the Chinese experience developed central and peripheral nervous system involvement, including cerebellar manifestations (2). SARS-CoV2 is thought to enter the central nervous system via the bloodstream or by retrograde neuronal transmission through the cribriform plate. It binds to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2) in bronchial alveoli, with internalization of the complex by the host cells (3), the same receptor identified in SARS-CoV, which also affected nervous system function (4).

Cerebellar ataxias (CAs) are a group of heterogeneous disorders from both the phenotypic and genetic standpoints. CAs include chronic neurodegenerative disorders such as the autosomal dominant spinocerebellar ataxias (SCAs), which affect cerebellar and extra-cerebellar structures, including brainstem and motor neurons, with widespread dysfunction of the motor system and other neurological domains. Patients with the various CAs are particularly vulnerable to COVID-19 for several reasons: their neurological syndrome is complex, comorbid medical illnesses are common, immune-mediated ataxias are managed with immunosuppressive medications such as rituximab, mycophenolate, and corticosteroids, which require frequent monitoring, CAs may affect elderly people, and all of these predispositions to severe response to the viral infection are compounded by cerebellum-specific neuropsychological impairments. General practitioners (GPs), who most frequently care for these patients and their families, are reporting that they are overwhelmed by the pandemic, with their usual meticulous engagement in managing their long-term course and supervening acute issues being superseded by the immediate need to care for the surging numbers of COVID-19 patients. Patients with CA in many centers are even finding that they are having difficulty connecting with their suddenly overburdened GPs. Adding to the stress on the CA patient population world-wide is the reality that in-person or at-home support services, including psychological counseling or therapy visits, have stopped, and necessary ambulatory care services such as speech, physical, and occupational therapy interventions have come to an abrupt halt. The consequence is that patients are reporting dramatically decreased levels of rehabilitative and maintenance care, which is having a demonstrable negative impact on their overall care and well-being.

All societies around the world, and most particularly the vulnerable populations, are severely challenged by the COVID-19 pandemic. There are, however, three considerations specific to patients and families dealing with CAs.

First, dysphagia, ataxic respiration, maintenance of airway protection, and aspiration pneumonia are an ever-present concern and risk in CAs (5). Should CA patients contract COVID-19, they are potentially at increased risk for pulmonary complications because dyspnea, cough, and fever, together with systemic ill-health and severe fatigue are among the earliest manifestations.

Second, there is intense pressure on healthcare systems due to limited numbers of beds in intensive care units (ICUs), which are facing an enormous challenge in terms of abrupt reorganization of their procedures and decisions to treat patients (6). Patients with CA may be at high risk now because our ICU colleagues might consider patients with CA to have irreversible neurological diseases with no hope of cure and who should therefore not benefit from ICU-level care. Genetic ataxias, such as Friedreich's ataxia (FA) with its cardiomyopathy and diabetes, represent a typical example of a neurological disorder with poor prognosis according to colleagues in ICUs. But not all CA patients are the same: a patient with late-stage FA with cardiomyopathy and diabetes is quite different than a young, otherwise medically healthy patient with FA or a late-onset adult FA patient whose disease resembles a more slowly evolving spinocerebellar ataxia. The same concept is true when distinguishing between a patient with multiple system atrophy of the cerebellar type and a patient with spinocerebellar ataxia type 6. Nuances of knowledge about the nature of the underlying disease of a CA patient are second-nature to neurologists and particularly to ataxiologists, but they are not necessarily familiar to internists, who need input and guidance from the neurologist expert in these disorders.

Third, the neurocognitive and behavioral-affective syndrome in CA patients manifests with impairments in executive function and visuo-spatial cognition and in personality changes, including blunting of affect or impaired behavior (7). Patients are at risk for severe depression and apathy, as well as reduced mental flexibility (8). Impulsive actions, propensity to rumination, and unawareness of social boundaries are not unexpected in some of the CAs. Impaired attentional control combined with illogical thought impacts daily life, with the consequence that patients with CA patients occupy the borderland of neurology and neuropsychiatry and require specialized management (9).

In our institutions, we have instituted the following seven practices and share these recommendations with neurologists caring for the CA patient population:

1. Emphasize that the recommendations to the general population to avoid contracting the infection need to be followed seriously and rigorously by CA patients, their families, and caregivers. This includes staying at home as long as the local/national authorities determine quarantine is still required, maintaining physical distancing if leaving the house or interacting with others outside the immediate household, adhering to the advertised protocols for hand-washing, avoiding touching the face, wearing masks when in contact with others outside the home, and meticulous cleansing and disinfecting of surfaces and of objects brought into the house. Take a pro-active approach to educating patients regarding travel restrictions.
2. Continue all necessary medications, whether for the symptoms and manifestation of the CA or for other medical conditions, for instance, 4-aminopyridine or acetazolamide in episodic ataxias. Patients with immune-mediated ataxias should not discontinue their immunosuppressive drugs. The dysphoria, anhedonia, and sometimes suboptimal decision-making encountered in CA patients may contribute to unjustified interruption of medications or undue influence by social media sites offering unsolicited and erroneous medical advice.
3. Promote rehabilitation efforts through speech and language therapy and physical and occupational therapy in CA patients. Discontinuation of rehabilitation is likely to exacerbate symptoms and worsen ataxia, as is already evident in our phone or video virtual visits with patients. Contact should be maintained with providers of these rehabilitation services to devise programs that can be carried out at home and monitored remotely. The effect of this cessation of in-person rehabilitation care provides an opportunity for quantitative research in the future to assess the impact of this unexpected change in the care model. Because neurological disorders are not uncommon in COVID-19, it may be relevant to remind patients, caregivers, and paramedics that the ataxic syndrome may worsen due to the lack of rehabilitation or the interruption of medications. This exacerbation should be distinguished from a new-onset COVID-19 infection, which is primarily characterized by fever, dry cough, tiredness, pains, nasal congestion, sore throat, or diarrhea.
4. Use the virtual visit platforms of telemedicine. We are fortunate to have this technology, which has emerged as the primary way to interact with and care for patients through telephone contact or real-time interactive video platforms in this environment in which in-person encounters for routine care are not possible. Whereas, telemedicine technology is not perfect or equipped to perform a comprehensive neurological examination, in our experience it is nevertheless adequate for assessing the overall mental state and speech and for examination of hyperkinetic movement disorders, ataxia, hand dexterity, and balance, while maintaining the social connection with patients and their families and giving them the confidence that they are cared for and are not being abandoned.
5. Emphasize the need for assessment and monitoring of patients' emotional and social health, which may be adversely affected in this time of great stress and anxiety and superimposed upon the real social isolation that many CA patients already feel because of the nature of their underlying disorder. Be aware that emotional and social impairments of cerebellar patients may render virtual interaction more difficult and taxing, so that extra encouragement might be needed to use virtual means. These patients may also have diminished understanding of the social duty to follow the strict hygiene measures necessary for the common welfare (10). The cognitive and affective deficits in some CA patients may prevent them from identifying or reporting the possible symptoms of the novel coronavirus infection. This is an additional reason to recommend that CA patients maintain frequent contact with families and caregivers, using the technology of virtual interactions if necessary (see also recommendation 4).
6. Take an active role in management decisions regarding CA patients stricken with COVID-19 whose illness may require ICU-level care in the context of reduced access to ventilator care. Current management strategies need to be fine-tuned in these instances (11). Internists and intensivists can benefit from the neurologist's understanding and experience of the preexisting CA condition and its implications, and the neurologist can advocate for these patients. Careful neurological examinations are also recommended, keeping in mind that coronavirus invasion in the brain may not trigger the classical inflammation cascade leading to the usual picture of infectious encephalitis (12). Nobody is better positioned than the neurologist to ascertain the neurological prognosis of CA patients. Collaborative thinking across disciplines should be promoted when facing ethical challenges that may arise in caring for patients with CA. In case of suspected or confirmed COVID-19 in CA patients with more severe manifestations, both the motor and non-motor features of the cerebellar syndrome need to be considered during quarantine or in the isolation room. Patients are typically clumsy and may require adaptation of the environment, for instance, access to food. They also require a case-by-case discussion for the management of neuropsychiatric manifestations. For CA patients with COVID-19 whose illness may require ICU-level care and intubation, consideration of hospice-level care may be appropriate if the underlying CA is severe and has a short life-expectancy. This decision poses its own challenges, as hospices may lack staff and equipment. Assistance choices for CA patients who are already in bad condition with short life-expectancy and stricken with COVID-19 requiring ICU-level care and intubation are ethically difficult. On one side, clinical pre-COVID-19 conditions must not preclude, a-priori, access to ICU. On the other, in case of limited resources, as is often the case in pandemic conditions, disaster medicine rules apply.
7. Be mindful in this unprecedented time that it is fully appropriate to be attuned to the needs of our medical and paramedical colleagues who are themselves in need of attention (13). Insomnia, anxiety, depression, and even suicide are now reported in healthcare providers exhausted by the workload and fearful of succumbing to the disease

themselves. An antidote to the emotional, intellectual, and physical depletion that is characterizing this global crisis is the international and multi-disciplinary discussion and collaboration focused on saving lives and advancing science, and we all play a role in the effort to emerge stronger once this scourge has been defeated.

None of us has ever personally encountered such a dire situation as is posed by this pandemic. This set of recommendations offered by the international panel of ataxia experts is based on our collective clinical experience and review of the rapidly expanding clinical and basic science literature. We expect that the results of clinical trials and larger studies of the pandemic in all its manifestations will enable us to provide more substantive and evidence-based guidelines for neurologists, including ataxiologists, in the future.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5. [Epub ahead of print].
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) e201127. doi: 10.1001/jamaneurol.2020.1127
3. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol*. (2020) 94:e00127–20. doi: 10.1128/JVI.00127-20
4. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Infect Dis*. (2005) 41:1089–96. doi: 10.1086/444461
5. Rönnefarth M, Hanisch N, Brandt AU, Mähler A, Endres M, Paul F, et al. Dysphagia affecting quality of life in cerebellar ataxia-a large survey. *Cerebellum*. (2020) 19:437–45. doi: 10.1007/s12311-020-01122-w
6. Qiu H, Tong Z, Ma P, Hu M, Peng Z, Wu W, et al. Intensive care during the coronavirus epidemic. *Intensive Care Med*. (2020) 46:576–8. doi: 10.1007/s00134-020-05966-y
7. Ahmadian N, van Baarsen K, van Zandvoort M, Robe PA. The cerebellar cognitive affective syndrome - a meta-analysis. *Cerebellum*. (2019) 18:941–50. doi: 10.1007/s12311-019-01060-2
8. Bolton C, Lacy M. Comparison of cognitive profiles in spinocerebellar ataxia subtypes: a case series. *Cerebellum Ataxias*. (2019) 6:13. doi: 10.1186/s40673-019-0107-4
9. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum*. (2007) 6:254–67. doi: 10.1080/14734220701490995
10. Van Overwalle F, Manto M, Leggio M, Delgado-García JM. The sequencing process generated by the cerebellum crucially contributes to social interactions. *Med Hypotheses*. (2019) 128:33–42. doi: 10.1016/j.mehy.2019.05.014
11. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF. Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. *Intensive Care Med*. (2020) 46:579–582. doi: 10.1007/s00134-020-05967-x
12. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol*. (2008) 82:7264–75. doi: 10.1128/JVI.00737-08
13. Zhang WR, Wang K, Yin L, Zhao WF, Xue Q, Peng M, et al. Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. *Psychother Psychosom*. (2020). p. 1–9 doi: 10.1159/000507639. [Epub ahead of print].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 29 May 2020
doi: 10.3389/fneur.2020.00579

Acute Neurological Care in the COVID-19 Era: The Pandemic Health System REsilience PROGRAM (REPROGRAM) Consortium Pathway

Sonu Bhaskar[1,2,3,4*], *Divyansh Sharma*[1,5], *Antony H. Walker*[1,6], *Mark McDonald*[1,7], *Bella Huasen*[1,8], *Abilash Haridas*[1,9], *Manoj Kumar Mahata*[1,10] *and Pascal Jabbour*[1,11]

[1] *Pandemic Health System REsilience PROGRAM (REPROGRAM) Consortium, REPROGRAM Acute Care Sub-committee*[†], *Sydney, NSW, Australia,* [2] *Department of Neurology, Liverpool Hospital, Liverpool, NSW, Australia,* [3] *Neurovascular Imaging Laboratory & NSW Brain Clot Bank, Ingham Institute for Applied Medical Research, Liverpool, NSW, Australia,* [4] *The University of New South Wales Sydney, UNSW Medicine, Sydney, NSW, Australia,* [5] *The University of New South Wales Sydney, UNSW Medicine, Sydney, NSW, Australia,* [6] *Lancashire Cardiac Centre, Blackpool Victoria Hospital, NHS, Lancashire, United Kingdom,* [7] *Department of Neurology, University of Virginia, Charlottesville, VA, United States,* [8] *Department of Interventional Neuroradiology, Lancashire University Teaching Hospitals, Preston, United Kingdom,* [9] *Pediatric Neurosurgery, Cerebrovascular and Skull Base Neurosurgery, St Joseph's Hospital, Tampa, FL, United States,* [10] *Department of Stroke and Neurointervention, Woodlands Multispeciality Hospital Limited, Kolkata, India,* [11] *Division of Neurovascular Surgery and Endovascular Neurosurgery, Thomas Jefferson University and Jefferson Hospital for Neuroscience, Philadelphia, PA, United States*

The management of acute neurological conditions, particularly acute ischemic stroke, in the context of Coronavirus disease 2019 (COVID-19), is of importance, considering the risk of infection to the healthcare workers and patients and emerging evidence of the neuroinvasive potential of the virus. There are variations in expert guidelines further complicating the picture for clinicians in acute settings. In this light, there is a compelling need for further formulation of recommendations that compile these variations seen in the numerous guidelines present. Health system protocols for managing ongoing acute neurological care and intervention need consideration of safety and well-being of the frontline healthcare workers and the patients. We examine existing pathways and their efficacy to mitigate viral exposure to the healthcare workers and patients and synthesize a systemic approach to manage patients with acute neurological conditions in the COVID-19 scenario. Early experiences with a COVID-19 positive stroke patient treated with endovascular thrombectomy is presented to highlight the urgent need for adequate personal protective equipment (PPE) during acute neuro-interventional procedures.

Keywords: Coronavirus disease 2019 (COVID-19), Personal Protective Equipment (PPE), safety, acute stroke, guidelines, reperfusion, neurointervention, surgery

OPEN ACCESS

Edited by:
Jesús Porta-Etessam, Hospital Clínico San Carlos, Spain

Reviewed by:
Juan Francisco Arenillas, Hospital Clínico Universitario de Valladolid, Spain
Susana Arias Rivas, Hospital Clínico Universitario de Santiago, Spain

***Correspondence:**
Sonu Bhaskar
sonu.bhaskar@health.nsw.gov.au

*[†] The COVID19 pandemic is causing an unprecedented public health crisis impacting healthcare systems, healthcare workers and communities. The COVID-19 Pandemic Health System **RE**SILIENCE **PROGRAM** (**REPROGRAM**) consortium is a think-tank of leading international healthcare physicians, researchers and policymakers formed to champion the safety of healthcare workers, policy development and advocacy for global pandemic preparedness and action.*

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *15 April 2020*
Accepted: *19 May 2020*
Published: *29 May 2020*

Citation:
*Bhaskar S, Sharma D, Walker AH, McDonald M, Huasen B, Haridas A, Mahata MK and Jabbour P (2020) Acute Neurological Care in the COVID-19 Era: The Pandemic Health System **RE**silience **PROGRAM** (**REPROGRAM**) Consortium Pathway. Front. Neurol. 11:579. doi: 10.3389/fneur.2020.00579*

INTRODUCTION

Neurotropism is a well-known feature of beta-coronaviruses, of which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus which causes Coronavirus Disease 2019 (COVID-19) (1), is one, with effects on the brain stem, and in particular, the cardiorespiratory center thought to result in breathing dysfunction (2). The Italian experience has displayed the

presence of neurological symptoms in COVID-19 positive patients (3). The Chinese study from Wuhan published in JAMA Neurology reported neurological manifestations in a significant proportion (36.4%) of patients with COVID-19 (4). Recent findings surrounding anosmia as an early symptom of COVID-19 have invoked further interest in this hypothesis (5). The role of the central component in hyposmia could also be suspected. Those presenting with symptoms of skeletal muscle damage are at higher risk of liver and kidney damage. It is evident that the virus is able to cross the blood-brain barrier (BBB), which is postulated to occur post-infection due to interactions with the Angiotensin-Converting Enzyme 2 (ACE2) receptor present at various sites within the cerebral circulation (6). Another case report on a female airline worker with COVID-19 positive status developing acute necrotizing hemorrhagic encephalopathy (7), a condition that is typically seen following cytokine storm in influenza, suggests possible BBB compromise. Independent of possible neurotropism, COVID-19 infection is associated with coagulopathy (elevated D-dimer and severe platelet reduction) and may disrupt blood pressure regulation through interaction with the ACE2 receptor. COVID-19 could possibly contribute to ischemic and hemorrhagic stroke aside from neurotropism (8). Taken together these anecdotal reports suggest a possible neuroinvasive potential of the virus.

ACUTE ISCHEMIC STROKE

Management of patients with acute ischemic stroke during COVID-19 pandemic could be challenging and certain precautions must be taken in order to protect healthcare workers, particularly in the delivery of endovascular treatment, where aerosol could be produced during the procedures, to prevent further vector transmission (9). As a result of this, various modifications of the traditional code stroke are being discussed amongst hospitals, and in particular, Khosravani et al. (10) propose the concept of the "Protected Code Stroke" whereby management of patients with a suspected stroke is modified in the context of the COVID-19 pandemic to protect healthcare workers. A conservative approach involving fever screening, history taking to rule out COVID-19 risks and the presence of infectious symptoms could replace routine "Code Stroke."

Minimizing healthcare workers in the same room as the patient, specifications surrounding personal protective equipment use, and the delegation of specific roles to limit the risk of infection have been suggested. However, this protocol is not ratified by other major associations and does not consider the surgical aspects associated with endovascular treatment, a major gap that must be addressed.

Various bodies have put forth guidelines into how surgery should be conducted in these times to minimize harm to patients and healthcare workers alike. However, they are non-specific to endovascular treatment. Nonetheless, general Intercollegiate Surgical Guidelines (11) are available, and emphasize the importance of not undertaking procedures that may result in poorly controlled aerosol production, minimization of theater staff, team changes required during a prolonged surgery, and intubation and extubation within the operation theater itself, with only necessary staff members present. This differs from the "*Society of American Gastrointestinal and Endoscopic Surgeons and The European Association of Endoscopic Surgery Recommendations Regarding Surgical Response to COVID-19 Crisis* (12)," which recommend that "unless there is an emergency, there should be no exchange of room staff."

Notably, neither of these guidelines are specific to endovascular treatment. The *Society of Neurointerventional Surgery* recently released "recommendations for the care of emergent neuro-interventional patients in the setting of COVID-19 (13)," which consider the management of patients before, during and after thrombectomy. They agree with the model proposed by Khosravani et al. (10) with regards to presuming COVID positive status unless proven otherwise. Notably, these guidelines concur with the "*Consensus Statement from Society for Neuroscience in Anesthesiology & Critical Care*" about "*Anesthetic Management of Endovascular Treatment of Acute Ischemic Stroke During COVID-19 Pandemic* (9)," in that general anesthesia should be used if there are concerns surrounding the need for mid-procedural conversion and intubation which could be very detrimental and could expose the whole team, a scenario that should be avoided at all cost. However, these latter guidelines do not address the issue of separating COVID-19 patients from others in terms of scanning equipment, radiology suites, and decontamination protocols.

RECOMMENDATIONS FOR TREATING PATIENTS WITH NEUROLOGICAL SYMPTOMS AND SUSPECTED ACUTE ISCHEMIC STROKE PATIENTS

Given the possible neuroinvasive potential of COVID-19, there is a need to consider both the short and long-term implications of COVID-19, and implement systems-level methods of assessing, addressing, and longer-term monitoring (**Figure 1**). We expect that there is a significant amount of variability based on institution and country with respect to COVID-19 testing. For example, the earliest possible result time for COVID testing at one of our hospitals is 7 h but the serology test that would take minutes to give a result was just Food and Drug Administration (FDA) approved and hopefully will be introduced soon but until this is available widely it will be practically difficult to rule out COVID-19 during code stroke (at least at many hospitals in the US and elsewhere), and as such, we propose that all patients undergoing code stroke be presumed COVID-19 positive. This is concurrent with the American Heart Association (AHA) emergency guidelines for stroke centers in the context of COVID-19 (14). All COVID-19 positive patients should be triaged into COVID-19 neuro or COVID-19 non-neuro wards depending upon the presence of neurological symptoms (6). Common neurological complaints include dizziness, headache, anosmia, and dysgeusia (14).

In patients with a suspected acute stroke:

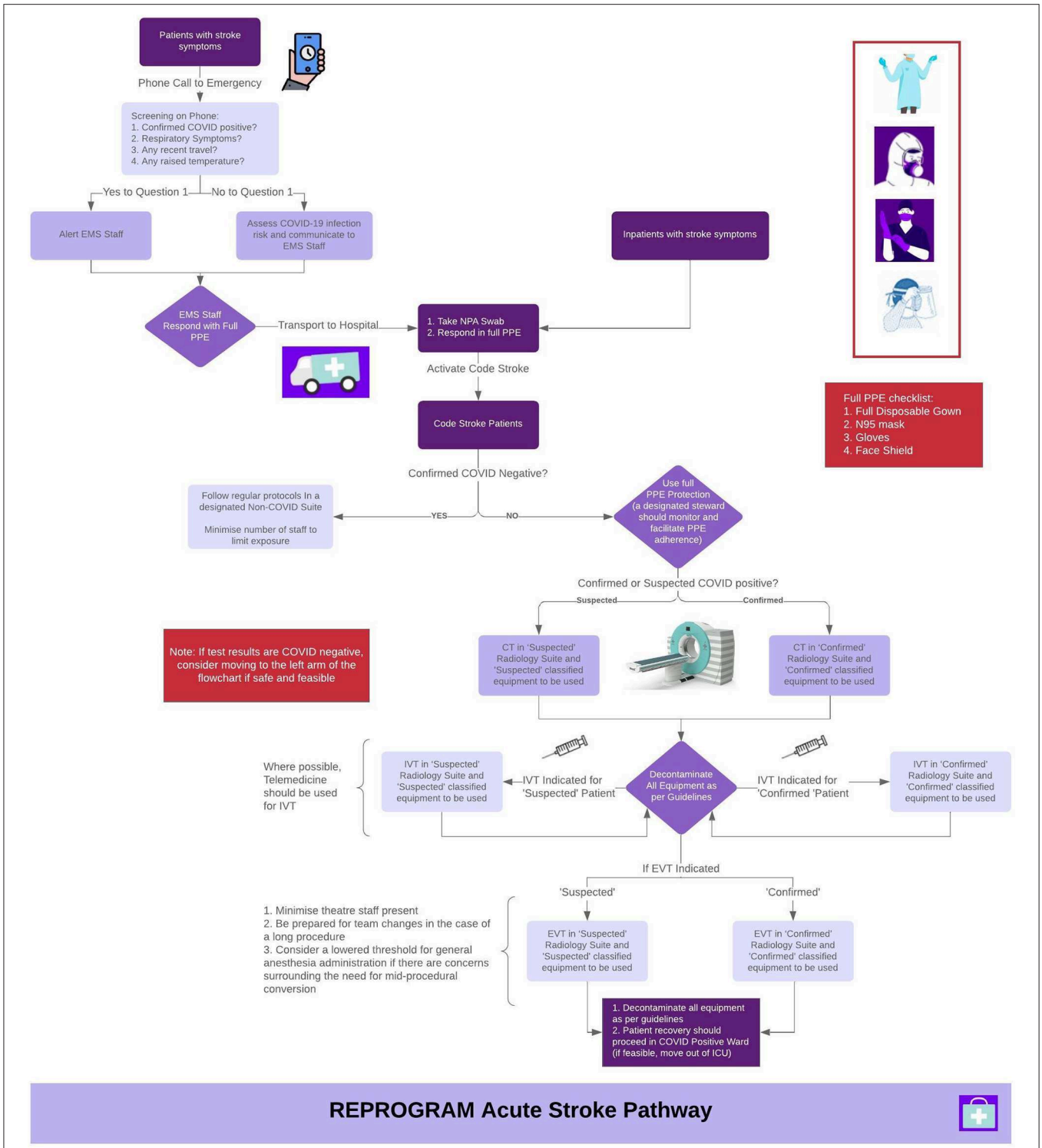


FIGURE 1 | Proposed acute stroke pathway in the setting of the coronavirus 2019 (COVID-19) pandemic**.** Notably, there are 3 different suite options recommended: Non-COVID, Suspected COVID and Confirmed COVID. EMS, Emergency Medical Services; NPA, Nasopharyngeal Aspirate; PPE, Personal Protective Equipment; IVT, Intravenous Thrombolysis; EVT, Endovascular Therapy; ICU, Intensive Care Unit; CT, Computed Tomography.

- All acute stroke patients should be treated as COVID positive until proven otherwise, and full Personal Protective Equipment (PPE) should be used when responding to a code stroke (10, 13).

- Telemedicine should be used to determine eligibility and perform intravenous thrombolysis [trans plasminogen activator (tPA)] to minimize potential exposure to infectious patients (14, 15). Patients who receive tPA do not need to be admitted to the ICU, if stable. Prior to the pandemic, it was standard practice in the US to admit all post-tPA patients to the ICU for 24 h. However, the AHA recommends that there is little evidence to support post-tPA ICU stay (14).
- Separate scanning equipment and radiology suites for negative, suspected, and confirmed COVID-19 patients, with clear decontamination protocols after each patient (16).
- Separate suites for endovascular treatment of negative and suspected/confirmed COVID-19 patients, with extra equipment stocked in the latter to prevent staff having to retrieve equipment. Clear decontamination protocols after each patient (13).
- In all theaters, minimize exposure to staff and the number of perioperative workers (10, 11).
- In the case of long procedures, team changes should be encouraged to minimize prolonged exposure to healthcare workers (11).
- A lowered threshold for general anesthesia administration in terms of concerns surrounding the need for mid-procedural conversion (9, 13).
- Where possible, post thrombectomy recovery should occur outside of ICU in the stroke unit if those beds are required for COVID-19 patients (14).
- It is recommended that suspected COVID-19 patients should be treated as COVID-19 positive until the polymerase chain reaction (PCR) diagnosis confirms otherwise, and such patients should be admitted to COVID-19 positive wards. Separate stroke units for COVID-19 positive and negative patients are recommended.
- To ensure the quality of stroke care for COVID-19 stroke patients, such patients could be admitted to other wards for COVID-19 positive patients. Dysphagia management, physical or logo therapy, and standard in-hospital rehabilitation of stroke patients should be provided; however, concerned staff should wear adequate PPE to prevent exposure and transmission.
- Healthcare workers in secondary hospitals and radiology facilities are recommended to wear adequate PPEs when caring for someone with a confirmed or suspected case of COVID-19.

It is advised that patients in which neurological symptoms are present:

- Patients should be monitored for short-term and/or possibly long term cognitive or neurological impairments. Cognitive impairment could be assessed using routine tests such as Mini-Mental State Examination (MMSE) by treating clinicians. Large scale community screening with good sensitivity/specificity could also be administered using telephone, by informant proxy or directly by post [such as Cognitive Assessment Screening Test (CAST)] provided the test has a good sensitivity/specificity balance (>85%) (17).
- For patients presenting with neurological symptoms in future, past COVID-19 infection should be ascertained, along with the clinical severity, and corroborating imaging findings.
- In addition, imaging could be used to assess the damage to the blood brain barrier (BBB) to examine whether COVID-19 induces a transient or long-term change. BBB assessment and permeability quantification could be done either: (a) semi-quantitatively by comparing the scans before and after contrast injection, or (b) quantitatively using perfusion-weighted or permeability magnetic resonance imaging (MRI) technique, vis a vis dynamic contrast-enhanced MRI (DCE-MRI) (18).

OTHER ACUTE NEUROLOGICAL CONDITIONS

For all acute neurological conditions, a major concern revolves around the decrease in the proportion of acute presentations due to fear of contracting COVID-19 while accessing health services and the presumption that all healthcare resources are now mobilized to prioritize COVID-19 patients (14). This could have negative consequences vis a vis long-term disability subsequent to permanent brain damage due to acute neurological emergencies such as traumatic brain injury (19). Similarly, earlier symptoms of emergent brain tumors, such as headache and ataxia (20) may be neglected or cranial neuropathies from mass effect of a brain aneurysm, due to the perceived cons of seeking help. As of yet, significant gaps exist in the literature pertaining to how to address delayed or absence of presentation. Use of telemedicine where possible, social distancing within clinics for patients coming to the hospitals and systems-level separation of patients with fever and respiratory symptoms from those without having been proposed as possible solutions to minimize the impact (21).

Public health campaigns surrounding measures that are in place to minimize infection transmission and ill consequences of failing to present with a condition that does indeed warrant medical attention need to be pursued. Also, the long-term negative impact of the delayed presentation should be emphasized. A recent case report identified a link between frequent convulsive seizures and COVID-19 infection in the context of emergent epilepsy (22). In light of these anecdotal findings, it is relevant that guidelines pertaining to seizure management in COVID-19 cases are not available, to the best of our knowledge. With regards to chronic epilepsy patients, longer-term medicine prescription, use of telemedicine, and optimal seizure management plans have been recommended (23). Similar issues exist with respect to the management of aneurysmal presentations as no specific guidelines exist in the COVID-19 scenario.

The number of COVID 19 positive patients under 18 years of age represent 1.7% of total lab-confirmed cases in the USA (24). Given the relatively low proportion of COVID-19 pediatric patients, neurological manifestations are very unlikely to be delineated.

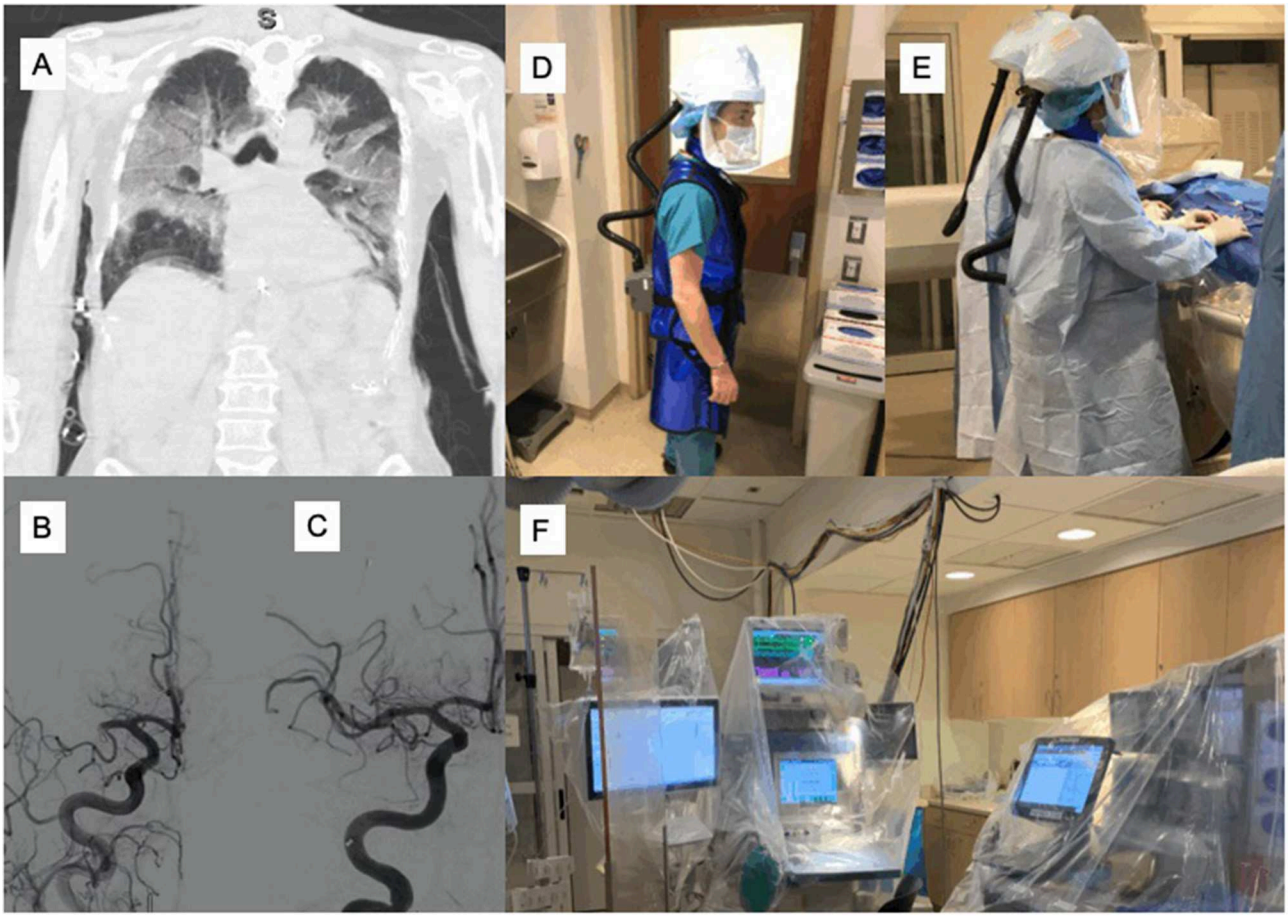


FIGURE 2 | Illustration of an acute stroke reperfusion work-up in a COVID-19 positive case. A patient in the age-group of 65–75 years, with a history of atrial fibrillation and on anticoagulation, presented to an outside facility with difficulty breathing (dyspnea), high temperature and severe cough. COVID-19 work-up was followed and the patient tested positive for COVID-19. Chest computed tomography (CT) revealed bilateral infiltrates **(A)**. The patient was intubated and sedated a day later. On Day 3, the nurse noticed that she was not moving the left side to painful stimuli; given the time of onset could not be determined (unknown), intravenous thrombolysis was not given. Baseline non-contrast computed tomography (NCCT) head was normal; the patient was transferred to the comprehensive stroke center. CT angiography (CTA) showed the right M1 and A2 occlusions. Pre-intervention digital subtraction angiography (DSA) confirmed occlusion in the right M1 and A2 arteries **(B)**. Endovascular thrombectomy (EVT) was performed successfully with complete angiographic reperfusion (thrombolysis in cerebral infarction (TICI) score of 3). The patient was still intubated by the time the manuscript was written. **(C)** Post-intervention DSA imaging demonstrated good reperfusion outcome (TICI3). A clinician with *3M™ Versaflo™ TR-600* Powered Air Purifying Respirator (PAPr) – personal protective equipment (PPE) for protection against the air-borne virus is shown **(D)**. The interventional neuroradiology (INR) team doing the EVT procedure while wearing their full PPEs (sterile gown, gloves and PAPr) is shown **(E)**. Post-procedure, all INR suite equipment including anesthesia machines and pyxis are secured using surgical drapes and equipment covers **(F)**. COVID-19, Coronavirus 2019; NCCT, Non-contrast computed tomography angiography; CTA, CT angiography; EVT, Endovascular thrombectomy; TICI, Thrombolysis in cerebral infarction score; DSA, Digital subtraction angiography; PAPr, Powered Air Purifying Respirator; PPE, Personal protective equipment; INR, Interventional neuroradiology.

SUPPORTING OUR HEALTHCARE WORKERS

This pandemic is adversely challenging the health systems, causing stress, fear to healthcare workers, with the pressures of lengthened hours, lack of PPE equipment and systemic changes that are having to be implemented to protect them (10, 14). Indeed many healthcare workers have expressed publicly in the media and on social media channels that the risk of infecting their families is a source of constant stress to them and impacting their intimate relationships significantly (25). Indeed it is also overlooked that the scarcity of resources can impact the management of patients and potentially result in some patient who may have ordinarily fared better having worse outcomes, another key factor in terms of mental health issues and also indeed the morale of healthcare workers, which can have longer terms impacts in terms of the efficiency and drive of health systems (26).

Considering public health ethics, and more specifically the concept of utilitarianism which forms a key part of this, the need to protect our frontline healthcare workers and support their health becomes evident. Utilitarianism refers to judging actions based on how much good they will do for the greatest number of people - thereby forming the backbone of ethics and health policy

debate underpinning the crisis (27). Protecting our healthcare workers gives the most benefit. This can, therefore, involve protecting them from contracting the infection, which could then be spread to their families, other patients, and resultantly the community, as well as focusing on their psychological health so they are able to discharge their duties efficiently and effectively. Various strategies have been proposed for addressing these issues.

Training

It is pivotal that any changes to protocols, such as those related to changes in how to carry out code stroke actions are well-rehearsed, which may include simulation training with the revised protocol (10). An extra healthcare worker on the team will be needed to observe the team while at work to try to detect any breach in the COVID-19 precaution protocols and at the end of a procedure to help undress the team and clean their PPEs.

Breaks

Managing a pandemic of this proportion can undeniably cause stress and fear. As such it has been proposed that healthcare workers, particularly those working with COVID-19 positive cases, be given regular breaks (16) and encouraged to recognize their limits (28). We also propose that healthcare workers be given information pertaining to relaxation and coping strategies; whilst many healthcare workers may already be aware of these, a reminder may be beneficial.

Team Cohesion and Peer Support

The World Health Organization "Mental health and psychosocial considerations during the COVID-19 outbreak" document advocates the role of a "buddy" or peer support system for more experienced clinicians to assist and support their less experienced colleagues, as a means to not only help manage stress but also learn how to efficiently enact the protocols that may be in place in an organization (29). This is especially relevant as the health systems are being reorganized and protocols are being revised regularly, sometimes on a daily basis (30). Online peer-support networks for discussions as well as social media and messaging chat groups may provide a valuable outlet for clinicians.

Supporting Home Environments

Planning how healthcare workers will interact with their families and reorganize their living arrangements can help de-escalate the stressors as reported in the media (25). The Victorian government in Australia has announced that all healthcare workers required to self-isolate or tested positive for COVID-19 will be provided hotel accommodation to minimize risks to them and to their families, with an indication to expand this model to other states and territories (31). It is important for these recommendations to be specific to avoid creating further anxiety among healthcare workers (32).

CONCLUSIONS

In the COVID-19 pandemic, acute neurological care is increasingly under stress due to ongoing reorganization and rationing of services to meet the demands of frontline COVID-19 cases. In this article, we have identified and proposed various considerations that may minimize the risk to health systems, healthcare workers, and the patients. The differential diagnosis of severe acute respiratory syndrome CoV (SARS-CoV2) infection should be considered in patients with neurological symptoms during the COVID-19 period (4). This is important to avoid missed or delayed diagnosis and prevent viral transmission. All patients amidst this pandemic should be screened for COVID-19 and telemedicine could be used to triage these patients and possibly deliver intravenous thrombolysis. For those who may be candidates for endovascular thrombectomy, extra precautions need to be taken to minimize procedural risks associated with the aerosol transmission of the COVID-19 virus and possible exposure to the healthcare staff. An example of reperfusion therapy work-up with PPEs in a COVID-19 stroke patient is illustrated in **Figure 2**. Public health campaigns to educate and increase awareness of the community about the need to seek urgent medical attention should acute neurological symptoms occur. Special considerations also apply for patients with traumatic brain injury and those requiring urgent aneurysm surgery or carotid endarterectomy. We are alarmed at the rising deaths of healthcare workers who are waging a war against the COVID-19 without the provision of adequate PPE to defend themselves. The cost of adopting the proposed protocol and its impact on the quality of care merits further study. The current consortium is expeditiously working toward rapid adoption of the proposed protocol. Further study on the impact and cost these measures may have on the quality of care and its results are envisaged. However, given the nature of the pandemic and emerging situation, the safety of healthcare workers' is paramount and thus justifies the heightened safety measures suggested in our protocol with an anticipation that this would hopefully limit the exposure. Minimizing the harm to healthcare workers should be a priority as potential exposure can not only compromise the health systems, expose other workers, and patients to COVID-19; but will also have a negative impact on the morale of professional colleagues.

ETHICS STATEMENT

Written, informed consent was obtained from the individual/legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SB devised the project, the main conceptual ideas and proof outline, encouraged DS to investigate and supervised the findings of this work. SB and DS wrote the first draft of the manuscript. All authors discussed the results and recommendations and contributed to the final manuscript. The consortium would like to thank PJ for sharing an illustrative case example included in the study. The opinions expressed in this article are those of the

authors and do not necessarily represent the decisions, official policy, or opinions of the affiliated institutions.

ACKNOWLEDGMENTS

We would like to acknowledge the REPROGRAM consortium members who have worked tirelessly over the last days in contributing to various guidelines, recommendations, policy briefs, and ongoing discussions during these unprecedented and challenging times despite the incredibly short timeframe. We would like to dedicate this work to our healthcare workers who have died due to COVID-19 while serving the patients at the frontline and to those who continue to serve during these challenging times despite lack of personal protective equipment.

REFERENCES

1. World Health Organisation. *Naming the Coronavirus Disease (COVID-19) and the Virus that Causes it*. (2020). Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-covid-2019-and-the-virus-that-causes-it (accessed April 7, 2020).
2. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. (2020). doi: 10.1002/jmv.25824. [Epub ahead of print].
3. Padovani A. *Special Report COVID-19: Neurologists Adapt in Northern Italy*. (2020). Available online at: https://www.eanpages.org/2020/04/01/special-report-covid-19-neurologists-adapt-in-northern-italy/ (accessed April 9, 2020)
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) e201127. doi: 10.1001/jamaneurol.2020.1127. [Epub ahead of print].
5. Hopkins C, Kumar N. *Loss of Sense of Smell as Marker of COVID-19 Infection*. London: The Royal College of Surgeons of England ENT UK (2020).
6. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. (2020) 11:995–8. doi: 10.1021/acschemneuro.0c00122
7. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology*. (2020). doi: 10.1148/radiol.2020201187. [Epub ahead of print].
8. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun*. doi: 10.1016/j.bbi.2020.03.031. [Epub ahead of print].
9. Sharma D, Rasmussen M, Han R, Whalin M, Davis M. Anesthetic Management of Endovascular Treatment of Acute Ischemic Stroke During COVID-19 Pandemic: Consensus Statement From Society for Neuroscience in Anesthesiology & Critical Care (SNACC)_Endorsed by Society of Vascular & Interventional Neurology (SVIN), Society of NeuroInterventional Surgery (SNIS), Neurocritical Care Society (NCS), and European Society of Minimally Invasive Neurological Therapy (ESMINT). *J Neurosurg Anesthesiol*. (2020). doi: 10.1097/ANA.0000000000000688. [Epub ahead of print].
10. Khosravani H, Rajendram P, Notario L, Chapman M, Menon B. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) Pandemic. *Stroke*. (2020). doi: 10.1161/STROKEAHA.120.029838. [Epub ahead of print].
11. Royal College of Surgeons of England. *Updated Intercollegiate General Surgery Guidance on COVID-19. 35-43 Lincoln's Inn Fields*. London: Royal College of Surgeons of England (2020).
12. Society of American Gastrointestinal and Endoscopic Surgeons and The European Association of Endoscopic Surgery. *SAGES and EAES Recommendations Regarding Surgical Response to COVID-19 Crisis*. Society of American Gastrointestinal and Endoscopic Surgeons (2020).
13. Fraser JF, Arthur A, Chen M, Levitt M, Mocco J, Albuquerque FC, et al. Society of NeuroInterventional Surgery recommendations for the care of emergent neurointerventional patients in the setting of COVID-19. *J Neurointerv Surg*. (2020) 12:539–41. doi: 10.1136/neurintsurg-2020-016098
14. Lyden P. Temporary emergency guidance to US stroke centers during the COVID-19 pandemic. *Stroke*. (2020). doi: 10.1161/STROKEAHA.120.030023
15. Burke JF, Chan AK, Mummaneni V, Chou D, Lobo EP, Berger MS, et al. Letter: The coronavirus disease 2019 global pandemic: a neurosurgical treatment algorithm. *Neurosurgery*. (2020). doi: 10.1093/neuros/nyaa116. [Epub ahead of print].
16. Huang Z, Zhao S, Li Z, Chen W, Zhao L, Deng L, et al. The battle against coronavirus disease 2019 (COVID-19): emergency management and infection control in a radiology department. *J Am Coll Radiol*. (2020). doi: 10.1016/j.jacr.2020.03.011. [Epub ahead of print].
17. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA. A review of screening tests for cognitive impairment. *J Neurol Neurosurg Psychiatry*. (2007) 78:790–9. doi: 10.1136/jnnp.2006.095414
18. Chassidim Y, Veksler R, Lublinsky S, Pell GS, Friedman A, Shelef I. Quantitative imaging assessment of blood-brain barrier permeability in humans. *Fluids Barriers CNS*. (2013) 10:9. doi: 10.1186/2045-8118-10-9
19. National Academies of Sciences EaM. *Evaluation of the Disability Determination Process for Traumatic Brain Injury in Veterans*. Washington, DC: The National Academies Press (2019).
20. Snyder H, Robinson K, Shah D, Brennan R, Handrigan M. Signs and symptoms of patients with brain tumors presenting to the emergency department. *J Emergency Med*. (1993) 11:253–8. doi: 10.1016/0736-4679(93)90042-6
21. American Headache Society. *Headache Clinic Workflows During the COVID-19 Pandemic*. (2020). Available online at: *https://americanheadachesociety.org/news/headache-clinic-workflows-covid-19/* (accessed April 7, 2020).
22. Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: a case report. *Iran Red Crescent Med J*. (2020) 22:e102828. doi: 10.5812/ircmj.102828
23. American Epilepsy Society. *COVID-19 Resources for Epilepsy Clinicians*. (2020). Available online at: *https://www.aesnet.org/about_aes/position_statements/covid-19/for-clinicians/* (accessed April 7, 2020).
24. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep*. (2020) 69:422–6. doi: 10.15585/mmwr.mm6914e4
25. Lewin E. *Risk of Infecting Others With COVID-19 Key Concern for Healthcare Workers*. (2020). Available online at: https://www1.racgp.org.au/newsgp/clinical/risk-of-infecting-others-with-covid-19-a-key-conce/ (accessed April 7, 2020).
26. Black Dog Institute. *Mental Health Ramifications of COVID-19*: Sydney: The Australian context Black Dog Institute (2020).
27. Torda A. *Ethics Cube*. (2017). Available online at: https://ethics.med.unsw.edu.au/ (accessed April 7, 2020).
28. Chen Q, Liang M, Li Y, Guo J, Fei D, Wang L et al. Mental health care for medical staff in China during the COVID-19 outbreak. *Lancet Psychiatry*. (2020) 7:e15–e6. doi: 10.1016/S2215-0366(20)30078-X
29. World Health Organisation. *Mental Health and Psychosocial Considerations During the COVID-19 Outbreak 2020*. (2020).

30. Greenberg N, Docherty M, Gnanapragasam S, Wessely S. Managing mental health challenges faced by healthcare workers during covid-19 pandemic. *BMJ*. (2020) 368:m1211. doi: 10.1136/bmj.m1211
31. Ilanbey S. *Healthcare Workers to be Given Free Accommodation Under $20m 'Hotels for Heroes' Plan*. (2020). Available online at: *https://www.theage.com.au/national/victoria/healthcare-workers-to-be-given-free-accommodation-under-20m-hotels-for-heroes-plan-20200405-p54h6b.html*. (accessed April 7, 2020).
32. Adams JG, Walls RM. Supporting the health care workforce during the COVID-19 Global epidemic. *JAMA*. (2020). doi: 10.1001/jama.2020.3972. [Epub ahead of print].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

OPINION
published: 29 May 2020
doi: 10.3389/fneur.2020.00578

Evolving Healthcare Delivery in Neurology During the Coronavirus Disease 2019 (COVID-19) Pandemic

Patrick M. Chen and Thomas M. Hemmen*

Department of Neurosciences, University of California, San Diego, San Diego, CA, United States

Keywords: COVID-19, pandemic, general neurology, healthcare workflow, stroke, PPE, telemedicine, burnout

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has led to the development of a rapidly evolving pandemic (1). The pandemic changed the assumptions made by most developed health care system: ample supplies and an overwhelmingly safe environment for patients and healthcare providers. Hospital resources and supply are no longer secure, and the potential risk to patients and caregivers is increased. As neurologists, we face these challenges in many areas.

Here, we discuss the impact of the pandemic on neurology work flow in four areas: inpatient care, outpatient care, research, and ethics.

INPATIENT MANAGEMENT

One key lesson from the COVID-19 experience internationally is the rapid depletion and scarcity of medical supplies [e.g., personal protective equipment (PPE) and mechanical ventilators], beds, and staff—an increasing occupational hazard for health care workers (2–4). We must critically evaluate our workflow and resource utilization in this crisis. Acute stroke alerts present the most direct potential interface with COVID-19 patients. Existing stroke alert paradigms focus on high sensitivity for stroke detection with generally low specificity, requiring high resource utilization (5).

Several new workflows and consensus statements have been proposed for "protected" stroke alerts (6–9). Overarching themes include expanded pre-screening in peri-hospital setting, widespread PPE training, designated "safety leaders" for monitoring proper precautions, limited examinations, and telemedicine. Similarly, we have demonstrated the practicality of implementing tele-stroke video technology in the emergency room for initial triage during the pandemic (10). Rapidly implementing a large-scale "protected code" policy requires multidisciplinary coordination with hospital administration, other subspecialties (e.g., emergency department), and frequent feedback on the policies effectiveness from the frontline (e.g., nursing, ancillary staff, and trainees). In the future, the stroke alert could consolidate other COVID-19-related tests, such as chest imaging. How these protected workflow trends will affect time metrics and stroke care outcomes is yet to be determined.

Neurologic admissions and transfers to the hospital must be triaged and prioritized. We previously had the luxury of prolonged observation and extended outpatient workups, but we must now consider the exposure risks of prolonged hospitalization. Surgical specialties have significantly reduced "elective" surgery (3). In a similar vein, we should be judicious in determining if the benefits of admission or intervention supersede the potential dangers and resource utilization in the current crisis. We often call upon the neurological intensive care unit (ICU) for co-management, though these beds and staff are also needed for COVID-19 overflow. In a pandemic, it is reasonable to reserve resources, such as thrombectomy, to patients that would benefit the most, according to

OPEN ACCESS

Edited by:
Jesús Porta-Etessam,
Hospital Clínico San Carlos, Spain

Reviewed by:
Patricio Sandoval,
Pontificia Universidad Católica de chile, Chile
Maria Nuria González García,
Hospital Clínico San Carlos, Spain

****Correspondence:***
Patrick M. Chen
pmc003@health.ucsd.edu

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *21 April 2020*
Accepted: *19 May 2020*
Published: *29 May 2020*

Citation:
Chen PM and Hemmen TM (2020) Evolving Healthcare Delivery in Neurology During the Coronavirus Disease 2019 (COVID-19) Pandemic. Front. Neurol. 11:578. doi: 10.3389/fneur.2020.00578

high-level (Class 1, Level A Evidence) guidelines (7). Ideally separate units should be used to isolate neurologic patients with COVID-19 from neurology patients without the disease.

Beyond stroke patients, neurologists interface with the COVID-19 population for symptoms including anosmia, encephalopathy, headache, or meningitis-encephalitis rule out. We must be cautious in pigeonholing a COVID-19 patient and must resist substituting proxy diagnostics for a clinical exam because of infection risk. Ancillary testing (e.g., EEG and CT scans) involve not only the machinery that will need to be disinfected but also personnel with risks for viral exposure. Yet, standard of care, if indicated, should not be withheld due to COVID-19. Given variability in individuals risk tolerance, a unified protocol may help remove these possible diagnostic biases in COVID-19 patients. Finally, with a need for mechanical ventilators and ICU resources, our teams will need to be practical but still thorough in prognostication of catastrophic neurologic disease to assist resource allocation.

Many institutions share similar policies to reduce COVID-19 transmission (9). At our institution, family visits are restricted, and all admitted patients receive a SARS-COV2 PCR test. Regarding PPE, aerosolized high-risk patients require N95 masks/powered air purifiers (PAPR) with eye protection, gowns, and gloves, while other inpatients require surgical masks, gloves, and eye protection (6). In circumstances of limited history, such as stroke codes or persons under investigation, an abundance of care should be taken. The possibility of asymptomatic COVID-19 carriers or occult history should be considered in our patients and consults, underpinning the importance of universal precautions and rapid COVID-19 testing when available. Team members at high risk (e.g., immunosuppression and those over age 60) are triaged to avoid direct contact (e.g., telemedicine role) when possible. Finally, should a team member be exposed to COVID-19 or show concerning symptoms, we follow the institutions policy regarding symptom monitoring, self-quarantine, and testing.

The day-to-day routines of neurologists in the hospital have changed. For our institution, rounds have been streamlined to one senior team member, and team rounds are carried out over video conferencing. We practice six feet of distance amongst staff and patients and consider telephone-video conversation when possible except for critical physical examinations. We perform limited, but practical, neurologic examinations (at minimum: mental status, cranial nerves, and gross motor skills) focused on localization that guides changes in management. COVID-19-positive or PUI patients are seen last to reduce transmission. Neurologists have the challenge of protecting the specialties tenants of diagnostic exactness and personalized patient rapport despite these limitations.

Finally, we have yet to see the long-term effects of COVID-19 on trainee education and mental health. The Accreditation Committee of General Medical Education have made new exceptions to previous training requirements considering the pandemic, though there is concern this may lead to suboptimal learning conditions. Currently, neurology trainees may be deployed to non-specialty services while primary teams are downsized. Didactics are converted to video conferences, clinics are conducted via telemedicine, and the tradition of neurology bedside rounds and examination are curtailed. Do these adaptations add to or deprive neurology training, and will these changes persist after the pandemic? Similarly little is known about the impact of COVID-19 on the psychological health of our team members who face a number of stresses: occupational risk, evolving policy changes, and unprecedented ethical decisions. The risk for trainee burnout—occupational, mental, emotional, and physical exhaustion—is high. A prophylactic solution to this by leadership should take the form of self-care initiatives, multidisciplinary mental health support groups, and frequent open forums (e.g., town halls) for trainees and all team members.

OUTPATIENT CARE AND TELEMEDICINE

A substantial portion of the neurologic population is classified by the Center for Disease Control (CDC) as "high risk" (e.g., elderly, neuromuscular, immunosuppressed) for COVID-19 illness (11, 12). How can we best protect this vulnerable population while providing continuity of care?

A review of current literature shows various subspecialties—multiple sclerosis (13), vascular (8), neuromuscular (14), and epilepsy (15)—have attempted to tackle this question in the form of consensus statements by subspecialty leaders. Recommendations are broad but share consistent themes: (1) screen all patients and use universal precautions in clinic visits; (2) prevent unnecessary medical facility visits; (3) triage diagnostic workups; (4) develop individualized contingency plans; and (5) avoid drastic regimen changes based on speculative links between COVID-19 and neurologic disease.

The use of telemedicine platforms is critical when providing care to high-risk populations. Pre-pandemic literature suggested telehealth was not inferior to face-to-face clinic visits for outcomes across neurologic subspecialties (16). The expansion of Medicare coverage beyond rural areas and relaxing tele-HIPAA requirements in response to the pandemic (17, 18) has catalyzed rapid and wide implementation. The technology is versatile and could be expanded to monitoring with remote devices (e.g., accelerometers in Parkinson's disease), neuro-rehabilitation, and providing a hotline to curb isolation in the elderly and disabled. Proponents of telemedicine highlight its role in the "4 Cs": better access to care, greater convenience, enhanced patient comfort, and better confidentiality. There is also an added new C—"contagion" (19). Telemedicine is limited in the funduscopic, neuromuscular, and vestibular exams, and there remain concerns regarding consistent technology access and consistent privacy standards. We urge neurologist to address previous methodological flaws in the literature through collection of outcomes with neuro-telehealth. By addressing past infrastructure gaps, we may develop a feasible telehealth system for a high-quality standard of care post-pandemic. This data will help establish the marginal benefits of in-person visits over tele-visits. In many situations, this benefit may be much smaller from a risk–benefit and cost analysis standpoint than traditionally thought.

A key question remains of how we will prepare for the return of neurologic patients with delayed diagnosis because of COVID-19. The number of stroke and myocardial disease hospital presentations decreased during the peak of the pandemic (20). These patients avoided and delayed health care due to isolation and quarantine, and this is likely applicable to other chronic neurologic conditions. As neurologists, we will need to explore the effects of isolation and fear on the outcomes of our neurologic patients. It is our responsibility to be proactive in educating our patients on the urgency of evaluation when appropriate, perhaps with more frequent tele-health follow-up, designated post-hospitalization follow-up coordinators, and large public organizational campaigns (e.g., Stroke F.A.S.T campaign). We expect to see an upsurge in delayed neurologic complications as pandemic restrictions lighten, which may further exacerbate healthcare resource limitations.

COVID-19 AND NEUROLOGY RESEARCH

The pandemic has created a fervor within the research community, and neurology is not an exception. A number of small, observational retrospective studies have emerged with reports of Guillain-Barre (21) syndrome, hemorrhagic encephalopathy (22), and stroke (23). There is speculation that anosmia may be from olfactory involvement of SARS-CoV2 (24). Yet, it remains unclear if these reported correlations also lend to causation. Editorial boards have pushed these findings to the forefront by offering pre-review releases, expedited review, and open access. While rapid information dissemination is important in uncertain times, we caution against the risk of "research exceptionalism" (25). As the pandemic matures, the mentality of "better than nothing" should be transitioned to similar rigorous pre-pandemic publication standards if the findings are to be of clinical meaning. Pandemic opportunism should not compromise the past standard of research integrity. Given this, we must be cautious in how we interpret findings, especially when considering diverging from pre-pandemic standard of care.

COVID-19 has posed many challenges to ongoing large clinical trials. Quarantine and travel restrictions have forced the pause of enrollment and rigid study protocols place several logistical strains on research staff. Nevertheless, there remains a moral obligation to current study participants to complete these studies. How this is handled is complex and individualized by the study group. As the pandemic recedes, the impact of the pandemic directly (e.g., loss of participants or data) and indirectly (e.g., infection as a confounder) will need to be accounted for in result analysis and explored further.

Ultimately, we must leverage our research focus and resources wisely. The societal drive to understand COVID-19 should not also come at the expense of our non-COVID-19 neurologic patients. While the neurologic complications have captured the public eye, we should consider questions around quality improvement, personnel wellness, and the impact of the aforementioned workflow changes. An important task moving forward is to be methodical in our collection of data for COVID-19 neurologic patients if we are the truly understand its role in the central nervous system. This will likely take the form of multi-center consortiums with a standardized protocol to create large prospective databases.

ETHICS AND ISSUES IN A RESOURCE LIMITED ENVIRONMENT

A myriad of potential ethical situations could arise for neurologists (26). Accounts of the Lombardy region of Italy detail harrowing decisions of life and death by ICU physicians (3). How do we weigh diseases such as Alzheimer's or Parkinson's against ventilated patients when asked about "life prognosis" or "prospective instrumental value to others" (4)? How do we factor in neurologic comorbidities when making triage decisions? While we hope to never reach this point, we must prepare for it. We must not categorically exclude those with chronic neurologic and cognitive disability. It is imperative we proactively discuss goals of care with patients outside the hospital to shield the frail from medical intervention that may provide potential harm. Now, is a time to develop a robust palliative care program for patients with limitation of therapeutic effort (LTE). Furthermore, these difficult ICU decisions should use advanced directives and living wills and be guided in a multidisciplinary fashion with ethical committees.

In the first weeks of the pandemic, we noticed many subtle clinical situations that already challenge our previous framework of clinical practice. A seemingly simple example is the extent of observation and work up in a transient ischemic attack. Does a patient on therapeutic anticoagulation and a low ABCD score for transient numbness warrant admission? Previously in our academic tertiary hospital, we would admit this patient and pursue an extensive stroke work up. Currently, the risk of exposure to COVID-19 in the hospital leads providers and patients to prefer outpatient workup, forgoing, or curtailing inpatient monitoring. How this impacts patient outcome is not certain. On the other hand, the risk of nosocomial infection previously existed, and the potential for harm was present in healthcare before COVID-19. How much higher this risk is now with COVID-19 is unexplored. These questions may lead to a fundamental risk assessment going forward where the marginal benefit of improved outcome for inpatient admission is weighed against the increased risks associated with hospital stay and procedures (27).

Our actions as specialists do not exist in a vacuum. We should note the impact our testing has on nurses and ancillary staff. For instance, we were consulted for abnormal neck movements in a prone-position COVID-19-positive patient. Our initial impulse was to order a 24-h EEG to capture this event. But a number of questions arose. What is the benefit of a 32-lead EEG established by an EEG technologist over a portable and limited EEG that can be established by a bedside provider who already had used PPE and was at the bedside? How does our diagnostic plan differ from pre-pandemic? What are the effects on patient outcome if we adjust our diagnostic and treatment algorithm in the setting of the COVID-19 pandemic? Our department is developing a collaborative protocol posed from these clinical questions.

Finally, how do we manage outpatients with progressive neurologic disease—the ones with limited life expectancy but who not ill enough to be in the hospital? An example is a man with longstanding amyotrophic lateral sclerosis (ALS) who is scheduled for outpatient gastrostomy tube placement. The interventional radiology team inquires if gastrostomy tube placement can be delayed as the healthcare system reduces use of equipment and staff for elective procedures. A fully informed discussion in a controlled setting with the patient and his family regarding the goals of care is important. We are still not sure how these discussions will be framed by the current crisis or used for triage, but we as neurologists are well-equipped for these discussions and should be proactive.

CONCLUSION

COVID-19 has disrupted the neurologic healthcare ecosystem in the inpatient, outpatient, and research setting. It is paramount that we aid in preserving limited hospital resources and protect our patients and teams by critically assessing all clinical practices. What emerges are striking changes in clinical workflow and a chance to develop telemedicine and potentially difficult clinical-ethical decisions. Moving forward, we should be diligent in data collection and strive to understand how these workflow changes impact our patients. The silver lining in this pandemic is we have the opportunity as a specialty to revisit our practices and change for the better.

AUTHOR CONTRIBUTIONS

PC: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. TH: analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. All authors read and approved the final manuscript.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–720. doi: 10.1101/2020.02.06.20020974
2. Truog RD, Mitchell C, Daley GQ. The toughest triage - allocating ventilators in a pandemic. *N Engl J Med.* (2020) 382:1973–5. doi: 10.1056/NEJMp2005689
3. Rosenbaum L. Facing Covid-19 in Italy - ethics, logistics, and therapeutics on the epidemic's front line. *N Engl J Med.* (2020) 382:1873–5. doi: 10.1056/NEJMp2005492
4. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of Covid-19. *N Engl J Med.* (2020) 382:2049–55. doi: 10.1056/NEJMsb2005114
5. Schneck M, Bruzzone M, Vlahovic L, Durazo-Arvizu R, Biller J, Flaster M, et al. Acute stroke code accuracy in the inpatient versus Emergency Department (ED) setting (S16.003). *Neurology*. (2016) 86.
6. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon KB. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) Pandemic. *Stroke*. (2020) 120029838. doi: 10.1161/STROKEAHA.120.029838. [Epub ahead of print].
7. Smith MS, Bonomo J, Knight WA IV, Prestigiacomo CJ, Richards CT, Ramser E. Endovascular therapy for patients with acute ischemic stroke during the COVID-19 pandemic: a proposed algorithm. *Stroke*. (2020) STROKEAHA120029863. doi: 10.1161/STROKEAHA.120.029863. [Epub ahead of print].
8. Dafer RM, Osteraas ND, Biller J. Acute stroke care in the coronavirus disease 2019 pandemic. *J Stroke Cerebrovasc Dis*. (2020) 104881. doi: 10.1016/j.jstrokecerebrovasdis.2020.104881. [Epub ahead of print].
9. Waldman G, Mayeux R, Claassen J, Agarwal S, Willey J, Anderson E, et al. Preparing a neurology department for SARS-CoV-2 (COVID-19): early experiences at Columbia University Irving Medical Center and the New York Presbyterian Hospital in New York City. *Neurology*. (2020) 94:886–891. doi: 10.1212/WNL.0000000000009519
10. Meyer D, Meyer BC, Rapp KS, Modir R, Agrawal K, Hailey L, et al. A stroke care model at an academic, comprehensive stroke center during the 2020 COVID-19 pandemic. *J Stroke Cerebrovascular Diseases*. (2020) 104927. doi: 10.1016/j.jstrokecerebrovasdis.2020.104927. [Epub ahead of print].
11. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:343–6. doi: 10.15585/mmwr.mm6912e2
12. Herman C, Mayer K, Sarwal A. Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19. *Neurology*. (2020). doi: 10.1212/WNL.0000000000009673. [Epub ahead of print].
13. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology*. (2020). doi: 10.1212/WNL.0000000000009507. [Epub ahead of print].
14. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. (2020). doi: 10.1212/WNL.0000000000009566. [Epub ahead of print].
15. French JA, Brodie MJ, Caraballo R, Devinsky O, Ding D, Jehi L, et al. Cross: keeping people with epilepsy safe during the Covid-19 pandemic. *Neurology*. (2020). doi: 10.1212/WNL.0000000000009632. [Epub ahead of print].
16. Hatcher-Martin JM, Adams JL, Anderson ER, Bove R, Burrus TM, Chehrenama M, et al. Telemedicine in neurology: telemedicine Work Group of the American Academy of Neurology update. *Neurology*. (2020) 94:30–8. doi: 10.1212/WNL.0000000000008708
17. C. f. M. M. S. (CMS): *Medicare Telemedicine Health Care Provider Fact Sheet* Baltimore, MD. (2020).
18. Hollander JE, Carr GB. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med.* (2020) 382:1679–81. doi: 10.1056/NEJMp2003539
19. Bloem BR, Dorsey ER, Okun SM. The coronavirus disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. *JAMA Neurol.* (2020). doi: 10.1001/jamaneurol.2020.1452. [Epub ahead of print].
20. Kansagra AP, Goyal MS, Hamilton S, Albers WG. Collateral effect of Covid-19 on stroke evaluation in the United States. *N Engl J Med.* (2020) NEJMc2014816. doi: 10.1056/NEJMc2014816. [Epub ahead of print].
21. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-barre syndrome associated with SARS-CoV-2. *N Engl J Med.* (2020) 19:383–4. doi: 10.1056/NEJMc2009191
22. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology*. (2020) 201187. doi: 10.1148/radiol.2020201187. [Epub ahead of print].

23. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) e201127. doi: 10.1001/jamaneurol.2020.1127. [Epub ahead of print].
24. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:10.1002/jmv.25728. doi: 10.1002/jmv.25824
25. London AJ, Kimmelman J. Against pandemic research exceptionalism. *Science*. (2020) 368:476–7. doi: 10.1126/science.abc1731
26. Kim SYH, Grady C. Ethics in the time of COVID: what remains the same and what is different. *Neurology*. (2020). doi: 10.1212/WNL.0000000000009520. [Epub ahead of print].
27. Becher EC, Chassin RM. Improving quality, minimizing error: making it happen. *Health Aff.* (2001) 20:68–81. doi: 10.1377/hlthaff.20.3.68

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 29 May 2020
doi: 10.3389/fneur.2020.00564

An Italian Neurology Outpatient Clinic Facing SARS-CoV-2 Pandemic: Data From 2,167 Patients

Carla Piano[1†], Enrico Di Stasio[1,2†], Guido Primiano[1], Delfina Janiri[1,3], Marco Luigetti[1,4], Giovanni Frisullo[1], Catello Vollono[1,4], Matteo Lucchini[1,4], Valerio Brunetti[1], Mauro Monforte[1], Valeria Guglielmi[1], Giacomo Della Marca[1,4], Amelia Evoli[1,4], Camillo Marra[1,4], Massimiliano Mirabella[1,4], Davide Quaranta[1,4], Enzo Ricci[1,4], Serenella Servidei[1,4], Gabriella Silvestri[1,4], Simone Bellavia[1], Sara Bortolani[1], Francesco Bove[1], Riccardo Di Iorio[1], Andrea Di Paolantonio[1], Danilo Genovese[1], Tamara Ialongo[1], Maria Rita Lo Monaco[1], Jessica Marotta[1], Agata Katia Patanella[5], Alessia Perna[1], Martina Petracca[1], Giorgia Presicce[1], Vittorio Riso[1], Eleonora Rollo[1], Angela Romano[5], Marina Romozzi[1], Cristina Sancricca[1], Irene Scala[1], Gregorio Spagni[1], Marcella Solito[1], Luca Tricoli[1], Paola Zinzi[1], Paolo Calabresi[1,4] and Anna Rita Bentivoglio[1,4]*

[1] Dipartimento Scienze dell'Invecchiamento, Neurologiche, Ortopediche e della Testa-Collo, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [2] Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy, [3] Department of Psychiatry and Neurology, Sapienza University of Rome, Rome, Italy, [4] Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy, [5] Centro Clinico, NEMO, Rome, Italy

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu, Hospital Clínico San Carlos, Spain

Reviewed by:
Naoto Kuroda, Wayne State University, United States
Francisco Javier Carod Artal, NHS Highland, United Kingdom

***Correspondence:**
Guido Primiano
guido.primiano@gmail.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *04 May 2020*
Accepted: *18 May 2020*
Published: *29 May 2020*

Citation:
Piano C, Di Stasio E, Primiano G, Janiri D, Luigetti M, Frisullo G, Vollono C, Lucchini M, Brunetti V, Monforte M, Guglielmi V, Della Marca G, Evoli A, Marra C, Mirabella M, Quaranta D, Ricci E, Servidei S, Silvestri G, Bellavia S, Bortolani S, Bove F, Di Iorio R, Di Paolantonio A, Genovese D, Ialongo T, Lo Monaco MR, Marotta J, Patanella AK, Perna A, Petracca M, Presicce G, Riso V, Rollo E, Romano A, Romozzi M, Sancricca C, Scala I, Spagni G, Solito M, Tricoli L, Zinzi P, Calabresi P and Bentivoglio AR (2020) An Italian Neurology Outpatient Clinic Facing SARS-CoV-2 Pandemic: Data From 2,167 Patients. Front. Neurol. 11:564. doi: 10.3389/fneur.2020.00564

Objective: Neurological sequelae of SARS-CoV-2 infection have already been reported, but there is insufficient data about the impact of the pandemic on the management of the patients with chronic neurological diseases. We aim to analyze the effect of COVID-19 pandemic and social restriction rules on these fragile patients.

Methods: Patients with chronic neurologic diseases routinely followed at the outpatient clinic of Gemelli University Hospital, Rome, were assessed for symptoms suggestive of SARS-CoV-2 infection in the pandemic period, consequences of social restrictions, and neurological disease features, concomitant medical conditions, current medical and disease-specific treatments. Data source: a dedicated telephone survey designed to encompass questions on COVID-19 symptoms and on pandemic effects in chronic neurologic conditions.

Results: Overall, 2,167 individuals were analyzed: 63 patients reported contact with COVID-19 positive cases, 41 performed the swab, and 2 symptomatic patients tested positive for COVID-19 (0.09%). One hundred fifty-eight individuals (7%) needed urgent neurological care, deferred due to the pandemic; 641 patients (30%) suspended hospital treatments, physiotherapy or other support interventions; 405 individuals (19%) reported a subjective worsening of neurological symptoms.

Conclusions: In our population, the presence of neurological chronic diseases did not increase the prevalence of COVID-19 infection. Nevertheless, the burden of neurological disorders has been worsened by the lockdown.

Keywords: neurology, infection, coronavirus, pandemic, health care, COVID-19, personalized medicine

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has spread across Italy since the end of February 2020 and resulted in an increase in total deaths of nearly 100% (1). On March 11th, the World Health Organization (WHO) characterized the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak as a pandemic (2). In response to this, the Italian Government implemented a series of emergency containment measures, including the restriction of social contacts and the quarantine of COVID-19 positive and suspect cases.

The principal manifestations of COVID-19 are fever, cough and dyspnea; the most severe complication of the infection is the acute respiratory distress syndrome (3). In a recent editorial Manji et al. (4) highlighted the concern of neurologists for vulnerability to COVID-19 in patients with neurological diseases. Patients on disease-modifying and immunosuppressant treatments and with respiratory impairment from neuromuscular weakness might be particularly at risk for severe COVID-19 complications (5). Nevertheless, there is insufficient data available on the outcomes of patients with pre-existing neurological disorders (4) or on the impact of the pandemic on their care management. This study aimed at filling this gap by describing the prevalence of symptoms suggestive of COVID-19 infection in a large neurological sample of 2,167 individuals. Furthermore, since recent studies stressed the negative impact of COVID-19 outbreak on quality of life outcomes (6), subjective worsening of neurological conditions and effects of social restrictions were also investigated by a dedicated telephone survey.

MATERIALS AND METHODS

Patient Population

Individuals with chronic neurological diseases who were regularly followed at the outpatient clinic of the Department of Neurology at Agostino Gemelli University Hospital Foundation IRCCS-Catholic University of the Sacred Heart in Rome were consecutively enrolled in the study if they had a scheduled visit during the lockdown.

Inclusion Criteria

Patients with chronic neurological diseases with scheduled visits during the lockdown period, postponed due to social restrictions.

Exclusion Criteria

Patients were excluded if they or their legal support administrator were unable to provide informed and valid consent at the time of the assessment. Patients with cognitive deterioration and not fluent in Italian were also excluded if a caregiver was not available for the interview.

Survey Design and Testing

The study was conducted through a telephone survey. Surveys started on April 1, 2020, and ended on April 15, 2020. A dedicated questionnaire, based on current evidence of SARS-CoV-2 (7), was adopted to collect information on symptoms suggestive of COVID-19 in patients with chronic neurological conditions and to evaluate the impact of social restrictions on the perception of illness. Specifically, the survey assessed: (1) Demographic and clinical characteristics, including age at onset, duration of illness, and disability measures (ADL/IADL) (8); (2) COVID-19 related questions, including history of recent travel in endemic areas, direct contacts with COVID-19 confirmed cases (COVID-19+), symptoms suggestive of COVID-19 infection started or worsened in the last 3 months (fever, cough/sore throat, asthenia, dyspnea, myalgia, and hyposmia/hypogeusia), and confirmatory testing for COVID-19 (nasal/pharyngeal swab test results); (3) information related to the impact of COVID-19 on disease burden, including subjective worsening of neurological symptoms, compliance with restrictions and specific effects of restriction measures on the perception of illness (need of urgent neurological care, discontinuation of pharmacological treatment or physiotherapy, difficulties in finding drugs). We chose the last 3 months as the period in which symptoms could be attributed to SARS-CoV-2 infection because the first case of COVID-19 in Italy was confirmed on January 30, 2020.

Comorbid medical conditions, smoking habits and current pharmacological treatments were also investigated. Drug classes potentially interfering with SARS-CoV-2 (9) (i.e., ACE-inhibitors, sartans, NSAIDs, steroids, immunosuppressant drugs) were distinguished from other pharmacological treatments, including specific treatments for neurological disease (i.e., levodopa, anticholinesterase drugs, memantine, xenazine, riluzole, botulinum toxin injections, and antiepileptic drugs).

Statistical Analysis

All the statistical analyses were carried out using the "Statistical Package for Social Science (SPSS)" program, version 25.0 (IBM Co., Armonk, NY). Collected data were analyzed for normality of distribution using the Kolmogorov-Smirnov test of normality and expressed as mean ± SD (continuous variables) and as frequencies (n, %) for categorical variables according to neurological diagnosis. Univariate correlations were calculated using the non-parametric Spearman correlation coefficient. After adjustment for multiple measures (Bonferroni correction), a $p < 0.01$ was considered statistically significant. The Mann–Whitney and χ^2 tests were used to assess the significance of the differences between subgroups, as appropriate. For major findings the effect size was also reported.

Standard Protocol Approvals, Registration, and Patient Consent

The Survey was reviewed and approved by the Agostino Gemelli University Hospital Foundation IRCCS-Catholic University of the Sacred Heart Ethics Committee, Rome. Because of the biological risks related to the pandemic, participants could not timely provide written informed consent. Therefore, during the phone call, verbal consent was obtained for study participation and use of anonymized data (immediate consent), according to information filed with the Ethics Committee. Participants were informed that written consent would be obtained at the first visit in the hospital (deferred consent).

Data Availability

Upon approved requests, anonymized data will be shared with qualified external researchers.

RESULTS

Two thousand two hundred and eighty-nine patients were surveyed; 122 participants were excluded for incomplete data, unavailability of legal support administrator at the time of the assessment. Twenty-nine patients (1.3%) refused to participate in the study. The final study sample included 2,167 patients. In the final sample, the male/female ratio was 1,066/1,101 (0.968), mean age was 59 ± 18 and mean illness duration was 12 ± 12 years.

Demographic and clinical characteristics of the sample (**Table 1**), COVID-19 related questions (**Table 2**), and information related to the impact of COVID-19 on disease burden (**Table 3**) are reported for each neurological diagnostic group.

Demographic and Clinical Characteristics

The main demographic and clinical characteristics of the sample are reported in **Table 1** for each neurological group. Furthermore, 1,207 individuals reported one concomitant medical condition and 653 participants reported two or more concomitant medical conditions; 844 individuals (39%) reported hypertension, with the highest prevalence among patients affected by stroke (82%), 411 were affected by heart disease (19%), and 233 by lung disease (11%); 270 participants presented with diabetes (13%), 188 reported cancer (9%), 64 chronic kidney diseases (3%), and 220 obesity (10%). Furthermore, 530 patients were current or former smokers (25%).

Among the 1,189 patients who were on drug treatment, 365 (17%) were on ACE-inhibitors, 301 (14%) on sartanics, 164 (8%) on non-steroidal anti-inflammatory drugs (NSAIDs), 154 (7%) on steroids, and 205 (9%) on immunosuppressant/immunomodulatory drugs. Hospital delivered, and infusion therapies, including botulinum toxin and other neurological disease–specific treatments, were reported by 1,387 individuals (64%).

COVID-19 Related Questions

Distribution of symptoms suggestive of COVID-19 infection and results of confirmatory testing are reported in **Table 2** for each neurological group. Sixty-three patients (3%), 10 of whom were cohabitants (0.5%), reported a contact with COVID-19+ individuals, and 58 patients (2.7%) had recently traveled in endemic areas. Forty-one individuals (1.9%) were tested with nasal/pharyngeal swabs, two were COVID-19+ (4.9% of screened patients, 0.09% of the total sample).

The first COVID-19+ was a 57-years-old woman with a 14-year history of secondary progressive multiple sclerosis (ADL score = 2/6) in treatment with azathioprine. During the stay in a rehabilitation clinic, she presented with high fever and fatigue for 2-days, followed by hypogeusia. Symptoms promptly resolved and she did not require hospitalization; nevertheless, she reported a transient worsening of neurological symptoms.

The second COVID-19+ was a 60-years-old woman, smoker, with an 8-year history of relapsing/remitting multiple sclerosis (ADL score = 6/6), on ocrelizumab treatment (last infusion in October 2019). After her mother developed COVID+ pneumonia, she reported moderate fever and cough lasting for 5 days. Thereafter, she spontaneously recovered and did not report any worsening of previous neurological symptomatology.

Correlations between the clinical condition suggestive of COVID-19 infection (at least 3 among fever, cough, asthenia, dyspnea, myalgia, hyposmia in the last 3 months) (10) and subjective worsening of neurological symptoms, disability and compliance to restriction measures are reported in **Table 4A**. We decided to evaluate these aspects in the patients with clinical conditions characterized by at least three of COVID-symptoms to increase the probability that these subjects were affected by COVID-19. We found a significant positive correlation between COVID-19 symptoms and subjective worsening of neurological symptoms and a negative association between COVID-19 symptoms and ability to walk. Among patients who experienced COVID-19 symptoms and asymptomatic individuals, 28 and 18% reported subjective worsening of neurological symptoms, respectively ($p = 0.002$, $h = 0.16$ – small); 7% of ambulatory subjects and 12% of non-ambulating patients presented with COVID-19 flu symptoms ($p = 0.001$, $h = 0.18$ – small). Finally, in our population, there was no correlation between the suggestive symptoms of COVID-19, either when considered individually or in combination of at least three symptoms, and the usage of steroid or immunosuppressant therapies.

Lockdown Consequences on Disease Burden

Information related to the impact of COVID-19 on disease burden is reported in **Table 3** for each neurological group.

Social restrictions were respected by 88% of the participants, ranging from 54% among patients with sleep disorders, to over 95% among patients with movement disorders, multiple sclerosis, and myopathies. One hundred and fifty-eight individuals (7%) needed urgent neurological care, which was deferred due to the lockdown; 641 patients (30%) suspended the hospital treatments (including botulinum toxin injection and infusion treatments of immunomodulatory drugs), physiotherapy or other support interventions, 76 patients (4%) complained about drug unavailability, 408 individuals (19%) reported a subjective worsening of neurological symptoms (**Table 3**). We reviewed our data about lockdown effects on function and disability in the group of patients aged seventy and older (695 subjects; 32%): 154 patients (22%) reported a subjective worsening of neurological symptoms; 62 individuals (9%) needed urgent neurological care; 222 patients (32%) suspended the hospital treatments, physiotherapy or other support interventions; 35 patients (5%) reported drug unavailability. In the same group, low ADL/IADL scores, indicating higher disability, was detected, respectively, in 180 (26%) and 331 (48%) subjects.

Correlations between subjective worsening of neurological symptoms and specific consequences of social restrictions are reported in **Table 4B**. Specifically, we found a direct

TABLE 1 | Demographic and disease characteristics.

Neurological diagnosis	N°	Mean age (y)	Male subjects	Disease duration (y)	Age at onset (y)	ADL ≤ 3	IADL ≤ 4	Ambulatory patients
ALS	84 (4%)	65 ± 11	54 (64%)	4 ± 3	62 ± 11	51 (61%)	57 (68%)	42 (50%)
CI	173 (8%)	76 ± 8	66 (38%)	4 ± 3	72 ± 9	52 (30%)	129 (75%)	146 (84%)
Dystonia	104 (5%)	68 ± 12	26 (25%)	16 ± 10	52 ± 15	1 (1%)	2 (2%)	104 (100%)
Epilepsy	107 (5%)	46 ± 18	47 (44%)	14 ± 13	32 ± 22	6 (6%)	18 (17%)	102 (95%)
HD & TS	100 (5%)	58 ± 13	46 (46%)	9 ± 7	50 ± 15	28 (28%)	57 (57%)	77 (77%)
Headache	97 (4%)	44 ± 16	24 (25%)	21 ± 15	24 ± 14	0 (0%)	2 (2%)	97 (100%)
MS	201 (9%)	45 ± 14	54 (27%)	12 ± 9	33 ± 12	19 (9%)	21 (10%)	172 (86%)
Myasthenia	111 (5%)	60 ± 17	51 (46%)	14 ± 10	47 ± 21	4 (4%)	9 (8%)	108 (97%)
Myopathies	371 (17%)	51 ± 15	198 (53%)	21 ± 12	30 ± 15	31 (8%)	11 (18%)	332 (89%)
Neuropathies	57 (3%)	62 ± 17	45 (79%)	8 ± 10	54 ± 20	6 (11%)	57 (19%)	49 (86%)
PD	255 (12%)	70 ± 11	163 (64%)	10 ± 7	60 ± 13	50 (20%)	113 (44%)	199 (78%)
SD	200 (9%)	56 ± 17	109 (55%)	9 ± 10	47 ± 19	8 (4%)	9 (5%)	192 (96%)
HSP & SCA	68 (3%)	50 ± 15	39 (57%)	21 ± 12	29 ± 18	15 (22%)	31 (46%)	48 (71%)
Stroke	239 (11%)	69 ±14	144 (60%)	0.9 ± 0.4	68 ± 14	61 (26%)	77 (32%)	199 (83%)
Total	2 167	59 ± 18	1,066 (49%)	12 ± 12	47 ± 22	332 (15%)	602 (28%)	1,867 (86%)

PD, Parkinson disease; HD & TS, Huntington disease and Tourette syndrome; CI, Cognitive Impairment; MS, Multiple Sclerosis; ALS, Amyotrophic Lateral Sclerosis; SD, Sleep Disorder; HSP & SCA, Hereditary spastic paraplegia and Spinocerebellar ataxia.

TABLE 2 | COVID-related variables.

Neurological diagnosis	Flu-related symptoms						Nasopharyngeal swab	
	Fever	Cough/Sore thorat	Asthenia	Myalgia	Dyspnoea	Hyspomia/ hypogeusia	Performed	Positive
ALS	3 (4%)	6 (7%)	4 (5%)	(2 (2%)	2 (2%)	1 (1%)	2 (2%)	0
CI	11 (6%)	25 (14%)	(14 (8%)	12 (7%)	4 (2%)	11 (6%)	1 (1%)	0
Dystonia	8 (8%)	18 (17%)	7 (7%)	3 (3%)	1 (1%)	0 (0%)	1 (1%)	0
Epilepsy	13 (12%)	16 (15%)	13 (12%)	11 (10%)	6 (6%)	3 (3%)	5 (5%)	0
HD & TS	10 (10%)	23 (23%)	12 (12%)	6 (6%)	5 (5%)	2 (2%)	2 (2%)	0
Headache	17 (19%)	30 (31%)	15 (15%)	12 (12%)	6 (6%)	4 (4%)	3 (3%)	0
Myasthenia	3 (3%)	12 (11%)	10 (9%)	2 (2%)	4 (4%)	1 (1%)	1 (1%)	0
Myopathies	40 (11%)	92 (25%)	30 (8%)	49 (13%)	13 (4%)	4 (1%)	3 (1%)	0
MS	30 (15%)	72 (36%)	39 (19%)	28 (14%)	7 (3%)	6 (3%)	3 (1%)	2 (1%)
Neuropathies	10 (18%)	14 (25%)	10 (18%)	7 (12%)	2 (4%)	2 (4%)	0 (0%)	0
PD	18 (7%)	30 (12%)	16 (6%)	10 (4%)	9 (4%)	31 (12%)	9 (4%)	0
SD	19 (10%)	42 (21%)	20 (10%)	13 (10%)	8 (4%)	8 (4%)	7 (4%)	0
HSP & SCA	2 (3%)	5 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
Stroke	22 (9%)	38 (16%)	33 (14%)	14 (6%)	11 (5%)	10 (4%)	4 (2%)	0
Total	206 (10%)	423 (20%)	223 (10%)	169 (8%)	78 (4%)	83 (4%)	41 (1.9%)	2 (0.09%)

PD, Parkinson disease; HD & TS, Huntington disease and Tourette syndrome; CI, Cognitive Impairment; MS, Multiple Sclerosis; ALS, Amyotrophic Lateral Sclerosis; SD, Sleep Disorder; HSP & SCA, Hereditary spastic paraplegia and Spinocerebellar ataxia.

correlation between the subjective worsening of neurological symptoms and need of urgent neurological care ($p < 0.001$, $h = 0.94$ - large) and discontinuation of hospital treatment or physiotherapy ($p = 0.002$; $h = 0.16$). Also low ADL/IADL scores, indicating higher disability, significantly correlated with subjective worsening of neurological symptoms during the pandemic ($p = 0.007$ and $p = 0.001$).

DISCUSSION

This study aimed to report the prevalence of COVID-19 infection/symptoms and to analyze the impact of restriction measures among patients with chronic neurological disorders. It included over 2,000 patients regularly followed at different services of our outpatient clinic.

TABLE 3 | Consequences of pandemic COVID-19 on neurology outpatients.

Neurological diagnosis	Subjective worsening of neurological condition	Suspension hospital treatments or physiotherapy	Difficulty finding drugs	Need for urgent consultation	Compliance social restriction	
					Before March 11th	After March 11th
ALS	40 (48%)	63 (75%)	2 (2%)	12 (14%)	61 (73%)	79 (94%)
CI	82 (47%)	37 (21%)	5 (3%)	33 (19%)	108 (62%)	127 (73%)
Dystonia	31 (30%)	101 (97%)	3 (3%)	1 (1%)	31 (30%)	102 (98%)
Epilepsy	7 (7%)	3 (3%)	5 (5%)	6 (6%)	55 (51%)	88 (82%)
HD & TS	10 (10%)	18 (18%)	8 (8%)	8 (8%)	57 (57%)	97 (97%)
Headache	20 (21%)	8 (8%)	1 (1%)	6 (6%)	48 (49%)	87 (90%)
MS	32 (16%)	53 (26%)	6 (3%)	11 (5%)	88 (44%)	194 (97%)
Myasthenia	12 (11%)	3 (3%)	4 (4%)	14 (13%)	51 (46%)	91 (82%)
Myopathies	33 (9%)	151 (41%)	2 (1%)	16 (4%)	231 (62%)	354 (95%)
Neuropathies	15 (26%)	15 (26%)	1 (2%)	3 (5%)	15 (26%)	50 (88%)
PD	64 (25%)	104 (41%)	21 (8%)	27 (11%)	102 (40%)	236 (93%)
SD	33 (17%)	5 (3%)	8 (4%)	12 (6%)	128 (64%)	108 (54%)
HSP & SCA	5 (7%)	29 (43%)	0 (0%)	1 (1%)	53 (78%)	67 (99%)
Stroke	24 (10%)	51 (21%)	10 (4%)	8 (3%)	134 (56%)	219 (92%)
Total	408 (19%)	641 (30%)	76 (4%)	158 (7%)	1,162 (54%)	1,899 (88%)

PD, Parkinson disease; HD & TS, Huntington disease and Tourette syndrome; CI, Cognitive Impairment; MS, Multiple Sclerosis; ALS, Amyotrophic Lateral Sclerosis; SD, Sleep Disorder; HSP & SCA, Hereditary spastic paraplegia and Spinocerebellar ataxia.

TABLE 4 | Reduced Correlation Matrix of univariate analysis [Spearman rho correlation coefficient (significance)].

	Subjective perception of worsening	Total ADL	Total IADL	Ambulatory patients	Compliance to social restriction before March 11th	Compliance to social restriction after March 11th
A						
Presence of 3+ flu symptoms	0.067 (0.002)	−0.051 (0.017)	−0.015 (0.484)	−0.068 (0.001)	0.021 (0.334)	0.029 (0.173)
	Need for urgent neurological visit	**Total ADL**	**Total IADL**	**Suspension of treatments**	**Difficulty finding drugs**	
B						
Subjective Worsening Perception	0.451 (<0.001)	−0.058 (0.007)	−0.075 (0.001)	0.065 (0.002)	−0.031 (0.151)	

Although patients with neurological diseases might be particularly at risk for SARS-CoV-2 (4), in our sample only two patients (0.09%) of 41 tested through nasal-pharyngeal swab (4.9%) received a diagnosis of SARS-CoV-2 infection. Furthermore, these two patients, both affected by multiple sclerosis, presented with a mild clinical picture, not requiring specific antiviral treatments or hospitalization. On April 15, 2020, out of 5,897,000 inhabitants in the Lazio region, 75,584 individuals had been screened through nasal-pharyngeal swab, of whom 5,232 (0.09%) were found to be COVID-19+. Accordingly, the prevalence of COVID-19 infection (positive swab) in our sample (0.09%) was consistent with the one observed in the general screened population. Therefore, our results suggest that chronic neurological disorders may not increase the risk for SARS-CoV-2 infection. Interestingly, the 2 COVID-19+ cases in our sample were both affected by multiple sclerosis and reported minor symptoms. Clinical deterioration during SARS-CoV-2 infection is correlated to a release of pro-inflammatory cytokines and, in our patients, chronic immunosuppressant therapy could have *per-se* mitigated the infection course (11). This possible interpretation need eventual confirmation in larger case series. In our sample a substantial proportion of patients reported fever and cough/sore throat (10 and 20% of the total sample, respectively). Despite it is possible that some of these individuals could have COVID-19, no severe clinical features needing hospitalization or deaths were reported. Previous studies reported that hyposmia is a frequent and specific indicator of SARS-CoV2-infection, when associated with flu-like symptoms, myalgia and asthenia (12, 13). A recent reduction of the sense of smell or taste, or a substantial modification compared to lifetime, were reported in 4% of the sample. Hyposmia is a common non-motor symptom in Parkinson's disease (PD), however in our sample 31 individuals with PD (12%) reported a recent further worsening or new onset of hyposmia.

Concerning the secondary aim of our study, we found a significant association between the presence of COVID-19

symptoms and the subjective worsening of neurological symptoms. This could be due to an objective worsening of underlying medical conditions or to concern about further medical complications in patients with chronic illnesses (14). Nevertheless, our results showed that the subjective worsening of neurological symptoms was associated with the consequences of social restrictions. As a matter of fact, among 408 individuals reporting subjective worsening of neurological symptoms, only 158 patients reported an unmet need for urgent neurological care. Proportions are unevenly distributed among different neurological diagnostic groups exceeding 10% in patients with Parkinsonian syndromes, cognitive impairment, myasthenia, and amyotrophic lateral sclerosis (ALS). We can suppose that this distribution reflects the complex clinical management of these diseases, often requiring a multidisciplinary team. Patients with the above-mentioned syndromes are often in treatment with polypharmacotherapy and with supportive therapies such as neuromotor, speech, and occupational therapies. Unfortunately, during the pandemic these treatments have been interrupted due to social restrictions. In particular, regarding the high percentage of patients affected by ALS that referred a progression of symptoms, we can speculate that this is partly attributable to the natural progression of the disease but could also be due to the impossibility of carrying out planned neurological and pneumological assessments, as well as physiotherapy. In our sample, 1,337 patients were under neurological disease–specific treatments, including botulinum toxin and infusion therapies for neuroinflammatory diseases, headache and other disorders; 30% of these patients could not receive the scheduled treatments due to restrained hospital routine.

Conversely, difficulties in obtaining pharmacological treatments were reported only by a small percentage of patients (8%), the majority in the Parkinson group. Overall, telephone contacts were extremely helpful in reassuring most patients and caregivers and allowed to postpone scheduled medical visits. Not clinically significant differences about lockdown effect on function and disability were detected in the group of patients aged 70 and older. These subjects, as expected, presented a lower ADL/IADL scores.

Finally, the lack of correlation between COVID-symptoms and the usage of steroid or immunosuppressant therapies does not suggest to interrupt or modify these treatments in patients with neurological disorders.

Our study has several limits. First, the present study is not a population-based analysis. Since our hospital is a referral center for rare neurological diseases, some of them were over-represented with respect to the Italian general population (15). At the same time, the broad spectrum of neurological diseases involved in this survey, encompassing subgroups characterized by a particular vulnerability to lockdown such as rare neurological diseases, can well-represent the impact of the pandemic on chronic neurological disorders followed in the Community hospitals and non-reference centers. Furthermore, results showed a high degree of variability in age at onset and illness duration, ranging from few months in the group of patients presenting with stroke, to many decades in the genetic diseases group. Another limitation was the lack of standardized questionnaires for cognition, mood or quality of life. However, all patients underwent a detailed neurological anamnesis which included the evaluation of these clinical aspects. In particular, the worsening of the patient's clinical condition was considered only if clearly distinguished from a worsening of mood or is reported by the caregiver in case of cognitive decline (i.e., Alzheimer disease, PD). Comorbid medical conditions and drug treatment were also unevenly distributed in the cohort. As expected, they were not related to the specific neurological conditions, but to individual risk factors and demographic variables (i.e., hypertension was more frequent among patients with stroke and in older individuals). Conversely, women and men were homogenously represented in the total sample (M/F: 49/51), and sex ratio in the specific diagnostic subgroups was in accordance with previous data in the specific neurological populations (**Table 1**). Second, even though results suggest that chronic neurological disorders may not increase the risk of COVID, only 41 patients underwent swab (1.9% of the sample). Therefore, the exact number of COVID+ cases among individuals presenting with flu-like symptoms suggestive of SARS-CoV-2 infection could not be precisely established. Moreover, asymptomatic cases may also underestimate the real prevalence of the infection. Third, the survey design required telephone contact rather than face-to-face assessment, as a consequence, the interview may be influenced by uncontrolled and recall bias. Finally, our observations and conclusions are limited by the study's retrospective and cross-sectional design.

In conclusion, our data suggest that chronic neurologic diseases did not increase the prevalence of COVID-19 infection. Lockdown restriction measures were associated with subjective worsening of neurological symptoms and may have exacerbated the burden of neurological disorders.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universitá Cattolica del Sacro Cuore Ethics Committee, Rome. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CP and ED designed and conceptualized study and collected and analyzed the data. GPri interpreted the data, revised the manuscript for intellectual content, and drafted the manuscript. PC and AB designed and conceptualized study, analyzed the data, and revised the manuscript for intellectual content. DJ, MLui, GF, CV, MLuc, VB, MMo, VG, GD, AE, CM, MMi, DQ, ERi,

SS, GSi, SBe, SBo, FB, RD, AD, DG, TI, MRL, JM, AKP, AP, MP, GPre, VR, ERo, AR, MR, CS, IS, GSp, MS, LT, and PZ collected and interpreted the data and revised the manuscript for intellectual content.

ACKNOWLEDGMENTS

GPri and SS acknowledge support for activities related to this work from the ERN EURO-NMD.

REFERENCES

1. Lazzerini M, Putoto G. COVID-19 in Italy: momentous decisions and many uncertainties. *Lancet Glob Health*. (2020) 8:e641–2. doi: 10.1016/S2214-109X(20)30110-8
2. The World Health Organization (2020). Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed March 22, 2020).
3. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. (2020) 13:e200994. doi: 10.1001/jamainternmed.2020.0994
4. Manji H, Carr AS, Brownlee WJ, Lunn MP. Neurology in the time of covid-19. *J Neurol Neurosurg Psychiatr*. (2020) 91:568–70. doi: 10.1136/jnnp-2020-323414
5. Almirall J, Serra-Prat M, Bolibar I, Balasso V. Risk factors for community-acquired pneumonia in adults: a systematic review of observational studies. *Respiration*. (2017) 94:299–311. doi: 10.1159/000479089
6. Moccia L, Janiri D, Pepe M, Dattoli L, Molinaro M, De Martin V, et al. Affective temperament, attachment style, and the psychological impact of the COVID-19 outbreak: an early report on the Italian general population. *Brain Behav Immun*. (2020) 20. doi: 10.1016/j.bbi.2020.04.048
7. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 10:e201127. doi: 10.1001/jamaneurol.2020.1127
8. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffee MW. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. (1963) 185:914–9.
9. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. (2020) 382:1653–9. doi: 10.1056/NEJMsr2005760
10. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
11. Novi G, Mikulska M, Briano F, Toscanini F Tazza F, Uccelli A, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? *Mult Scler Relat Disord*. (2020) 42:102120. doi: 10.1016/j.msard.2020.102120
12. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. (2020) 26:ciaa330. doi: 10.1093/cid/ciaa330
13. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, et al. Acute-onset smell and taste disorders in the context of Covid-19: a pilot multicenter PCR-based case-control study. *Eur J Neurol*. (2020) 22. doi: 10.1111/ene.14273
14. Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, et al. Focal status epilepticus as unique clinical feature of COVID-19: a case report. *Seizure*. (2020) 78:109–12. doi: 10.1016/j.seizure.2020.04.009
15. Pugliatti M, Sobocki P, Beghi E, Pini S, Cassano GB, Altamura AC, et al. Cost of disorders of the brain in Italy. *Neurol Sci*. (2008) 29:99–107. doi: 10.1007/s10072-008-0868-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 24 June 2020
doi: 10.3389/fneur.2020.00664

OPEN ACCESS

Edited by:
Ricardo F. Allegri,
Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Argentina

Reviewed by:
Paolo Martelletti,
Sapienza University of Rome, Italy
Matilde Leonardi,
Carlo Besta Neurological Institute (IRCCS), Italy
Amos D. Korczyn,
Tel Aviv University, Israel

***Correspondence:**
Sonu Bhaskar
sonu.bhaskar@health.nsw.gov.au

† The COVID19 pandemic is causing an unprecedented public health crisis impacting healthcare systems, healthcare workers and communities. The COVID-19 Pandemic Health System **RE**silience **PROGRAM** (**REPROGRAM**) consortium is an international not-for-profit think-tank established to champion the safety of healthcare workers, policy development and advocacy for global pandemic preparedness and action

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 30 April 2020
Accepted: 03 June 2020
Published: 24 June 2020

Citation:
Bhaskar S, Bradley S, Israeli-Korn S, Menon B, Chattu VK, Thomas P, Chawla J, Kumar R, Prandi P, Ray D, Golla S, Surya N, Yang H, Martinez S, Ozgen MH, Codrington J, González EMJ, Toosi M, Hariya Mohan N, Menon KV, Chahidi A and Mederer Hengstl S (2020) Chronic Neurology in COVID-19 Era: Clinical Considerations and Recommendations From the REPROGRAM Consortium. Front. Neurol. 11:664. doi: 10.3389/fneur.2020.00664

Chronic Neurology in COVID-19 Era: Clinical Considerations and Recommendations From the REPROGRAM Consortium

Sonu Bhaskar[1,2,3]*, Sian Bradley[1,4], Simon Israeli-Korn[1,5], Bindu Menon[1,6], Vijay Kumar Chattu[1,7], Pravin Thomas[1,8], Jasvinder Chawla[1,9], Rajeev Kumar[1,10], Paolo Prandi[1,11], Daniel Ray[1,12], Sailaja Golla[1,13], Nirmal Surya[1,14], Harvey Yang[1,15], Sandra Martinez[1,16], Mihriban Heval Ozgen[1,17,18], John Codrington[1,19], Eva María Jiménez González[1,20], Mandana Toosi[1,21], Nithya Hariya Mohan[1,22], Koravangattu Valsraj Menon[1,23], Abderrahmane Chahidi[1,24,25,26] and Susana Mederer Hengstl[1,27]

[1] Pandemic Health System REsilience PROGRAM (REPROGRAM) Consortium, Chronic Neurology REPROGRAM Sub-committee†, [2] Department of Neurology and Neurophysiology, Liverpool Hospital, Sydney, NSW, Australia, [3] Neurovascular Imaging Laboratory & NSW Brain Clot Bank, Ingham Institute for Applied Medical Research and South West Sydney Clinical School, The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [4] The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [5] Department of Neurology, Sheba Medical Center, Tel Hashomer, Ramat Gan and Sackler School of Medicine, Movement Disorders Institute, Tel Aviv University, Tel Aviv-Yafo, Israel, [6] Department of Neurology, Apollo Hospitals, Nellore, India, [7] Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada, [8] Department of Neurology, University Hospitals NHS Foundation Trust, Birmingham, United Kingdom, [9] Department of Neurology, Loyola University Medical Center & Hines VA Hospital, Chicago, IL, United States, [10] Department of Psychiatry, Hamad Medical Center, Qatar & Australian National University, Canberra, ACT, Australia, [11] Department of Neurology, University of Eastern Piedmont Amedeo Avogadro, Novara, Italy, [12] Farr Institute of Health Informatics, University College London (UCL) & NHS Foundation Trust, Birmingham, United Kingdom, [13] Texas Institute for Neurological Disorders, Dallas, TX, United States, [14] Department of Neurology, Bombay Hospital & Medical Research Centre, and Epilepsy Foundation India, Mumbai, India, [15] Department of Neurology, Academic Hospital Paramaribo & Anton de Kom Universiteit van Suriname Faculteit der Medische Wetenschappen, Paramaribo, Suriname, [16] Department of Neurology, Hospital da Restauração, Recife, Brazil, [17] Department of Psychiatry, Parnassia Psychiatric Institute, The Hague, Netherlands, [18] Curium-Leiden University Medical Centre, Oegstgeest, Netherlands, [19] Department of Laboratory Medicine, Academic Hospital Paramaribo and Anton de Kom Universiteit van Suriname Faculteit der Medische Wetenschappen, Paramaribo, Suriname, [20] Department of Forensic Psychology, Forensic Psychology and Forensic Sciences Institute, Ministry of Justice, Granada, Spain, [21] LodeStone Center for Behavioral Health and Eastern Illinois University, Chicago, IL, United States, [22] Chengalpattu Medical College and Hospital, Chengalpattu, India, [23] Department of Psychiatry, South London and Maudsley NHS Foundation Trust, Kings Health Partners, London, United Kingdom, [24] ED 268, DR 178, Sorbonne Nouvelle University, Paris, France, [25] Moroccan Society of Neurophysiology, Marrakech, Morocco, [26] Morocco and Basic and Clinical Neurosciences Research Laboratory, University Medical School of Marrakech, Marrakech, Morocco, [27] Department of Neurology, Complejo Hospitalario de Pontevedra, Pontevedra, Spain

With the rapid pace and scale of the emerging coronavirus 2019 (COVID-19) pandemic, a growing body of evidence has shown a strong association of COVID-19 with pre- and post- neurological complications. This has necessitated the need to incorporate targeted neurological care for this subgroup of patients which warrants further reorganization of services, healthcare workforce, and ongoing management of chronic neurological cases. The social distancing and the shutdown imposed by several nations in the midst of COVID-19 have severely impacted the ongoing care, access and support of patients with chronic neurological conditions such as Multiple Sclerosis, Epilepsy, Neuromuscular Disorders, Migraine, Dementia, and Parkinson disease. There is a

pressing need for governing bodies including national and international professional associations, health ministries and health institutions to harmonize policies, guidelines, and recommendations relating to the management of chronic neurological conditions. These harmonized guidelines should ensure patient continuity across the spectrum of hospital and community care including the well-being, safety, and mental health of the patients, their care partners and the health professionals involved. This article provides an in-depth analysis of the impact of COVID-19 on chronic neurological conditions and specific recommendations to minimize the potential harm to those at high risk.

Keywords: coronavirus disease 2019 (COVID-19), chronic neurological disease, healthcare services, guidelines, neurodegenerative disorders, protocols, pandemics, recommendations

INTRODUCTION

Coronavirus 2019 (COVID-19), officially severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV2) (1), was declared by the World Health Organization (WHO) to have reached pandemic status on the 11th March 2020 (2). The global reach of the disease continues to promote fear and panic amongst members of the public and healthcare workers. In the COVID-19 pandemic, chronic neurological care is increasingly under stress due to ongoing reorganization and rationing of services to meet the demands of frontline COVID-19 cases. Patients with chronic neurological diseases are forced to balance their pre-existing conditions with this rapidly evolving threat of COVID-19 (3, 4). Specific considerations for clinical management of these patients and of health services are warranted in the background of huge social and economic costs associated with long-term morbidity. This article pursues to discuss the ongoing approaches to neurological patient management in the COVID-19 era and provides comprehensive recommendations for specific chronic neurological conditions. Patients with chronic neurological diseases such as Multiple Sclerosis, Epilepsy, Neuromuscular Disorders, Migraine, Dementia, and Parkinson disease would benefit from a targeted strategy to minimize harm and prevent long-term associated costs to society and to the economy. Mental health implications of COVID-19 on chronic neurological patients and healthcare workers are also discussed. A triage and management protocol for chronic neurological patients presenting to the emergency in the COVID-19 period is also proposed (**Figure 1**).

CURRENT APPROACHES IN CHRONIC NEUROLOGICAL PATIENTS DURING COVID-19

COVID-19 positive patients could be classified into three categories depending upon the presenting neurological symptoms: neurological manifestations in patients with underlying disease [headache, dizziness, impaired consciousness (5), ataxia, seizures or epileptic manifestations (6, 7), and stroke (5)]; neuro-peripheral origin associated neurological expressions (hypo-ageusia, hyposmia, neuralgia) and symptoms of skeletal muscle damage (5, 8, 9). The prevalence rates of hypogeusia and hyposmia in COVID-19 patients are variable in the literature. The prevalence of hyposmia and hypogeusia was 5.1 and 5.6% in a study on 214 hospitalized patients with COVID-19 from Wuhan (China), respectively (5). In a multi-center European study on 417 mild-to-moderate COVID-19 patients, olfactory, and gustatory dysfunctions were reported by 85.6 and 88% of patients, respectively (10). Hyposmia or anosmia was present in ∼78% of patients without nasal obstruction or rhinorrhoea (10). A Korean study reported a prevalence of acute anosmia or ageusia in 15.3 and 15.7% in the early stage of COVID-19 and in patients with asymptomatic-to-mild disease severity, respectively (11). Chemosensory dysfunction was present in ∼19.4% of patients in Italy (12). With emerging evidence concerning anosmia presenting as an early symptom of COVID-19, dedicated testing for anosmia could be useful in early detection of COVID-19 infection (9).

Several countries have imposed strict social distancing measures. In the United Kingdom (UK), strict social distancing is recommended for those with chronic neurological conditions, such as Multiple Sclerosis (MS), Motor Neuron Disease (MND), Myasthenia Gravis (MG), inflammatory myopathies, autoimmune neuropathies, epilepsy, Parkinson's Disease (PD), Alzheimer's disease, and immunosuppressed individuals (13). Social distancing or quarantine could have further detrimental effects both mentally and physically on patients who require physical therapy, mobilization, and assistance as these resources become increasingly difficult to access or become less available.

A number of approaches to the management of patients with chronic neurological conditions during the time of COVID-19 have been explored worldwide to maintain patient continuity. Measures including remote triaging, reliance on telemedicine for outpatient consultations, separation of COVID and non-COVID patients in emergency departments (ED) and working across subspecialties are being applied (14). Such patients and those with vascular comorbidities need to be supported so that issues such as discontinuing previous medications out of fear, canceled outpatient appointments, and general anxiety can be managed. The Association of British Neurologists has released an outline of risks posed to chronic neurological patients generally, as well as risk stratification of particular

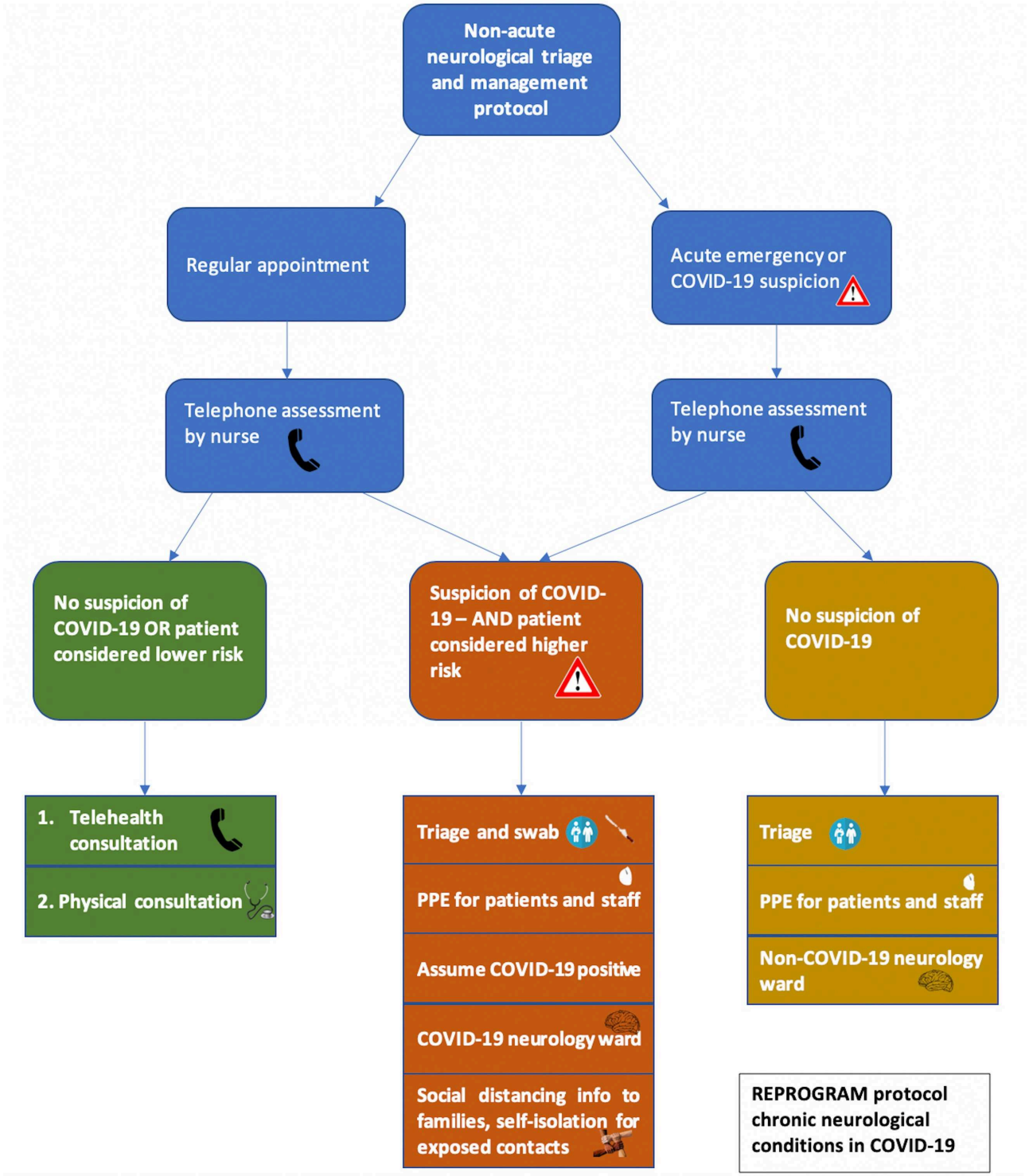


FIGURE 1 | Proposed flow chart outlining the triage and management decisions for patients with chronic neurological conditions in the COVID-19. This flow chart applies to chronic patients who need to make a regular appointment, such as for scheduled check-ups or prescription refills, or for acute emergency presentations due to possible COVID-19 cases or acute neurological symptoms. In both situations, an initial telephone conversation should screen patients to assess the possibility of a COVID-19 infection. This will involve asking about fever, cough, sore throat, fatigue, shortness of breath, anosmia, and potential COVID-19 contact. For those patients without COVID-19 symptoms or who are at low risk and don't require presentation to hospital, telehealth consultation with their neurologist or primary physician can be undertaken. Where this is not possible, physical consultation may be required. If there is suspicion that the patient may have COVID-19 and they are

(Continued)

FIGURE 1 | considered at higher risk to their health, they should present to the hospital and receive point-of-entry triage and swabbing for COVID-19 infection. PPE should be worn by both staff and patients. Patients should be assumed to be COVID-19 positive until proven otherwise and be taken to a designated COVID-19 neurology ward. Close relatives and attendees of the patient should also practice social isolation whilst awaiting test results. For patients who require acute neurological care and are not suspected of having a COVID-19 infection, they should receive point-of-entry triage, PPE should be supplied to patients and staff and they should be admitted to a non-COVID-19 neurology ward if necessary. Triage assessment will involve stratification by mild, moderate, severe, and critical risk, according to **Table 1**.

diseases (15). Those presented with higher risks include those with high doses of immunotherapy, multiple immunotherapies, active disease, swallowing or respiratory muscle weakness, and comorbidities (15). The American Academy of Neurology (AAN) has also issued guidelines on telemedicine for management of chronic neurological patients (16). The American Headache Society recommends the use of telemedicine where possible for COVID-19 symptoms screening and recommends the need for triage for the presentation to clinics (17). In the advent of an emergency during the COVID-19 era, patients with chronic neurological conditions should be separated from non-neurological patients, due to the greater risk posed to their health (18). We will now critically examine the impact of COVID-19 on various neurological conditions and provide strategies and recommendations to improve patient management and reduce negative impact during the current pandemic.

MULTIPLE SCLEROSIS

Multiple Sclerosis is a neuroinflammatory disorder, which confers risk to those affected due to the prevalence of immunotherapy, as well as potential swallowing and breathing difficulties. Media reports have shown patients with MS to be anxious given their immunocompromised state and the reduced availability of services in the COVID-19 crisis (19). This is a worldwide concern, as, amongst young people, MS is the most common neurological cause of disability, with the highest prevalence and incidence rates being in Europe with over 750,000 affected individuals (20, 21). To alleviate some concern, several MS associations have released guidelines on disease-modifying therapy (DMTs) (15, 22). Patients may be tempted to cease their immunotherapy due to fears of infection risk, however, the general consensus amongst physicians and associations is that changes to medication should not be made without consulting their neurologist. In the case that patients become infected with COVID-19, it might become necessary to cease immunotherapy depending on the severity of the infection. Certain DMTs may be considered immunomodulators, with little to some immunosuppression abilities, whilst others are considered definitive immunosuppressants (23, 24). It is unknown what risk immunosuppression gives in relation to COVID-19, however, it remains prudent for those with MS to consult their physicians and practice social-distancing and good hygiene practices.

The move to telemedicine for neurological patients can be helpful in the ongoing management of MS patients. The Northwestern University Multiple Sclerosis Clinic has demonstrated the ability to rely on telemedicine for such patients, with exceptions including necessary transfusions and potential relapse investigation (25). A further area for consideration is in the cognitive health of COVID-19 positive patients, and whether the COVID-19 induced infection will accelerate the severity of the MS and/or hence the associated increased rate of brain atrophy. Age-matched and severity-matched comparisons of COVID-19 positive and COVID-19 negative chronic neurological patients could help determine whether there is a putative long-term impact.

NEUROMUSCULAR DISEASES

Patients with neuromuscular diseases are at heightened risk of COVID-19 infection. No data currently exist on how COVID-19 affects people with neuromuscular disorders including MND, MG, autoimmune or inflammatory neuropathies, or inflammatory myopathies, etc. There are no clear guidelines as to how this will impact patients taking immunosuppressive therapies. We need to assume that patients on immunosuppressive therapies and/or with bulbar/respiratory muscle weakness such as MG or Lambert Eaton myasthenic syndrome, are at higher risk of contracting the infection or experiencing severe manifestations of COVID-19 (26). Patients with MND often suffer severe disability involving bulbar or respiratory muscle weakness and are hence considered at a higher risk, particularly due to the threat of pneumonia development in the COVID-19 scenario (27).

Furthermore, some patients may already require interventions such as non-invasive ventilation (NIV) or bilevel positive airway pressure (biPAP), and it is essential that any personal breathing equipment is being regularly cleaned and maintained. The American Academy of Sleep Medicine recommends that the use of continuous positive airway pressure (CPAP) and biPAP in a home setting should only be undertaken by COVID-19 patients who already used PAP at home, and it should be done so in an isolated room (28). Neuromuscular patients who are dependent on biPAP may also require use in hospitalization. There is a lack of international consensus on guidelines despite the availability of a considerable number of recommendations.

The International MG/COVID Working Group have provided guidance on patients with MG and Lambert Eaton myasthenic syndrome (LEMS) and the use of therapies during the COVID-19 pandemic (26). It is anticipated that some patients with neuromuscular diseases who require maintenance infusions would require hospital or infusion center visits. From a health system organizational perspective, health care providers need to consider providing information on protocols concerning access to these facilities and precautions that must be adhered by those available in them. Alternative options

such as home infusion could be considered. However, this may require additional training for self-administration that could be provided remotely using tele-neurology. Immunoglobulin infusion and/or plasmapheresis haven't been shown to increase potential COVID-19 infection risk. Routine blood monitoring required with certain medications needs to be streamlined and based on individual needs and regional COVID-19 prevalence. The possibility of corticosteroid dose escalation in MG patients might be considered during COVID-19 times. Temporary suspension of immunosuppressive therapies would be required in patients with comorbid sepsis-associated hospitalization. Pharmacological profile and characteristics, such as longer wash-out periods and rebuilding therapeutically optimal levels on resuming therapy of individual immunosuppressive drugs need to be weighed (26). In essence, the treatment escalation or change decisions need to be individualized based on the relative severity of COVID-19 infection and underlying neuromuscular disorder.

Patients with neuromuscular diseases are advised to adhere to public health measures as invoked by their respective local and national bodies. Patients should be reassured to continue their ongoing treatment and any changes to the treatment regimen and dosage should only be made on the advice and approval of the treating physician. Patients should be educated and advised to follow strict social distancing, regular handwashing, and avoiding non-essential travel (27). Online order facilities to procure groceries/daily provisions and stocking up on non-perishables to reduce grocery trips should be pursued. It is advised that patients have adequate stock of essential items, such as medication and feeding-tube supplies. A concurrent issue is that many MND patients are reliant on carers. Recommendations by the New Zealand MND organization to ensure continuity of care include having a list of medications, dosages and healthcare providers; ensuring strict hygiene of self and environment and utilization of MND support resources in addition to familial and community support (29).

The impact on individual patients with neuromuscular disease relying on novel treatment remains to be seen. MND poses a unique worry due to a lack of curative treatment options and the dependence of a substantial number of patients on clinical trials. There is an indication that some clinical trials have been halted, as well as a lack of new trial or recruitment opportunities. It should, therefore, be recognized that there may be some distress in the MND community at this time and that ongoing support will be required. It is hoped that this will only be a temporary issue, however, the impact on individual patients relying on novel treatment remains to be seen.

EPILEPSY

There are conflicting opinions as to whether patients with epilepsy are considered more vulnerable to the disease than the general population (30, 31). Whilst some epilepsy organizations do not consider this population especially vulnerable, it is important to recognize that patients with epilepsy are widely varied in their presentations and a significant proportion (∼80%) of epilepsy patients live in a low or middle-income country (LMIC) (32). Patients with seizures that are triggered by fever and infection may be considered at a relatively higher risk and could consider taking antipyretics if a fever develops. As typical antiepileptic medications do not suppress the immune system, it is imperative that patients do not cease their anti-epileptic drugs (AED) for fear of COVID-19 or due to inability to get scripts (33). In the present circumstances, any patients with new-onset seizures should be tested for COVID-19 as it has been reported that COVID-19 could present as seizures due to encephalopathy, however, patients should be treated as per epilepsy protocol with AED (34). Concern for patients is the unavailability of AEDs and there need to be guidelines from the government to allow pharmacists to refill old prescriptions. This is important as many people living in rural areas may not have smartphone access to digital prescription. The use of telemedicine could be key for follow up, guidance and counseling for people with epilepsy.

If a patient has mobility or cognitive disabilities associated with their epilepsy, they could also be considered vulnerable and should avoid exposure and be provided with support. Given the disproportionate burden of epilepsy in LMIC countries, relatively limited access and provision of specialist care and absence of targeted and available guidelines in their respective languages from the epilepsy organizations and support networks; it is notable that patients with epilepsy may be at a significantly higher disadvantage in these specific regions. In case of expected bed shortages, rationing of non-acute neurological testing including cancellation of elective epilepsy monitoring could be explored. However, individual case-mix and case-by-case approach are preferred as deferring diagnostic tests or monitoring could result in a possible case scenario where a patient might end up having a severe episode of seizure that would require emergency admission. While these measures are taken globally, the Epilepsy Foundation has also provided some guidelines, including when to go to the emergency room, medications and common concerns about COVID-19 and epilepsy (35).

PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

Patients with Parkinson's Disease (PD), although not at higher risk *per se*, should be considered a vulnerable population due to older age, bulbar symptoms, respiratory dysfunction, frailty and cognitive impairment with respect to measures taken to minimize their potential exposure to COVID-19 as well as to ensure monitoring for compliance (36). Patients with PD are more likely to develop pneumonia, and infections can lead to sudden motor and cognitive changes. Healthcare workers treating COVID-19 patients should, therefore, be equipped to manage PD patients, as well as being prepared for potential cases of delirium (37).

Notably, PD is associated with anosmia often prior to diagnosis (38), and hence this may not be a useful indication of potential COVID-19 infection (39). Nursing and care homes need to ensure that PD patients remain in quarantine. Continuation of Botox® for symptomatic control of dystonia and post-stroke spasticity should be made on a case by case basis. Due to close proximity between the physician and the

patient, both masks and eye protection should be used (40). Special considerations also apply for invasive procedures. This should be on a case-by-case basis, but non-urgent elective procedures: percutaneous endoscopic gastrostomy (PEG) for Duodopa, focused ultrasound thalamotomy (FUT), and deep brain stimulation (DBS) should be postponed, if and whenever possible. However, implantable pulse generator (IPG) battery replacements should still be performed because of the risks of the neuroleptic malignant syndrome with sudden battery failure (41).

Lastly, along with the importance of telemedicine in these patients to ensure continuity of care, tele-exercise and tele-physiotherapy are very important in patients with PD as well as other clinical populations with neurological and non-neurological chronic disease. The psychosocial aspects of the impact of COVID-19 infection and of increased social isolation and sudden change to the daily routine, are of particular clinical relevance in Parkinson's disease patients. On the other hand, with adequate psychosocial support, the experience of being isolated at home together with everyone else in the country may, in fact, be somewhat normalizing in the sense that being socially isolated (owing to mobility constraints or stigma/shame relating to their diagnosis/symptoms), no longer results in them experiencing the feeling of missing out.

MIGRAINE AND SEVERE HEADACHES

Migraine and severe headaches are one of the most frequent outpatient presentations in neurology clinics. To minimize risks of infection to healthcare workers, patients and the health system, all non-emergent procedures (such as Botox® injections) should be deferred. During the COVID-19 period, the goal is to keep people at home with the appropriate treatment provided via telemedicine unless absolutely essential to bring patients to hospitals. Face to face consultations and follow-up visits should be done remotely via telephone/video call (telemedicine) (42). A recent randomized control trial showed telemedicine was an effective mode of treatment and improves physician productivity and patient satisfaction (43). Treating neurologists and/or headache specialists must maintain and encourage patient-continuity using telemedicine such as through video or telephone visits. Tele-consultation for worsening headaches should include a red-flag checklist for secondary headaches: only those with red/orange/yellow flags should be brought in, prioritized in that order. In resource-constrained settings, where there is a lack of manpower for doctors to deal with headaches, specialist nurses/physician assistants and junior doctors could be assigned to take calls.

Botox® should be deferred for all migraine patients; however, "high-risk" patients, especially those with severe depression and/or at suicide risk, who are likely to come to the emergency in the advent of a severe headache episode could be considered for outpatient Botox® therapy to limit exposure. Should a need for urgent in-person patient consultation be felt by the treating physician, remote screening for COVID-19 symptoms and any previous history of travel or contact with a COVID-19 infected person could be done over the phone. All acute headache presentations must be screened, along with a swab for COVID-19, should there be any suspicion of COVID-19. Concomitant concerns have been raised regarding the use of ACE2-stimulating drugs, such as renin-angiotensin system (RAS) blockers and the non-steroid anti-inflammatory drug (NSAID) ibuprofen, and an increased risk of COVID-19 infection and developing severe fatal COVID-19 viral infection (44, 45). Patients with migraine and severe headaches should not change therapy unless clinically indicated (44, 46). In COVID-19 infected patients, ACE2-stimulating drugs should be switched to another drug, such as specific human immunoglobulin under close clinical supervision, until the infection abates (47). For acute migraines in suspected or confirmed COVID-19 cases, NSAIDs and beta-blockers (owing to bronchospasm complications in COVID-19 associated respiratory flare) should be avoided (48). However, it's important to note that termination of beta-blockers can cause withdrawal symptoms and have been linked to death in specific patients with cardiac conditions such as unstable angina and those who underwent coronary bypass surgeries (49–51).

Triptans should be used with caution in males with hypertension and older age because of the greater risk of stroke with COVID-19 (52, 53). Paracetamol (acetaminophen) with antiemetics are recommended for acute migraine headaches as this should relieve nausea and vomiting (54). Caution should be exercised in the use of steroids for non-COVID-19 patients as these patients would be immunocompromised with their use.

There is a propensity for thrombophilic disorders in neuro-COVID and hence headache patients should have a low threshold for investigations for cerebral venous sinus thrombosis (CVST) and secondary idiopathic intracranial hypertension (IIH) (55). IIH patients who are at high risk for impending visual loss need to be rapidly assessed. Based on a teleconsultation, patients who have a worsening of IIH could be brought to the hospital and in order to minimize hospital stay and improve compliance, a telemetric intracranial pressure monitoring or cerebrospinal fluid (CSF) shunting procedures may be considered. Patients with other chronic disabling headaches such as trigeminal autonomic cephalalgias and trigeminal neuralgia, who are scheduled for interventional procedures such as Gasserian ganglion blocks and multiple cranial nerve blocks, and neuromodulation treatment such as occipital nerve stimulation and DBS need to be reassessed on the treatment immediacy in COVID-19 period.

Necessary precautions must be taken by the healthcare workers and patients including the use of personal protective equipments (PPEs) and face masks to limit risks of possible COVID-19 transmission. Lumbar puncture and fundoscopy should be considered as aerosol-generating procedures and full PPE is recommended: double gloves, mask for the patient (for fundoscopy) and clinician. The clinician should also use an FFP3 mask (56). The removal and disposal of PPE are equally important.

STROKE

Recent reports have indicated concerning trend of large vessel strokes in COVID-19 cases, especially among young COVID-19

patients who are asymptomatic or with mild symptoms (57). Stroke survivors at high risk of contracting the COVID-19 are the elderly, patients with the co-morbid disease such as obesity and those with swallowing difficulties. The most common comorbid diseases seen in COVID-19 patients are hypertension, diabetes, and coronary heart disease (58, 59). A study evaluating the clinical characteristics of 99 patients found cardiovascular and cerebrovascular diseases in 40% of patients as comorbid diseases (60). Patients are also relatively more susceptible to severe pneumonia in the case of contracting COVID-19. The medication regimen need not be changed in view of the present situation. In the event of limited access to outpatient services, patients should maintain regular compliance with medication and utilize telemedicine facilities to seek an appropriate expert opinion. Patients should follow the protocol of FAST symptom recognition and contact the emergency services. Triaging and rapid assessment will take into account the patient as well as the safety of the healthcare workers. An infection control and travel history screen would need to be completed by the paramedical team. Acute stroke protocols including "Protected Code Stroke" have been suggested for stroke patients in COVID-19 times (61). The current consortium has also developed a pathway targeting covering a broad spectrum of acute neurological emergencies, including acute ischemic stroke and transient ischemic attack (TIA), specifically for COVID-19 and takes into account considerations for infection risks and control toward minimizing exposure of healthcare workers during the entire continuum of acute stroke (62).

PERIPHERAL NEUROPATHY AND GUILLAIN-BARRÉ SYNDROME

Neurological conditions affecting the PNS and muscle reported in COVID-19 include (63): peripheral motor neuropathy (64), Guillain-Barré Syndrome (GBS) (65–70), Miller Fisher syndrome (71), polyneuritis cranialis (71), acute myelitis (72, 73), and viral myopathy with rhabdomyolysis (74). Patients with peripheral neuropathy are not specifically at a greater risk of COVID-19 infection. However, precautions may be taken to prevent potential COVID-19 infection. A case of 69-year male from Northern Ireland has been reported presenting as peripheral motor neuropathy, with bilateral lower limb weakness, manifesting before the onset of the COVID-19 typical flu-like symptoms (64).

GBS is a post-viral autoimmune complication that was seen with both SARS and MERS. A case study of a 61-year-old lady from Wuhan who developed symptoms of GBS at the same time as COVID-19 showed the potential that GBS could be parainfectious, rather than just post-infectious, similarly seen with Zika virus (65). This report in isolation is inconclusive, but it indicates a need to consider potential neurological manifestations of COVID-19. A case series from Italy reported 5 cases of GBS with patients developing GBS symptoms in the mean of 5–10 days after onset of COVID-19 infection symptoms (66). It is not evident if having GBS prior to contracting COVID-19 will affect outcomes; however, if the patient is already ventilated or experiencing neuromuscular weakness this could confer additional risk (15). GBS is an acute and emergent presentation that can involve sensorimotor, bulbar or respiratory manifestation, dysautonomia, and nerve pain. In those that recover, it can be associated with life-long disabilities (75). It can also be fatal and has the potential to progress to Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). The development of GBS associated with COVID-19 is hence a serious complication that could have permanent ramifications. It should be noted that GBS or CIDP patients who are being treated with chronic immunosuppressive drugs should be wary of increased infection risk and reduce exposure wherever possible (76). There should be tight surveillance of any accelerated increases in GBS diagnosis after the COVID-19 crisis rests due to the associated morbidity risks and disability.

NEUROVIROLOGICAL MANIFESTATIONS

Studies investigating the neurovirological manifestations of COVID-19 are being conducted increasingly, as growing evidence demonstrates the ability of the virus to cross the blood-brain barrier and due to involvement of angiotensin-converting enzyme 2 (ACE2) receptor (77). The mechanism of entry into the CNS is not known, however, comparison to the SARS-COV and MERS-COV viruses display a common link across the neuroinvasive potential of coronaviruses (78). A retrospective study of 214 hospitalized patients with COVID-19 infection aimed at investigating the neurological manifestation of the disease, where 36.4% of the patients developed a CNS, PNS or skeletal muscle manifestations (5). Causes of suspicion include the virus being found in cerebrospinal fluid (CSF) samples and the symptom of anosmia. It is of particular concern that the virus could involve the brainstem.

A COVID-19-associated acute necrotizing haemorrhagic encephalopathy in a lady in her 50s has been reported (79). This is a rare form of encephalopathy that has been associated with other viruses (79). This complication is associated with a cytokine storm, and it is a consideration that cytokine storm syndrome could present in severe COVID-19 cases. Furthermore, cytokine storms associated with severe COVID-19 cases have been hypothesized to be related to secondary hemophagocytic lymphohistiocytosis (sHLH), a hyperinflammatory syndrome (80). It is proposed that immunosuppression may be necessary for such patients. This demonstrates the need to monitor inflammatory markers in COVID-19 positive patients. Furthermore, an investigation of associated neuroinflammation and COVID-19 would be beneficial, involving long-term follow-up and monitoring of early signs of neuroinflammation. This is important as neuroinflammation can translate to poor morbidity outcomes. It should hence also be a concern of health workers involved in the frontline clinical care of COVID-19 cases to monitor for any neurological changes, and neurologists could

consider COVID-19 infection as a risk factor when encountering patients with new neurological manifestations in future.

AUTISM AND PEDIATRIC NEUROLOGICAL CONDITIONS

Most pediatric neurologists globally are offering telemedicine services for non-acute pediatric neurological disorders. It is quite challenging to have children at home, missing school, and doing school online while many parents are working from home. Autism Speaks has useful information and resources for children and adults affected with Autism spectrum disorders (81). Some of the information includes practical tips for parents, useful websites, school services, and information (81). Elective pediatric surgeries, those that are neither urgent or emergent, should be limited or rescheduled given the limited resources and anticipated surge in capacity to limit COVID-19 exposure to pediatric patients, their families and healthcare workers (82). Proactive approaches to identify pediatric neurological patients who might be at the risk of progressing from "semi-urgent" (non-symptomatic) to "urgent" (symptomatic) condition could be useful in preventing exposure due to emergency presentation.

ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Patients with Alzheimer's disease and related dementias (ADRD) are at increased COVID-19 infection risk and its associated morbidity and mortality (83). They are less likely to adhere to public health restrictions and recommendations. Dementia patients have a higher prevalence of the cardiovascular disease, diabetes and pneumonia—which confers them an increased risk of severe illness after COVID-19 infection (83). The strain on healthcare services has also adversely impacted the diagnosis and clinical management of ADRD patients. ADRD patients living in a group and assisted living environments as well those in long-term care or nursing homes are especially vulnerable to an infection outbreak in their facilities (83, 84). Any outbreak can have disproportionately high attack rate and case fatality rate. Several authorities and governments have imposed strict restrictions on visits and access to these facilities. However, this has led to further social isolation and stress among residents (84). Close monitoring of patients via telemedicine is required. Identifying patients who are at "high-risk" of developing an acute event and continual assessment of the risk-benefit ratio of some medications are a priority (83).

MENTAL HEALTH RAMIFICATIONS FOR PATIENTS, CARERS, AND PROVIDERS

The psychological and psychiatric impact of COVID-19 on patients and carers is a matter of ongoing debate and concern (85). Given social distancing has been imposed by several governments; it will be relevant and also necessary to study the long-term negative consequences on both physical and mental health should this be prolonged. Patients with chronic conditions might be experiencing a sense of hopelessness and frustration during this crisis leading to non-compliance and potential relapse. Patients requiring carers will need to have backup plans in place to ensure continuity of care. For patients such as those with MS and MND who have experience managing infection risk, the extra measures such as social distancing and changes to care could add to anxiety about their health. As outlined by the European Association of Neurologists, patients with dementia are also affected by the closure of care facilities; they may become more agitated or anxious, there may be a breakdown in communication and live-in carers and family may experience deterioration in their own mental health (86). The Alzheimer's Disease International and international dementia expert panel has called for an urgent need of mental health and psychosocial support, in addition to physical protection from COVID-19 infection, for people living with dementia and their carers (84). Clinicians are experiencing an increasing number of calls with concerns about an irrational fear of contracting COVID-19 leading to worsening of a previous anxiety disorder, new-onset illness anxiety, and even engaging in repeated ritualistic behaviors such as excessive cleaning [obsessive-compulsive disorder (OCD)-like symptoms]. There are also reports on patients avoiding regular follow-ups. There is a worry as to what the delay in appointments and elective operations will mean for long-term patient outcomes.

The COVID-19 pandemic has had major impacts on the mental health of patients, carers and healthcare workers. The physical and emotional burnout among physicians is also a major long-term concern, and symptoms of burnout such as loss of empathy should be recognized (87). Another important consideration in the COVID-19 pandemic is the impact of adjustment disorder, acute stress disorder and post-traumatic stress disorder (PTSD) symptoms on clinicians, providers and those working in direct contact with patients. These individuals experience recurring exposure to the morbid effects on their patients as well as recurring exposure to the virus and thus awareness of threats to their own lives (88). It is imperative to actively investigate early PTSD symptoms, their trends and indications so that they could inform strategies for early and optimal treatment. The reorganization of medical staff is another point of stress for both staff and patients (85). As neurologists are being or soon-to-be repurposed, the ability of current patients to contact their physicians will be impacted and physicians will have to manage ongoing patients as well as increasing workload. It is harmful to patient care if there is ambiguity in the prioritization of patients. It is important to recognize the vulnerable nature of some of these patients during the pandemic and the necessity that they not be overlooked. A systematic review and meta-analysis on psychiatric and neuropsychiatric presentations associated with severe coronavirus infections (SARS, MERS, and COVID-19) observe, should SARS-CoV-2 follows a similar trajectory to that of SARS-CoV or MERS-CoV, a significant proportion of patients should recover without experiencing mental illness (89). However, the study highlighted the prevalence of delirium in

acute stages in a significant proportion of COVID-19 patients (89). Long-term psychiatric manifestations, in COVID-19 infected patients, such as depression, PTSD, fatigue, anxiety, and rarer neuropsychiatric syndromes could be expected by clinicians (89). Telehealth or telepsychiatry services could provide mental health support during and beyond this pandemic (90).

RECOMMENDATIONS AND DISCUSSIONS

Patients with chronic neurological diseases suffer from a disability, restricted mobility, and associated challenges that interfere with the independent quality of living. It is recommended that chronic neurological patients in general, and those with immunocompromised conditions in particular, must self-isolate if at high-risk and ensure that sufficient provision of medications are available for a prolonged time as the pandemic inflicted shut-down continues. Patients with chronic neurological conditions should be considered of higher risk of COVID-19 infection should they present to the hospital and appropriate personal protective safety equipment could be provided as per the clinical assessment. We propose a triage and management algorithm specific for patients with underlying chronic neurological diseases while following strict personal protective measures including PPEs for healthcare workers and patients as appropriate (**Figure 1**). Risk based triage of chronic neurological patients during the COVID-19 era is also proposed (**Table 1**). Patients with confirmed or suspected COVID-19 should be separated into COVID-19 Neuro and COVID-19 non-Neuro wards at the point of triage. Impact of COVID-19 on various chronic neurological conditions and corresponding additional recommendations from this consortium (along with existing guidelines) have been summarized in **Table 2**. We acknowledge that our algorithm may have limitations via a visa application in case of LMICs where facilities for neurological patients are limited or lacking. However, recommendations applicable to these settings have been provided for specific conditions such as epilepsy.

The role of population health and accurately coded data on COVID-19 patients is poignant as it could enable analysis and tracking of patients to help inform forward onward management of patients with similar dispositions and toward longitudinal follow-up to study the long-term impact on the physical and emotional health of COVID-19 patients with or without underlying neurological diseases. Technological solutions such as telemedicine consultation should be explored as a priority to minimize risk to patients and clinicians alike especially for patients with MS, PD, MG, ADRD, and ALS. Upper respiratory infections can be relatively severe and possibly fatal in immunocompromised, ALS, PD, and MG patients. It may be considered that neurologists collaborate with primary care physicians so that responsibilities could be shared especially at times when neurologists may be repurposed, and health systems are being reorganized for tending to frontline COVID-19 case triage and management. Comorbidities such as cardiovascular disease, diabetes, and obesity also warrant a targeted approach in COVID-19 (91) and this also applies to chronic neurological conditions who carry an increased risk of these comorbidities (92). Mental health implications of COVID-19, health system reorganization and self-isolation on patients with chronic neurological conditions warrant attention (9, 85, 89). Ongoing monitoring of mental health impact of COVID-19 on healthcare workers, patients and carers would help identify those at higher risk of mental health problems (90).

Institutions need to consider alternative ways to maintain continuity of care given the restrictions and limited availability of public transport amidst lockdowns, patients increasingly are at a disadvantage and sometimes unable to access regular or ongoing consultations. It is also relevant that chronic neurological patients would benefit from targeted education and outreach through their respective support networks or organizations around taking necessary anti-COVID-19 preventative measures such as hand hygiene, masks, etc. Patients must be encouraged to follow public health advice issued by their concerned authorities on hand hygiene, cough etiquette and should practice social distancing to minimize the COVID-19 infection and spread. Patients who are on immunosuppressant therapy, discussion with their physician and ongoing close monitoring in COVID-19 era should be undertaken.

TABLE 1 | Risk-based triage for non-acute neurological patients.

Risk level	Characteristics
Mild risk	· Person with no COVID-19 symptoms (fever, cough, sore throat, fatigue, shortness of breath, anosmia) · Person with mild COVID-19 symptoms, no shortness of breath, fever <38°C
Moderate risk	· Stable patient presenting with COVID-19 symptoms · Oxygen Saturation >92% in room air · Fever >38°C · Fatigue · Extra care should be taken with chronic neurological patients being treated with immunosuppressants or who have bulbar, respiratory or chewing issues Such patients should be placed within a neurology-only COVID-19 ward
Severe risk	· Patients presenting with both respiratory and systemic COVID-19 symptoms · Respiratory rate >30 brpm · Oxygen Saturation <92% in room air · Fever >38°C · Reduced alertness · Systolic blood pressure <90 mmHg · Diastolic BP <60 mmHg · Chronic neurological patients with severe muscle, bulbar and respiratory issues or who already require breathing assistance
Critical risk	· Patients in respiratory failure, hypotension, impaired consciousness or respiratory distress · Patients who are ventilated yet still deteriorated

Adapted from a–d:

a. Lewin E Push to include anosmia as a recognized COVID-19 symptom newsGP: racgp; 2020.

b. National COVID-19 clinical evidence taskforce Management of patients with moderate to severe COVID-19 disease: covid19evidence, 2020.

c. National COVID-19 clinical evidence task force Management of patients with severe to critical COVID-19 disease: covid19evidence, 2020.

d. All India Institute of Medical Sciences COVID-19 management protocol 2020.

TABLE 2 | Summary of the impact of COVID-19 on chronic neurological conditions and recommendations for their management.

Non-acute neurological condition	Impact of COVID-19 infection/crisis	Recommendations/guidelines for management by professional bodies/health authorities	Recommendations by REPROGRAM consortium
Multiple sclerosis	Reduced availability of services in the COVID-19 crisis Risk due to an immunocompromised state	Guidelines by some Multiple Sclerosis associations released on disease-modifying treatments (DMTs)	Telemedicine Consider long-term association with brain atrophy
Neuromuscular disorders (including Motor Neuron Disease)	At higher risk due to bulbar or respiratory weakness, may already require breathing assistance Higher risk of pneumonia Clinical trials halted Loss of trust in caregivers	Maintenance of breathing equipment Adequate supply of medication, essential items, and feeding tube supplies Strict social distancing, avoiding non-essential travel Ensure continuity of care through communication with caregivers	Use online order facilities Neurologists should be cognizant of interruptions to clinical trials
Epilepsy	Overrepresentation in LMIC Risk of fever-triggered seizures Possible mobility and cognitive disabilities	Do not cease antiepileptic medications Discussions with physicians about any current immunosuppressants Epilepsy Foundation guidelines	Rationing of non-acute neurological testing including cancellation of elective epilepsy monitoring could be explored Individual case-mix and case-by-case approach preferred Government should consider allowing pharmacists to refill epilepsy scripts during COVID-19
Parkinson's Disease and other movement disorders	Often elderly, vulnerable population Possible bulbar and respiratory issues Cognitive impairments could impact compliance Infections may lead to sudden motor and behavioral changes	Healthcare workers must have knowledge on PD and be prepared for delirium Masks and eye protection should be worn during Botox® procedures	Physicians should recognize that anosmia is already a PD symptom Nursing and care homes need to ensure PD patients stay quarantined Elective procedures (PEG, FUT, and DBS) should be postponed IPG battery replacements should still be performed Tele-exercise and tele-physiotherapy should be utilized
Migraine and severe headache	Require frequent outpatient consultations	Use Telemedicine	Minimize all non-emergent procedures If physical consultation is required, ensure telephone, and front-desk screening for COVID-19
Stroke	Residual impairments including dysphagia May be elderly with the comorbid disease Pneumonia risk	FAST protocol Protected-code stroke	Medication regime needs no change Use of telemedicine Triage, rapid assessment, and infection screening REPROGRAM Acute Stroke Pathway for broad spectrum of acute neurological emergencies including stroke and transient ischemic attack
Guillain-Barré Syndrome	Possible parainfectious profile Post-infection complication Potential for life-long disability and CIDP Maybe immunosuppressed	GBS and CIDP patients are only deemed at higher risk if on immunosuppressants	Tight surveillance of any accelerated increases in GBS diagnosis after the COVID-19 crisis rests
Neuro-virological manifestations	Involvement of ACE2 receptor, neurological involvement	Limited or non-specific guidelines	Monitor inflammatory markers and signs of neuroinflammation Monitor COVID-19 patients for any neurological change Neurologists could consider COVID-19 infection as a risk factor when encountering patients with new neurological manifestations in future
Autism and pediatric neurological conditions	Disruption to daily life and managing children at home	Autism Speaks guidelines	Limit elective pediatric surgeries Proactively identify patients at risk of progressing from semi-urgent to urgent

Prepared by the authors based on the evidence from the studies discussed in the paper.
DMT, disease-modifying treatments; LMIC, low- and middle-income countries; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; COVID-19, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-2 converting enzyme; PD, Parkinson's Disease.

Utilizing electronic patient records to understand the impact of underlying neurological conditions and comorbidities on the outcomes of patients who are COVID-19 positive will be fundamental. There also needs to be increased communication between neurologists and primary care physicians about compliance to and provision of medications, and physicians should be proactively cognizant of any relevant disruptions to a patient's clinical trials. Compliance to ongoing treatment is crucial and it is anticipated that this may be increasingly challenging for patients who are already under severe emotional distress and anxiety. Ensuring that such patients are able to seek timely and appropriate medical consultation will help ease their ongoing struggle and possibly limit non-compliance risks. The importance of email communication, outreach and touching base with patients should not be underestimated. Patients living in nursing homes or elderly care facilities should be encouraged to get pneumonia and influenza vaccinations. Carers and nursing home staff must take added precautions and measures to ensure that any suspected staff or visitors who may have COVID-19 symptoms should not be allowed in the facilities so that ongoing quarantine is maintained.

AUTHOR CONTRIBUTIONS

SBh devised the project, the main conceptual ideas, and proof outline. SBh and SBr wrote the first draft of the manuscript, and to investigate and supervised the findings of this work. SBh, SBr, SI-K, BM, VC, PT, JCh, RK, PP, DR, SG, AC, NS, HY, SMa, MO, EG, MT, NH, KM, JCo, and SMe discussed the results and recommendations, and contributed to the final manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to acknowledge the REPROGRAM consortium members who have worked tirelessly over the last days in contributing to various guidelines, recommendations, policy briefs, and ongoing discussions during these unprecedented and challenging times despite the incredibly short timeframe. We would like to dedicate this work to our healthcare workers who have died due to COVID-19 while serving the patients at the frontline and to those who continue to serve during these challenging times despite lack of personal protective equipment.

REFERENCES

1. Gorbalenya AE, Baker SC, Baric RS, de Groot RJ, Drosten C, Gulyaeva AA, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* (2020) 5:536–44. doi: 10.1038/s41564-020-0695-z
2. World Health Organisation. *WHO Director-General's Opening Remarks at the Media Briefing on COVID-19*. (2020). Available online at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020 (accessed June 1, 2020).
3. Helmich RC, Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *J Parkinsons Dis.* (2020) 10:351–4. doi: 10.3233/jpd-202038
4. Multiple Sclerosis International Federation. *The Coronavirus and MS – Global Advice*. (2020). Available online at: www.msif.org/news/2020/02/10/the-coronavirus-and-ms-what-you-need-to-know/ (accessed March 24, 2020).
5. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020). doi: 10.1001/jamaneurol.2020.1127. [Epub ahead of print].
6. Li Y, Li H, Fan R, Wen B, Zhang J, Cao X, et al. Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. *Intervirology.* (2016) 59:163–9. doi: 10.1159/000453066
7. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. *Epilepsia.* (2020). doi: 10.1111/epi.16524. [Epub ahead of print].
8. Talan J. COVID-19: neurologists in italy to collegues in us: look for poorly-defined neurologic conditions in patients with the coronavirus. *Neurology Today*. https://journals.lww.com/neurotodayonline/blog/breakingnews/pages/post.aspx?PostID=920 (accessed April 8, 2020).
9. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* (2020). doi: 10.1001/jamaneurol.2020.2065. [Epub ahead of print].
10. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* (2020). doi: 10.1007/s00405-020-05965-1. [Epub ahead of print].
11. Lee Y, Min P, Lee S, Kim SW. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. *J Korean Med Sci.* (2020) 35:e174. doi: 10.3346/jkms.2020.35.e174
12. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. *Laryngoscope.* (2020). doi: 10.1002/lary.28692. [Epub ahead of print].
13. Public Health England. *Guidance on social distancing for everyone in the UK*. (2020). Available online at: https://www.gov.uk/government/publications/covid-19-guidance-on-social-distancing-and-for-vulnerable-people/guidance-on-social-distancing-for-everyone-in-the-uk-and-protecting-older-people-and-vulnerable-adults (accessed April 5, 2020).
14. Kreimer S. In and out of the hospital, neurohospitalists shift course for the surge in COVID-19. *Neurology Today*: AAN (2020). Available online at: https://journals.lww.com/neurotodayonline/fulltext/2020/05070/in_and_out_of_the_hospital_neurohospitalists.5.aspx (accessed June 1, 2020).
15. Association of British Neurologists. *Association of British Neurologists Guidance on COVID-19 for People with Neurological Conditions, Their Doctors and Carers*. (2020). Available online at: https://cdn.ymaws.com/www.theabn.org/resource/collection/6750BAE6-4CBC-4DDB-A684-116E03BFE634/ABN_Neurology_COVID-19_Guidance_22.3.20.pdf (accessed June 1, 2020).
16. American Academy of Neurology. *Position Statement: Telemedicine*. (2020). Available online at: https://www.aan.com/siteassets/home-page/policy-and-guidelines/policy/position-statements/18_telemedicineps_v304.pdf (accessed April 17, 2020).
17. American Headache Society. *COVID-19 Workflows for Headache Clinics*. (2020). Available online at: https://americanheadachesociety.org/news/headache-clinic-workflows-covid-19/ (accessed April 5, 2020).
18. Stetka BS. What neurologists can expect from COVID-19. *Medscape Neurology*. (2020). Available online at: https://www.medscape.com/viewarticle/927562 (accessed March 26, 2020).
19. Powell J. I'm choosing to let my spirit shine during the COVID-19 crisis. *Multiple Sclerosis News Today*. (2020). Available online at: https://multiplesclerosisnewstoday.com/news-posts/2020/03/30/my-spirit-shines-amid-covid-19-a-choice-to-thrive-with-spms/ (accessed June 1, 2020).
20. European Brain Council. *Rethinking MS in Europe: Prioritising Integrated Services for People With Multiple Sclerosis*. (2019). Available online at: https://www.braincouncil.eu/projects/rethinkingms/ (accessed June 1, 2020).

21. Rolak LA. Multiple sclerosis: it's not the disease you thought it was. *Clin Med Res.* (2003) 1:57–60. doi: 10.3121/cmr.1.1.57
22. Giovannoni G, Hawkes C, Lechner-Scott J, Levy M, Waubant E, Gold J. The COVID-19 pandemic and the use of MS disease-modifying therapies. *Mult Scler Relat Disord.* (2020) 39:102073.doi: 10.1016/j.msard.2020.102073
23. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology.* (2020) 94:949–52. doi: 10.1212/wnl.0000000000009507
24. National Multiple Sclerosis Society. *MS Treatment Guidelines during Coronavirus.* (2020). Available online at: https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/ms-treatment-guidelines-during-coronavirus#section-0\relax$\@@underline\hbox{}\mathsurround\z@$\relax (accessed June 1, 2020).
25. Collins T. COVID-19: How Neurologists Are Defining Those 'Essential' Visits for Migraine, Stroke, Epilepsy, and Multiple Sclerosis. *Neurology Today*: AAN publications (2020). Available online at: https://journals.lww.com/neurotodayonline/fulltext/2020/05070/covid_19__how_neurologists_are_defining_those.6.aspx (accessed June 1, 2020).
26. Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, Howard JF, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci.* (2020) 412:116803. doi: 10.1016/j.jns.2020.116803
27. ALS Association. *Coronavirus Disease Outbreak COVID-19*. (2020). Available online at: http://www.alsa.org/assets/pdfs/COVID-19_Facts.pdf (accessed April 5, 2020).
28. American Academy of Sleep Medicine. *COVID-19: FAQs for Sleep Clinicians*. (2020). Available online at: https://aasm.org/covid-19-resources/covid-19-faq (accessed March 11, 2020).
29. MND New Zealand. *COVID-19 Updates*. (2020). Available online at: https://mnd.org.nz/covid-19-updates/ (accessed April 5, 2020).
30. Epilepsy Society UK. *Epilepsy and the Coronavirus (COVID-19) FAQs*. (2020). Available online at: https://www.epilepsysociety.org.uk/epilepsy-and-coronavirus-covid-19-faqs#.XondK9P7Q6W (accessed April 5, 2020).
31. Epilepsy Centre. *Epilepsy and COVID-19*. (2020). Available online at: https://epilepsycentre.org.au/what-is-epilepsy/epilepsy-and-covid-19/ (accessed April 5, 2020).
32. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. *Lancet.* (2019) 393:689–701. doi: 10.1016/s0140-6736(18)32596-0
33. von Oertzen TJ, McGinty R, Holtkamp M, Kalviainen R, Ruegg S, Trinka E, et al. Impact of COVID-19 on management of epilepsy. *European Association of Neurologists*. (2020) Available online at: https://www.eanpages.org/2020/04/03/impact-of-covid-19-on-management-of-epilepsy/ (accessed April 5, 2020).
34. Karimi N, Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: a case report. *Iran Red Crescent Med J.* (2020) 22:e102828. doi: 10.5812/ircmj.102828
35. Epilepsy Foundation. *Concerns about COVID-19 and Epilepsy*. (2020). Available online at: https://epilepsyfoundation.org.au/wp-content/uploads/2020/03/Concerns-About-Coronavirus-and-Epilepsy-1.pdf (accessed June 1, 2020).
36. Association APD. *COVID-19 Overview for the Parkinson's Community*. (2020). Available online at: https://www.apdaparkinson.org/article/covid-19-overview-for-pd-community/ (accessed April 5, 2020).
37. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Critical Care.* (2020) 24:176. doi: 10.1186/s13054-020-02882-x
38. Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *bioRxiv.* (2020). doi: 10.1101/2020.03.25.009084. [Epub ahead of print].
39. Tarakad A, Jankovic J. Anosmia and ageusia in Parkinson's disease. *Int Rev Neurobiol.* (2017) 133:541–56. doi: 10.1016/bs.irn.2017.05.028
40. Khunti K, Greenhalgh T, Chan XH, Durand-Moreau Q, Straube S, Devane D, et al. *What is the Efficacy of Eye Protection Equipment Compared to No Eye Protection Equipment in Preventing Transmission of COVID-19-Type Respiratory Illnesses in Primary and Community Care?* (2020). Available online at: https://www.cebm.net/covid-19/what-is-the-efficacy-of-eye-protection-equipment-compared-to-no-eye-protection-equipment-in-preventing-transmission-of-covid-19-type-respiratory-illnesses-in-primary-and-community-care/ (accessed April 24, 2020).
41. Azar J, Elinav H, Safadi R, Soliman M. Malignant deep brain stimulator withdrawal syndrome. *BMJ Case Rep.* (2019) 12:e229122. doi: 10.1136/bcr-2018-229122
42. American Migraine Foundation. *Navigating Migraine & Headache Treatment during the COVID-19 Global Pandemic*. (2020). Available online at: https://americanmigrainefoundation.org/resource-library/migraine-treatment-during-covid-19/ (accessed April 7, 2020).
43. Friedman DI, Rajan B, Seidmann A. A randomized trial of telemedicine for migraine management. *Cephalalgia.* (2019) 39:1577–85. doi: 10.1177/0333102419868250
44. MaassenVanDenBrink A, de Vries T, Danser AHJ. Headache medication and the COVID-19 pandemic. *J Headache Pain.* (2020) 21:38. doi: 10.1186/s10194-020-01106-5
45. Chatterjee S. Important steps to control COVID-19/SARS-CoV-2 infection. *SN Compr Clin Med.* (2020) 1–2. doi: 10.1007/s42399-020-00271-7
46. Talreja H, Tan J, Dawes M, Supershad S, Rabindranath K, Fisher J, et al. A consensus statement on the use of angiotensin receptor blockers and angiotensin converting enzyme inhibitors in relation to COVID-19 (corona virus disease 2019). *N Z Med J.* (2020). [Epub ahead of print].
47. Panati K, Narala VR. COVID-19 outbreak: an update on therapeutic options. *SN Compr Clin Med.* (2020) 2:379–80. doi: 10.1007/s42399-020-00264-6
48. Little P. Non-steroidal anti-inflammatory drugs and covid-19. *BMJ.* (2020) 368:m1185. doi: 10.1136/bmj.m1185
49. Brown JD. Antihypertensive drugs and risk of COVID-19? *Lancet Respir Med.* (2020) 8:e28. doi: 10.1016/s2213-2600(20)30158-2
50. Frishman WH. Beta-adrenergic blocker withdrawal. *Am J Cardiol.* (1987) 59:F26–32. doi: 10.1016/0002-9149(87)90038-5
51. Prins KW, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of beta-blocker withdrawal in acute decompensated heart failure. A systematic review and meta-analysis. (2015) 3:647–53. doi: 10.1016/j.jchf.2015.03.008
52. Raschi E, Poluzzi E, De Ponti F. Stroke, migraine and triptans: from bedside to bench. *EBioMedicine.* (2016) 6:14–5. doi: 10.1016/j.ebiom.2016.03.045
53. Diener HC. The risks or lack thereof of migraine treatments in vascular disease. *Headache.* (2020) 60:649–53. doi: 10.1111/head.13749
54. Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev.* (2013) 2013:Cd008040. doi: 10.1002/14651858.CD008040.pub3
55. Tietjen GE, Collins SA. Hypercoagulability and migraine. *Headache.* (2018) 58:173–83. doi: 10.1111/head.13044
56. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS ONE.* (2012) 7:e35797. doi: 10.1371/journal.pone.0035797
57. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the Young. *N Engl J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787
58. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect.* (2020) 80:639–45. doi: 10.1016/j.jinf.2020.03.019
59. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* (2020) 395:1054–62. doi: 10.1016/s0140-6736(20)30566-3
60. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
61. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected code stroke. *Stroke.* (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.029838

62. Bhaskar S, Sharma D, Walker AH, McDonald M, Huasen B, Haridas A, et al. Acute neurological care in the COVID-19 era: the pandemic health system REsilience PROGRAM (REPROGRAM) consortium pathway. *Front Neurol.* (2020) 11:579. doi: 10.3389/fneur.2020.00579
63. Román GC, Spencer PS, Reis J, Buguet A, Faris MEA, Katrak SM, et al. The neurology of COVID-19 revisited: a proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. *J Neurol Sci.* (2020) 414:116884. doi: 10.1016/j.jns.2020.116884
64. Abdelnour L, Eltahir Abdalla M, Babiker S. COVID 19 infection presenting as motor peripheral neuropathy. *J Formos Med Assoc.* (2020) 119:1119–20. doi: 10.1016/j.jfma.2020.04.024
65. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* (2020) 19:383–4. doi: 10.1016/S1474-4422(20)30109-5
66. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain–Barré syndrome associated with SARS-CoV-2. *N Engl J Med.* (2020). doi: 10.1056/NEJMc2009191. [Epub ahead of print].
67. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: a case report. *J Clin Neurosci.* (2020) 76:233–5. doi: 10.1016/j.jocn.2020.04.062
68. Scheidl E, Canseco DD, Hadji-Naumov A, Bereznai B. Guillain-Barré syndrome during SARS-CoV-2 pandemic: a case report and review of recent literature. *J Peripher Nerv Syst.* (2020). doi: 10.1111/jns.12382. [Epub ahead of print].
69. Ottaviani D, Boso F, Tranquillini E, Gapeni I, Pedrotti G, Cozzio S, et al. Early Guillain-Barré syndrome in coronavirus disease 2019 (COVID-19): a case report from an Italian COVID-hospital. *Neurol Sci.* (2020) 41:1351–4. doi: 10.1007/s10072-020-04449-8.
70. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan.* (2005) 14:113–9.
71. Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas R, et al. Miller fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology.* (2020). doi: 10.1212/wnl.0000000000009619. [Epub ahead of print].
72. Zhao K, Huang J, Dai D, Feng Y, Liu L, Nie S. Acute myelitis after SARS-CoV-2 infection: a case report. *medRxiv.* (2020). doi: 10.1101/2020.03.16.20035105. [Epub ahead of print].
73. Munz M, Wessendorf S, Koretsis G, Tewald F, Baegi R, Krämer S, et al. Acute transverse myelitis after COVID-19 pneumonia. *J Neurol.* (2020). doi: 10.1007/s00415-020-09934-w. [Epub ahead of print].
74. Jin M, Tong Q. Rhabdomyolysis as potential late complication associated with COVID-19. *Emerg Infect Dis.* (2020). doi: 10.3201/eid2607.200445. [Epub ahead of print].
75. Barnes SL, Herkes GK. Guillain-Barré syndrome: clinical features, treatment choices and outcomes in an Australian cohort. *Intern Med J.* (2019). doi: 10.1111/imj.14705. [Epub ahead of print].
76. GBS CIDP Foundation International. *A Statement from the GBS|CIDP Foundation Regarding the COVID-19*. (2020). Available online at: https://www.gbs-cidp.org/a-statement-from-the-gbscidp-foundation-regarding-the-covid-19/ (accessed June 1, 2020).
77. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:552–5. doi: 10.1002/jmv.25728
78. Nath A. Neurologic complications of coronavirus infections. *Neurology.* (2020) 94:809. doi: 10.1212/WNL.0000000000009455
79. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. *Radiology.* (2020) 201187. doi: 10.1148/radiol.2020201187
80. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* (2020) 395:1033–4. doi: 10.1016/s0140-6736(20)30628-0
81. Autism Speaks. *COVID-19 Information and Resources*. (2020). Available online at: https://www.autismspeaks.org/covid-19-information-and-resources (accessed April 6, 2020).
82. Coronavirus in Context: *How a Pediatric Hospital Prepares for Potential COVID-19 Influx*. (2020). Available online at: https://www.webmd.com/coronavirus-in-context/video/anthony-sandler (accessed April 7, 2020).
83. Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and mitigating the impact of the COVID-19 pandemic on Alzheimer's disease and related dementias. *Am J Geriatr Psychiatry.* (2020). doi: 10.1016/j.jagp.2020.04.010. [Epub ahead of print].
84. Wang H, Li T, Barbarino P, Gauthier S, Brodaty H, Molinuevo JL, et al. Dementia care during COVID-19. *Lancet.* (2020) 395:1190–1. doi: 10.1016/S0140-6736(20)30755-8
85. Pereira-Sanchez V, Adiukwu F, El Hayek S, Bytyçi DG, Gonzalez-Diaz JM, Kundadak GK, et al. COVID-19 effect on mental health: patients and workforce. *Lancet Psychiatry.* (2020) 7:e29–30. doi: 10.1016/S2215-0366(20)30153-X
86. European Academy of Neurology. *Management Group of the EAN Dementia panel*. Available online at: Dementia Scientific Panel Report - COVID-19 (2020). https://www.eanpages.org/2020/04/03/dementia-scientific-panel-report-covid-19/ (accessed June 1, 2020).
87. Leonardi S, Camporotondo R, Totaro R, Costantino I, Gnecchi M, Oltrona L. *Patients: Scared and Alone - Pavia, Italy*. Washington, DC: American Psychiatric Association (2020). Available online at: https://www.escardio.org/Education/COVID-19-and-Cardiology/patients-scared-and-alone-pavia-italy (accessed June 1, 2020).
88. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders – DSM-5*. 5th ed. doi: 10.1176/appi.books.9780890425596
89. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*. doi: 10.1016/S2215-0366(20)30203-0. [Epub ahead of print].
90. Zhou X, Snoswell CL, Harding LE, Bambling M, Edirippulige S, Bai X, et al. The role of telehealth in reducing the mental health burden from COVID-19. *Telemed J E Health.* (2020) 26:377–9. doi: 10.1089/tmj.2020.0068
91. Bhaskar, Rastogi A, Chattu VK, Adisesh A, Thomas P, Alvarado N, et al. Key strategies for clinical management and improvement of healthcare services for cardiovascular disease and diabetes patients in the coronavirus (COVID-19) settings: recommendations from the REPROGRAM consortium. *Front. Cardiovasc. Med.* 6:26. doi: 10.3389/fcvm.2020.00112
92. Cragg JJ, Kramer JK, Borisoff JF. Relationship between neurological disorders and heart disease: a national population health survey. *Neuroepidemiology.* (2015) 44:64–5. doi: 10.1159/000373925

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The Reviewer AK declared a shared affiliation with one of the author, SI-K to the handling editor at time of review.

frontiers in Neurology

OPINION
published: 26 June 2020
doi: 10.3389/fneur.2020.00722

Decision Making on Telemedicine for Patients With Epilepsy During the Coronavirus Disease 2019 (COVID-19) Crisis

*Naoto Kuroda**

Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI, United States

Keywords: epilepsy, COVID-19, telemedicine, decision making, algorithm, epilepsy surgery, novel coronavirus

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Chih-Sheng Yang,
Taichung Tzu Chi General Hospital, Taiwan
Poh-Shiow Yeh,
Chi Mei Medical Center, Taiwan

****Correspondence:***
Naoto Kuroda
naoto.kuroda@wayne.edu

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *27 May 2020*
Accepted: *15 June 2020*
Published: *26 June 2020*

Citation:
Kuroda N (2020) Decision Making on Telemedicine for Patients With Epilepsy During the Coronavirus Disease 2019 (COVID-19) Crisis. Front. Neurol. 11:722. doi: 10.3389/fneur.2020.00722

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak initially occurred in Wuhan, China, in late 2019, and is spreading globally (1). Society, in general, is required to adapt to the changes induced by the COVID-19 crisis.

Epilepsy is a neurological chronic disorder characterized by a spontaneous recurrence of unprovoked seizures. In the field of neurology, as well as other departments, telemedicine is recommended as an alternative option for outpatient practice during the COVID-19 crisis to avoid the risk of exposure to SARS-CoV2 (2). The clinicians are trying to change the practice style to telemedicine owing to the worldwide COVID-19 crisis. Telemedicine was already in use before the COVID-19 crisis for some patients who had difficulty accessing medical facilities. However, the COVID-19 crisis has made telemedicine an option that should be actively considered in most patients, not just some patients who have difficulty accessing medical facilities. In the field of epilepsy, the importance of telemedicine is emphasized during this crisis; however, no consensus about decision making is available (2).

The present study article emphasizes the decision-making process by clinicians for patients with epilepsy via telemedicine during the COVID-19 crisis. Considering the decision-making factors, a decision-making tree has been proposed (**Figure 1**).

DECISION MAKING ON TELEMEDICINE

Strength and Weakness of Telemedicine

Telemedicine consultation between clinicians and patients with epilepsy has certain advantages. First, the patients can save time, consultation fees, and travel expenses required to visit their doctors (3). Second, Patients living in areas with poor medical resources can have access to professional doctors of the required fields (3). Third, patients can avoid public exposure, which is highly recommended during COVID-19 crisis (2).

In contrast, telemedicine has certain limitations compared to physical consultation. It is difficult to examine the patients online, the effectiveness is limited, and remains unauthenticated (4). In general, patients cannot undergo clinical tests associated with epilepsy such as blood test, cerebrospinal-fluid test, neuroimaging, and electroencephalogram, thereby indicating that patients requiring such examination have to physically visit the testing centers despite the exposure risk to SARS-CoV-2.

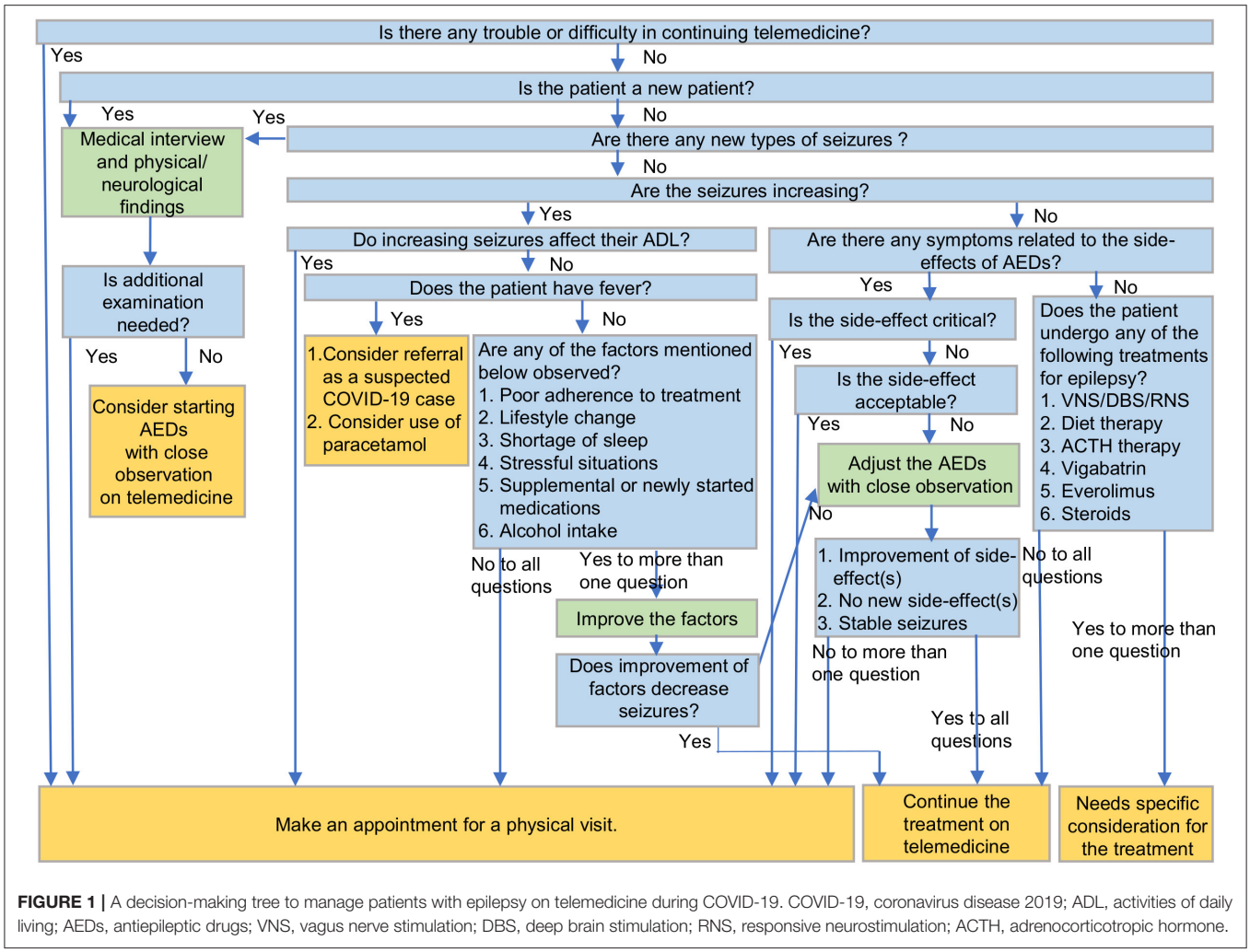


FIGURE 1 | A decision-making tree to manage patients with epilepsy on telemedicine during COVID-19. COVID-19, coronavirus disease 2019; ADL, activities of daily living; AEDs, antiepileptic drugs; VNS, vagus nerve stimulation; DBS, deep brain stimulation; RNS, responsive neurostimulation; ACTH, adrenocorticotropic hormone.

Decision Making by Clinicians for Patients With Epilepsy via Telemedicine During COVID-19 Crisis

Based on the above-mentioned advantages and limitations of telemedicine, physicians should recommend both outpatient consultation at clinic and telemedicine appropriately. During telemedicine consultation, the doctors should decide whether the patients require a visit to the clinics.

Access to the System of Telemedicine

To continue telemedicine, the feasibility and accessibility for patients remain one of the most important factors. Some factors disturb the patients to continue the telemedicine (2). People who are blind or hard of hearing may be more inconvenienced by telemedicine. Some patients are unable to use a video-call system for a variety of reasons, such as difficulty accessing the internet, location, or financial situation. Patients in such situations should be encouraged to visit the clinics. It is more important to provide continued medical care.

New Patients

In the cases of new patients, we would collect general information, including clinical history, family history, seizure semiology, medical history, and birth and developmental history. In addition, we would check the physical and neurological findings. If additional testing is needed, including blood test, tap test, electroencephalogram, or neuroimaging, an appointment can be made for the patient to come into the clinic. In cases where more examinations are not needed, we can continue with telemedicine.

The Presence of New Seizure Type

The occurrence of seizure types would indicate acute symptomatic seizure due to onset of new diseases including COVID-19 (5). Even for patients with epilepsy as a neurological chronic disorder, the new types of seizures should be distinguished from the original seizures and must be examined in detail. The diseases which cause seizures include cerebrovascular disease, head trauma, central nervous system infection, auto immune encephalitis, and intoxication (6). We should also

remember that psychogenic non-epileptic seizures are a disorder that is often difficult to differentiate from epilepsy (7). Therefore, epileptologists should confirm the presence of seizure types, differing from the original seizures.

Seizure Frequency

While consulting outpatients with epilepsy, an essential factor is the change in seizure frequency. Several factors affect the seizure control (8). If the seizure frequency increases, clinicians should consider all factors responsible for the loss of seizure control.

In the cases of increasing seizures, clinicians have to confirm several factors associated with seizure occurrence. Changing lifestyle, such as change of sleep duration, decreased medication compliance, and stressful/anxious situations can affect the seizure control. Alcohol consumption is a known trigger for seizures in patients with epilepsy. It is widely known that people under stressful situation tend to consume alcohol more frequently (9). Moreover, it is widely known that anxiety and mental stress can increase seizures (10). To control seizure, medication compliance is essential. During the COVID-19 crisis, lifestyle changes are bound to occur, which may decrease the medication compliance (11). Considering prevention or supportive therapy of COVID-19, patients with epilepsy might be exposed to various supplements or newly started medications. As reported, some antiviral therapy used for COVID-19 may interact with the antiepileptic drugs (AEDs) (12). According to The Italian League Against Epilepsy (https://www.lice.it/pdf/Antiepileptic_drugs_interactions_in_COVID-19.pdf), some AEDs (gabapentin, levetiracetam, lorazepam, pregabalin, clonazepam, ethosuximide, et al.) have relatively few interactions with antiviral medications and are easy to combine with them. O the other hand, some AEDs (carbamazepine, phenytoin, phenobarbital, et al.) have strong interaction with antiviral drugs. In addition, some combinations can induce fatal arrhythmias in patients. Therefore, clinicians should consider the effects of interaction between such medications and AEDs.

We should first confirm such factors, including medication adherence, lifestyle, shortage of sleep, stressful situations, alcohol intake, and supplemental or new medications. If there is no change in terms of these factors, we would consider about adjustment of AEDs. If the increase in seizures disturbs the patients' daily activities, physician could encourage making appointment for physical consultation, whatever the causes of exacerbation might be.

Patients' General State

Any person could be infected by SARS-CoV-2. Therefore, clinicians should ask the patients with epilepsy whether they have any symptoms of COVID-19. Similar to the general population, patients with epilepsy who have comorbidities, such as smoking, obesity, diabetes, heart disease, lung disease, and cancer, are at a higher risk of developing COVID-19 (13). Among the COVID-19 symptoms, fever should be appropriately monitored as it could decrease the threshold of seizures (14). If required, the clinicians should consider prescription of antifebrile medications. In particular, for patients with Dravet syndrome, the management of fever is critical (15). Moreover, it is reasonable to use paracetamol if patients with Dravet syndrome have a fever (16). In addition to patients with Dravet syndrome, those with epilepsy can also be prescribed antifebrile medications, such as paracetamol.

Side-Effect of AEDs

If the patients with increased seizure lack the aforementioned factors (medication adherence, lifestyle, shortage of sleep, stressful situations, alcohol intake, supplemental or new medication, and patients' general state) or when improvement in such factors does not decrease the seizure frequency, clinicians may consider adjusting the AEDs.

While adjusting AEDs on telemedicine, the side-effect of AEDs should be considered. Telemedicine allows us to weigh the side-effects of the treatment (17). In case of critical side-effects, clinicians may consider physical consultation. We may consider continuing the AEDs if the side-effects are mild and acceptable to both clinician and patients. However, if the side-effects are critical, an appointment at the clinic will be needed. We need to consider discontinuing or changing the therapeutic drug on telemedicine if the side effects are not critical, and are unacceptable to either the physician or the patient. If the side-effects do not improve despite decreasing or stopping the AEDs, the patient should be encouraged to physically visit the clinician for further evaluation.

Other Treatments for Epilepsy

Some patients with epilepsy resort to the diet-therapy to control seizures. Diet-therapy would be vulnerable under the effect of COVID-19 crisis owing to the difficulty of obtaining the required foods for diet-therapy (18). Therefore, the clinicians should confirm the compliance to diet-therapy on telemedicine. Few patients with diet-therapy would need online-dietary-counseling by dieticians.

Patients with epilepsy who underwent surgeries, such as vagus nerve stimulation, deep brain stimulation, or responsive neurostimulation, require the adjustment of parameter for stimulation. In the present scenario, clinicians have no alternative options to manage and control such procedure on telemedicine. In particular, patients who are not very long post-operatively or who need to have parameters set may need an actual visit even in a COVID-19 situation.

Some patients take medications, such as everolimus or corticosteroid, which affect the immune system. Under normal conditions, such medications are normally prescribed to control seizures (12). However, these medications may need to be discontinued for a short period for patients with exposure to SARS-CoV-2 or diagnosed as COVID-19 positive (19).

Vigabatrin is an AED often used for patients with tuberous sclerosis complex. Clinicians can continue prescribing this medication on telemedicine if approved by the opthalmologists, as it is known to cause visual field defect (20).

Some patients with infantile spasm might have undergone adrenocorticotropic hormone (ACTH) therapy for epilepsy (21). This therapy is generally provided on admission; however, during the COVID-19 crisis, physicians could consider using oral steroid

as an alternative option for ACTH therapy on telemedicine to reduce the risk of virus exposure (21, 22).

CONCLUSION

The present study summarizes and suggests the management of patients with epilepsy on telemedicine during the COVID-19 crisis. Epileptologists are required to manage their outpatients using telemedicine due to COVID-19 pandemic. Decision-making tree prescribed in this article would be helpful for the epileptologists to manage their patients on telemedicine. In COVID-19 situations, patients are exposed to various aspects of psychological stress. Therefore, in addition to decision-making, understanding and listening to the patient's stress in the telemedicine is important during the COVID-19 crisis. It is also important to establish a medical system that allows for the continuation of telemedicine in the long term, even after the COVID-19 crisis. Research will also be needed to evaluate the effectiveness and safety of telemedicine in the COVID-19 crisis.

AUTHOR CONTRIBUTIONS

NK: study/article design, data collection, and manuscript writing.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
2. Bloem BR, Dorsey ER, Okun MS. The coronavirus disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. *JAMA Neurol.* (2020) 26:2020. doi: 10.1001/jamaneurol.2020.1452
3. Patterson V. Managing epilepsy by telemedicine in resource-poor settings. *Front Public Health.* (2019) 7:321. doi: 10.3389/fpubh.2019.00321
4. Lo MD, Gospe SM Jr. Telemedicine and child neurology. *J Child Neurol.* (2019) 34:22–26.
5. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. *Epilepsia.* (2020) 26:2020. doi: 10.1111/epi.16524
6. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsia.* (2010) 51:671–75. doi: 10.1111/j.1528-1167.2009.02285.x
7. Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? *J Neurol Neurosurg Psych.* (2010) 81:719–25. doi: 10.1136/jnnp.2009.197996
8. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med.* (2011) 365:919–26. doi: 10.1056/NEJMra1004418
9. Becker HC. Influence of stress associated with chronic alcohol exposure on drinking. *Neuropharmacology.* (2017) 122:115–26. doi: 10.1016/j.neuropharm.2017.04.028
10. Kotwas I, McGonigal A, Bastien-Toniazzo M, Bartolomei F, Micoulaud-Franchi JA. Stress regulation in drug-resistant epilepsy. *Epilepsy Behav.* (2017) 71:39–50. doi: 10.1016/j.yebeh.2017.01.025
11. Brown MT, Bussell J, Dutta S, Davis K, Strong S, Mathew S. Medication adherence: truth and consequences. *Am J Med Sci.* (2016) 351:387–99. doi: 10.1016/j.amjms.2016.01.010
12. Kuroda N. Epilepsy and COVID-19: associations and important considerations. *Epilepsy Behav.* (2020) 108:107122. doi: 10.1016/j.yebeh.2020.107122
13. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ.* (2020) 368:m1198. doi: 10.1136/bmj.m1198
14. Kasahara Y, Ikegaya Y, Koyama R. Neonatal seizure models to study epileptogenesis. *Front Pharmacol.* (2018) 9:385. doi: 10.3389/fphar.2018.00385
15. Wheless JW, Fulton SP, Mudigoudar BD. Dravet syndrome: a review of current management. *Pediatr Neurol.* (2020) 107:28–40. doi: 10.1016/j.pediatrneurol.2020.01.005
16. Dravet Syndrome UK. *Latest Coronavirus Guidance for Children and Adults With Dravet Syndrome*. (2020). Available online at: https://www.dravet.org.uk/news/coronavirus-advice (accessed May 10, 2020).
17. Liptrott S, Bee P, Lovell K. Acceptability of telephone support as perceived by patients with cancer: a systematic review. *Eur J Cancer Care.* (2018) 27:e12643. doi: 10.1111/ecc.12643
18. The Epilepsy Foundation New England. *Coronavirus Information For People Affected By Epilepsy In New England.* (2020). Available online at: https://epilepsynewengland.org/news/coronavirus-information-for-people-affected-by-epilepsy-in-new-england (accessed May 10, 2020).
19. Al-Ani AH, Prentice R, Rentsch C, Johnson D, Ardalan Z, Heerasing N, et al. Review article: prevention, diagnosis and management of COVID-19 in the inflammatory bowel disease patient. *Aliment Pharmacol Ther.* (2020) 26:2020. doi: 10.1111/apt.15779
20. Curatolo P, Nabbout R, Lagae L, Aronica E, Ferreira JC, Feucht M, et al. Management of epilepsy associated with tuberous sclerosis complex: updated clinical recommendations. *Eur J Paediatr Neurol.* (2018) 22:738–48. doi: 10.1016/j.ejpn.2018.05.006
21. Kelley SA, Knupp KG. Infantile spasms-have we made progress? *Curr Neurol Neurosci Rep.* (2018) 18:27. doi: 10.1007/s11910-018-0832-8
22. Gonzalez-Giraldo E, Stafstrom CE, Stanfield AC, Kossoff EH. Treating infantile spasms with high-dose oral corticosteroids: a retrospective review of 87 children. *Pediatr Neurol.* (2018) 87:30–5. doi: 10.1016/j.pediatrneurol.2018.06.011

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 03 July 2020
doi: 10.3389/fneur.2020.00737

Epilepsy Care in the Time of COVID-19 Pandemic in Italy: Risk Factors for Seizure Worsening

Giovanni Assenza[1†], Jacopo Lanzone[1], Francesco Brigo[2], Antonietta Coppola[3], Giancarlo Di Gennaro[4], Vincenzo Di Lazzaro[1], Lorenzo Ricci[1], Andrea Romigi[5], Mario Tombini[1] and Oriano Mecarelli[6]*

[1] Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, University Campus Bio-Medico of Rome, Rome, Italy, [2] Division of Neurology, "Franz Tappeiner" Hospital, Merano, Italy, [3] Department of Neurosciences, Reproductive Sciences and Odontostomatology, University Federico II of Naples, Naples, Italy, [4] Epilepsy Surgery Center, IRCCS NEUROMED, Pozzilli, Italy, [5] Sleep Medicine Center, IRCCS NEUROMED, Pozzilli, Italy, [6] Department of Human Neurosciences, "Sapienza" University of Rome, Rome, Italy

OPEN ACCESS

Edited by:
Rodrigo Rocamora,
Pompeu Fabra University, Spain

Reviewed by:
Estevo Santamarina,
Vall D'Hebron University Hospital, Spain
Mariusz Stanisław Wiglusz,
Medical University of Gdansk, Poland

***Correspondence:**
Giovanni Assenza
g.assenza@unicampus.it

†ORCID:
Giovanni Assenza
orcid.org/0000-0002-6160-4348

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 28 April 2020
Accepted: 16 June 2020
Published: 03 July 2020

Citation:
Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, Ricci L, Romigi A, Tombini M and Mecarelli O (2020) Epilepsy Care in the Time of COVID-19 Pandemic in Italy: Risk Factors for Seizure Worsening. Front. Neurol. 11:737. doi: 10.3389/fneur.2020.00737

Objective: In early 2020, Italy struggled with an unprecedented health emergency related to the COVID-19 pandemic. Medical care of chronic neurological diseases, such as epilepsy, is being sorely neglected. In this national survey, we aimed at understanding the impact of COVID-19 lockdown on the care of people with epilepsy (PwE) and identifying PwE risk factors for seizure worsening to direct telemedicine efforts.

Methods: We administered a 48-items online survey (published on April 11, 2020) including socio-demographic, epilepsy-related, and psychometric variables (BDI-II for depression, GAD-7 for anxiety, and PSQI for sleep) to PwE and people without epilepsy (PwoE). Regression analysis identified predictors of seizure worsening.

Results: We collected responses from 456 PwE (344 females) and 472 PwoE (347 females). Outpatient examinations of PwE were postponed in 95% of cases. One-third of PwE complained of issues with epilepsy management, but only 71% of them reached the treating physician and solved their problems. PwE had worse depressive and anxiety symptoms (higher BDI-II and GAD-7 scores; $p < 0.001$) than PwoE. Sleep quality was equally compromised in both groups (47 and 42%). Sixty-seven PwE (18%) reported seizure worsening, which was best explained by the number of anti-seizure medications (ASM) of chronic therapy and the severity of sleep disorder.

Conclusions: During the current COVID-19 pandemic, a significant percentage of PwE experienced difficulties in follow-up and a seizure number increase, in particular those chronically taking more ASMs and with poor sleep quality. This dramatic experience outlines the urgent need for validation and implementation of telemedicine services for epileptic patients in order to provide regular follow-up.

Keywords: epilepsy, COVID-19, sleep, depression, anxiety

INTRODUCTION

Italy is facing an unprecedented health emergency represented by the COVID-19 pandemic due to the SARS-CoV-2 virus. The government imposition of quarantines, travel bans, and lockdown throughout the country has been producing the first effects in limiting the spread of the viral infection. The COVID-19 pandemic led to strict measures of isolation (www.apple.com/covid19/mobility) throughout the Italian peninsula. Almost inevitably, isolation is accompanied by either the onset or the worsening of sleep, mood, and anxiety disorders (1). It is also associated with an increased risk of an inadequate level of medical care for chronic disorders, including epilepsy. The social and behavioral consequences of COVID19 lockdown might increase seizure frequency in people with epilepsy (PwE). Furthermore, the COVID-19 viral infection itself can induce a febrile status, which in turn can reduce seizure threshold (2). The industry lockdown hampers anti-seizure medication (ASM) supplies, whereas the reduced care services limited to emergencies make it difficult for PwE to receive regular follow-up and to keep in touch with their treating physicians. To address these difficulties, Italian neurologists are using several communication strategies (e.g., emails, phone, electronic messages, web conference calls, etc.) to maintain contact with their patients, while continuing to manage the increased need for intensive medical assistance.

In this national survey, we aimed at understanding the real impact of COVID-19 breakdown on PwE in Italy by evaluating the seizure frequency, needs, and behaviors of patients in order to identify possible risk factors for seizure worsening and thus to better focus the implementation of telemedicine strategies.

MATERIALS AND METHODS

An online survey was created using the free open-access Google^{TM} Forms (https://www.google.com/forms/about/) application. The survey included an informed consent verification, making it possible for those who did not agree with its terms of use to end the survey without further questions. No personally identifiable information was collected, and data were treated according to the European regulation GDPR n. 2016/679. The survey was published on April 11, 2020, on the Facebook webpage of the LICE (Lega Italiana Contro Epilessia, the Italian chapter of the International League Against Epilepsy, ILAE) Foundation, a non-profit organization promoting research, training, and public awareness about epilepsy.

We set a convenience sample of at least 300 PwE. We planned also to include people without epilepsy (PwoE) as a control group. Subjects younger than 18 years old were excluded from the survey since the psychiatric scales used in the questionnaire are validated for adults only. The survey continued until there was a reduction of >90% in the number of daily answers compared to the 1st day of online publication. The survey was closed at 23:59, April 16, 2020.

The questionnaire contained the following sections:

- Introduction with a brief description of the aim of the study
- Informed consent (mandatory)
- Demographic and social data (age, sex, region, educational level, and marital, and working status)
- Changes in working activities during the COVID-19 period
- Anamnesis for depression and anti-depressant therapy
- The assumption of new anti-depressants, anxiolytics, hypno-inducers, or antipsychotics during the COVID-19 period
- Epilepsy-related questions (for PwE group):
    - seizure frequency during COVID-19 period and pre-COVID-19 period, number and dosages of ASM in chronic therapy, subjective seizure worsening (PwE were asked "Did your epilepsy worsen, with an increased number or severity of seizures, in the lockdown period? Yes or No"), scheduled neurological examinations/outpatient visits and their deferral (if there were any), rising epilepsy-related issues (ASM availability, adverse effects of ASM, anxiety, depression, need to increase therapy), attempts to contact the neurologist, successes in contacting the neurologist, successes in resolving epilepsy-related issues, adherence to the ASM therapy.
- Psychiatric assessment: Beck depression inventory scale II for depressive symptoms (BDI-II), General Anxiety Disorder-7 (GAD-7) for anxiety symptoms, and Pittsburg Sleep Quality Index (PSQI) for sleep.

The BDI-II is a 21-item self-report measure of common depressive symptoms (3). Each item has four possible responses, and higher total scores are indicative of a greater number and severity of depressive symptoms. Scores ranging from 0 to 13 indicate minimal/no symptoms, 14–19 indicate mild depression, 20–28 indicate moderate depression, and 29–63 indicate severe depression.

The GAD-7 is a valid and efficient tool for screening for anxiety symptoms and assessing their severity in clinical practice and research (4). Scores of 5, 10, and 15 represent cut-off scores for mild, moderate, and severe anxiety symptoms, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater.

Subjective quality of sleep was assessed through the PSQI (5), a self-rated questionnaire that assesses sleep quality and its disturbance over 1 month. We used the validated Italian version of PSQI (6) consisting of a 19-items scale, in which responses are given for the last month, that measures sleep disturbances according to seven dimensions: subjective sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbances (C5), use of sleep medication (C6), and daytime dysfunctions (C7). The scores from these seven areas were gathered together, creating a global score considered an indicator of relevant sleep disturbances if >5. As PSQI was one of the variables best at predicting seizure worsening in PwE, we performed a principal component analysis, which helps to reduce the dimensionality of data, on PSQI components in order to evaluate which items are responsible of the variation in total PSQI score in our sample.

The social lockdown started on March 11, 2020, in Italy. We therefore defined the COVID-19 period as the 31 days before the questionnaire was published (March 11 to April 10, 2020),

whereas the period between February 9 and March 10, 2020, was defined as the pre-COVID-19 period.

Data were automatically stored on a private account and downloaded as a ".csv" text file.

STATISTICAL ANALYSIS

Data management and statistical analysis were performed in R 3.6.2 using R studio software. Data manipulation was performed in the tidyverse grammar for R.

Normally distributed data were reported as mean ± standard deviation; normality was checked by quantile-quantile plotting. Non-normally distributed data were reported as median and range. The main items of data were subdivided according to the responder's answer to the following questions: "Do you have a diagnosis of epilepsy?" "Did your epilepsy worsen, with an increased number or severity of seizures in the lockdown period?" According to the answers, subjects were divided into PwE and PwoE. The PwE group was further divided into patients experiencing worsening (WPwE) and those without worsening (nWPwE). This subjective variable was chosen to merge qualitative (intensity, duration, post-ictal symptoms) and quantitative (number) changes to seizures in PwE. However, to check for possible biases caused by the subjectivity of the PwE evaluation of seizure worsening, we compared the seizure frequency changes between WPwE and nWPwe in terms of both absolute number and percentage change (percentage change of seizure frequency in the COVID-19 period with respect to the pre-COVID-19 period).

Differences among groups were described with a *t*-test for continuous normal variables, the *U*-Mann-Whitney test for non-normal continuous variables, and Chi-squared for frequencies. Significant correlations (Pearson's correlation for normally distributed variables, Spearman's correlation for non-normally distributed variables) were calculated for psychometric variables in the PwE and PwoE groups. As, in Italy, the number of COVID-19 infections was higher in the Northern regions of Lombardia, Veneto, and Piemonte (www.salute.gov.it), we also performed a comparison between participants coming from those regions and those resident in the rest of the peninsula.

In order to better describe which variables influenced the worsening of epilepsy in PwE during the lockdown period, we designed a logistic regression model. We selected dependent variables through a stepwise backward model, with selection based on the Akaike information criterion (AIC), which was implemented using the MASS library for R. Categorical variables were dummy-coded prior to entering the logistic regression. Variables in the initial entry were chosen among those showing potential differences between the worsened and non-worsened group ($p < 0.1$). We added to these variables some factors that, in our experience, could increase the likelihood of worsening, such as number of ASMs or previous diagnosis of depressive disorders.

Since PSQI showed to be a significant predictor of seizure worsening, we investigated which component of PSQI contributed the most to the variability of the total score. To better describe the PSQI sub-scores, we performed a principal component analysis (PCA) to reduce the dimensionality of data, choosing components that explained most of the variability (elbow method) and showing which sub-items weighed the most in those components.

The alpha level was set at 0.05 for statistical significance.

RESULTS

A total of 953 subjects accessed the online survey, and 928 of them (97.4%) gave their consent to proceed with the questionnaire.

Demographic Data

We collected the answers of 456 PwE (344 females) and 472 PwoE (347 females). Females represented 78% of the whole sample. PwoE were older than PwE (43.9 ± 12.3 years, range 18–89 years vs. 37.82 ± 12.48, range 18–86 years; $p < 0.0001$). Regional residence frequency was, in alphabetical order: Abruzzo 24, Basilicata 3, Calabria 16, Campania 123, Emilia-Romagna 53, Friuli venezia giulia 20, Lazio 315, Liguria 9, Lombardia 112, Marche 11, Molise 10, Piemonte 48, Puglia 49, Sardegna 16, Sicilia 16, Toscana 30, Trentino alto adige 19, Umbria 9, Valle d'aosta 0, and Veneto 42.

We did not find any difference between responders from the regions of Lombardia, Veneto and Piemonte and those from other Italian regions with regard to age, sex, and number of PwE and PwoE.

Socio-Demographic and Occupational Data

The socio-demographic and occupational data are summarized in **Table 1**.

PwE had a lower percentage of occupation (55.7%, employees + freelancers) than PwoE (76.1% employees+freelancers); 54% of PwE and 83.5% of PwoE reported a reduction in their working activities during COVID-19 lockdown (**Table 1**). Of all respondents, 79.7% reported that they stayed at home around the clock.

Depression

A history of depression was reported by 89 PwE (19%) and 80 PwoE (17%), with 35 PwE (8%) and 39 PwoE (8%) taking anti-depressant drugs at the moment of the survey.

Furthermore, 44 PwE and 32 PwoE reported that since the COVID-19 isolation began, they had started taking new psychotropic drugs (anxiolytics 46.5%, anti-depressants 8.5%, antipsychotics 2.8%, and hypnotics 42.3%) for insomnia (38.2%), depression (14.5%), and anxiety (47.4%).

SARS-CoV-2 Infection

Symptoms of COVID-19 infection was specifically investigated. It was found that 32 PwE reported fever (6.6%) and 16 PwE (3.5%) underwent a nasopharingeal swab test for *SARS-CoV-2* (one positive, 0.2%, no hospitalization was required), while 30 PwoE (5.3%) had fever and 29 (6.1%) underwent the swab test (two positives, 0.4%, one with hospitalization, one with

TABLE 1 | Socio-demographic data.

Variable		PwE		PwoE		Stat. sig.
		N	%	*N*	%	
Total		456	100	472	100	
Females		344	75.4	347	79.9	0.6263
Age (mean ± *SD*)		37.9 ± 12.5		42,3 ± 12,32		**<0.0001**
Marital status						**0.0001**
	Single	189	41.4	112	23.7	
	Married	164	36.0	224	47.5	
	Cohabiting	77	47.0	93	19.7	
	Separated/Divorced	25	5.5	38	8.1	
	Widowed	1	0.6	5	1.1	
Education						**0.0001**
	Primary school	12	2.6	2	0.4	
	Secondary school	69	15.1	30	6.4	
	High School	211	46.3	167	35.4	
	Bachelors	131	28.7	189	40.0	
	PhD/residency	26	5.7	82	17.4	
	No answer	7	1.5	2	0.4	
Working status						**<0.0001**
	Employee	198	43.4	276	58.5	
	Unemployed	147	32.2	74	15.7	
	Freelancer	56	12.3	83	17.6	
	Retired	45	9.9	32	6.8	
	Laid off	10	7.6	7	1.5	
Job reduction during COVID-19 period						**<0.0001**
	No job reduction	119	45.9	42	16.5	
	Laid off	42	16.2	46	18.1	
	Forced private job shutdown	30	11.6	60	23.6	
	Forced holidays	15	5.8	38	15.0	
	Fired	8	3.1	3	1.2	
	Job hours reduction	45	17.4	65	25.6	
Depression						>0.3
	Positive history	89	19.5	80	16.9	
	Use of anti-depressants at the moment of the survey	35	7.7	39	8.3	
COVID-19 symptoms						>0.06
	Fever	30	6.6	30	6.3	
	Swab sample	16	3.5	29	6.1	
	Positive swab	1	0.2	2	0.4	
	Hospitalization for COVID-19	0	0	1	0.2	

Bold is used for significant values.
SD, standard deviation.

spontaneous recovery). No significant differences between PwE and PwoE were found.

Psychiatric Questionnaires

Depressive Symptoms

Overall, PwE had more sever depressive symptoms (higher BDI-II scores) than PwoE (PwE 12.0 ± 10, PwoE 9.8 ± 7.7; $p = 0.0001$).

Among PwE, 297 subjects (65.1%) had normal BDI-II values (score ≤ 13), 69 (15.1%) had mild depressive symptoms (14–19 score), 53 (11.6%) had moderate depressive symptoms (20–28 scores), and 37 (8.1%) had severe depressive symptoms (>28 score). In PwoE, 357 subjects (75.6%) had normal BDI-II values, 64 (13.6%) had mild depressive symptoms, 33 (7%) had moderate depressive symptoms, and 18 (3.8%) had severe depressive symptoms.

No difference was found between responders from the regions of Lombardia, Veneto, and Piemonte (the areas most severely affected by the outbreak) and those from other Italian regions.

Anxiety Symptoms

PwE had more severe anxiety symptoms (higher GAD-7 scale scores) than PwoE (8 ± 5.3 and 6.8 ± 4.9, respectively; $p = 0.0002$).

Among PwoE, 135 (47.5%) had normal GAD-7 values, 128 cases (32.4%) had mild anxiety symptoms, 142 (12.9%) had moderate anxiety symptoms, and 34 (7.2%) had severe anxiety symptoms.

Among PwE, 111 (39.5%) had normal values, 92 cases (28.9%) had mild anxiety symptoms, 162 (21.3%) had moderate anxiety symptoms, and 47 (10.3%) had severe anxiety symptoms.

No difference was found between the GAD-7 values of responders from the regions of Lombardia, Veneto, and Piemonte, and those from other Italian regions.

Sleep Quality

PSQI scale scores did not differ between PwE and PwoE (6.8 ± 3.7 and 6.6 ± 3.8, respectively; $p = 0.3117$), and 214 PwE (46.9%) and 200 PwoE (42.4%) had PSQI values out of normal range (>5).

The first three components of the PSQI explained 75% of the variance of the total PSQI score. The sub-items explaining most of the variance of total PSQI were, in order of relevance: C1: Subjective evaluation of sleep quality; C2: Sleep Latency; C3: Sleep duration. Full PCA data and weights are shown in **Table S1**.

No difference was found in sleep quality between responders from the regions of Lombardia, Veneto, and Piemonte, and those from other Italian regions.

Epilepsy

Seizures in PwE

PwE reported having generalized epilepsy in 188 cases (41.2%) and focal epilepsy in 139 cases (30.5%), whereas the remaining 129 PwE (28.3%) were not aware of the epilepsy type they suffered from. Among the whole sample of PwE, 212 (46%) had been free of seizure in the last year.

In non-seizure-free patients, PwE reported to take a median of 2 ASMs (range 0–7) and had a median of 1 seizure (range 0–100) in the pre-COVID-19 period, and a median of 1 seizure during the COVID-19 period (0–100; Wilcoxon signed ranks test Z−1-138, asympt sign. 0.255).

Sixty-two patients (13%) reported that they had experienced at least one generalized tonic-clonic seizure during the COVID-19 lockdown.

We did not find any difference between responders from the regions of Lombardia, Veneto, and Piemonte, and those from other Italian regions with regard to number of seizures.

Worsening of seizures

A worsening of seizures during the COVID-19 period was reported by 67 (18%) PwE (WPwE). In WPwE, but not in not-worsening PwE (nWPwE), the number of seizures was higher in the COVID-19 period (median 1, range 0–50) compared to the pre-COVID-19 period (median 3, range 0–80; $p = 0.0003$). WPwE had a percentual worsening of seizure frequency, with a median value of 25% (0–60%) (**Figure 1**). Compared with nWPwE, WPwE more frequently had a positive history of depression ($p = 0.01$), anti-depressant use ($p < 0.0001$), tonic-clonic seizures during COVID-19 ($p < 0.0001$), and epilepsy-related issues during COVID-19 ($p < 0.0001$); conversely, seizure freedom was less frequent in WPwE ($p < 0.0001$). In the psychiatric questionnaires, WPwE had more severe depression and anxiety symptoms and more disturbed sleep than the rest of the PwE group ($p < 0.001$).

Improvement of Seizures

We identified 61 PwE (13%) patients that, according to their self-reported seizure frequency, had improved during the lockdown period. These PwE had an average reduction of seizures according to their self-report of 4.8 ± 4 seizures/month, with an average percentage improvement in seizure frequency of 72 ± 31%.

We compared their psychometric scores with those of the WPwE group.

No significant difference was found in total BDI scores between the two groups (WPwE: BDI = 17.69 ± 9.99; improved PwE: BDI = 15.25 ± 12.02; $T = 1.23$, $p = 0.216$), and PSQI total score was significantly lower (better quality of sleep) in improved PwE (WPwE: PSQI = 9.4 ± 4; Improved PwE: PSQI = 6.59 ± 3.17; $T = 3.8$ $p = 0.00002$). Anxiety symptoms were less severe (lower GAD scores) in improved PwE (WPwE: GAD = 10.84 ± 5.4; improved PwE: GAD = 8.69 ± 5.48; $T = 2.23$, $p = 0.02$).

Epilepsy-related issues during COVID-19

Of PwE, 172 (38%) reported to have a scheduled outpatient visit during the COVID-19 period; 166 of them (96%) did not receive it. Among the whole PwE sample, 169 (37%, **Figure 2**) persons reported negative issues related to the management of epilepsy (61% of these patients had a planned examination that was deferred). Also, 68 PwE (40%) had problems with ASM availability, 20 PwE (12%) had to increase their therapy, six (3%) experienced ASM-related adverse effects, and 75 (44%) had anxiety/mood problems. All of these subjects attempted to contact the treating neurologist using short text message (SMS)/WhatsApp messages (43%), emails (25%), personal mobile calls (22%), or direct doctor's office calls (9%). Of 169 PwE, 120 (71%) managed to reach their neurologist, and all of them solved their problem thanks to the advice given by the treating physician. No PwE patient was hospitalized for epilepsy-related problems. PwE complaining of problems with ASM availability were taking the eight ASM molecules carbamazepine, clonazepam, eslicarbazepine acetate, lamotrigine, levetiracetam, phenobarbital, valproic acid, and zonisamide, either alone, or in different combinations.

Therapy compliance

Of PwE, 424 (93%) reported having taken their ASMs regularly during the COVID-19 period, whereas 32 (7%) reported

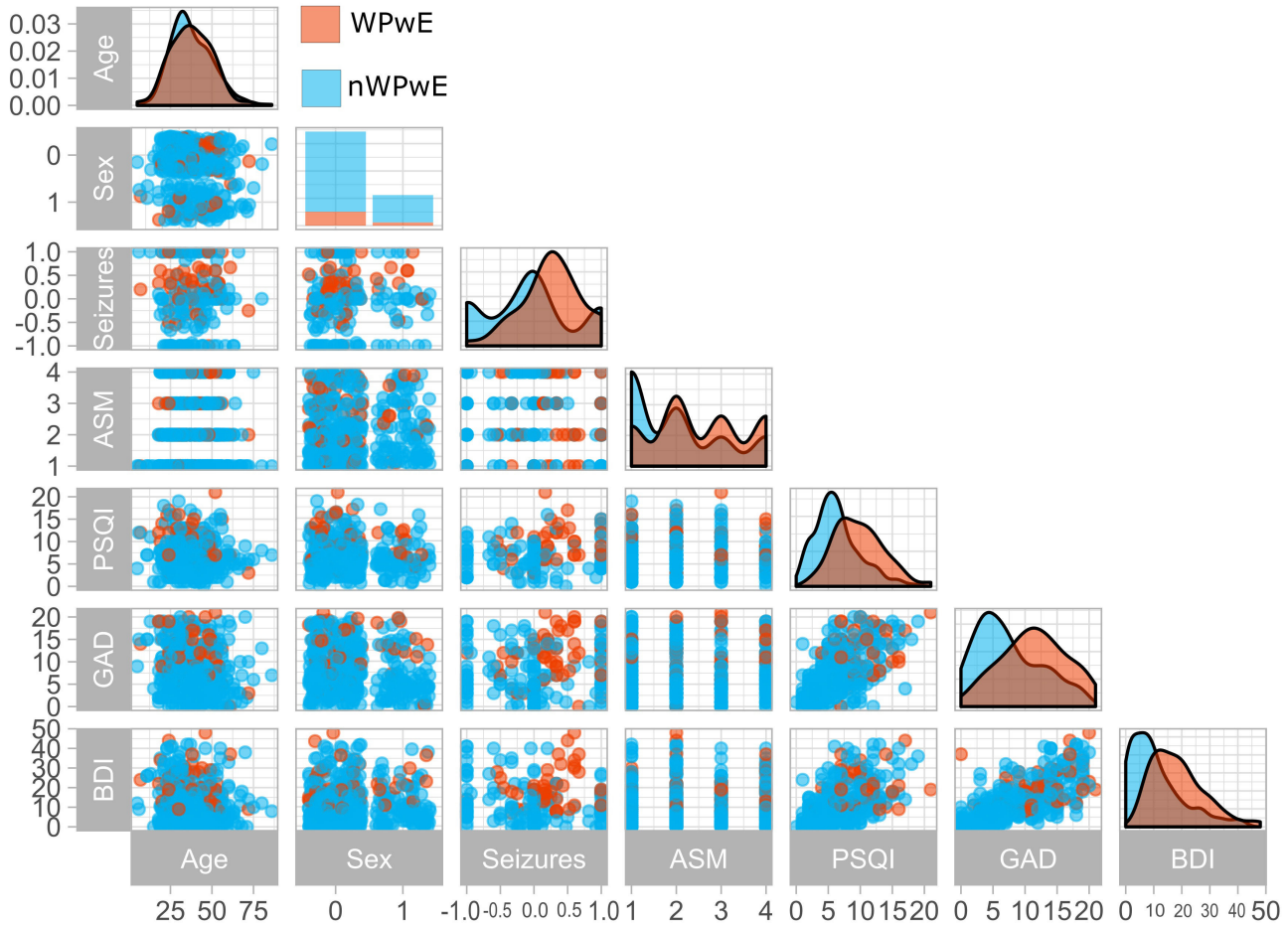


FIGURE 1 | Clinical variables in people with epilepsy according to seizure worsening during the COVID-19 pandemic. The figure displays a paired plot that highlights differences between PwE who experienced worsening (Orange) and those who did not (Blue). WPwE, Worsened People with Epilepsy; nWPwE, non-Worsened People with Epilepsy; ASM, Anti-Seizure Medications; GAD, Generalized Anxiety Disorder 7; PSQI, Pittsburgh Sleep Quality Index; BDI, Beck Depression Inventory; Sex (0 = Female,1 = Male); Seizures (Percentage increase/decrease in seizure frequency compared to previous months).

inadequate adherence due to forgetfulness (70%), demotivation (15%), adverse events (10%), or difficulties in ASM supply (5%). No PwE reported low adherence to ASM therapy because of a difficulty in contacting the referring physician, though 94 PwE (22%) complained of issues in the retrieval of ASMs. Also, 13 (2.6%) patients had a vagus nerve stimulator; three (23%) of them had problems with their device, and these were solved by contacting their neurologists.

Correlations

We performed a correlation analysis among the three psychometric scales, age, number of seizures, and variation in seizures between the pre-COVID-19 period and the COVID-19 period.

BDI-II, GAD-7, and PSQI were highly correlated with each other ($r > 0.530$, $p = 0.0001$; **Figure 3**) and with the presence of tonic-clonic seizures (rho > 0.160; $p \leq 0.001$).

Age was negatively correlated with BDI-II and GAD-7 ($r = -0.119$, $p = 0.011$; $r = -0.148$, $p = 0.002$).

The number of ASMs was correlated with the number of seizures either in the pre-COVID-19 (rho $= 0.332$, $p = 0.0001$) or during the COVID-19 period (rho $= 0.238$, $p = 0.0001$).

LOGISTIC REGRESSION

Logistic regression was performed to ascertain the effects on the likelihood of seizure worsening (WPwE) dependent on the following variables: "Age," "Sex," "GAD7," "BDI," "PSQI," "Change in work condition," "History of depression," "Number of ASMs," and "Number of seizures in the pre-COVID-19" (**Table 2**). The variables were introduced into the model with a stepwise backward method, with choice based on the Akaike information criterion (AIC). The logistic regression model was statistically significant for the only two variables surviving after stepwise selection: Number of ASMs and PSQI (**Figure 3**). Number of ASMs: odds ratio = 1.58 (95% C.I.= 1.12–2.2), Standard Error = 0.17, z-value = -2.67, $p = 0.001$; PSQI: odds

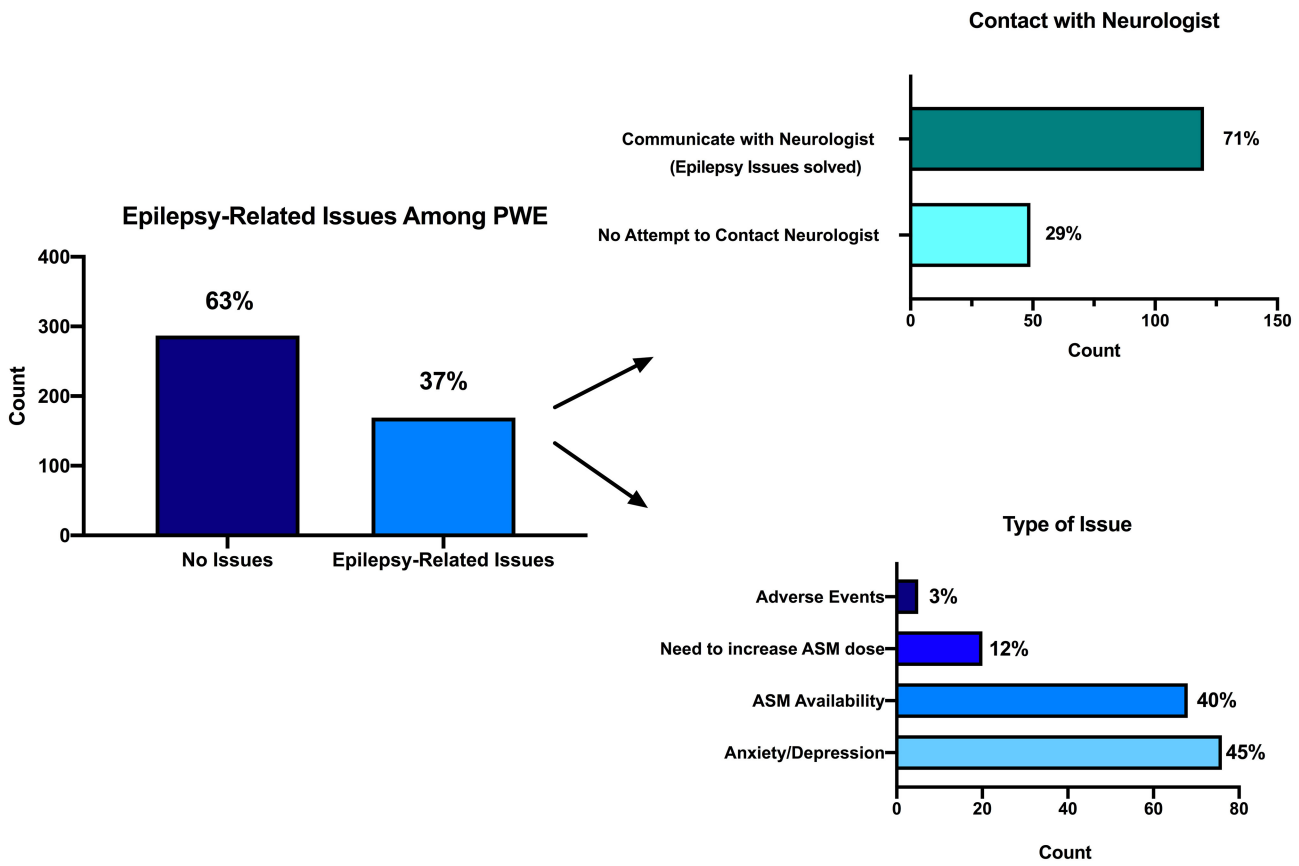


FIGURE 2 | Epilepsy-related issues during the COVID-19 pandemic. Among the whole PwE sample, 169 (37%, in this figure) persons reported negative issues related to the management of epilepsy (left). Attempt to contact treating neurologist (right up): 120 (71%) out of 169 PwE managed to reach their neurologist, and all of them solved their problem thanks to the advice given by the treating physician. Types of issues they were concerned about (right down): 68 PwE (40%) had problems with ASM availability, 20 PwE (12%) had to increase their therapy, 6 (3%) experienced ASM-related adverse effects, and 75 (44%) had anxiety/mood problems.

ratio = 1.20 (95% C.I. 1.10–1.30), Standard Error = 0.04, z-value = 4.09, $p = 0.0001$. The model showed an accuracy of 87% in predicting seizure worsening.

DISCUSSION

Our survey was conducted during the most severe phase of governmental restrictions on mobility, work, and public services caused by the COVID-19 pandemic in Italy. We aimed at investigating the impact of the lockdown on PwE care, identifying epilepsy-specific issues that they had to struggle with.

Epilepsy is a common chronic neurologic disorder, and PwE (particularly those with drug-resistance) need long-term care for managing ASMs, adverse drug effects, and possible behavioral disturbances. In our sample, more than one-third of PwE had a planned outpatient evaluation during the COVID-19 lockdown, and this was postponed in almost all cases. Furthermore, one in three PwE of the whole sample complained of epilepsy-related problems requiring a neurologist's intervention. All of these PwE tried to reach the treating neurologist by phone, messaging, and emails, but only three out of four succeeded. When the PwE achieved contact with the treating neurologist, they always solved their epilepsy-related concerns. Remarkably, no PwE were hospitalized for epilepsy-related problems.

Present data accurately reflect the main features of epilepsy medical care in Italy. Our data confirm the strict personal contact that Italian neurologists have with their patients, which often goes beyond what it is merely due by public health assistance. Furthermore, our data strongly emphasize the need to improve and implement organized telemedicine assistance in the public health system, because in most cases, a simple phone/message/email could resolve medical issues, avoiding unnecessary emergency room, or outpatient examinations. A telemedicine program appears of utmost importance in this historical moment due to the governmental restrictions caused by pandemic but also for the so-called "phase 2" of the pandemic, when restrictions will be progressively waived. Reducing outpatient examinations could decrease the number of in-hospital contacts, minimizing preventable COVID-19 contagions among physicians, and patients themselves, and contributing to the efficiency of public medical assistance throughout the emergency period.

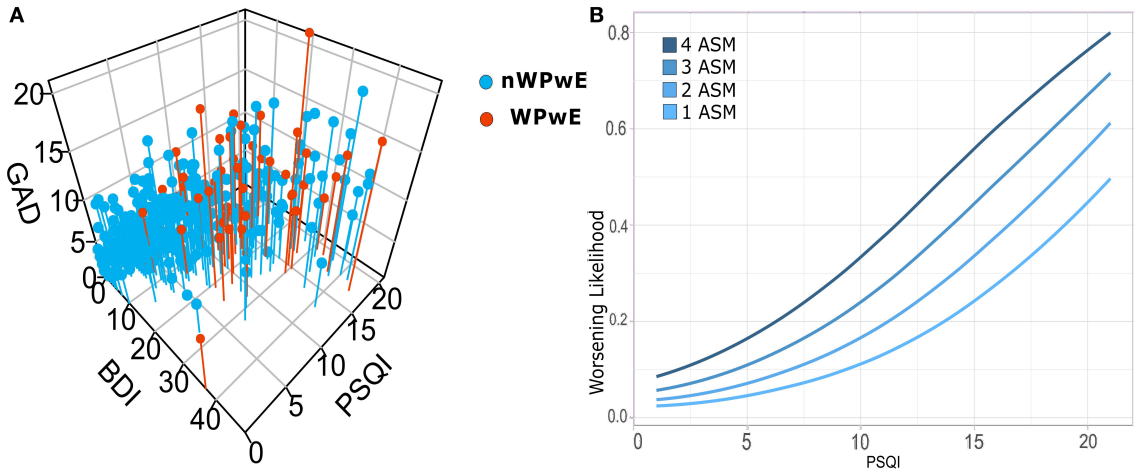


FIGURE 3 | (A) Correlations among psychiatric scales for depression (BDI), anxiety (GAD7), and sleep (PSQI), and logistic regression for seizure worsening in PwE. Illustrates the relationship among psychometric (PSQI, GAD, BDI) tests in people with epilepsy; subjects that underwent worsening (WPwE) are color-coded (red). In the 3D plot, it can be noted that WPwE tend to fall within a widespread cluster of subjects with more impairment, while there is a dense cluster of subjects with normal tests that do not report worsening. **(B)** In order to evaluate which psychometric test and variable did independently influence the likelihood of worsening, we designed a logistic regression model that identified the number of ASMs and the PSQI score as significant predictors. We show the increase in the likelihood of worsening for each score of PSQI and for each number of ASMs. WPwE, Worsened People with Epilepsy; nWPwE, non-Worsened People with Epilepsy; ASM, Anti-Seizure Medications; GAD, Generalized Anxiety Disorder 7; PSQI, Pittsburgh Sleep Quality Index; BDI, Beck Depression Inventory.

TABLE 2 | Factors influencing seizure worsening.

Features	WPwE	NWPwE	Predictor (OR)
Age	37.6 ± 12	41.19 ± 12	n.s.
Sex	54 F; 13 M	290 F; 54 M	n.s.
GAD-7	10.8 ± 5.4	7.5 ± 5.12	n.s.
BDI-II	17.69 ± 9.99	10.99 ± 9.64	n.s.
PSQI	9.40 ± 4.07	6.40 ± 3.52	**1.20**
Work situation change	41 Yes; 26 No	260 Yes; 84 No	n.s.
History of depression	9 Yes; 58 No	26 Yes; 363 No	n.s.
Number ASM	2.5 ± 1	1.9 ± 1	**1.58**
N. Seizures/month pre-COVID-19	5.18 ± 4	2.26 ± 4	n.s.

ASM, anti-seizure medication; BDI-II, Beck Depression Inventory-II; PSQI, Pittsburgh Sleep Quality Index; n.s., not significant. Bold values are for statistically significant variables surviving after stepwise selection during the logistic regression.

Our survey also suggests that a large part of the medical care for PwE could be effectively managed through telemedicine, particularly for stable patients or those with lower risk of seizure aggravation.

Among PwE, almost one in five reported seizure worsening during the COVID-19 period.

The rate of seizure worsening in PwE reported here is consistent with a small body of previous evidence exploring the impact of environmental stressors on seizure occurrence. Specifically, a retrospective study investigated the frequency of seizures during the Persian Gulf War in 1991 and found that about 10% (eight out of 82 PwE) reported increased frequency (7). During flood evacuation in the Netherlands in 1995, eight out of 30 (26%) interviewed PwE reported seizure worsening (8).

In our sample, we showed that most of the WPwE tended to have severe depressive, anxiety, and sleep disturbance symptoms, while PwE with scores in the normal range were less likely to experience worsening. To investigate the most relevant risk factors that influenced worsening, we focused on socio-demographic and clinical variables and psychometric factors. Logistic regression showed that the number of chronic ASMs and the score of sleep quality (PSQI) significantly influenced the likelihood of worsening. Remarkably, the number of ASMs taken was even superior to the seizure frequency in predicting worsening; this probably reflects a concomitant drug-resistance. With the aim of developing an efficient telemedicine program, the number of ASMs is a more objective parameter assess compared to seizure frequency [which is sometimes difficult to assess objectively and accurately by patients and caregivers (9)]. In addition, the number of ASMs may represent the expression of an overtreatment condition, where patients are taking unnecessary high doses of combination therapy (polypharmacy), and polytherapy-itself may increase side effects and lower adherence, inducing seizure worsening in a vicious circle (10, 11). The analysis we conducted on sleep quality demonstrated that the reduction of sleep time and, generally, insomnia-related issues were the factors most influencing the reported sleep concerns. Interestingly, sleep disturbances did not differ between PwE and PwoE, and abnormal values of PSQI were found in almost half of the subjects, a finding that is consistent with results from general population studies (12). Poor sleep quality could be related to the sudden changes in lifestyle that affected both PwE and PwoE during the lockdown (13). Sleep quality deterioration is often related to depressive (14) and anxiety symptoms (15), but these factors did not enter our regression model. Even if PwE complained of more

severe depressive and anxiety symptoms than PwoE, these features did not influence the probability of seizure worsening according to our model. This pronounced effect of sleep is probably related to the strong pathophysiological connection that sleep shares with epilepsy. The bidirectional interactions between sleep, epilepsy, and ASMs are well-known; however, recently, several authors highlighted the rhythmic patterns of epileptic seizures and EEG discharges related to vigilance states and circadian variation in excitatory and inhibitory balance (16, 17). The overall impairment of the sleep-wake cycle due to the COVID-19 emergency may affect both PwE and PwoE; however, sleep fragmentation and sleep deprivation may induce in PwE an increase of EEG epileptiform abnormalities (18) and seizure worsening even through an increase in cortical excitability (19).

It is worth reporting that, in our sample, there was also a small portion of PwE who reported a reduction of seizure frequency and a better sleep quality rather than a worsening. This likely reflects the reduction of chronic working and familial load and furtherly confirms the beneficial effect of sleep on seizure control.

Other Epilepsy-Related Negative Issues During the COVID-19 Pandemic

Anxiety and depression symptoms were identified as the most frequent epilepsy-related issues reported by PwE during the COVID-19 pandemic. Population-based studies demonstrated that one in every three PwE experiences a psychiatric disorder in the course of life, with mood and anxiety disorders being the most frequently documented comorbidities in adults and children (20, 21). It was expected that in a condition of stress, as the COVID-19 isolation surely is, both depression and anxiety would worsen. Furthermore, their exacerbation could have also been favored by the concurrent seasonal changes, which are factors aggravating psychiatric disorders in people with depression and anxiety (22). Depressive symptoms in PwE are known to correlate with seizure frequency and intensity (21). However, we assessed the depressive and anxiety symptoms only during the COVID-19 period and not in the pre-COVID-19 period, so we cannot discuss modifications induced by the COVID-19 pandemic.

The second most relevant epilepsy-related issue of PwE during COVID-19 was ASM availability. At the time of the survey, there was no advice on the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) website about the lack of availability of ASMs in Italy during the COVID-19 period. However, in March, the LICE website published a note about the reduced availability of one ASM (valproic acid), which was caused by production problems at the pharmaceutical company. However, the problems related to drug availability involved eight different ASM molecules and were not restricted to valproic acid alone.

Adverse events and necessity of increasing the dosage of ASMs were the other two epilepsy-related problems reported.

Among our PwE, only 7% reported reduced compliance with ASM treatment; this number is quite low compared to data on self-reported non-adherence available in the literature [for a review, see (23)]. We can hypothesize that home isolation may have favored compliance for therapy due to a lack of possible distracting factors, such as work, school, or recreational and leisure activities.

COVID-19 Infections

Among our responders, we found a 0.2–0.4% rate of positivity to SARS-CoV-2 virus infection. This corresponds perfectly to the Italian national trend (152,271 COVID-19 positive cases by April 11, 2020 (data provided by the Minister of Health, www.salute.gov.it), in an Italian population of 5,9433,744 (data from the ISTAT, the National Institute of Statistics, www.istat.it 2011 census), with a resultant 0.2% rate of infection). We did not find any difference in the number of contagions between PwE and PwoE, thus supporting the notion that PwE do not have a higher risk of contagion with respect to the general population.

Differences Between PwE and PwoE

In our sample, we found some socio-demographic differences between PwE and PwoE, which are consistent with those previously described in the literature. In particular, PwE had a lower educational level, were less occupied, and less likely to be married/cohabiting than PwoE. These are factors depending either on epilepsy itself (unpredictability of seizures, impairment of consciousness during seizures, cognitive, and motor disability, behavioral problems) and its consequences (e.g., driving limitations) or on epilepsy-related stigma (24).

The consistency of these socio-demographic data, but also those regarding drug-resistance (25) and psychometric findings, reveal that our sample is accurately representative of the entire epileptic population.

Limitations

We received answers that were unbalanced for sex, with a clear predominance of females. However, our percentage of female respondents was quite similar to the proportion of female users on the Facebook social network in Italy (female:male ratio 2:1, https://wearesocial.com/it/digital-2020-italia). While for depressive symptoms, there is no gender prevalence in either the general population (26) or PwE (21), anxiety symptoms are more frequent in females in the general population (27) but not in PwE (28). Sleep quality does not have a gender prevalence in PwE (29), while, in the general population, sleep disturbances seem to be more prevalent in males (30). Thus, anxiety and sleep quality scores in the present manuscript could be influenced by the unbalanced distribution of genders, but the proportion of females was not different among PwE and PwoE, so it is unlikely that it could affect differences among these groups.

Secondly, most of our responders were young adults, and the sample could not therefore be representative of the general prevalence of epilepsy across the entire lifespan (31). However, it probably reflects the age distribution of people more acquainted with the use of the Internet (32), which was the channel of distribution of our questionnaire. We are aware that the use of this channel introduced several biases, but our scope was to reach the highest number of PwE nationwide during the lockdown phase of maximal restrictions and, thus, the Internet offered the best opportunities to achieve our goal. Thus, our data could

not reflect those of persons most affected by the SARS-CoV-2 virus (older than 65 years) and may underestimate the impact of the viral infection on PwE. However, the rate of COVID-19 positivity in our sample fitted the Italian mean of contagions. Furthermore, our principal aim was to explore the social and medical consequences of the COVID-19 lockdown on PwE epilepsy management and not how the viral infection influenced the epilepsy symptoms. The reduced number of elderly people could also bias the number of reported seizures, drug-resistance rate, and consequently, number of anti-seizure medications, which are often lower in this portion of the population. The use of the Internet for questionnaire diffusion did not allow PwE with moderate-severe cognitive impairment, who represent a relevant subpopulation in PwE, to participate, and thus this type of PwE was not explored at all by our survey.

A further limitation of our study was that we did not execute an analysis of differences between generalized and focal epilepsies. We chose to not perform this analysis for two main reasons: about one in three patients declared that they did not know the classification of their own epilepsy, so we are conscious that the reliability of the reported diagnosis could be very low. In fact, the differential diagnosis between generalized and focal epilepsy is sometimes a difficult issue also for a neurologist/epileptologist.

In our survey, only 2.6% of patients had a vagus nerve stimulator; this reflects the more severe cognitive impairment that can often affect PwE, and this can explain the low number of these patients participating in the survey.

Our sample was not equally distributed across the country, with a higher contribution of PwE coming from the Lazio region, which was not the region with the highest number of COVID-19 cases. However, the aim of our study was to explore the scenario of social isolation induced by the "lockdown" and its influence on epilepsy care. In this regard, it is important to note that governmental restrictions on mobility and access to health services were homogeneous throughout the country, in particular in the 1st month of the lockdown, when our survey was conducted. Furthermore, none of our epilepsy-related and psychometric scales were different when comparing the values of the regions with the highest number of contagions with the rest of Italy.

Another limitation of the study is that it does not provide data on the impact of lockdown on depressive and anxiety symptoms because they were assessed only during the lockdown, without any question on the preceding period. However, we designed to use psychometric scales only as covariates to understand their contribution to seizure modifications and not as the main outcome variable of our study on lockdown impact on PwE.

We are aware that an observational online survey provides low strength of scientific evidence. However, the global lockdown did not allow any other kind of contact with our patients, except for the emergency room. Thus, we decided to promote this survey to understand the real and current needs of our PwE to improve the implementation of remote medical assistance in epilepsy.

CONCLUSIONS

The enormous and unprecedented social restrictions caused by the COVID-19 pandemic really put the Italian National Health System to the test and negatively impacted medical care for epilepsy. PwE struggled with difficulties in follow-up and attempted to reach their doctors in many different ways for answers to their complaints but did not always succeed. The number of chronically taken ASMs and sleep deterioration were the major factors influencing the risk of seizure worsening experienced by some patients. Special attention should be paid to these factors to prevent seizure worsening in PwE and to help set up an efficient telemedicine program devoted to epilepsy care.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The dataset will be provided to reviewers if required. Requests to access these datasets should be directed to g.assenza@unicampus.it.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was implied via the completion of the questionnaire.

AUTHOR CONTRIBUTIONS

GA: design and conceptualized study. JL: major role in methods creation, statistical analysis, and interpretation. FB: major role in statistical analysis. AC, GD, AR, and MT: major role in acquisition of data. VD and OM: interpreted the data and revised the manuscript for intellectual content. LR: major role in iconographic creation. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors would give their great thanks to Prof. Amedeo Bianchi, President of the LICE Foundation, for authorizing the publication of the survey contained in this manuscript on the Facebook web page of the LICE Foundation.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00737/full#supplementary-material

REFERENCES

1. Chou K-L, Liang K, Sareen J. The association between social isolation and DSM-IV mood, anxiety, and substance use disorders: wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* (2011) 72:1468–76. doi: 10.4088/JCP.10m06019gry
2. Frucht MM, Quigg M, Schwaner C, Fountain NB. Distribution of seizure precipitants among epilepsy syndromes. *Epilepsia.* (2000) 41:1534–9. doi: 10.1111/j.1499-1654.2000.001534.x
3. Beck A, Steer R, Brown G. Beck depression inventory-II. *San Antonio.* (1996) 12–5. doi: 10.1037/t00742-000
4. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092
5. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4
6. Curcio G, Tempesta D, Scarlata S, Marzano C, Moroni F, Rossini PM, et al. Validity of the Italian version of the Pittsburgh sleep quality index (PSQI). *Neurol Sci.* (2013) 34:511–9. doi: 10.1007/s10072-012-1085-y
7. Neufeld MY, Sadeh M, Cohn DF, Korczyn AD. Stress and epilepsy: the Gulf war experience. *Seizure.* (1994) 3:135–9. doi: 10.1016/S1059-1311(05)80204-3
8. Swinkels WAM, Engelsman M, Kasteleijn-Nolst Trenité DGA, Baal MG, De Haan GJ, Oosting J. Influence of an evacuation in February 1995 in The Netherlands on the seizure frequency in patients with epilepsy: a controlled study. *Epilepsia.* (1998) 39:1203–7. doi: 10.1111/j.1528-1157.1998.tb01312.x
9. Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav.* (2012) 24:304–10. doi: 10.1016/j.yebeh.2012.04.128
10. Alexandre V, Monteiro EA, Freitas-Lima P, Pinto KD, Velasco TR, Terra VC, et al. Addressing overtreatment in patients with refractory epilepsy at a tertiary referral centre in Brazil. *Epileptic Disord.* (2011) 13:56. doi: 10.1684/epd.2011.0411
11. Perucca E, Kwan P. Overtreatment in epilepsy. *CNS Drugs.* (2005) 19:897–908. doi: 10.2165/00023210-200519110-00001
12. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. *Sleep Med Rev.* (2016) 25:52–73. doi: 10.1016/j.smrv.2015.01.009
13. Gemignani A, Piarulli A, Menicucci D, Laurino M, Rota G, Mastorci F, et al. How stressful are 105 days of isolation? Sleep EEG patterns and tonic cortisol in healthy volunteers simulating manned flight to Mars. *Int J Psychophysiol.* (2014) 93:211–9. doi: 10.1016/j.ijpsycho.2014.04.008
14. Tsuno N, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry.* (2005) 66:1254–69. doi: 10.4088/JCP.v66n1008
15. Ramsawh HJ, Stein MB, Belik S-L, Jacobi F, Sareen J. Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. *J Psychiatr Res.* (2009) 43:926–33. doi: 10.1016/j.jpsychires.2009.01.009
16. Khan S, Duan P, Yao L, Hou H. Shiftwork-mediated disruptions of circadian rhythms and sleep homeostasis cause serious health problems. *Int J Genomics.* (2018) 2018:8576890. doi: 10.1155/2018/8576890
17. Daley JT, DeWolfe JL. Sleep, circadian rhythms, and epilepsy. *Curr Treat Options Neurol.* (2018) 20:47. doi: 10.1007/s11940-018-0534-1
18. Pratt KL, Mattson RH, Weikers NJ, Williams R. EEG activation of epileptics following sleep deprivation: a prospective study of 114 cases. *Electroencephalogr Clin Neurophysiol.* (1968) 24:11–5. doi: 10.1016/0013-4694(68)90061-8
19. Manganotti P, Bongiovanni LG, Fuggetta G, Zanette G, Fiaschi A. Effects of sleep deprivation on cortical excitability in patients affected by juvenile myoclonic epilepsy: a combined transcranial magnetic stimulation and EEG study. *J Neurol Neurosurg Psychiatry.* (2006) 77:56–60. doi: 10.1136/jnnp.2004.041137
20. Ribot R, Kanner AM. Neurobiologic properties of mood disorders may have an impact on epilepsy: should this motivate neurologists to screen for this psychiatric comorbidity in these patients? *Epilepsy Behav.* (2019) 98:298–301. doi: 10.1016/j.yebeh.2019.01.026
21. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, Ulivi M, et al. Depressive symptoms and difficulties in emotion regulation in adult patients with epilepsy: association with quality of life and stigma. *Epilepsy Behav.* (2020) 107:107073. doi: 10.1016/j.yebeh.2020.107073
22. Eastwood MR, Stiasny S. Psychiatric disorder, hospital admission, and season. *Arch Gen Psychiatry.* (1978) 35:769–71. doi: 10.1001/archpsyc.1978.01770300111012
23. Malek N, Heath CA, Greene J. A review of medication adherence in people with epilepsy. *Acta Neurol Scand.* (2017) 135:507–15. doi: 10.1111/ane.12703
24. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, De Mojà R, et al. Epilepsy-associated stigma from the perspective of people with epilepsy and the community in Italy. *Epilepsy Behav.* (2019) 98:66–72. doi: 10.1016/j.yebeh.2019.06.026
25. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the *ad hoc* Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia.* (2010) 51:1069–77. doi: 10.1111/j.1528-1167.2009.02397.x
26. Malhi GS, Mann JJ. Depression. *Lancet.* (2018) 392:2299–312. doi: 10.1016/S0140-6736(18)31948-2
27. Ruscio AM, Hallion LS, Lim CCW, Aguilar- S, Al-hamzawi A, Alonso J, et al. Cross-sectional comparison of the epidemiology of DSM-5. *JAMA Psychiatry.* (2017) 74:465–75. doi: 10.1001/jamapsychiatry.2017.0056
28. Pham T, Sauro KM, Patten SB, Wiebe S, Fiest KM, Bulloch AGM, et al. The prevalence of anxiety and associated factors in persons with epilepsy. *Epilepsia.* (2017) 58:e107–10. doi: 10.1111/epi.13817
29. Gutter T, Callenbach PMC, Brouwer OF, de Weerd AW. Prevalence of sleep disturbances in people with epilepsy and the impact on quality of life: a survey in secondary care. *Seizure.* (2019) 69:298–303. doi: 10.1016/j.seizure.2019.04.019
30. Madrid-Valero JJ, Martínez-Selva JM, Ribeiro do Couto B, Sánchez-Romera JF, Ordoñana JR. Age and gender effects on the prevalence of poor sleep quality in the adult population. *Gac Sanit.* (2017) 31:18–22. doi: 10.1016/j.gaceta.2016.05.013
31. Sander JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol.* (2003) 16:165–70. doi: 10.1097/01.wco.0000063766.15877.8e
32. Holt K, Shehata A, Strömbäck J, Ljungberg E. Age and the effects of news media attention and social media use on political interest and participation: do social media function as leveller? *Eur J Commun.* (2013) 28:19–34. doi: 10.1177/0267323112465369

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 July 2020
doi: 10.3389/fneur.2020.00781

Neurological Comorbidity Is a Predictor of Death in Covid-19 Disease: A Cohort Study on 576 Patients

OPEN ACCESS

Edited by:
Jesús Porta-Etessam,
Hospital Clínico San Carlos, Spain

Reviewed by:
Rodrigo Guerrero,
University of the Andes, Chile
Juan Carlos Garcia-Monco,
Hospital de Basurto, Spain

***Correspondence:**
David García-Azorín
davilink@hotmail.com;
dgazorin@ucm.es

Specialty section:
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

Received: 03 June 2020
Accepted: 25 June 2020
Published: 07 July 2020

Citation:
García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, Talavera B, Simón-Campo P, de Lera M, Chavarría-Miranda A, López-Sanz C, Gutiérrez-Sánchez M, Martínez-Velasco E, Pedraza M, Sierra Á, Gómez-Vicente B, Guerrero Á, Ezpeleta D, Peñarrubia MJ, Gómez-Herreras JI, Bustamante-Munguira E, Abad-Molina C, Orduña-Domingo A, Ruiz-Martin G, Jiménez-Cuenca MI, Juarros S, del Pozo-Vegas C, Dueñas-Gutierrez C, de Paula JMP, Cantón-Álvarez B, Vicente JM and Arenillas JF (2020) Neurological Comorbidity Is a Predictor of Death in Covid-19 Disease: A Cohort Study on 576 Patients. Front. Neurol. 11:781. doi: 10.3389/fneur.2020.00781

David García-Azorín[1]*, Enrique Martínez-Pías[1], Javier Trigo[1], Isabel Hernández-Pérez[1], Gonzalo Valle-Peñacoba[1], Blanca Talavera[1], Paula Simón-Campo[1], Mercedes de Lera[1], Alba Chavarría-Miranda[1], Cristina López-Sanz[1], María Gutiérrez-Sánchez[1], Elena Martínez-Velasco[1], María Pedraza[1], Álvaro Sierra[1], Beatriz Gómez-Vicente[1], Ángel Guerrero[1,2], David Ezpeleta[3], María Jesús Peñarrubia[4], Jose Ignacio Gómez-Herreras[5], Elena Bustamante-Munguira[6], Cristina Abad-Molina[7], Antonio Orduña-Domingo[7], Guadalupe Ruiz-Martin[8], María Isabel Jiménez-Cuenca[9], Santiago Juarros[10], Carlos del Pozo-Vegas[11], Carlos Dueñas-Gutierrez[12], Jose María Prieto de Paula[12], Belén Cantón-Álvarez[13], Jose Manuel Vicente[13] and Juan Francisco Arenillas[1,2,14]

[1] Department of Neurology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [2] Department of Medicine, University of Valladolid, Valladolid, Spain, [3] Department of Neurology, Hospital Universtitario Quironsalud Madrid, Madrid, Spain, [4] Department of Hematology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [5] Department of Anestesiology and Reanimation, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [6] Department of Intensive Care Medicine, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [7] Department of Microbiology and Immunology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [8] Department of Clinical Chemistry, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [9] Department of Radiology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [10] Department of Pneumology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [11] Emergency Department, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [12] Department of Internal Medicine, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [13] Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [14] Neurovascular Research Laboratory, Instituto de Biología y Genética Molecular, Universidad de Valladolid – Consejo Superior de Investigaciones Científicas, Madrid, Spain

Introduction: Prognosis of Coronavirus disease 2019 (Covid-19) patients with vascular risk factors, and certain comorbidities is worse. The impact of chronic neurological disorders (CND) on prognosis is unclear. We evaluated if the presence of CND in Covid-19 patients is a predictor of a higher in-hospital mortality. As secondary endpoints, we analyzed the association between CND, Covid-19 severity, and laboratory abnormalities during admission.

Methods: Retrospective cohort study that included all the consecutive hospitalized patients with confirmed Covid-19 disease from March 8th to April 11th, 2020. The study setting was Hospital Clínico, tertiary academic hospital from Valladolid. CND was defined as those neurological conditions causing permanent disability. We assessed demography, clinical variables, Covid-19 severity, laboratory parameters and outcome. The primary endpoint was in-hospital all-cause mortality, evaluated by multivariate cox-regression log rank test. We analyzed the association between CND, covid-19 severity and laboratory abnormalities.

Results: We included 576 patients, 43.3% female, aged 67.2 years in mean. CND were present in 105 (18.3%) patients. Patients with CND were older, more disabled, had more vascular risk factors and comorbidities and fewer clinical symptoms of Covid-19. They presented 1.43 days earlier to the emergency department. Need of ventilation support was similar. Presence of CND was an independent predictor of death (HR 2.129, 95% CI: 1.382–3.280) but not a severer Covid-19 disease (OR: 1.75, 95% CI: 0.970–3.158). Frequency of laboratory abnormalities was similar, except for procalcitonin and INR.

Conclusions: The presence of CND is an independent predictor of mortality in hospitalized Covid-19 patients. That was not explained neither by a worse immune response to Covid-19 nor by differences in the level of care received by patients with CND.

Keywords: SARS-CoV-2, nervous system diseases, stroke, mortality, prognosis

INTRODUCTION

Hypertension, diabetes, cardiovascular disorders, pulmonary disorders, and cancer have been associated with an increased risk of severe Coronavirus disease 2019 (Covid-19) and mortality (1–6). Since the first edition of the clinical management protocol of Covid-19 with severe acute respiratory infection, the World Health Organization (WHO) recommended that those patients, even if they present with mild symptoms, should be admitted to a designated unit for close monitoring (7).

The frequency, type and implications of neurological comorbidity in Covid-19 patients is largely unexplored. A recent review found a frequency ranging from 1.4 to 40%, with a pooled percentage of having a pre-existing neurological disease of 8.0% (8). The possible reasons for the heterogeneous results were the varying definitions, the lack of specific studies and underreported frequency. The impact of neurological comorbidities in Covid-19 disease is yet unknown. Covid-19 patients requiring intensive care unit (ICU) admission had prior history of cerebrovascular disease more frequently (3), but in some series, cerebrovascular disorders were classified together with cardiovascular disease (9). The aim of this study was to evaluate if the presence of comorbid chronic neurological disorders is associated with a worse prognosis in patients with Covid-19 disease.

METHODS

Study Design

This study was done according to the registry of neurological symptoms in Covid-19 patients of the Spanish Society of Neurology and designed by the investigators. The study was done according to the strengthening the reporting in observational studies in epidemiology (STROBE) (10) statement. The study was done in the Clinic University Hospital, tertiary public hospital from Valladolid, Spain, free of charge for patients. Data were collected, analyzed and interpreted by the authors. All the authors reviewed and approved the final version of manuscript.

Data Sources

We collected data from the electronic medical records. The data about the history prior to the admission was collected from the admission report, emergency department (ED) history and primary care electronic records. The local authorities created a reference contact phone line, that followed patients with typical Covid-19 symptoms daily or every other day. Regarding the hospitalization period data, we gathered the medical records. Patients were treated according to the national Covid-19 management protocol standard of care (SOC) (11). The study period included all consecutive patients that were admitted to the hospital with a Covid-19 confirmed diagnosis between March 8th and April 11th, 2020. The information was reviewed from April 21st to May 1st. The source of the data was the admission department and the department of microbiology records, whilst notification of every Covid-19 positive was mandatory during the time of the study.

Covid-19 Disease Diagnosis

Covid-19 diagnosis was based on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay (LightMIx Modular SARS-CoV (COVID19) E-gene and LightMIx Modular SARS-CoV (COVID19) RdRP, Roche Diagnostics S.L.) of oropharyngeal-nasopharyngeal swab, sputum or lower respiratory tract sample; or was based on the presence of anti-SARS-CoV-2 IgM+IgA antibodies (COVID-19 ELISA IgM+IgA; Vircell, S.L. Granada, Spain) in serological test in patients with clinical symptoms, according to the WHO protocols (12). Patients without laboratory-confirmed diagnosis were not included. Recruitment was probabilistic and all consecutive patients were included. Only hospitalized patients were included. Data was extracted according to a predefined protocol by 13 neurologists that were involved in the treatment of Covid-19 patients. The needed time to review it patient was 20–30 min.

Chronic Neurological Disorders Definition

We used the WHO definition of disabling chronic neurological disorders (CND), as those neurological disorders that (a) caused persistent disability, (b) limited the individual's functioning, and (c) interfered with the person's ability to engage in activities (13). We included conditions affecting both mental and physical function. CND included dementia, movement disorders, prior stroke with long-term sequelae, neuromuscular disorders,

spinal disorders, symptomatic central nervous system cancer, chronic encephalopathies or neuro-inflammatory disorders. (Full definitions in **Supplementary Material**). Researchers specifically assessed the presence of prior history of neurological diseases and only those conditions fulfilling (a), (b), and (c) criteria were included.

Variables

We analyzed demographic variables, prior medical history, clinical presentation, the course of the disease and treatment. Demographic variables included age, sex, date of symptoms onset. Regarding comorbidities, we analyzed the presence of hypertension (systemic blood pressure higher than 140/90 mmHg in two prior determinations), diabetes (fasting blood glucose >126 mg/dl on two separate tests, HbA1c > 6,5%, blood glucose level >200 mg after oral glucose overload or blood glucose level >200 mg/dl with diabetes symptoms), smoking habit (current or in the preceding 6 months), cardiovascular diseases (coronary artery disease, congenital heart diseases, cardiomyopathies, arrythmias, valvular heart disease, aortic aneurysms, and peripheral artery disease), chronic respiratory diseases (chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases, interstitial lung diseases and pulmonary hypertension), cancer (excluding epidermoid and basal cell carcinoma), immunocompromised state (congenital or acquired). We specifically evaluated the presence of CND. We analyzed baseline performance status by using the modified Ranking scale (mRS), ranging from 0 (no symptoms) to 6 (dead), being defined 3 as the presence of moderate disability and need of assistance (14).

Concerning the clinical presentation, we evaluated if the source of contagion was suspected or not, the time between the first symptom and the emergency department (ED) presentation. We analyzed the general symptoms, including fever (defined as axillary temperature equal or higher than 37.5%), asthenia, cough, cutaneous rash, dyspnea, diarrhea, chest pain, expectoration, headache, myalgia, nausea, odynophagia, rhinorrhea, and vomiting. We describe the type of Covid-19 diagnosis, either by RT-PCR or serological tests. We analyzed the frequency of abnormal chest imaging, either by X-ray or Computerized Tomography (CT). We evaluated the laboratory results on admission and the worst values during the hospitalization. The analyzed parameters were leukocytes [cell count $\times$ 10^9 / L, reference value (RV):4–10], lymphocytes (count $\times$ 10^9/L, RV: 0.9–5.2), platelets (count $\times$ 10^9 /L, RV: 150–400), hemoglobin (g/dL, RV: 12–16), international normalized ratio (INR, RV: 0.8–1.3), D-dimer (ng/dL, RV: <500), lactate dehydrogenase (U/L, RV: 135–250), creatine-kinase (U/L, RV: 20–170), glomerular filtration rate corrected by body area (ml/min/1.73 m^2, RV > 90), C-reactive protein (mg/L, RV: 1–5), procalcitonin (ng/mL, RV: <5), interleukine-6 (pg/mL, RV <5.9), ferritin (ng/mL, RV: 15–150). Interleukine-6 and ferritin were not available on admission. We evaluated the percentage of patients that presented abnormal results on admission and during the hospitalization. We describe the received treatment, that according to the local SOC, being the possible drug dose regimes hydroxychloroquine 400 mg bid for 5 days, lopinavir/ritonavir 400/100 mg bid, methylprednisolone 250 mg three consecutive days and interferon beta-1b (11). We also report the need of oxygen therapy, the use of mechanical ventilation, the need of Intensive Care Unit (ICU) admission and the all-cause mortality. The severity of the Covid-19 disease was defined according to the American Thoracic Society guidelines for community-acquired pneumonia (15) (**Supplementary Material**). We defined severe Covid-19 disease as the presence of either severe pneumonia or acute respiratory distress syndrome (ARDS) (16).

Study Endpoints

The primary endpoint was in-hospital mortality of Covid-19 in patients with CND, calculated by multivariate regression and survival probability by Cox regression, adjusted by the possible confounders and effect modifiers. As secondary endpoints, we aimed to analyze the Covid-19 severity in CND patients and the presence of Covid-19 related laboratory abnormalities.

Statistical Analysis

Qualitative and ordinal variables are expressed as frequency and percentage. Continuous variables are presented as medians, interquartile range (IQR), and minimum-maximum value or mean and standard deviation (SD). Missing data was managed by complete case analysis. In the statistical analysis we employed Chi^2 test or Fisher's Exact test for the contrast of categorical variables, adjusting *p*-value by Bonferroni method for multiple comparisons correction. We employed Student *T*-test for the contrast of categorical and continuous variables. The level of significance threshold was set in 0.05, after adequate adjustment. Due to the exploratory nature of the study, we did not calculate sample size.

For the primary endpoint, we conducted a univariate regression analysis of all baseline variables and all the variables that showed statistical association with higher odds of death and a *p*-value lower or equal than 0.1, were included in a multivariate regression analysis. All CND were analyzed together. We present the odds ratio (OR) and the 95% confidence interval (CI). Survival probability over time was assessed by Cox-regression analysis with hazard ratio (HR) and the corresponding 95% CI analysis, adjusted by all the covariates that were significant in the univariate regression analysis. Differences in Kaplan Meier Curves were analyzed by the log-rank test.

For the secondary endpoint severe-Covid-19 disease, we repeated the same analysis as for the primary endpoint. To evaluate if laboratory parameters were more often abnormal in patients with CND, we created a regression analysis adjusting for age, mRS and sex. Statistical analysis was performed with SPSS v.26 (IBM Corp. Armonk, NY) by DGA. All datasheets are available for other researchers under reasonable request.

Ethical Aspects

The study protocol was approved by the institutional review board of Valladolid Este health area (PI-20-1751). Written informed consent was waived given the risk of contagion and the urgent need of data.

Data Availability

Datasheets are available for other researchers under reasonable request.

RESULTS

During the study period, 580 consecutive patients were admitted and hospitalized to our hospital with a positive test for SARS-CoV-2, being excluded four of them. **Supplementary Figure 1** shows the flow diagram of patients. The sample included thus 576 patients, 250 (43.3%) female, with a mean age of 67.2 (sd:14.7), ranging from 23 to 98 years. One hundred and five (18.3%) patients had one or more chronic neurological disorders (CND). The frequency of specific disorders was 40 (6.9%) patients with cerebrovascular disease, 32 (5.5%) patients with cognitive disorders, 24 (4.1%) patients with neuromuscular and spinal diseases, 16 (2.7%) patients with movement disorders, four (0.7%) patients with symptomatic central nervous system tumors, two (0.3%) patients with multiple sclerosis and isolated cases of Neurobehçet disease, neurolupus and one malformation syndrome. The full list of patients is available in **Supplementary Materials**. Patients with CND were older, more disabled at baseline and had hypertension and diabetes more often. **Table 1** shows demographic variables, vascular risk factors frequency and comorbidities.

The source of the contagion was suspected in 282 (49%) of all cases, without differences between patients with CND (58 (55.2%) cases) and the rest of the patients (224 (47.6%) cases).

TABLE 1 | Demographic variables, vascular risk factors frequency and comorbidities.

	All patients (n = 576)	Chronic neurological disorders (n = 105)	No-neurological comorbidity (n = 471)	Adjusted p-value
Mean age	67.18 (14.75)	74.97 (12.69)	65.45 (14.63)	<0.001†
Female sex	250 (43.4%	50 (47.6%)	200 (42.5%)	0.384‡
Hypertension	300 (52.1%)	75 (71.4%)	225 (47.8%)	<0.001‡
Diabetes	113 (19.6%)	34 (32.4%)	79 (16.8%)	0.001‡
Smoking habit	118 (20.5%)	22 (21.0%)	96 (20.4%)	0.894‡
Cardiac disease	154 (26.7%)	41 (39.0%)	113 (24.0%)	0.002‡
Respiratory disease	145 (25.2%)	31 (29.5%)	114 (24.2%)	0.264‡
Cancer	94 (16.3%)	22 (21.0%)	72 (15.3%)	0.188‡
Immunodepression	32 (5.6%)	10 (0.5%)	22 (4.7%)	0.059‡
Mean mRS	0.61 (1.12)	1.73 (1.48)	0.36 (0.84)	<0.001†

mRS, Modified Rankin Scale; †Student T-Test; ‡Two-sided Fisher's Exact test.

The most frequent symptoms on presentation were fever and cough. Patients with CND had less frequently cough, asthenia, diarrhea, myalgia, chest pain, headache or lightheadedness. The frequency and type of general presenting symptoms is shown in **Supplementary Table 3**.

Latency Between Symptom Onset and ED Presentation

The mean time between symptom onset and ED visit in patients with neurological comorbidities was 5.27 (sd: 7.72) days, compared with 7.81 (sd: 5.66) days in those without prior neurological history. After adjusting for age, mRS, sex, vascular risk factors and comorbidities, linear regression analysis was significant (B coefficient −1.436, 95% CI: −2.844- −0.28, p = 0.046). **Figure 1** shows the interval between symptom onset and ED visit in patients with and without neurological comorbidities in patients with and without CND.

Diagnosis and Management of Patients

Diagnosis was confirmed by RT-PCR in 546 (94.8%) of cases and/or serology in 175 (30.4%). Chest imaging was abnormal in 549 patients (95.3%). Patients with CND received hydroxychloroquine (83.8 vs. 92.6%, p = 0.008) and lopinavir/ritonavir (81.9 vs. 92.1%, p = 0.003) less frequently. Frequency of methylprednisolone or interferon use was similar. Need of oxygen therapy was more frequent in CND patients (83.8 vs. 66.2%, p = 0.001). Frequency of ventilatory support or ICU admission was similar.

Course of the Disease

Concerning the clinical course, 393 (68.2%) of patients had a severe pneumonia or ADRS and 127 (22.0%) died. Nine patients had not pneumonia but had severe illness because of septic shock 5 (0.8%), pulmonary embolism without pneumonia 2 (0.3%), and one case (0.1%) of lithium intoxication and one case (0.1%) of fatal gastrointestinal bleed. Patients with CND had non-severe pneumonia less frequently (12.4 vs. 27.4%, p = 0.002) and ADRS more frequently (30.5 vs. 19.6%, p = 0.020). Mortality of CNS patients was 44.8%, compared with 17% in the rest of the sample (p < 0.001). **Supplementary Table 4** describes treatment and severity of Covid-19 disease.

Primary Endpoint: Predictors of Mortality

In the univariate regression analysis, baseline disability, age, hypertension, diabetes, smoking habit, cardiac disorders, cancer and chronic neurological disorders were associated with higher odds of mortality, whereas female sex was associated with a lower odd of death. In the multivariate regression analysis, including all the variables that were statistically significant in the univariate analysis, baseline disability, age and chronic neurological disorders remained statistically significant (OR: 1.76, 95% CI: 1.014–3.06). **Table 2** presents the results of the univariate and multivariate regression analysis.

Cox regression analysis patients with CND had lower survival over time than patients without prior history of CND (HR: 2.13, 95% CI: 1.382–3.280, p = 0.001), adjusted by all the variables included in the multivariate regression analysis (age,

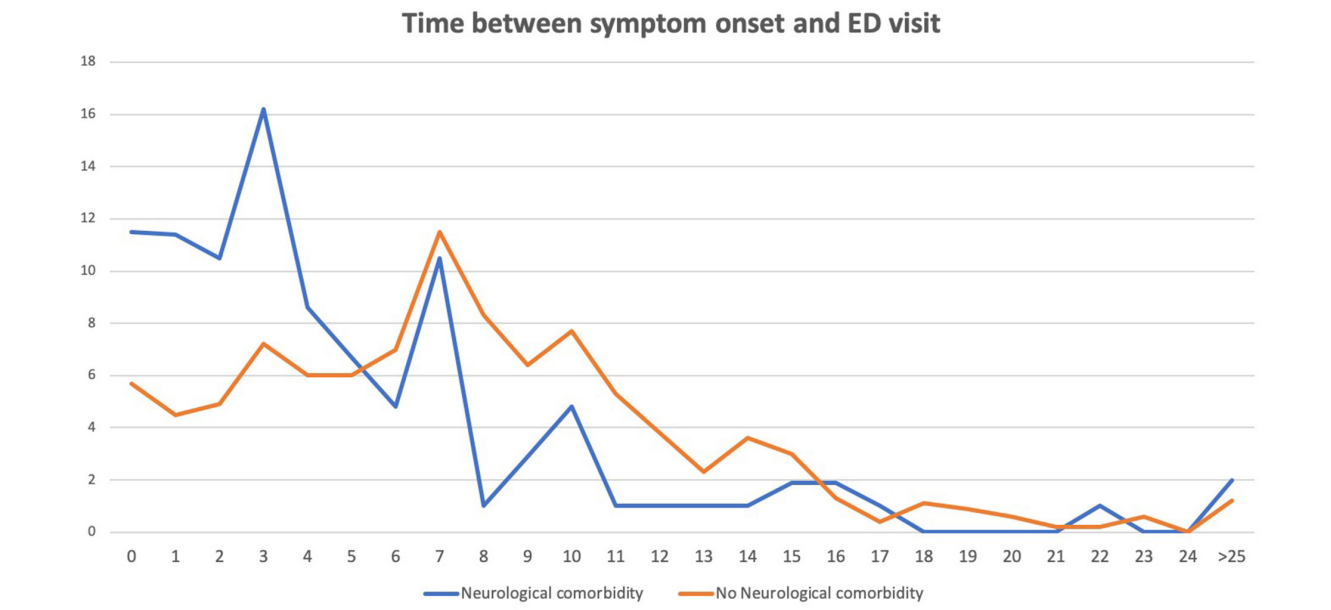


FIGURE 1 | Time between the first symptom and the emergency department (ED) visit in days. *Y axis: Percentage of patients. X axis: Days since the first symptom to the ED presentation*.

TABLE 2 | Predictors of mortality: univariate and multivariate regression analysis.

	Type of analysis	OR	95% CI	*p*-value
mRS≥3	Univariate	11.371	6.376–20.278	<0.001
	Multivariate	4.100	2.088–8.050	<0.001
Age	Univariate	1.090	1.069–1.112	<0.001
	Multivariate	1.064	1.040–1.089	<0.001
Female sex	Univariate	0.682	0.454–1.024	0.065
	Multivariate	0.770	0373–1.052	0.077
Hypertension	Univariate	3.534	2.272–5.495	<0.001
	Multivariate	1.369	0.806–2.325	0.246
Diabetes	Univariate	2.129	1.353–3.351	0.001
	Multivariate	1.221	0.710–2.098	0.471
Smoking	Univariate	1.589	1.004–2.514	0.048
	Multivariate	1.720	0.955–3.096	0.701
Cardiological disorders	Univariate	2.955	1.950–4.478	<0.001
	Multivariate	1.208	0.730-1.999	0.462
Pulmonary disorders	Univariate	1.434	0.928–2.217	0.105
	Multivariate	0.931	0.543–1.596	0.794
Cancer	Univariate	1.641	1.001–2.690	0.049
	Multivariate	1.209	0.676–2.162	0.523
Chronic neurological disorders	Univariate	3.961	2.516–6.234	<0.001
	Multivariate	1.763	1.014–3.064	0.044
Immunosuppression	Univariate	1.295	0.405–4.138	0.663

mRS, Modified Rankin Scale; OR, Odds Ratio; CI, Confidence Interval.

mRS, sex, presence of hypertension, diabetes, smoking habit, prior history of cardiac disorders, pulmonary diseases, and history of cancer). **Figure 2** shows cumulative survival curves. **Supplementary Table 5** presents the results of all the variables included in the analysis.

Predictors of Severe Covid-19 Disease

All the variables that were associated with higher odds of mortality except by cancer were associated with a higher odd of severe Covid-19 disease in the univariate regression analysis. In the multivariate analysis, only age, female sex and diabetes remained statistically significant, with a trend to signification in smoking habit ($p = 0.066$) and CND ($p = 0.063$). **Table 3** shows results of univariate and multivariate regression analysis.

Laboratory Findings

The median laboratory values on admission and the worst values during hospitalization is available in **Supplementary Table 6**. All the laboratory parameters were more frequently abnormal during the hospitalization than upon admission (all $p < 0.001$), **Supplementary Table 7**. Patients with CND had higher odds of having increased INR during hospitalization (OR: 1.85, 95% CI: 1.14–3.01) and higher odds of having increased procalcitonin levels during hospitalization (OR: 1.845, 95% CI: 1.08–3.15), after adjusting for age, mRS, sex, and prior history of hypertension, diabetes, smoking habit and other comorbidities. **Supplementary Table 8** shows the full results of the regression analysis.

DISCUSSION

Most of the Covid-19 management protocols coincide that patients with comorbidities should be closely monitored (7, 11), however specific recommendations for neurological comorbidities are sparse. Frequency of CND comorbidities in Covid-19 patients have not been considered in most of the studies (8). To our knowledge, this is the first study that analyzes the implication of CND presence. CND was an independent

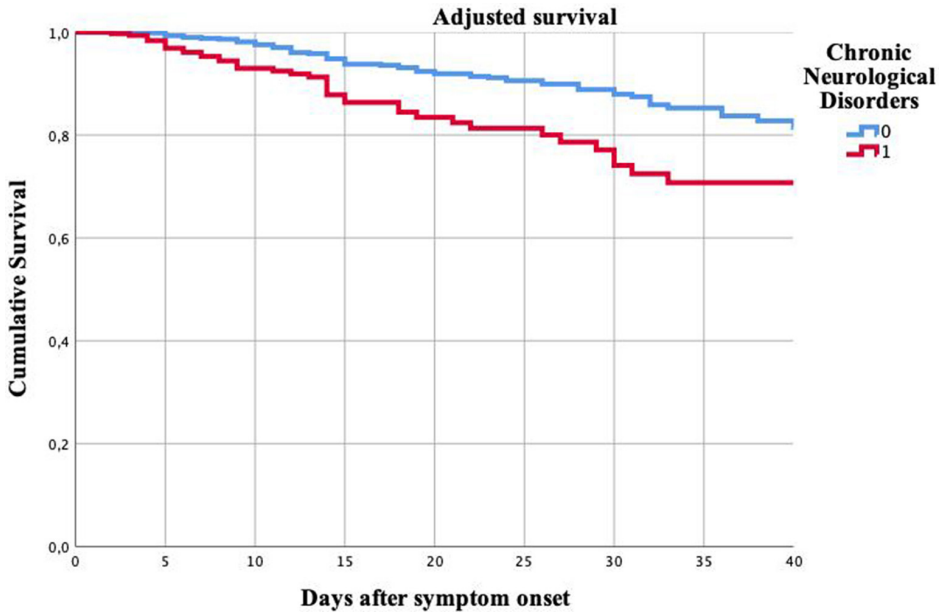


FIGURE 2 | Cumulative survival of patients with and without chronic neurological disorders. Kaplan Meier curves. *Y axis: Cumulative survival. X axis: Days after the symptoms onset*.

TABLE 3 | Predictors of severe Covid-19 disease. Univariate and multivariate regression analysis.

	Type of analysis	OR	95% CI	*p*-value
mRS>2	Univariate	2.437	1.241–4.786	0.010
	Multivariate	1.272	0.587–2.756	0.542
Age	Univariate	1.031	1.019–1.044	<0.001
	Multivariate	1.029	1.013–1.045	<0.001
Female sex	Univariate	0.584	0.410–0.832	0.003
	Multivariate	0.642	0.437–0.942	0.024
Hypertension	Univariate	1.485	1.044–2.113	0.028
	Multivariate	0.802	0.522–1.232	0.314
Diabetes	Univariate	2.714	1.600–4.603	<0.001
	Multivariate	2.200	1.256–3.855	0.006
Smoking	Univariate	2.083	1.279–3.392	0.003
	Multivariate	1.648	0.967–2.809	0.066
Cardiological disorders	Univariate	1.527	1.008–2.314	0.046
	Multivariate	0.834	0.516–1.350	0.460
Pulmonary disorders	Univariate	1.812	1.172-2.801	0.008
	Multivariate	1.399	0.874–2.240	0.162
Cancer	Univariate	1.534	0.924-2.547	0.098
	Multivariate	1.182	0.689–2.027	0.523
Chronic neurological disorders	Univariate	2.418	1.421–4.115	0.001
	Multivariate	1.750	0.970–3.158	0.063
Immunosuppression	Univariate	1.289	0.405–4.103	0.668

ADRS, Acute Distress Respiratory Syndrome; mRS, Modified Rankin Scale; OR, Odds Ratio; CI, Confidence Interval.

predictor of in-hospital mortality, and death occurred faster in CND patients.

As expected, patients with CND were older, more disabled and had higher frequency of vascular risk factors and other comorbidities. All of those have been associated with higher mortality in most of the Covid-19 series (1–6). The clinical presentation of Covid-19 disease was pauci symptomatic in CND patients, as some typical symptoms such as cough, chest pain or asthenia were less frequent. Also, the most frequently reported neurological symptoms, myalgia, and headache (17–19), were less common. Despite of that, CND patients experienced ADRS more often and had a higher death rate.

Considering the more severe disease, the worst baseline performance and the scanty clinical expression, the reason for the different outcome could be related with a delayed ED presentation. However, in our sample, patients with CND came earlier, even after adjusting for age, mRs, sex, and the rest of comorbidities. Hence, we could not attribute the worse prognosis to the delay in the care provision (6).

Then, we tried to find out if patients with CND received standard care and/or intensive care less often. More than 80% of CND patients received pharmacological treatment according to the local SOC. Even though the clinical benefit of those drugs is not yet clear (20), we could not attribute the worse prognosis to the restriction of the received therapy. Due to the collapse of the sanitary system, ICU guidelines deemed to prioritize the resource allocation to those patients with a higher potential benefit (21). Nevertheless, in our sample, patients with CND benefited from ICU admission as frequently as those without it.

Since the need of oxygen therapy was more frequent in patients with CND, a possible explanation of the higher mortality was the more severe Covid-19 disease. As the simple comparison of mean or median values of laboratory findings was not adequate due to the imbalanced populations, we analyzed if patients with CND had abnormal laboratory values more frequently than the rest of the patients, adjusting by all the variables that deemed potential confounders. Only increased INR and procalcitonin remained statistically significant. The reason why INR is more frequently increased in patients with CND is elusive and could be

related with hepatic failure caused by sepsis, low K vitamin levels, or acute liver failure (22). In the case of procalcitonin, patients with CND are more vulnerable to nosocomial infections (23), so the bacterial co-infection could be the most likely explanation (24, 25). It has been pointed as an independent predictor of fatal outcome in Covid-19 patients (26).

Henceforth, if we could not attribute the worse prognosis of CND patients neither to a delayed presentation to the ED nor a different management (27), a plausible explanation could be the higher fragility and lower reserve of CND population. It is well-known that CND are independent predictors of mortality in hospitalized patients (28, 29). Prior history of stroke has been related with a higher odds of severe Covid-19 illness, as well (30). The possible reasons seem varied, including frequency of delirium (18, 19), malnutrition (31), impaired respiratory function (32), and worse self-management (33). Many of them can be worsened by Covid-19 disease and the use of personal protective equipment makes its management arduous. Covid-19 should be prevented and detected early in CND patients, whose close monitoring could prevent complications and improve the prognosis (34). In addition, the worse prognosis of patients with CND could be linked with immuno-senescence, an enhanced inflammatory state, favored by an angiotensin II induced vasoconstriction and inflammatory response, leading to lymphopenia, cytokine release and macrophage activation (35).

This study has notable limitations. First, the sample size was modest, implying the possibility of some false-negative results. The number of CND was not high enough to perform sub-studies by different specific conditions, but all the patients were consecutive. We tried to create an operative definition of CND, based on the persistent impact on functionality, however the definition is imperfect and not every neurological disorder might be equally relevant. Further studies should focus on the specific impact of the different neurological comorbidities and analyze them separately. Second, this was a single center study, it would be desirable to create multicentric studies to clarify the impact of other variables, such as the type of hospital care and the different management of patients. Future studies should be multinational, as the reported adjusted mortality rates are highly variable between the different countries. It is not yet known if it could be attributed to genetic predisposition for severe Covid-19 or different healthcare systems. This was a retrospective study and despite the information was carefully reviewed, some information could be incomplete. It was a limitation that there were many different researchers involved in the study, albeit all of them were neurologists and followed a pre-defined protocol. We did not include long-term follow up of the patients, some patients remained admitted at the time of data cutoff, mortality might be underestimated in some cases. Also, the sample is not representative of the whole population, as it only included hospitalized patients, which could influence the results.

CONCLUSION

The presence of pre-existing chronic neurological disorders was an independent predictor of mortality in hospitalized Covid-19 patients.

Death occurred faster after admission in patients with CND, and CND was associated with an earlier presentation at ED. Presence of CND was not associated with a worse inflammatory response or with differences in the level of care provided to the patients.

The course of Covid-19 in patients with CND appears to be faster and more aggressive, and therefore protocols should consider these patients as a very high-risk population.

Future Covid-19 studies should consider the presence of CND in the evaluation of risk of mortality.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Datasheets are available upon reasonable request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Valladolid Este Ethics Review Board. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

DG-A and JA designed and conceptualized the study. DG-A, EM-P, JT, IH-P, GV-P, BT, PS-C, ML, AC-M, CL-S, MG-S, EM-V, and MP collected the data. DG-A and JA analyzed and interpreted the data. DG-A drafted the manuscript. ÁS, BG-V, ÁG, DE, MJP, JG-H, EB-M, CA-M, AO-D, GR-M, MJ-C, SJ, CP-V, CD-G, JP, BC-Á, and JV revised the manuscript for intellectual content. All authors agreed and approved the publication.

ACKNOWLEDGMENTS

The authors thank all the people who faced Covid-19.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00781/full#supplementary-material

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. (2020) 323:1061–9. doi: 10.1001/jama.2020.1585

4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
5. Guan WJ, Ni ZY, Hu Y, Lian W, Ou C, He J, et al. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
6. Wu C, Chen X Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress síndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. (2020) 13:e200993. doi: 10.1001/jamainternmed.2020.0994
7. The World Health Organization. *Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (2019- nCoV) Infection is Suspected: Interim Guidance*. (2020). Available online at: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf (accessed June 3, 2020).
8. Herman C, Mayer K, Sarwal A. Scoping review of neurologic comorbidities in patients hospitalized for COVID-19. *Neurology*. (2020). doi: 10.1212/WNL.0000000000009673. [Epub ahead of print].
9. Du, RH, LR Liang, Yang CQ, Wang W, Cao T, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Resp J*. (2020) 55:2000524. doi: 10.1183/13993003.00524-2020
10. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. (2007) 4:e296. doi: 10.1371/journal.pmed.0040296
11. Ministry of Health. Technical documents. *Hospital Management of COVID-19*. (2020). Available online at: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Protocolo_manejo_clinico_ah_COVID-19.pdf (accessed May 16, 2020).
12. The World Health Organization. *Coronavirus Disease (COVID-19) Technical Guidance: Laboratory Testing for 2019-nCoV in Humans*. (2020). Available online at: https://www.who.int/publications/i/item/10665-331501 (accessed May 16, 2020).
13. Dua T, Janca A, Kale R, Montero F, Muscetta A, Peden M. Public health principles and neurological disorders. In: Aarli JA, Avanzini G, Bertolote JM, de Boer H, Breivik H, Dua T, Graham N, Janca A, Kesselring J, Mathers C, Muscetta A, Prilipko L, Saraceno B, Saxena S, Steiner TJ, editors. *World Health Organization: Neurological Disorders: Public Health Challenges*. Geneva: World Health Organization (2006). p. 16–21.
14. Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified rankin scale: a systematic review. *Stroke*. (2009) 40:3393–5. doi: 10.1161/STROKEAHA.109.557256
15. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia: an official clinical practice guideline of the American thoracic society and infectious disease society of America. *Am J Respir Crit Care Med*. (2019) 200:e45–67. doi: 10.1164/rccm.201908-1581ST
16. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. (2012) 307:2526–33. doi: 10.1001/jama.2012.5669
17. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. *J Neurol Sci*. (2020) 43:116832. doi: 10.1016/j.jns.2020.116832
18. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
19. Mao L, Wang M, Hu Y, Chen S, He Q, Chang J, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
20. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacological treatments for coronavirus disease 2019 (Covid-19). A review. *JAMA*. (2020). doi: 10.1001/jama.2020.6019. [Epub ahead of print].
21. White DB, Lo B. A framework for rationing ventilators and critical care beds during the Covid-19 pandemic. *JAMA*. (2020). doi: 10.1001/jama.2020.5046. [Epub ahead of print].
22. Harrison MF. The misunderstood coagulopathy of liver disease: A review for the acute setting. *West J Emerg Med*. (2018) 19:863–71. doi: 10.5811/westjem.2018.7.37893
23. Yuan M, Li F, Tian X, Wang W, Jia M, Wang X, et al. Risk factors for lung infection in stroke patients: a meta-analysis of observational studies. *Expert Rev Anti Infect Ther*. (2015) 13:1289–98. doi: 10.1586/14787210.2015.1085302
24. Wirz Y, Meier MA, Bouadma L, Luyt CE, Wolff M, Chastre J, et al. Effect of procalcitonin-guided antibiotic treatment on critical outcomes in Intensive Care Unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials. *Crit Care*. (2018) 22:191. doi: 10.1186/s13054-018-2125-7
25. Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. *PLoS ONE*. (2018) 13:e0206527. doi: 10.1371/journal.pone.0206527
26. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. *Chest*. (2020) 158:97–105. doi: 10.1016/j.chest.2020.04.010
27. Piano C, Di Stasio E, Primiano G, Janiri D, Luigetti M, Frisullo G, et al. An Italian Neurology outpatient clinic facing SARS-CoV-2 pandemic: data from 2,167 patients. *Front Neurol*. (2020) 11:564. doi: 10.3389/fneur.2020.00564
28. Schwartz N, Sakhinini, Bisharat N. Predictive modeling of inpatient mortality in departments of internal medicine. *Intern Emerg Med*. (2018) 13:205–11. doi: 10.1007/s11739-017-1784-8
29. Smolin B, Levy Y, Sabbach-Cohen E, Levi L, Mashiach T. Predicting mortality of elderly patients acutely admitted to the department of internal medicine. *Int J Clin Pract*. (2015) 69:501–8. doi: 10.1111/ijcp.12564
30. Aggarwal G, Lippi G, Henry BM. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): a pooled analysis of published literature. *Int J Stroke*. (2020) 15:385–9. doi: 10.1177/1747493020921664
31. Lopez Espuela F, Roncero-Martín R, Pedrera JD, Rey-Sanchez P, Ailaga-Vera I, Portilla Cuenca JC, et al. Controlling nutritional status (CONUT) score as predictor of al-cause mortality at 3 months in Stroke patients. *Biol Res Nurs*. (2019) 21:564–70. doi: 10.1177/1099800419860253
32. Ashima SS, Wolfe L. Respiratory care in neuromuscular diseases. *Respir Care*. (2018) 63:601–8. doi: 10.4187/respcare.06210
33. Rae-Grant A, Turner AP, Sloan A, Miller D, Hunziker J, Haselkorn JK, et al. Self-management in neurological disorders: systematic review of the literature and potential interventions in multiple sclerosis care. *J Rehabil Res Dev*. (2011) 48:1087–100. doi: 10.1682/JRRD.2010.08.0159
34. Matías-Guiu J, Porta-Etessam J, López-Valdes E, Garcia-Morales I, Guerrero-Sola A, Matías-Guiu JA. Management of neurological care during the COVID-19 pandemic. *Neurologia*. (2020) 35:233–7. doi: 10.1016/j.nrl.2020.04.001
35. Romoli M, Jelcic I, Bernard-Valnet R, García Azorín D, Mancinelli L, Akhvlediani T, et al. A systematic review of neurological manifestations of SARS-CoV-2 infection: the devil is hidden in the details. *Eur J Neurol*. (2020). doi: 10.1111/ene.14382. [Epub ahead of print].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with several of the authors DG-A, MG-S.

frontiers in Neurology

ORIGINAL RESEARCH
published: 10 July 2020
doi: 10.3389/fneur.2020.00806

Neurological Manifestations in Critically Ill Patients With COVID-19: A Retrospective Study

Siyuan Fan[1†], Meng Xiao[2†], Fei Han[1†], Peng Xia[3], Xiaoyin Bai[4], Huan Chen[5], Hongmin Zhang[5], Xin Ding[5], Hua Zhao[5], Jing Zhao[6], Xuefeng Sun[6], Wei Jiang[7], Chunyao Wang[7], Wei Cao[8], Fan Guo[9], Ran Tian[9], Peng Gao[9], Wei Wu[9], Jie Ma[3], Dong Wu[4], Zhengyin Liu[8], Xiang Zhou[5], Jinglan Wang[6], Tianjia Guan[10], Yan Qin[3], Taisheng Li[8], Yingchun Xu[2], Dong Zhang[2], Yu Chen[2], Jing Xie[2], Yongzhe Li[2], Xiaowei Yan[9], Yicheng Zhu[1], Bin Peng[1], Liying Cui[1], Shuyang Zhang[9†] and Hongzhi Guan[1*†]*

[1] Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [2] Department of Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [3] Department of Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [4] Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [5] Department of Intensive Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [6] Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [7] Department of Medical Intensive Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [8] Department of Infectious Disease, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [9] Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China, [10] School of Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

OPEN ACCESS

Edited by:
Jesús Porta-Etessam, Hospital Clínico San Carlos, Spain

Reviewed by:
Rodrigo Guerrero, University of the Andes, Chile
Julián Benito León, University Hospital October 12, Spain

***Correspondence:**
Shuyang Zhang
shuyangzhang103@163.com
Hongzhi Guan
pumchghz@126.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *05 May 2020*
Accepted: *29 June 2020*
Published: *10 July 2020*

Citation:
Fan S, Xiao M, Han F, Xia P, Bai X, Chen H, Zhang H, Ding X, Zhao H, Zhao J, Sun X, Jiang W, Wang C, Cao W, Guo F, Tian R, Gao P, Wu W, Ma J, Wu D, Liu Z, Zhou X, Wang J, Guan T, Qin Y, Li T, Xu Y, Zhang D, Chen Y, Xie J, Li Y, Yan X, Zhu Y, Peng B, Cui L, Zhang S and Guan H (2020) Neurological Manifestations in Critically Ill Patients With COVID-19: A Retrospective Study. Front. Neurol. 11:806. doi: 10.3389/fneur.2020.00806

Background: The complications of coronavirus disease 2019 (COVID-19) involved multiple organs or systems, especially in critically ill patients. We aim to investigate the neurological complications in critically ill patients with COVID-19.

Methods: This retrospective single-center case series analyzed critically ill patients with COVID-19 at the intensive care unit of Tongji Hospital, Wuhan, China from February 5 to April 2, 2020. Demographic data, clinical and laboratory findings, comorbidities and treatments were collected and analyzed.

Results: Among 86 patients with confirmed COVID-19, 54 patients (62.8%) were male, and the mean (SD) age was 66.6 (11.1) years. Overall, 65% patients presented with at least one neurological symptom. Twenty patients (23.3%) had symptoms involving the central nervous system, including delirium, cerebrovascular diseases and hypoxic-ischemic brain injury, while 6 patients (7%) had neuromuscular involvement. Seven of 86 patients exhibited new stroke and 6 (7%) cases were ischemic. A significantly higher prevalence of antiphospholipid antibodies was observed in patients with ischemic stroke than in those without stroke (83.3 vs. 26.9%, $p < 0.05$). Patients with ischemic stroke were more likely to have a higher myoglobulin level, and a lower hemoglobin level.

Conclusions: The clinical spectrum of neurological complications in critically ill patients with COVID-19 was broad. Stroke, delirium and neuromuscular diseases are common neurological complications of COVID-19. Physicians should pay close attention to neurological complications in critically ill patients with COVID-19.

Keywords: COVID-19, neurological manifestations, critically ill, stroke, neuromuscular diseases

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) began in Wuhan, Hubei Province in December 2019 and has rapidly spread throughout China (1–3). It is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1), which is similar to the zoonotic SARS-CoV from 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) from 2012 (4). In a short time, COVID-19 has spread worldwide. On March 11, 2020, the World Health Organization (WHO) characterized COVID-19 as a pandemic (5, 6).

The clinical spectrum of the SARS-CoV-2 infection, COVID-19, appears to be wide, including asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death (2). Furthermore, various complications beyond the respiratory system, such as acute myocardial injury, acute kidney injury and gastrointestinal complications, have been investigated (2–4, 7–12).

With the increasing number of confirmed cases and accumulating clinical data, neurological complications associated with COVID-19 have been a challenge for clinical management and have generated considerable concern. Recent data from Wuhan, China, reported neurological complications in 36% of 214 COVID-19 patients (13). The neurological manifestations can vary from mild and unspecific symptoms, such as headache and hyposmia, to catastrophic symptoms, including stroke, acute hemorrhagic necrotizing encephalopathy, encephalitis/meningitis and Guillain-Barré syndrome (13–25). However, neurological features of COVID-19 infection in critically ill patients, have not been fully investigated. Herein, we conducted a retrospective study to analyze the neurological manifestations of critically ill patients with COVID-19 in intensive care units (ICU) to explore various pathophysiological mechanisms that could contribute to neurological complications in these patients.

MATERIALS AND METHODS

Participants and Study Design

This is a single-center, retrospective, observational study performed at the Tongji Hospital, Wuhan, China. A designated ICU was established and specialized for critically ill patients with COVID-19 and was managed by the National Medical Team from Peking Union Medical College Hospital, Beijing, China. We retrospectively analyzed patients with COVID-19 who were diagnosed according to the criteria for critically ill patients with confirmed COVID-19 in our ICU from February 5, 2020 to April 2, 2020. All patients included were confirmed cases with positive reverse transcription-polymerase chain reaction (RT-PCR) results for SARS-CoV-2 before admission or positive serological tests for anti-SARS-CoV-2 specific immunoglobulin (Ig) M and G during hospitalization. The diagnosis and classification of disease severity of COVID-19 were made according to Chinese Management Guidance for COVID-19 Diagnosis and Treatment (7th version) (26). Patients who met one of the following conditions were classified as critically ill: (1) Respiratory failure requiring mechanical ventilation (MV). (2) Shock. (3) Patients complicated with other organ failure who required ICU monitoring and treatment.

All individual-level medical information, including demographic characteristics, medical history, clinical, radiological and laboratory findings, treatments and outcome data, were retrieved from the electronic medical records.

This study was approved by the institutional review board of Peking Union Medical College Hospital (No. S-K1151). Written informed consent was waived as this retrospective study was carried out to investigate an emerging infectious disease. The study was performed in accordance with the Declaration of Helsinki.

Laboratory and Neuroimaging Evaluation

Head CT scans were performed for patients with severe neurological complications after February 28, 2020 using a transport ventilator. Antiphospholipid syndrome (APS) panels, including serum levels of anticardiolipin IgG, IgM and IgA, and anti-β2-glycoprotein 1 (aβ2GP1) IgG, IgM and IgA were determined using a chemiluminescence assay (QUANTA Flash® assays, Inova) according to the manufacturer's instructions. Metagenomic next-generation sequencing of patients CSF samples was performed according to a standard flow, which has been described elsewhere (27, 28).

Definitions

Lymphocytopenia was defined as a lymphocyte count $<1.1 \times 10^9$/L. Coagulopathy was defined as a 3-s extension of prothrombin time or a 10-s extension of activated partial thromboplastin time. Delirium was defined according to Diagnostic and Statistical Manual of Mental Disorders, 6th edition. Flaccid paralysis was defined as bilateral paralysis with the loss of muscle tone and absence of tendon reflexes. Stroke was defined as a syndrome of rapidly emerging clinical signs of focal or global disturbance of cerebral function lasted at least 24 h, or detection of cerebral lesions in accordance with vascular origin on neuroimaging examination. Strokes were further verified and classified into ischemic stroke or spontaneous intracerebral hemorrhage based on neuroimaging results. Hypoxic ischemic brain injury is used to describe diffuse brain injury as a result of hypoxia or reduction of oxygen. The outcome is defined as the condition evaluated on April 2, 2020.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 17.0 and EXCEL 1810. Data are expressed as medians with the interquartile range (IQR) or means ± standard deviation (SD) according to the distribution. Analysis of variance (ANOVA), Student's *t*-test, or the Mann–Whitney test (non-normal distributions) were used to analyze continuous variables.

TABLE 1 | Demographic and clinical findings of critically ill patients with COVID-19.

	All patients (*n* = 86)	Patients without AIS (*n* = 80)	Patients with AIS (*n* = 6)
Age, years, mean ± *SD*	66.6 ± 11.1	66.5 ± 11.5	68.2 ± 2.1
Sex			
Male, *n* (%)	54 (62.8)	49 (61.3)	5 (83.3)
Presenting symptoms			
Fever, *n* (%)	75 (87.2)	69 (86.3)	6 (100)
Cough, *n* (%)	65 (75.6)	61 (76.3)	4 (66.7)
Myalgia, *n* (%)	15 (17.4)	12 (15.0)	3 (50.0)
Fatigue, *n* (%)*	46 (53.5)	40 (50.0)	6 (100)
Headache, *n* (%)	8 (9.3)	7 (8.8)	1 (16.7)
Dizziness, *n* (%)	6 (7.0)	5 (6.3)	1 (16.7)
PMH			
Hypertension, *n* (%)	44 (51.1)	41 (51.3)	3 (50.0)
Diabetes, *n* (%)	19 (22.1)	17 (21.3)	2 (33.3)
CAD, *n* (%)	16 (18.6)	14 (17.5)	2 (33.3)
Ischemic stroke, *n* (%)	7 (8.1)	5 (6.3)	2 (33.3)
Intracranial hemorrhage, *n* (%)	4 (4.7)	4 (5.0)	0 (0)
Smoking, *n* (%)	12 (14.0)	11 (13.8)	1 (16.7)
Complications			
Arrhythmia, *n* (%)	29 (33.7)	28 (35.0)	1 (16.7)
AF, *n* (%)	16 (18.6)	15 (18.8)	1 (16.7)
Coagulopathy, *n* (%)	49 (57.0)	46 (57.5)	3 (50.0)
AKI, *n* (%)	35 (40.1)	31 (38.8)	4 (66.7)
Liver injury, *n* (%)	34 (39.5)	32 (40.0)	2 (33.3)
Delirium, *n* (%)	11 (12.8)	11 (13.8)	0 (0)
Intracerebral hemorrhage, *n* (%)	1 (1.2)	1 (1.3)	0 (0)
Hypoxic-ischemic brain injury, *n* (%)	2 (2.3)	2 (2.5)	0 (0)
Flaccid paralysis, *n* (%)	5 (6.3)	1 (1.3)	4 (66.7)
Rhabdomyolysis	2 (2.3)	2 (2.5)	0 (0)
Treatment			
Antiviral therapy, *n* (%)	67 (77.9)	62 (77.5)	5 (83.3)
Immunotherapy, *n* (%)			
IVIg, *n* (%)	70 (81.4)	65 (81.3)	5 (83.3)
Steroids, *n* (%)	71 (82.6)	67 (83.8)	4 (66.7)
Anticoagulation, *n* (%)*	48 (55.8)	42 (52.5)	6 (100)
Aspirin, *n* (%)	10 (11.6)	8 (10.0)	2 (33.3)
Invasive MV, *n* (%)	70 (81.4)	64 (80.0)	6 (100)
ECMO	5 (5.8)	5 (6.3)	0 (0)
CRRT, *n* (%)	16 (18.6)	15 (18.8)	1 (16.7)
Outcome			
Death, *n* (%)*	55 (64.0)	54 (67.5)	1 (16.7)
Follow-up duration, d, median (IQR)	35.0 (20.6, 43.5)	30.0 (20.0, 39.0)	66.5 (54.8, 69.3)

COVID-19, corona virus disease 2019; AIS, acute ischemic stroke; SD, standard deviation; PMH, past medical history; CAD, coronary artery disease; AF, atrial fibrillation; AKI, acute kidney injury; IVIg, intravenous immunoglobulin; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; IQR, interquartile range.
*$P < 0.05$.

Pearson χ^2 test or a Fisher's exact test were used to analyze categorical variables. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

We finally included 86 critically ill patients with confirmed COVID-19 after excluding 10 patients without available key information, 11 patients with suspected COVID-19, and two patients with a mild or moderate disease course. Of 86 patients, 54 (62.8%) were male, and the mean (SD) age was 66.6 (11.1) years old. The demographic and clinical features of these patients are summarized in **Table 1**.

Most of these patients presented with fever (87.2%) and cough (75.6%). Fifty-six (65.1%) patients presented with at least one type of neurological symptom (headache, dizziness, myalgia, fatigue or hyposmia), including 15 patients with myalgia, 46 patients with fatigue, 8 patients with headache, 6 patients with dizziness, and none patient complaining of hyposmia.

Underlying cardiovascular diseases, including hypertension, diabetes, coronary artery disease, and stroke, as well as smoking were prevalent in critically ill patients with COVID-19, while hypertension was the most common comorbidity and occurred in 44 (51.1%) patients. A total of 12 (14.0%) patients had a past medical history of stroke, including 7 cases of ischemic stroke, 4 cases of intracranial hemorrhage and 1 case of subarachnoid hemorrhage. One patient reported a medical history of myasthenia gravis; and one patient reported a medical history of Alzheimer disease.

The complications of COVID-19 involved multiple organs or systems, including the lymphohematopoietic system, kidney, liver and heart. Coagulopathy was common and occurred in 49 (57.0%) patients. Sixteen (18.6%) patients were complicated with atrial fibrillation during the disease course of COVID-19.

Of the 86 patients, 70 (81.4%) received invasive MV, 5 (5.8%) received extracorporeal membrane oxygenation, and 16 (18.6%) received continuous renal replacement therapy. Most critically ill patients received antiviral therapy (77.9%) and immunotherapy (81.4% received intravenous immunoglobulin and 82.6% received steroids). Forty-eight (55.8%) patients received anticoagulation therapy because of underlying coagulopathy or thromboembolic events. The fatality rate was high; 55 (64.0%) patients died through April 2, 2020 (the median follow-up duration was 35 days).

Laboratory Findings on ICU Admission

The laboratory findings of the patients are summarized in **Table 2**. Lymphocytopenia was common and occurred in 77 (89.5%) patients. Lactate dehydrogenase was elevated in 78 (90.7%) patients. Creatine kinase was elevated in 29 (33.7%) patients and myoglobulin elevation was documented in 26 (30.2%) patients. N terminal pro B type natriuretic peptide (NT-proBNP) was elevated in 60 (69.8%) patients, and cardiac troponin I (cTnI) was elevated in 48 (55.8%) patients. D-dimer was elevated in 55 (64.0%) patients. High-sensitive C-reactive protein was elevated in 80 (93.0%) patients. Interleukin−6 was elevated in 66 (76.7%) patients. Twelve of the 32 (37.5%) tested patients were positive upon APS panel testing.

TABLE 2 | Laboratory findings on admission in critically ill patients with COVID-19.

	All patients (n = 86)	Patients without AIS (n = 80)	Patients with AIS (n = 6)
WBC count, 10^9/L, median (IQR)	12.0 (8.7, 17.1)	12.0 (8.9, 17.4)	12.0 (5.2, 17.6)
Lymphocyte count, 10^9/L, median (IQR)	0.56 (0.36, 0.80)	0.56 (0.38, 0.86)	0.66 (0.25, 0.73)
Platelets, 10^9/L, median (IQR)	159 (97, 229)	159 (101, 230)	130 (54, 219)
Hemoglobin, g/L, median (IQR) *	122 (99, 134)	123 (104, 136)	95 (90, 107)
ALT, U/L, median (IQR)	27 (18, 43)	27 (18, 43)	22 (11,47)
LDH, U/L, median (IQR)	486 (241, 650)	493 (350, 642)	375 (280, 741)
Creatinine, μmol/L, median (IQR)	75.5 (51.0, 113.5)	72.5 (51.0, 111.2)	96.0 (72.5, 129.0)
Creatine kinase, U/L, median (IQR)	90 (48, 225)	99 (49, 259)	63 (30, 100)
Myoglobulin, ng/mL, median (IQR) *	148.0 (74.1, 365.6)	114.0 (71.2, 365.3)	281.6 (167.0, 443.7)
cTnI, pg/mL, median (IQR)	43.3 (13.8, 270.1)	42.2 (13.1, 300.8)	106.7 (32.6, 235.5)
NT-proBNP, pg/mL, median (IQR)	992 (398, 3,930)	939 (394, 3,771)	3,110 (2,236, 6,895)
LDL-C, mmol/L, mean ± *SD*	1.84 ± 0.78	1.88 ± 0.76	1.34 ± 0.86
Prothrombin time, s, median (IQR)	16.1 (15.1, 17.7)	16.1 (15.1, 18.0)	16.4 (15.0, 17.3)
aPTT, s, median (IQR)	42.8 (37.4, 47.1)	42.1 (37.3, 46.9)	44.4 (40.5, 49.6)
D-dimer, μg/mL, median (IQR)	9.0 (2.8, 21.0)	9.3 (2.8, 21.0)	3.7 (2.6, 12.0)
Procalcitonin, ng/mL, median (IQR)	0.31 (0.14, 0.81)	0.26 (0.12, 0.80)	0.53 (0.28, 1.30)
hsCRP, mg/L, mean ± *SD*	95.8 ± 67.4	94.5 ± 68.5	112.7 ± 53.8
IL-2R, U/mL, median (IQR)	1,090 (638, 1,650)	1,083 (595, 1,445)	1,593 (1,145, 1,921)
IL-6, pg/mL, median (IQR)	60.4 (29.2, 168.2)	59.8 (28.9, 180.3)	69.4 (47.1, 286.5)
IL-8, pg/mL, median (IQR)	28.6 (18.9, 77.3)	29.5 (16.6, 79.1)	28.2 (22.1, 39.5)
IL-10, pg/mL, median (IQR)*	10.9 (5.7, 17.1)	11.4 (5.7, 18.9)	6.1 (5.3, 6.3)
TNF-α, pg/mL, median (IQR)	10.3 (6.8, 19.6)	10.1 (6.8, 20.3)	11.8 (7.0, 13.9)
APS panel positivity, *n (%)**	12 (37.5)	7 (26.9)	5 (83.3)

COVID-19, corona virus disease 2019; AIS, acute ischemic stroke; WBC, white blood cell; ALT, alanine transaminase, cTnI, High-sensitive cardiac troponin I; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LDL-C, low-density-lipoprotein cholesterol; aPTT, activated partial thromboplastin time; hsCRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; IQR, interquartile range. APS, antiphospholipid syndrome. APS panel included lupus anticoagulant, antibodies against the membrane phospholipid cardiolipin (IgG, IgM, and IgA isotypes) and antibodies against β2GP1 (IgG, IgM, and IgA isotypes).

The normal range for the parameters: LDH, 135–225 U/L; Creatine kinase, ≤ 170 U/L; Myoglobulin, ≤ 154.9 ng/mL; cTnI, ≤ 34.2 pg/mL; NT-proBNP, < 486 pg/mL; D-Dimer, < 0.5 μg/mL FEU; hsCRP, < 1 mg/L; IL-2R, 223–710 U/mL; IL-6, < 7.0 pg/mL; IL-8, < 62 pg/mL; IL-10, < 9.1 pg/mL; TNFα, < 8.1 pg/mL.

**P < 0.05.*

Neurological Complications During the Disease Course

Neurological complications involving the central nervous system (CNS) were common, and 20 (23.3%) patients had at least one neurological complication of the CNS (delirium, acute ischemic stroke, intracerebral hemorrhage and hypoxic-ischemic brain injury). Delirium was presented in 11 (12.8%) patients, which was a reason that patients could not tolerate non-invasive MV and were admitted to the ICU for invasive MV. Two patients had hypoxic-ischemic brain injury, and one of these patients received cardiopulmonary resuscitation.

Acute ischemic stroke (AIS) occurred in six patients (7.0%, **Figure 1**, **Table 3**, **Supplementary Figures 1–10**), and intracranial hemorrhage occurred in one case. Additionally, two patients presented with acute focal neurologic deficit without neuroimaging evaluation. Of the six patients with AIS, two were deeply sedated, and infarctions were first revealed by head CT in these patients. Five patients were male. Notably, patients with AIS exhibited a significantly higher prevalence of APS panel positivity than those without AIS (83.3 vs. 26.9%, $p < 0.05$). Moreover, patients with AIS were more likely to have a higher myoglobulin level, and a lower hemoglobin level (**Table 2**). The cTnI and NT-proBNP levels seemed to be higher in patients with AIS, although there was no statistically significant difference between the two groups. All patients with AIS received anticoagulant therapy. Five of six patients with AIS were alive until the end of the follow-up period, and the median survival duration was 66.5 days for these patients.

Neurological complications of the peripheral nervous system and musculature were also observed in critically ill patients with COVID-19. Persistent flaccid paralysis was observed in four patients after withdrawal of sedation. Two patients had rhabdomyolysis.

Other Notable Neurological Evaluation

Lumbar puncture was performed in two critically ill patients with COVID-19. Protein levels were slightly elevated in one patient with persistent flaccid paralysis, while the opening pressure, white blood cell count and glucose levels were normal. SARS-CoV-2 was not detected in these two patients, either on RT-PCR or on metagenomic next-generation sequencing (**Supplementary Table 1**).

DISCUSSION

This retrospective study yields new insight into neurological manifestations in the critically ill patients with COVID-19. Of the 86 critically ill patients with COVID-19 included in this study, 65% presented with at least one neurological symptom. The clinical spectrum of neurological complications in critically ill patients with COVID-19 was broad, including delirium, acute ischemic stroke, intracerebral hemorrhage, hypoxic-ischemic brain injury, flaccid paralysis and rhabdomyolysis. Notably, that cerebrovascular disease was a common comorbidity, and the prevalence of previous stroke in our study was 14%. Moreover, 8% of patients exhibited new stroke during the course of disease,

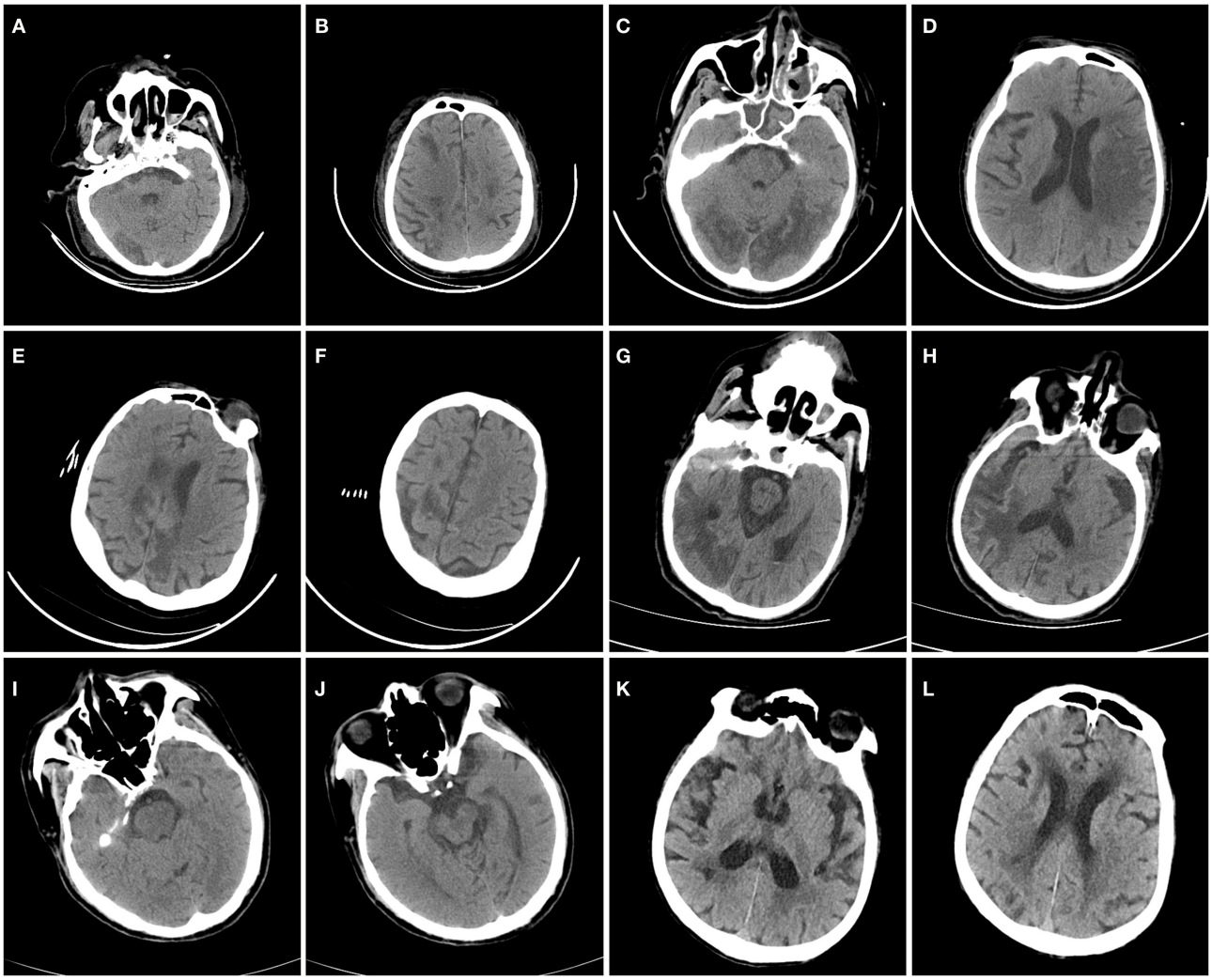


FIGURE 1 | Head CT scans of coronavirus disease 2019 patients with acute ischemic stroke. In Case 1 **(A,B)**, head CT revealed low-density lesions in the right occipital lobe and bilateral frontal and parietal lobes. In Case 2 **(C,D)**, head CT revealed low-density lesions in the bilateral occipital and temporal lobes and the left hemisphere. In Case 3 **(E,F)**, head CT revealed low-density lesions in the bilateral frontal and parietal lobes. In Case 4 **(G,H)**, head CT revealed low-density lesions in the right hemisphere. In Case 5 **(I,J)**, head CT revealed low-density lesions in the left midbrain. In Case 6 **(K,L)**, head CT revealed low-density lesions on the right side of the periventricular area.

and most strokes were ischemic. Positivity of antiphospholipid antibodies was highly prevalent in patients with ischemic stroke.

CNS symptoms were the main neurological complications in critically ill patients with COVID-19. Only two types of human coronaviruses, namely HCoV-OC43 and E299 were found to be neuroinvasive and can spread from the respiratory tract to the CNS (30). Invasion of CNS by SARS-CoV-2 has been suggested by researchers from the University of Yamanashi, and SARS-CoV-2 RNA can be detected in the CSF of patients with COVID-19 (18). Furthermore, autopsy reports have revealed the presence of virus in neural and capillary endothelial cells in frontal lobe tissue (31), as well as secondary brain damage and neuronal degeneration without evidence of viral encephalitis (32, 33). Recent studies illustrated that COVID-19 has the potential to cause nervous system damage. We performed lumbar puncture in two patients with COVID-19 and neurological manifestations in our ICU; however, neither patient showed signs of significant inflammation in the CSF. Furthermore, RT-PCR assays of the virus and metagenomic next-generation sequencing in the CSF samples were negative. Our findings were consistent with the previous observational report on severe COVID-19 patients, which indicated that RT-PCR assays of the CSF samples were negative for SARS-CoV-2 in all 7 tested patients (23). Whether and how CNS involvement is related to the direct invasion of the virus remains to be addressed in future studies.

Accumulating evidence suggested that neuroimaging features of hospitalized COVID-19 patients were variable, dominated by acute ischemic infarction and intracranial hemorrhages (19–24).

TABLE 3 | Clinical characteristics of COVID-19 patients complicated with stroke*.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age range, y	65–70	65–70	65–70	65–70	65–70	65–70	65–70
Sex	Male	Male	Female	Male	Male	Male	Female
PMH	HTN, DM, CAD, stroke[a]	Not notable	HTN, DM, CAD, hyperlipidemia	HTN, stroke[b], nasopharyngeal carcinoma	MI after COVID-19 onset	COPD	HTN, DM
Diagnosis	Acute ischemic stroke	Acute ischemic stroke	Acute ischemic stroke	Acute ischemic stroke	Acute ischemic stroke	Acute ischemic stroke	Intracerebral hemorrhage
Days after COVID-19 onset when stroke was diagnosed	Day 17	Day 55	Day 32	Day 8	Day 65	Day 19	Day 25
New onset neurological symptoms	Fall, irrelevant answer	Deep sedation, revealed by head CT	Deep sedation, revealed by head CT	LOC	LOC	Slurred speech	Severe headache, LOC
Notable neurological examination	Weakness of four limbs with decreased muscle tone, bilateral Babinski sign (+)	Weakness of four limbs with decreased muscle tone, right Babinski sign (+)	Weakness of four limbs with decreased muscle tone, left Babinski sign (+)	Weakness of four limbs (more severe on the left side), left Babinski sign (+)	Weakness of right limbs, right Babinski sign (+)	Slurred speech	NA (deep sedation after stroke onset)
Head CT	Low density lesions in right occipital lobe and bilateral frontal and parietal lobes	Low density lesions in bilateral occipital and temporal lobes and left hemisphere	Low density lesions in bilateral frontal and parietal lobes	Low density lesions in right hemisphere	Low density lesions in left midbrain	Low density lesions in peri-ventricular area	High density in lateral ventricles and subarachnoid space
Vascular territory	Right PCA, and watershed pattern between right MCA and ACA	Bilateral PCAs, and left MCA	Bilateral ACAs	Right MCA and PCA	Left PCA	Cerebral small vessel disease	-
APS panel	Positive	Positive	Positive	Positive	Positive	Negative	Negative
Outcome	Hosp	Hosp	Hosp	Hosp	Hosp	Died	Hosp

COVID-19, corona virus disease 2019; CT, computerized tomography; NA, not applicable; LOC, loss of consciousness; PMH, past medical history; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; APS, antiphospholipid syndrome; PCA, posterior cerebral artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; Hosp, hospitalization.

**Some information of case 1, case 3, and case 4 had been reported previously (29).*

[a]Case 1 reported a past history of ischemic stroke and recovered well with modified Rankin score 0 point.

[b]Case 4 reported a past history of ischemic stroke and the previous infarct was located in the cerebellum.

Besides, leptomeningeal enhancement, hypoxic-ischemic brain injury, cortical signal abnormalities that may be caused by systemic toxemia were also reported (23, 34, 35). Hypodensities localized in multiple brain areas on CT scans, which were in line with vascular origin were observed in case 1 to case 6 in our series. The lesions of five patients (case 1–5) indicated large artery involvement, while four of them had multiterritory infarcts. Case 6 presented with sudden onset of focal neurological deficit (slurred speech) after admission with a moderate background of cerebral small vessel disease on head CT scan, ischemic stroke of small vessel disease subtype was diagnosed.

Stroke is not uncommon in patients with coronavirus infection. AIS has been reported in patients with SARS and MERS (36–39). To date, 2.3–13.5% of patients with severe COVID-19 have been reported to have comorbid cerebrovascular disease (3, 9). Although stroke has been recognized as a complication of COVID-19 (usually in the severe cases), the exact incidence is not fully investigated (2, 3, 9, 10, 12, 40, 41). Data from Wuhan, China, reported that acute cerebrovascular disease (mainly ischemic stroke) was more common among 88 patients with severe COVID-19 than those with non-severe disease (5.7 vs. 0.8%) (13). In recent case series, ischemic stroke of both large artery- and small vessel- etiology have been reported (19–24). In the present study, stroke was diagnosed in 7 of 86 critically ill patients with COVID-19 and 6 cases were classified as ischemic stroke. This incidence might be higher because neuroimaging examinations were not performed for all patients with acute focal neurologic deficits because of a rapid deterioration of the conditions the result in death. The exact mechanism of ischemic stroke in COVID-19 remains under investigation. Possible explanations include the following.

First, abnormal coagulation results, especially markedly elevated D-dimer and fibrin degradation product, are quite prevalent in critically ill patients with COVID-19, which indicates a common coagulation activation and secondary hyperfibrinolysis condition (42). We also found coagulopathy and antiphospholipid antibodies in critically ill patients with COVID-19 in our cohort (29). Our results indicated that five of the six cases of ischemic stroke had large artery or embolic origin. Similarly, in a previous report of COVID-19 patients with ischemic stroke, all six stroke patients had large-vessel occlusion and three of them had multiterritory infarcts (21). The high incidence of thrombotic complications and the principal subtypes of ischemic strokes verified the existence of a pro-coagulant state in critically ill patients with COVID-19. D-Dimer levels were repeatedly measured in some patients in our study and showed a trend of decreasing, which might be related to anticoagulant therapy. Furthermore, compared with patients without a cerebrovascular event, a significantly higher prevalence of antiphospholipid antibodies was observed in stroke patients. Previous studies have shown an increased risk of developing antiphospholipid antibodies in various viral infections (43). Our results indicate that clinicians should be aware of the increased risk and consider testing for antiphospholipid antibodies in patients with COVID-19 infection and clinical manifestations suggestive of APS. All of the six patients complicated with ischemic stroke received anticoagulant therapy, and five improved or stabilized, which may indicate that critically ill patients with COVID-19 with ischemic stroke may benefit from anticoagulant therapy. Previous studies have also suggested that anticoagulant treatment was necessary and beneficial for severe COVID-19 patients with coagulopathy (44–46).

Second, virus-induced vascular inflammation might be responsible for stroke. In patients with COVID-19, the imbalanced response among T helper cell subtypes could precipitate a cytokine storm syndrome (36). Our results indicated that inflammatory markers were markedly elevated in most critically ill patients with COVID-19. Viral infection and the subsequent immune responses could cause lymphocytic infiltration, necrosis of smooth muscle, endothelial dysfunction and occlusion of large vessel walls. Furthermore, angiotensin-converting enzyme 2 (ACE2), which is a cardio-cerebral vascular protection factor, has been identified as the functional target for SARS-CoV-2 (47). The virus could interact with ACE2 expressed in the endothelium and further attack the vascular system. For patients with underlying cardiovascular disease, SARS-CoV-2 infection can further damage vessel walls through reduction of cerebral blood flow, decreases in oxygen supply and destabilization of arterial plaque. However, we have not been able to demonstrate an association of COVID-19 with vessel wall damage.

Third, there is evidence suggesting that patients with myocardial injury have an increased risk of occurrence of future cerebrovascular events compared with those without myocardial injury (48). Myocardial injury, evidenced by elevated cardiac biomarkers or new electrocardiogram or echocardiographic abnormalities, was recognized among early COVID-19 cases in China (8). In our cohort, more than 50% of critically ill patients had elevated high-sensitivity troponin I and NT-proBNP levels. Myoglobulin level was significantly higher in patients with AIS. Although no statistically significant difference was found because of the small number of stroke patients, higher levels of both cTnI and NT-proBNP levels were observed in patients with COVID-19 with incident ischemic stroke than in those without this event. Furthermore, 18% of the patients were complicated with atrial fibrillation. We speculated that myocardial injury and the concomitant atrial fibrillation may further contribute to the occurrence of ischemic stroke.

Finally, a higher prevalence of anemia was also observed in patients with ischemic stroke in our cohort. Anemia is associated with an increased risk of cerebrovascular events because of decreased tissue oxygen delivery as well as a hyperkinetic state, which disturbs endothelial function and may lead to thrombus formation. Our results indicated that correcting anemia in critically ill patients with COVID-19 might have positive effect on stroke prevention.

In addition to CNS involvement, neuromuscular manifestations, including persistent flaccid paralysis and rhabdomyolysis, were also observed in patients with severe coronavirus infection, which have previously been reported for SARS and MERS (37–39, 49). In a case series study consisting of four patients with SARS who had concomitant neuromuscular problems, the neuromuscular involvement was considered to be

critical-illness polyneuropathy or myopathy (50). Significantly elevated inflammatory cytokine levels and immune activation may play a role in neuromuscular injury. We noticed that the prevalence of flaccid paralysis was higher in patient with AIS (66.7%), compared with those without AIS (1.3%). Possible explanations included the longer time at ICU and the more serious clinical conditions for stroke patients. On the other hand, the mortality rate of non-AIS group was high, which limited our ability to withdraw sedatives and determine whether flaccid paralysis exists in these patients. Further electrophysiological and pathological studies are necessary to determine the relationship between COVID-19 and neuromuscular involvement.

Our study has several limitations. First, only 86 patients with confirmed COVID-19 were included in the present analysis, and a large, multi-center study is warranted to verify the neurological manifestations of COVID-19. Second, most of the critically ill patients in our ICU were receiving intensive sedation because of invasive MV, which may have resulted in underestimation of the incidence of neurological complications. Third, some specific information regarding neurological complications, such as brain MRI, imaging evaluations of large intracranial arteries, electrophysiological examinations and CSF profiles were not available. The data were incomplete because of the highly infectious nature of COVID-19, the serious clinical conditions of critically ill patients and the limited conditions for examination in the isolation ward. Thus, we restricted examinations to only those that could have a direct effect on patient management. Fourth, the relatively small number of stroke patients limited the accurate comparisons between patients with AIS and those without. Finally, some patients with neurological complications were still hospitalized at the time of analysis, which may limit the assessment of the ultimate clinical outcome and natural course of the disease, and further long-term observation is needed.

CONCLUSIONS

Stroke, delirium and neuromuscular diseases are major neurological complications of COVID-19. Neurological manifestations might be underestimated in critically ill patients with COVID-19, and physicians should pay close attention to neurological complications. Patients with COVID-19 complicated with ischemic stroke might benefit from anticoagulant therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Peking Union Medical College Hospital (No. S-K1151). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HG and SZ supervised, coordinated and designed the study. SF and FH drafted the manuscript. SF, MX, PX, XB, HC, HZhang, XD, HZhao, JZ, XS, WJ, CW, WC, FG, RT, PG, WW, JM, DZ, and YC collected the clinical data. SF, MX, FH, and JX participated in the interpretation of the data. SF and TG participated in statistical analysis. DW, ZL, XZ, JW, YQ, TL, YX, YL, XY, YZ, BP, and LC supervised and coordinated the study. All authors read and approved the final manuscript.

FUNDING

This work was supported by the National Key Research and Development Program of China, Grant No. 2016YFC0901500.

ACKNOWLEDGMENTS

The authors thank the patients and people in Wuhan.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00806/full#supplementary-material

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
4. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation.* (2020) 141:1648–55. doi: 10.1161/CIRCULATIONAHA.120.046941
5. World Health Organization. *WHO Director-General's Opening Remarks at the Media Briefing on COVID-19.* (2020). Available online at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed April 2, 2020).
6. World Health Organization. *Coronavirus Disease (COVID-2019) Situation Reports.* (2020). Available online at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_6 (accessed April 2, 2020).
7. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut.* (2020) 69:1002–9. doi: 10.1136/gutjnl-2020-320926

8. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* (2020) 27:e201017. doi: 10.1001/jamacardio.2020.1017
9. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* (2020) 8:475–81. doi: 10.1016/S2213-2600(20)30079-5
10. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ.* (2020) 368:m606. doi: 10.1136/bmj.m606
11. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
12. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* (2020) 368:m1091. doi: 10.1136/bmj.m1091
13. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
14. Eliezer M, Hautefort C, Hamel A L, Verillaud B, Herman P, Houdart E, et al. Sudden and complete olfactory loss function as a possible symptom of COVID-19. *JAMA Otolaryngol Head Neck Surg.* (2020). doi: 10.1001/jamaoto.2020.0832. [Epub ahead of print].
15. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology.* (2020). doi: 10.1148/radiol.2020201187. [Epub ahead of print].
16. Sun T, Guan J. Novel coronavirus and central nervous system. *Eur J Neurol.* (2020). doi: 10.1111/ene.14227. [Epub ahead of print].
17. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* (2020) 19:383–4. doi: 10.1016/S1474-4422(20)30109-5
18. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis.* (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
19. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. *Stroke.* (2020) 51:e124–7. doi: 10.1161/STROKEAHA.120.030153
20. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol.* (2020) 20:1–8. doi: 10.1007/s00415-020-09885-2
21. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiaty.* (2020). doi: 10.1136/jnnp-2020-323586. [Epub ahead of print].
22. Tunç A, Ünlübaş Y, Alemdar M, Akyüz E. Coexistence of Covid-19 and acute ischemic stroke report of four cases. *J Clin Neurosci.* (2020) 77:227–9. doi: 10.1016/j.jocn.2020.05.018
23. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med.* (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
24. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787
25. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* (2020). doi: 10.1001/jamaneurol.2020.2065. [Epub ahead of print].
26. National Health Commission of the People's Republic of China. *Chinese Management Guideline for COVID-19* (version 7.0). Available online at: http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml (accessed April 2, 2020).
27. Fan S, Ren H, Wei Y, Mao C, Ma Z, Zhang L, et al. Next-generation sequencing of the cerebrospinal fluid in the diagnosis of neurobrucellosis. *Int J Infect Dis.* (2018) 67:20–4. doi: 10.1016/j.ijid.2017.11.028
28. Guan H, Shen A, Lv X, Yang X, Ren H, Zhao Y, et al. Detection of virus in CSF from the cases with meningoencephalitis by next-generation sequencing. *J Neurovirol.* (2016) 22:240–5. doi: 10.1007/s13365-015-0390-7
29. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med.* (2020) 382:e38. doi: 10.1056/NEJMc2007575
30. Morfopoulou S, Brown JR, Davies EG, Anderson G, Virasami A, Qasim W, et al. Human coronavirus OC43 associated with fatal encephalitis. *N Engl J Med.* (2016) 375:497–8. doi: 10.1056/NEJMc1509458
31. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus—2 (SARS-CoV-2). *J Med Virol.* (2020) 92:699–702. doi: 10.1002/jmv.25915
32. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* (2020) 8:420–2. doi: 10.1016/S2213-2600(20)30076-X
33. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological Features of Covid-19. *N Engl J Med.* (2020). doi: 10.1056/NEJMc2019373. [Epub ahead of print].
34. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. *Radiology.* (2020). doi: 10.1148/radiol.2020201697. [Epub ahead of print].
35. Mahammedi A, Saba L, Vagal A, Leali M, Rossi A, Gaskill M, et al. Imaging in neurological disease of hospitalized COVID-19 Patients: an italian multicenter retrospective observational study. *Radiology.* (2020). doi: 10.1148/radiol.2020201933. [Epub ahead of print].
36. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* (2020) 87:18–22. doi: 10.1016/j.bbi.2020.03.031
37. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological complications during treatment of middle east respiratory syndrome. *J Clin Neurol.* (2017) 13:227–33. doi: 10.3988/jcn.2017.13.3.227
38. Algahtani H, Subahi A, Shirah B. Neurological complications of middle east respiratory syndrome coronavirus: a report of two cases and review of the literature. *Case Rep Neurol Med.* (2016) 2016:3502683. doi: 10.1155/2016/3502683
39. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan.* (2005) 14:113–9.
40. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA.* (2020) 323:1612–4. doi: 10.1001/jama.2020.4326
41. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: A retrospective observational study. *Am J Respir Crit Care Med.* (2020) 201:1372–9. doi: 10.1164/rccm.202003-0543OC
42. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* (2020) 18:844–7. doi: 10.1111/jth.14768
43. Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. *Lupus.* (2018) 27:572–83. doi: 10.1177/0961203317731532
44. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* (2020) 18:1094–9. doi: 10.1111/jth.14817
45. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.013

46. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of coronavirus disease 2019. *Crit Care Med.* (2020). doi: 10.1097/CCM.0000000000004458. [Epub ahead of print].
47. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* (2020) 11:995–8. doi: 10.1021/acschemneuro.0c00122
48. Rydén L, Roos A, Holzmann MJ. chronic myocardial injury and risk for stroke. *Am J Med.* (2019) 132:833–9. doi: 10.1016/j.amjmed.2019.01.027
49. Stainsby B, Howitt S, Porr J. Neuromusculoskeletal disorders following SARS: a case series. *J Can Chiropr Assoc.* (2011) 55:32–9.
50. Tsai LK, Hsieh ST, Chao CC, Chen YC, Lin YH, Chang SC, et al. Neuromuscular disorders in severe acute respiratory syndrome. *Arch Neurol.* (2004) 61:1669–73. doi: 10.1001/archneur.61.11.1669

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 28 July 2020
doi: 10.3389/fneur.2020.00780

Stroke Care Services in Singapore During COVID-19 Pandemic—A National Perspective

*Narayanaswamy Venketasubramanian**

Raffles Neuroscience Centre, Raffles Hospital, Singapore, Singapore

Stroke is a significant cause of admission to Singapore's acute care hospitals. Because of the current COVID-19 pandemic, there have been major changes in the stroke care system. On calling for the public ambulance, those suspected to have COVID-19 infection are taken to the National Center for Infectious Diseases. Otherwise, on arrival at the emergency room, all cases with fever or respiratory symptoms [COVID-19 suspect patients (CSPs)] are evaluated separately by staff wearing full personal protective equipment (PPE). Triage is not delayed. CSPs needing hyperacute therapies are sent to a specially prepared scanner; if not, imaging is deferred to the latter part of the day. CSPs are managed in isolation rooms, and sent to the acute stroke unit (ASU) if two consecutive COVID-19 swabs are negative. Investigation and rehabilitation are done within the room. ASU rounds are attended by essential members, communication by electronic means. Multidisciplinary team rounds have largely ceased, and discussions are via electronic platforms. Patient transfer and staff movement are minimized. All hospital staff wear face-masks, infection control is strictly enforced. Visitors are not allowed; staff make daily calls to update families. Mild stroke patients may be sent home with rehabilitation advice. Out-patient rehabilitation centers are closed. Patients return for out-patient visits only if needed; medications are sent to their home, and nurses make essential home visits. Stroke support and rehabilitation activities have started on-line. Continuing medical education activities are mainly by webinars. Stroke research has been severely hampered. Overall, evidence-based stroke care is delivered in a re-organized manner, with a clear eye on infection control.

Keywords: stroke, services, COVID-19, Singapore, stroke unit

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Po-Yu Lin,
National Cheng Kung University Hospital, Taiwan
Chih-Hao Chen,
National Taiwan University Hospital, Taiwan

***Correspondence:**
Narayanaswamy Venketasubramanian
drnvramani@gmail.com

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *24 May 2020*
Accepted: *25 June 2020*
Published: *28 July 2020*

Citation:
Venketasubramanian N (2020) Stroke Care Services in Singapore During COVID-19 Pandemic—A National Perspective. Front. Neurol. 11:780. doi: 10.3389/fneur.2020.00780

INTRODUCTION

The current COVID-19 pandemic has had a significant impact on global economic, political, social, emotional, and medical health. Stroke is a major cause of death and disability throughout the world (1), especially in Asia (2). Stroke occurs in 5.9% of COVID-19 patients, largely ischemic, but with a few hemorrhagic strokes (3, 4). Among patients with COVID-19, cerebrovascular disease is associated with increased mortality and severe COVID-19 infection (5); patients with prior stroke have a more severe COVID-19 infection (6, 7). While there is current interest in hypercoagulable states, vasculitis, and cardioembolism from cardiomyopathy as the mechanism for the stroke, others including large artery atherosclerosis, small artery disease, and other cardioembolic sources such as atrial fibrillation should not be forgotten (8, 9). There has been a noticeable drop in the number of stroke patients arriving at Emergency Rooms (10–12), or

they come late (12, 13), or when they are more severe (14). This could be possibly out of fear of entering an environment where there may be COVID-19 patients (15), or due to the reduced availability of ambulances or prompt medical services due to resource diversion to managing COVID-19. All these impact on the provision of evidence-based stroke care that have been proven to reduce death, disability, and stroke recurrence (16).

Singapore is a small tropical island city-state of 5.7 million people situated in the heart of South-East Asia. Stroke is a major cause of death and disability, with an incidence of 1.8/1,000, prevalence of 3.65% among those aged above 50 years, and is among the top 10 causes of hospitalization to our acute care government-funded restructured hospitals that provide heavily subsidized care for more than 95% of acute stroke patients (17).

The number of people diagnosed with COVID-19 in Singapore has been rising (18). The Singapore government quickly established a high-level Multi-Ministry Taskforce on 22 January 2020. It comprises 10 members, all ministers, and is co-chaired by the Minister of Health and the Minister of National Development, with the Deputy Prime Minister as its Advisor. The Taskforce's roles are to direct the national whole-of-government response to the novel coronavirus outbreak; coordinate the community response to protect Singaporeans and stay vigilant against the spread of the disease; and work with the international community to respond to the outbreak. This has resulted in a seamless collaborative response, tapping on the resources of many ministries, so as to swiftly and effectively respond to the infection.

Prior to the COVID-19 pandemic, patients calling for the national ambulance service who were assessed as possibly having a stroke were transported directly to one of three thrombolysis/thrombectomy centers if they met the time windows, or, if not, to the nearest of the seven restructured hospitals or a collaborating private hospital scattered throughout the country. The few patients who arrived via their own transportation means and who met the time windows would receive thrombolysis at whichever center they arrived at, but if they needed thrombectomy, they were then transported to one of the three thrombectomy centers; a small number of thrombectomies were performed at a few private hospitals. Intravenous thrombolysis and thrombectomy services were available 24 h a day. In all hospitals, after emergent triage, patients were, where possible, neuro-imaged while still in the emergency department, before being sent to the acute stroke unit (ASU) of that hospital to be managed by a multidisciplinary stroke team. Those requiring in-patient rehabilitation were transferred to the rehabilitation department or to a nearby community hospital. On discharge, they were followed up by the specialist if necessary, or by the primary care physician. Community-based resources were available including out-patient rehabilitation, home medical and nursing and rehabilitation (19). Stroke support was provided by the Singapore National Stroke Association (SNSA), the oldest national-level support group for stroke survivors and their carers (20, 21).

There have been a few publications with details on how the stroke care has been reorganized due to the COVD-19 situation. Some are hospital-based (22, 23) some only address a specific issue e.g., thrombectomy in that hospital (24). There are no publications on stroke care re-organization at a regional or national level, to my knowledge. In Singapore's response to the COVID-19 epidemic, there were significant changes to the well-coordinated stroke care system, bolstered by lessons learnt from the 2002–2003 SARS-CoV-1 epidemic. This paper aims to present these changes, and what efforts have been made to maintain the provision of high-quality care for those with acute stroke and after discharge, as well as ancillary stroke activities at a national level. The information may be valuable to clinicians, administrators and policy makers involved in stroke care coordination beyond a single hospital, involving hospital and care networks.

PRE-HOSPITAL

At a national level, on calling for the public ambulance, patients are screened for possible COVID-19 infection or if they are at high risk of having COVID-19 (HrCP). The definition includes return from a country with high numbers of COVID-19 patients, in close contact with persons who have COVID-19 (e.g., same household as, cared for, or exposed for more than 30 min within two meters of a COVID-19 patient), or have been served a quarantine, leave of absence or stay-home order due to contact with a COVID-19 patient. These HrCP are taken directly to the National Center for Infectious Diseases (NCID) where they are assessed and isolated for further care. This policy of sending HrCP to the NCID may be reviewed if the center gets overloaded with patients. There have been no noticeable delays in emergency service response times—the public ambulance service is centrally coordinated and has adequate staff and necessary ambulances; the provision for dealing with large numbers of ambulance requests has been in place for many years, probably based on prior experiences with large disasters and tragedies causing mass casualties. All others who meet the criteria for intravenous thrombolysis or thrombectomy are still taken to the three dedicated centers; if they do not meet the criteria, they are taken to any of the restructured hospitals, as before. Ambulance staff wear full PPE at all times. Each ambulance is fully equipped with adequate stores so that this can be achieved. The staff are all trained on how to quickly don their PPE with minimal delay. Patients may still choose to use their own transportation means for getting to their preferred hospital. There is no practice change here.

EMERGENCY ROOM, NEUROIMAGING AND HYPERACUTE THERAPIES (FIGURE 1)

At a hospital level, existing stroke pathways had to be modified in each hospital to meet the needs for strict infection control. In all hospitals, on arrival at the emergency room, all cases are screened again for possible COVID-19 infection and fever; those who are HrCPs are immediately sent to NCID—again this policy may be amended. The NCID is located next to the

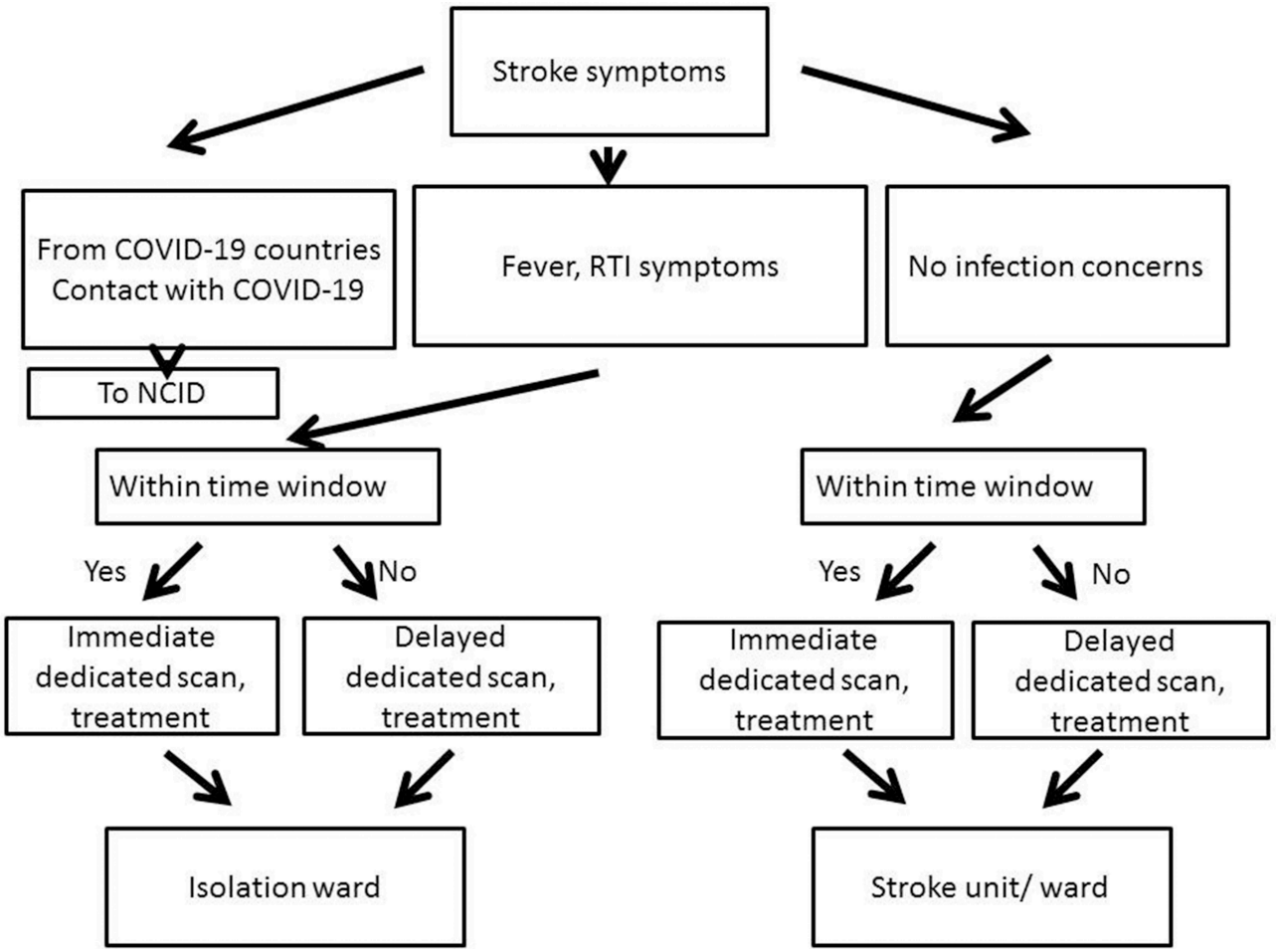


FIGURE 1 | Workflow in the Emergency Department. All patients arriving within the time window for hyperacute therapy are sent for immediate imaging; those who arrive beyond the time window are scanned later at the next available slot, usually later that same day. This applies to both with and without infection concerns (NCID, National Center for Infectious Diseases; RTI, Respiratory Tract Infection).

National Neuroscience Institute (NNI); the neurologist is able to see the stroke patient immediately. NCID has a designated CT scan negative-pressure room that is staffed 24 h a day and used only for COVID-19 patients. By protocol, all thrombectomy patients are prophylactically intubated and sent to a pre-specified operating theater which has negative pressure and a separate ventilation system. They are subsequently managed in the NCID Intensive Care Unit, and later in the NCID wards. The NNI neurologist consults on the patient on a daily basis to collaborate on stroke patient care. It is unlikely that acute stroke therapy was delayed by pre-triage to or subsequent management in NCID (25).

Those with fever or respiratory tract infection symptoms (e.g., cough, breathlessness, sore throat, runny nose) are defined as COVID-19 suspect patients (CSPs) and are evaluated separately in an area set aside for this purpose, with staff wearing PPE, and the patient in a face mask (FM). Triage, assessment for urgent therapies, imaging are performed without delay for all CSPs and non-CSPs as per the hospital stroke protocol. CSPs needing hyperacute therapies are sent to a scan machine in a minimally equipped room prepared for them, and the scanning room is thoroughly disinfected after each patient; if not for hyperacute therapy, the imaging is delayed to the latter part of the day. The three hospitals with the dedicated thrombolysis-thrombectomy services are able to reserve a scan room just for CSPs. Telemedicine is used where possible to reduce staff members entering this area.

Intravenous thrombolysis commences in the scan room, if possible, for all patients. CSPs who need thrombectomy are prepared in a negative-pressure room if available, and aerosol-generating activities are minimized. Non-CSPs are managed in the usual manner. There is a pool of interventional radiologists and trained staff, allowing for multiple thrombectomy teams in each of the three dedicated centers, in order to cater for the eventuality that if one EVT team unfortunately encounters a confirmed COVID-19 case without adequate protection, that whole team may need to be quarantined for many days.

TABLE 1 | Care in isolation room vs. acute stroke unit.

	Isolation room	Acute stroke unit
Patient	Face mask	Face mask +/−
Staff	PPE when entering patient's room Face mask when not in patient's room	Face mask
Blood tests Electrocardiography Telemetry set-up	Bedside	Bedside
Neurosonology	Bedside	Neurosonology laboratory Radiology department
Echocardiography, Holter set-up	Bedside	Cardiac laboratory
Chest x-ray	Bedside	Radiology department
Neuroimaging	Scan performed in dedicated scanner later in the day	Scan performed as schedule allows
Rehabilitation	Bedside	Bedside Rehabilitation center

ACUTE STROKE UNIT/ISOLATION ROOM

CSPs in all hospitals are managed in isolation rooms, usually within a 'fever ward' or if possible within the acute stroke unit (ASU), with staff in PPE, patients in FM. CSPs are swabbed for COVID-19 daily, and only sent out to the ASU for further care if two consecutive swabs are negative—the results of each swab are ready within 24 h; if positive, the patient is transferred to the NCID. Venepunctures, x-rays, neurosonology, echocardiography, arrhythmia monitoring, and rehabilitation are done within the isolation room by dedicated technicians and staff, based on the clinical need, but may be deferred until the patient has been moved to the ASU if it's less urgent. If repeat imaging is needed, the CSP is transported wearing a FM to the specially-prepared scanner, with imaging performed in the latter part of the day whenever possible. Non-CSPs are managed as usual in the ASU, and have their investigations performed in the usual venues e.g., radiology department, neurosonology laboratory, cardiac laboratory (**Table 1**).

ASU daily rounds are attended only by essential members, communication is by electronic means wherever possible, as all hospitals have electronic medical records including review of imaging and laboratory test results. Multidisciplinary team rounds have largely ceased; discussions are held via electronic platforms. Patient transfer and staff movement are minimized, with ward-based teams where possible. All hospital staff wear FM, infection control is strictly enforced especially hand-washing; social distancing enforced as far as is practicable. Care pathways continue to be followed. Non-urgent surgeries have been postponed.

Visitors are not allowed, except perhaps if the patient is in intensive care (one named visitor throughout hospital stay), or if caregiver training is being provided pre-discharge. Doctors and nurses call the patient's family daily with updates, patients are allowed easy access to ward telephones, wi-fi is provided free where possible. Hospital visits by volunteer befrienders from the SNSA have been halted, but communication over the phone may continue.

Rehabilitation is provided as before, but with social distancing, with patients kept at least one meter apart in the gyms. Transfers to rehabilitation units and community hospitals may be delayed by repeat screening for COVID-19 infection; mild strokes may be sent home with rehabilitation advice.

POST-DISCHARGE CARE

Out-patient rehabilitation centers are closed, which may increase functional limitations and hinder recovery (26). Online rehabilitation services are being tried, but elderly patients are usually unable to manage the required steps, further challenged by their physical disabilities. Traditional Chinese Medicine services have ceased. At the patient level, patients return for out-patient visits only if needed; many are fearful. They may still visit their family physicians. Home visits by nurses are performed where necessary (e.g., to change nasogastric tubes, urine catheters and dressings). Doctors call selected patients to determine progress. Medications are sent to the patient's home for a small fee to maintain compliance. Teleconsultation is available but not actively taken up by elderly patients. Some stroke support activities by SNSA have started on-line e.g., exercises, aphasia therapy, but again disabled elderly who are not familiar with the use of online services may not participate.

PROFESSIONAL MATTERS

All healthcare professionals are regularly recertified by their respective professional boards (e.g., Singapore Medical Council for doctors), usually by participating in continuing medical education (CME) activities (27). Professional recertification requirements have not been relaxed—full-practice doctors still need to earn at least 50 points over 2 years. But the availability of CME activities by electronic means via webinars has greatly increased; COVID-19 CMEs are popular and well-attended. Stroke research has been severely hampered as subjects are fearful to come to hospital, movements around the hospital is strictly controlled. But some researchers are taking the opportunity provided by reduced out-patient work to write their previously-shelved papers.

OTHER SOLUTIONS

There have been a number of publications of stroke systems of care during the COVID-19 epidemic. Pre-hospital triage, advance notice by the ambulance to the Emergency Room, adequate training and use of PPE to reduce staff infection, adequate respiratory management en-route, care in appropriately equipped hospitals, and minimizing transfers is important (28, 29). Existing stroke pathways may need to be revised (23), including for endovascular therapy (30, 31). Rehabilitation should not be neglected (32, 33). It can be managed with stream-lined protocols, use of telemedicine/telerehabilitation,

attending to COVID-19-related adverse events (such as fever and respiratory symptoms), enforcing social distancing and adequate sterilization of equipment (34, 35). While trying to provide the best of care to patients, staff safety cannot be neglected (36). A protocol specifically for the management of stroke among patients with COVID-19 may be helpful (22) and needs to be practiced (37). In effect, the entire system of care may needs to be reorganized (38). Guidelines and suggestions for stroke care have been proposed (39–44), but each center had best develop its own or tailor existing guidelines to meet and fit its needs. Consent for research, usually performed face-to-face, may be taken remotely (45), either electronically or by phone; follow-ups may need to be by phone (46). Challenges for stroke care are even greater in developing countries (47).

CONCLUSIONS

The COVID-19 pandemic has posed some challenges to the provision of stroke care in Singapore. There is no overall change in pre-hospital and hyperacute stroke care policies, but CSPs are cared for in isolation; stroke support services and stroke research are majorly affected. Still, evidence-based stroke care is delivered in a re-organized manner, with a clear eye on infection control. The future is likely to see the greater use of electronic communication and telemedicine.

AUTHOR CONTRIBUTION

NV wrote the paper and agrees to be accountable for the content of the work.

REFERENCES

1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:439–58. doi: 10.1016/S1474-4422(18)30499-X
2. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in south, east, and south-east Asia: a review. *J Stroke.* (2017) 19:286–94. doi: 10.5853/jos.2017.00234
3. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol.* (2020). doi: 10.1136/svn-2020-000431
4. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *JAMA Neurol.* (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
5. Pranata R, Huang I, Lim MA, Wahjoepramono PEJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 - systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis.* (2020) 29:104949. doi: 10.1016/j.jstrokecerebrovasdis.2020.104949
6. Larson AS, Savastano L, Kadirvel R, Kallmes DF, Hassan AE, Brinjikji W. COVID-19 and the cerebro-cardiovascular systems: what do we know so far? *J Am Heart Assoc.* (2020) 9:e016793. doi: 10.1161/JAHA.120.016793
7. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019 (COVID-19): a pooled analysis of published literature. *Int J Stroke.* (2020) 15:385–9. doi: 10.1177/1747493020921664
8. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. *Transl Stroke Res.* (2020) 11:322–5. doi: 10.1007/s12975-020-00818-9
9. Venketasubramanian N. Hennerici MG. Stroke in coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome (SARS). *Cerebrovasc Dis.* (2020) 26:1–2. doi: 10.1159/000508370
10. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center: cover title: falling stroke rates during COVID-19. *J Stroke Cerebrovasc Dis.* (2020) 29:104953. doi: 10.1016/j.jstrokecerebrovasdis.2020.104953
11. Morelli N, Rota E, Terracciano C, Immovilli P, Spallazzi M, Colombi D, et al. The baffling case of ischemic stroke disappearance from the casualty department in the COVID-19 Era. *Eur Neurol.* (2020) 1–3. doi: 10.1159/000507666
12. Pop R, Quenardelle V, Hasiu A, Mihoc D, Sellal F, Dugay MH, et al. Impact of the COVID-19 outbreak on acute stroke pathways - insights from the Alsace region in France. *Eur J Neurol.* (2020) 11:1073–9. doi: 10.1111/ene.14316
13. Teo KC, Leung WCY, Wong YK, Liu RKC, Chan AHY, Choi OMY, et al. Delays in stroke onset to hospital arrival time during COVID-19. *Stroke.* (2020) 51:2228–31. doi: 10.1161/STROKEAHA.120.030105
14. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS2-CoV-2 and stroke in a New York healthcare system. *Stroke.* (2020) 51:2002–11. doi: 10.1161/STROKEAHA.120.030335
15. Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke.* (2020) 51:1996–2001. doi: 10.1161/STROKEAHA.120.030225
16. Markus HS, Brainin M. COVID-19 and stroke-a global World Stroke Organization perspective. *Int J Stroke.* (2020) 15:361–4. doi: 10.1177/1747493020923472
17. Venketasubramanian N, Chen CL. Burden of stroke in Singapore. *Int J Stroke.* (2008) 3:51–4. doi: 10.1111/j.1747-4949.2008.00181.x
18. Singapore: Ministry of Health. Available online at: https://covidsitrep.moh.gov.sg/ (accessed May 24, 2020).
19. Venketasubramanian N, Chan BP, Lim E, Hafizah N, Goh KT, Lew YJ, et al. Stroke disease management–a framework for comprehensive stroke care. *Ann Acad Med Singapore.* (2002) 31:452–60.
20. Singapore National Stroke Association. Available online at: http://www.snsa.org.sg/ (accessed May 24, 2020).
21. Venketasubramanian N, Yin A, Lee LB, De Silva DA. Two decades of nation-wide community-based stroke support - The Singapore National Stroke Association. *Int J Stroke.* (2017) 12:297–301. doi: 10.1177/1747493016676620
22. Wang X, Chen Y, Li Z, Wang D, Wang Y. Providing uninterrupted care during COVID-19 pandemic: experience from Beijing Tiantan Hospital. *Stroke Vasc Neurol.* (2020) 5:180–4. doi: 10.1136/svn-2020-000400
23. Baracchini C, Pieroni A, Viaro F, Cianci V, Cattelan AM, Tiberio I, et al. Acute stroke management pathway during Coronavirus-19 pandemic. *Neurol Sci.* (2020) 41:1003–5. doi: 10.1007/s10072-020-04375-9
24. Alqahtani SA, Alnaami I, Alhazzani A. Protected stroke mechanical thrombectomy code during the coronavirus (COVID-19) pandemic: southwestern part of Saudi Arabia stroke unit local protocol. *Cureus.* (2020) 12:e7808. doi: 10.7759/cureus.7808
25. Christopher SYH, Carol TH, Yu-lin W. Challenges in adapting existing hyperacute protocols by a tertiary neuroscience centre for patients with COVID-19 in Singapore. *Int J Cerebrovasc Dis Stroke.* (2020) 3:125. doi: 10.29011/2688-8734.000025
26. Boldrini P, Garcea M, Brichetto G, Reale N, Tonolo S, Falabella V, et al. Living with a disability during the pandemic. "Instant paper from the field" on rehabilitation answers to the COVID-19 emergency. *Eur J Phys Rehabil Med.* (2020). doi: 10.23736/S1973-9087.20.06373-X. [Epub ahead of print].
27. Singapore Medical Council. Available online at: https://www.healthprofessionals.gov.sg/smc/continuing-medical-education-(cme)-for-doctors (accessed May 24, 2020).
28. Goyal M, Ospel JM, Southerland AM, Wira C, Amin-Hanjani S, Fraser JF, et al. AHA/ASAstroke council science subcommittees: emergency neurovascular Care(ENCC), the Telestroke and the Neurovascular Intervention

Committees. Prehospital triage of acute stroke patients during the COVID-19 pandemic. *Stroke*. (2020) 51:2263–7. doi: 10.1161/STROKEAHA.120.030340
29. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) pandemic. *Stroke*. (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.030243
30. Smith MS, Bonomo J, Knight WA 4th, Prestigiacomo CJ, Richards CT, Ramser E, et al. Endovascular therapy for patients with acute ischemic stroke during the COVID-19 pandemic: a proposed algorithm. *Stroke*. (2020) 51:1902–9. doi: 10.1161/STROKEAHA.120.029863
31. Nguyen TN, Abdalkader M, Jovin TG, Nogueira RG, Jadhav AP, Haussen DC, et al. Mechanical thrombectomy in the Era of the COVID-19 pandemic: emergency preparedness for neuroscience teams: a guidance statement from the society of vascular and interventional neurology. *Stroke*. (2020) 51:1896–901. doi: 10.1161/STROKEAHA.120.030629
32. Leocani L, Diserens K, Moccia M, Caltagirone C. Disability through COVID-19 pandemic: neurorehabilitation cannot wait. *Eur J Neurol*. (2020). doi: 10.1111/ene.14320. [Epub ahead of print].
33. Carda S, Invernizzi M, Bavikatte G, Bensmaïl D, Bianchi F, Deltombe T, et al. COVID-19 pandemic. What should PRM specialists do? A clinician's perspective. *Eur J Phys Rehabil Med*. (2020). doi: 10.23736/S1973-9087.20.06317-0. [Epub ahead of print].
34. Bikson M, Hanlon CA, Woods AJ, Gillick BT, Charvet L, Lamm C, et al. Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic. *Brain Stimul*. (2020) 13:1124–49. doi: 10.31234/osf.io/82bmu
35. Chang MC, Boudier-Revéret M. Usefulness of telerehabilitation for stroke patients during the COVID-19 pandemic. *Am J Phys Med Rehabil*. (2020) 99:582. doi: 10.1097/PHM.0000000000001468
36. Leira EC, Russman AN, Biller J, Brown DL, Bushnell CD, Caso V, et al. Preserving stroke care during the COVID-19 pandemic: potential issues and solutions. *Neurology*. (2020). doi: 10.1212/WNL.0000000000009713
37. Kurz MW, Ospel JM, Daehli Kurz K, Goyal M. Improving stroke care in times of the COVID-19 pandemic through simulation: practice your protocols! *Stroke*. (2020) 51:2273–5. doi: 10.1161/STROKEAHA.120.030091
38. Sheth SA, Wu TC, Sharrief A, Ankrom C, Grotta JC, Fisher M, et al. Early Lessons from world war COVID: reinventing our stroke systems of care. *Stroke*. (2020) 51:2268–72. doi: 10.1161/STROKEAHA.120.030154
39. Rodríguez-Pardo J, Fuentes B, Alonso de Leciñana M, Campollo J, Calleja Castaño P, Carneado Ruiz J, et al. en nombre del Grupo Multidisciplinar del Plan Ictus Madrid. Acute stroke care during the COVID-19 pandemic. Ictus Madrid Program recommendations. *Neurologia*. (2020) 35:258–63. doi: 10.1016/j.nrleng.2020.04.007
40. Qureshi AI, Abd-Allah F, Alsenani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. *Int J Stroke*. (2020). doi: 10.1177/1747493020923234. [Epub ahead of print].
41. AHA/ASA Stroke Council Leadership. Temporary emergency guidance to us stroke centers during the coronavirus disease 2019 (COVID-19) pandemic: on behalf of the American Heart Association/American Stroke Association Stroke Council Leadership. *Stroke*. (2020) 51:1910–2. doi: 10.1161/STROKEAHA.120.030023
42. Dafer RM, Osteraas ND, Biller J. Acute stroke care in the coronavirus disease 2019 pandemic. *J Stroke Cerebrovasc Dis*. (2020) 29:10488. doi: 10.1016/j.jstrokecerebrovasdis.2020.104881
43. Zhao J, Rudd A, Liu R. Challenges and potential solutions of stroke care during the coronavirus disease 2019 (COVID-19) outbreak. *Stroke*. (2020) 51:1356–7. doi: 10.1161/STROKEAHA.120.029701
44. Bhatia R, Sylaja PN, Srivastava MVP, Khurana D, Pandian JD, Suri V, et al. Consensus statement - suggested recommendations for acute stroke management during the COVID-19 pandemic: expert group on behalf of the Indian Stroke Association. *Ann Indian Acad Neurol*. (2020) 23(Suppl 1):S15–S23. doi: 10.4103/aian.AIAN_302_20
45. Rai AT, Frei D. A rationale and framework for seeking remote electronic or phone consent approval in endovascular stroke trials - special relevance in the COVID-19 environment and beyond. *J Neurointerv Surg*. (2020) 12:654–7. doi: 10.1136/neurintsurg-2020-016221
46. Meschia JF, Barrett KM, Brown RD Jr, Turan TN, Howard VJ, Voeks JH, et al. The CREST-2 experience with the evolving challenges of COVID-19: a clinical trial in a pandemic. *Neurology*. (2020) 95:29–36. doi: 10.1212/WNL.0000000000009698
47. Sylaja PN, Srivastava MVP, Shah S, Bhatia R, Khurana D, Sharma A, et al. The SARS-CoV-2/COVID-19 pandemic and challenges in stroke care in India. *Ann N Y Acad Sci*. (2020). doi: 10.1111/nyas.14379. [Epub ahead of print].

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 12 August 2020
doi: 10.3389/fneur.2020.00845

Neurological Manifestations of Severe SARS-CoV-2 Infection: Potential Mechanisms and Implications of Individualized Mechanical Ventilation Settings

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu,
Servicio de Neurología, Hospital Clínico San Carlos, Spain

Reviewed by:
Patrick M. Chen,
Massachusetts General Hospital, Harvard Medical School, United States
Cristina Valencia-Sanchez,
Mayo Clinic Arizona, United States

***Correspondence:**
Denise Battaglini
battaglini.denise@gmail.com

† These authors share senior authorship

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: 27 May 2020
Accepted: 07 July 2020
Published: 12 August 2020

Citation:
Battaglini D, Brunetti I, Anania P, Fiaschi P, Zona G, Ball L, Giacobbe DR, Vena A, Bassetti M, Patroniti N, Schenone A, Pelosi P, Rocco PRM and Robba C (2020) Neurological Manifestations of Severe SARS-CoV-2 Infection: Potential Mechanisms and Implications of Individualized Mechanical Ventilation Settings. Front. Neurol. 11:845. doi: 10.3389/fneur.2020.00845

Denise Battaglini[1]*, Iole Brunetti[1], Pasquale Anania[2], Pietro Fiaschi[2,3], Gianluigi Zona[2,3], Lorenzo Ball[1,4], Daniele Roberto Giacobbe[5], Antonio Vena[5], Matteo Bassetti[5], Nicolò Patroniti[1,4], Angelo Schenone[3,6], Paolo Pelosi[1,4], Patricia R. M. Rocco[7,8,9†] and Chiara Robba[1†]

[1] Department of Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy, [2] Department of Neurosurgery, San Martino Policlinico Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy, [3] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy, [4] Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genoa, Italy, [5] Infectious Disease Unit, San Martino Policlinico Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy, [6] Department of Neurology, San Martino Policlinico Hospital, IRCCS for Oncology and Neuroscience, Genoa, Italy, [7] Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [8] Ministry of Science, Technology, and Innovation, Brasília, Brazil, [9] Rio de Janeiro Network on Neuroinflammation, Carlos Chagas Filho Foundation for Supporting Research in the State of Rio de Janeiro (FAPERJ), Rio de Janeiro, Brazil

In December 2019, an outbreak of illness caused by a novel coronavirus (2019-nCoV, subsequently renamed SARS-CoV-2) was reported in Wuhan, China. Coronavirus disease 2019 (COVID-19) quickly spread worldwide to become a pandemic. Typical manifestations of COVID-19 include fever, dry cough, fatigue, and respiratory distress. In addition, both the central and peripheral nervous system can be affected by SARS-CoV-2 infection. These neurological changes may be caused by viral neurotropism, by a hyperinflammatory and hypercoagulative state, or even by mechanical ventilation-associated impairment. Hypoxia, endothelial cell damage, and the different impacts of different ventilatory strategies may all lead to increased stress and strain, potentially exacerbating the inflammatory response and leading to a complex interaction between the lungs and the brain. To date, no studies have taken into consideration the possible secondary effect of mechanical ventilation on brain recovery and outcomes. The aim of our review is to provide an updated overview of the potential pathogenic mechanisms of neurological manifestations in COVID-19, discuss the physiological issues related to brain-lung interactions, and propose strategies for optimization of respiratory support in critically ill patients with SARS-CoV-2 pneumonia.

Keywords: COVID-19, SARS-CoV-2, coronavirus, neurological manifestations, neurotropism

INTRODUCTION

In December 2019, an outbreak of disease caused by a novel coronavirus (2019 novel coronavirus, 2019-nCoV) was reported in Wuhan, China (1). On February 11, 2020, the novel virus was renamed the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses, and on the same day, the disease it causes was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) (2). The rising number of daily confirmed cases globally led the WHO to characterize the outbreak as a pandemic on March 11, 2020 (3–8). The typical manifestations of COVID-19 include fever, dry cough, fatigue, and respiratory distress (9). Among patients with symptoms requiring hospitalization, 5–20% require invasive mechanical ventilation and admittance to an intensive care unit (10). COVID-19 is a complex, multisystem disease, perhaps best defined as a multiple organ dysfunction syndrome (MODS-CoV-2) (11) which includes neurologic manifestations (9). In a recent meta-analysis (12), headache was identified as one of the most common neurologic symptoms in the early stages of the disease (occurring in 3.5 to 34% of patients), followed by dizziness. More specific neurological manifestations were also observed, including impairment of smell, taste, or vision; limb weakness; acute cerebrovascular disease; and seizures. The causative mechanisms for neurological involvement in COVID-19 are still under-investigated because of a lack of prospective studies (12, 13). Furthermore, mechanical ventilation, commonly used in the management of COVID-19 patients, can itself induce an inflammatory response, causing distal organ failure. Thus, a complex cross-talk between the lungs and other organs, including the brain (14), may occur during severe COVID-19. Despite the paucity of evidence, there are three key hypotheses for the neurological manifestations of COVID-19 patients (**Figure 1**): (1) viral neurotropism; (2) a hyperinflammatory and hypercoagulable state; and (3) brain–lung crosstalk. While neuroinvasion may be restricted to most severe cases, other cases may be epiphenomena of systemic disease (11). The latter hypothesis is particularly interesting because it may be amenable to adjustment of ventilator settings to minimize lung and brain injury. Within this context, the aim of this manuscript is to provide an updated overview of the potential pathogenic mechanisms of neurological manifestations in COVID-19, discuss the physiological issues related to brain-lung interactions, and propose strategies for optimization of respiratory support in critically ill patients with SARS-CoV-2 pneumonia.

Abbreviations: ACE2, angiotensin-converting enzyme-2; ANE, acute necrotizing encephalopathy; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; BBB, blood brain-barrier; CA, Ammon's horn; CD, cluster of differentiation; CI, confidence interval; CNS, central nervous system; CoV, coronavirus; COVID-19, coronavirus disease 2019; CT, computed tomography; CXCR, chemokine receptor; DIC, disseminated intravascular coagulation; DO_2, oxygen delivery; DPP4, dipeptidyl dipeptidase-4; ECMO, extracorporeal membrane oxygenation; FiO_2 fraction of inspired oxygen; FOX, forkhead box; HLH, hemophagocytic lymphohistiocytosis; ICAM, intracellular adhesion molecule; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IFN, interferon; MERS, Middle East respiratory syndrome; MHV, mouse hepatitis virus; MRI, magnetic resonance images; nCoV, novel coronavirus; OR, odds ratio; $PaCO_2$, partial pressure of carbon dioxide; PaO_2 partial pressure of oxygen; $PbtO_2$ brain tissue oxygenation tension; PCR, polymerase chain reaction; PEEP, positive end-expiratory pressure; PRES posterior reversible encephalopathy syndrome; RM, recruitment maneuvers; RNA, ribonucleic acid; SARS, severe acute respiratory syndrome; TLRs, toll-like receptor; TMPRSS2 transmembrane serine protease 2; TNF, tumor necrosis factor; WHO, World Health Organization.

VIRAL NEUROTROPISM

Pathogenesis

The coronaviruses are large, enveloped, non-segmented, single-stranded, positive-sense ribonucleic acid (RNA) viruses. Seven coronaviruses in two genera have been identified as possibly infectious in humans, of which SARS-CoV-1, Middle East respiratory syndrome (MERS-CoV), and SARS-CoV-2 can cause life-threatening respiratory failure (15, 16). Genomic and structural analyses have shown that SARS-CoV-1 binds to angiotensin-converting enzyme-2 (ACE2) receptors and transmembrane serine protease-2 (TMPRSS2) (17). MERS-CoV instead binds to dipeptidyl dipeptidase-4 (DPP4) receptors, which are mainly present on the epithelium of the lower respiratory tract, small intestine, liver, kidneys, and immune cells (18). ACE2 receptors are widely distributed in the lung alveolar epithelial cells, nasopharyngeal and oral mucosa, endothelium and vascular smooth muscle cells in the brain, vascular endothelium and smooth muscle cells of the liver, vascular and red pulp sinus endothelium of the spleen, and cytoplasm of distal tubules and collecting ducts in the kidney (17). However, binding to ACE2 and DPP4 receptors alone is not enough to make host cells susceptible to infection. Some human epithelial cells which overexpress these receptors are not infected, whereas other cells with lower expression of these receptors, such as central nervous system (CNS) cells, have shown SARS-CoV-1 and MERS-CoV infection (19). As with the other coronaviruses, the classical route of SARS-CoV-2 infection is the passage of infected droplets through the upper airway and binding to ACE2 receptors. Ocular transmission has also been proposed as a possible alternative route for SARS-CoV-2 infection, since the aqueous humor contains ACE2 receptors (20). SARS-CoV-2 enters the host cell by endocytosis. After viral uncoating, the virion is released, followed by translation, replication, virion assembly, and new virion coating, a process which induces programmed cell death (21). A cascade of cerebral involvement in SARS-CoV-2 infection has been proposed by many authors (22–24). Coronaviruses may pass from the systemic to the cerebral circulation by several routes. Trans-synaptic passage through infected neurons via the olfactory bulb has been demonstrated with other coronaviruses, which are able to invade peripheral nerve terminals and spread in a retrograde fashion through synapses into the CNS; neuroimaging evidence from COVID-19 patients suggests SARS-CoV-2 can do so as well. SARS-CoV-2 can also spread across the blood–brain barrier (BBB) by two distinct mechanisms: (a) leukocyte migration across the BBB (named the *Trojan horse mechanism*); and (b) sluggish movement of blood within the microcirculation, crossing the BBB by binding to endothelial

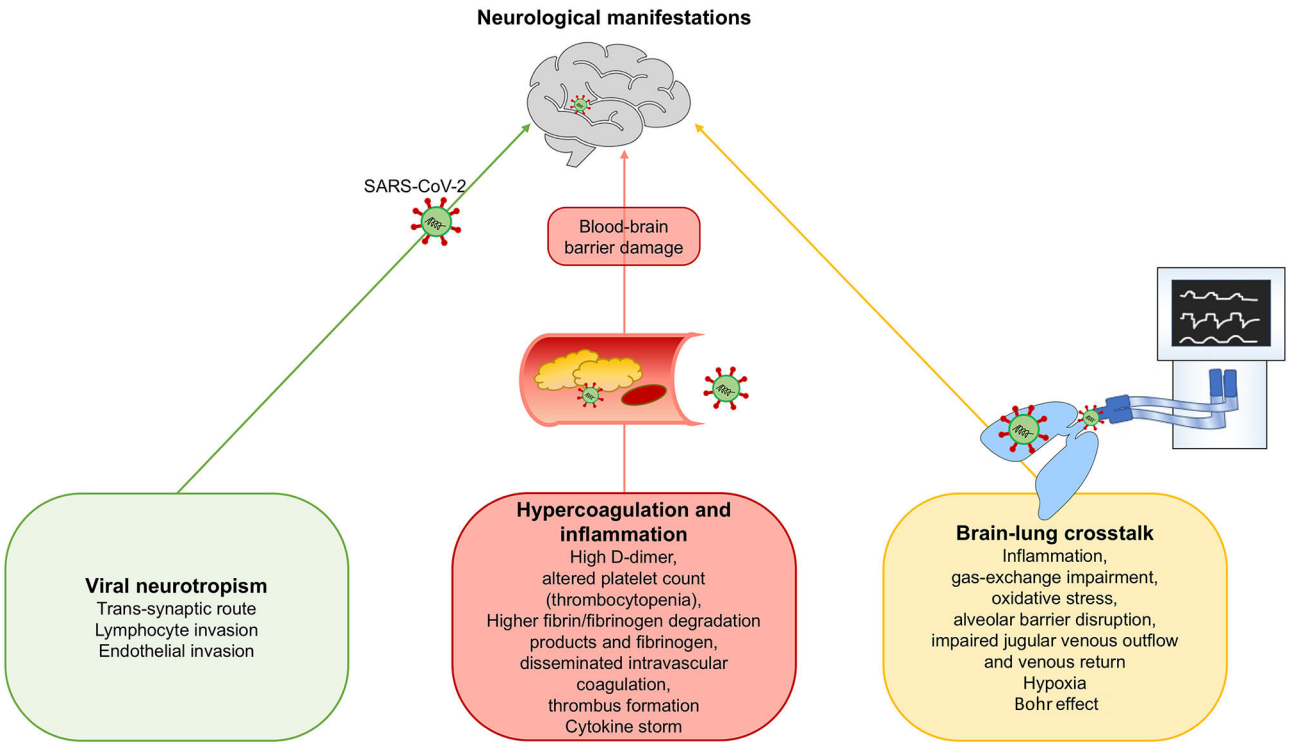


FIGURE 1 | Proposed mechanisms for neurological manifestations in SARS-CoV-2 infection. We hypothesize three possible mechanisms for neurological manifestations in SARS-CoV-2 infection: (1) Viral neurotropism; (2) Hypercoagulation and inflammation, and (3) Brain-lung crosstalk.

cells (17). Infected leukocytes can bind to ACE2 receptors and cross the BBB, migrating into the CNS (22–26). Expression of ACE2 receptors has been demonstrated in neurons, astrocytes, oligodendrocytes, the motor cortex, the cytoplasm of neurons, and sympathetic pathways (22). Binding to ACE2 produces vasodilatation and counteracts inflammation, while binding to the Mas receptor exerts neuroprotective and cardioprotective effects (27).

Experimental and Clinical Evidence

Trans-synaptic Spread

Literature from the previous SARS epidemic revealed that the virus primarily infects pneumocytes, but can also enter neuronal cells (28). Trans-synaptic spread has been demonstrated in experimental studies; in SARS-CoV-1 infected mice, extensive virus replication in brain cells was mediated by cerebral invasion through the olfactory epithelium (29). This has been also confirmed by another murine study with human coronavirus OC43 (30). In the clinical setting, SARS-CoV-1 genome sequences were detected in brain cells of infected patients by electron microscopy, real time-polymerase chain reaction (PCR), and light microscopy. Among brain areas, the thalami, cerebellum, white matter, and brainstem were primarily affected, with edema and scattered red degeneration of neurons (31). SARS-CoV-1 has been also detected in cerebrospinal fluid, probably reflecting spread through the BBB (29). Coronaviruses can also spread to the medullary cardiorespiratory center, which may at least partially account for the acute respiratory failure of SARS (32). Although previous literature on other coronaviruses clearly suggests neuronal involvement, data specific to SARS-CoV-2 are still limited; magnetic resonance imaging (MRI), autopsy findings, and brain biopsies should unravel the mystery. As with other coronaviruses, SARS-CoV-2 could potentially enter the nervous system through the olfactory bulb and spread to specific brain areas (33). This trans-synaptic spread theory is corroborated by multiple retrospective reports of anosmia and ageusia in COVID-19 patients (9, 29, 34). Most recently, anosmia and hyposmia were identified in 5.6% of 214 hospitalized patients (9), while 33.9% of 20 patients who completed a questionnaire experienced either olfactory or taste disorder and 18.6% experienced both (35). Smell and taste disorder were detected in 39.2% of 79 patients who were positive for COVID-19 PCR vs. 12.5% of 40 controls (adjusted odds ratio [OR] 21.4, confidence interval [CI] 95% 2.77–165.4, $p = 0.003$). Of these, 25 (80.6%) reported smell disorders and 28 (90.3%) reported taste disorders (34). A single center study on 1,480 patients with influenza-like symptoms revealed that smell and taste loss occurred in the majority of patients who tested positive for SARS-CoV-2, was significantly associated with COVID-19 ($p < 0.001$), and resolved after illness remission (36). A multicenter European study of 417 COVID-19 patients identified olfactory and gustatory dysfunctions as prevalent, early symptoms, which can indeed be used to identify SARS-CoV-2 infection (37). Finally, this hypothesis was

confirmed *in vivo* by MRI evidence of cortical hyperintensity in the right gyrus rectus and olfactory bulb, suggesting viral invasion of the brain—although not all the patients who develop olfactory dysfunction present with abnormal brain imaging (38)—and in post-mortem brain MRI studies, which found olfactory bulb and tract impairment without brainstem involvement (39). This provides very compelling evidence of SARS-CoV-2 entry via the olfactory tract and subsequent spread to specific brain areas, although limited to isolated cases (2).

Endothelial and Lymphocyte Invasion

Electron microscopy studies have recently demonstrated that SARS-CoV-2 can cross the BBB by binding to endothelial cells (40). SARS-CoV-2 neurotropism was further confirmed in autopsies of infected patients who died of cardiorespiratory failure (>65 years old) and massive intracranial hemorrhage (younger). In both groups, all patients showed lymphocytic pan-encephalitis and meningitis (41), confirming the neurotropic hypothesis, perhaps guided by leukocyte invasion.

Irrespective of mechanism, neurotropism is thus clearly demonstrated. When brain involvement does occur, the presence and persistence of human coronaviruses in the CNS, as occurs in mice, can determine long-term neurological sequelae. Mice surviving acute coronaviral encephalitis exhibited long-term sequelae associated with decreased activity in an open field test and a reduced hippocampus, with neuronal loss in the Ammon's horn (CA)1 and CA3 areas (42). It has also been hypothesized that human coronaviruses may play a triggering role in long-term neurological conditions, such as multiple sclerosis. Although research has not led yet to a direct link to any specific virus, an association of coronaviruses with multiple sclerosis has been suggested (43, 44). A significantly higher prevalence of human CoV-OC43 was observed in the brains of multiple sclerosis patients than in controls (45). Moreover, during infection by human CoV-OC43 and CoV-229E, an autoreactive T-cell response directed to both viral and myelin antigens was discovered in multiple sclerosis patients, but not in controls (46, 47). This underlines the possibility that long-term infection of the CNS by human coronaviruses may play a role in the onset of multiple sclerosis-like demyelinating lesions, as reported during the COVID-19 pandemic (48). Evidence of CNS infection by SARS-CoV-2 has been associated with poor prognosis, worse clinical condition, and sudden death in COVID-19 patients (9). However, there is limited evidence to confirm this hypothesis, since the majority of observed cerebrospinal fluid (CSF) samples have been negative for SARS-CoV-2 infection (49, 50). This makes it difficult to confirm that neurotropism could be the main mechanism of neurological complications in COVID-19.

HYPER-INFLAMMATION AND HYPERCOAGULABILITY

Pathogenesis

SARS-CoV-2 may pass across the respiratory epithelium and spread from the alveolar-epithelial barrier to the systemic circulation, enhancing the local inflammatory response (51) and producing a systemic "cytokine storm," affecting other organs such as the brain (52). Furthermore, inflammation is one of the main mechanisms that trigger the coagulation cascade and promote hypercoagulability. In severe SARS-CoV-2 infection, recent findings suggest a key role of endothelial cells (ECs) in vascular dysfunction, immunothrombosis, and inflammation (53). Histopathological studies have provided evidence of direct viral infection of ECs, diffuse endotheliitis, and micro- and macrovascular thrombosis, both in the venous and arterial circulations. The pro-inflammatory cytokine storm, with elevated levels of interleukin-6 (IL-6), IL-2 receptor, and tumor necrosis factor (TNF)-α, could also participate in endothelial dysfunction and leukocyte recruitment in the microvasculature. COVID-19-induced endotheliitis may explain the systemic impaired microcirculatory function in different organs observed in COVID-19 patients. Next, we will discuss the role of hyperinflammation and hypercoagulability as potential mechanisms for secondary brain involvement in COVID-19.

On the immune side, after antigen binding to the host receptor, monocytes are activated, with the release of pro-inflammatory cytokines (such as MMP9, which increases BBB permeability, and TNF-α, which that increases expression of intracellular adhesion molecule [ICAM]-1 on endothelial cells). Infected and activated monocytes cross the damaged BBB, inducing the local release of pro-inflammatory cytokines and resulting in oligodendrocyte and neuronal damage. Coronavirus primarily infects monocyte-derived macrophages, which produce chemokines and then present CoV antigens to T-cells and other pro-inflammatory cells (51). Astrocytes may also release other chemokines that will recruit other leukocytes. This hyperactive neuroinflammatory response could induce immune-mediated neuropathology (2, 51). On the coagulation side, increased consumption and decreased production of platelets in the damaged lungs are all factors that can contribute to thrombocytopenia (54). As a consequence, it seems reasonable that infected patients are more prone to developing posttraumatic or spontaneous intracranial hemorrhage (55), as well as these alterations suggest a trend of SARS-CoV-2 infection to induce consumption coagulopathy, which, if unchecked, could lead to disseminated intravascular coagulation (DIC) and an unfavorable clinical course (56). In fact, viral infections may lead to sepsis, which represents the most common cause of DIC. DIC is determined by the release of injury-related cytokines, which activate monocytes and endothelial cells, leading to overexpression of tissue factors and secretion of von Willebrand factor. The presence of free thrombin in the circulation can activate platelets, stimulating fibrinolysis (57).

Experimental and Clinical Evidence

Inflammation

Inflammatory involvement was recently confirmed by an experimental murine model of murine coronavirus (MHV-A59), which can enter the brain via intranasal or intracerebral exposure and whose virulence is mediated by cytokine secretion.

In one experimental study, injection of mouse hepatitis virus (MHV), a member of the *Coronaviridae* family, into the murine CNS demonstrated that coronavirus infection elicits both innate and adaptive immune responses (58). The genomic RNA is then translated, replicated, assembled, and coated for future release and infection of other cells. As replication increases with the aid of macrophages, microglia, astrocytes, and oligodendrocytes, the virus can spread from the ependyma to the brain parenchyma. By this point, inflammation is established, and is followed by BBB damage and enhanced innate and adaptive immune responses (58). Immunofluorescence and immunohistochemistry revealed that microglia and astrocytes are involved in activation of the innate immune system of the brain, releasing cytokines that are involved in the pathogenesis of encephalitis (59). A study on human autopsy specimens showed that SARS-CoV-1 was able to infect brain tissue, with necrosis of neuronal cells and gliocyte hyperplasia. These studies suggested that neuronal involvement in SARS was characterized by a massive inflammatory process, especially with enhancement of monokine expression in gliocytes induced by interferon (IFN)-γ (60). An experimental study on bronchoalveolar lavage fluid (BALF) of COVID-19 patients identified that SARS-CoV-2 infection of the airway leads to pro-inflammatory cytokine and chemokine release. This enhances the interaction with receptors expressed on thoracic sensory neurons of the lung, thus causing the release of neuropeptides, followed by vasodilation, immune-cell recruitment, neurogenic inflammation, and potential pain. This mechanism could be theoretically involved in the hyperinflammatory state, which first involves the lung and then extends to the nervous system, with sensory neurons thus potentially acting as drivers of neurogenic pulmonary dysfunction (61). In a retrospective cohort cited above, severe patients were more likely to exhibit impaired consciousness and acute cerebrovascular disease than non-severe patients ($p < 0.001$ and $p < 0.05$, respectively). Severe patients also showed a more florid inflammatory response (higher white blood cell and neutrophil counts, lower lymphocyte counts, higher C-reactive protein levels) and higher D-dimer levels than non-severe patients, and developed more extensive multiple organ involvement (9). Acute necrotizing encephalopathy (ANE) has been related to a brain cytokine storm, which results in BBB disruption (62). ANE has been previously reported as a rare complication of viral infections such as influenza (62). Radiological findings from computed tomography (CT) scans and MRI in COVID-19 have been recently published (62). ANE was also identified in a patient with aplastic anemia (63). Non-contrast CT scan demonstrated bilateral symmetric hypoattenuation in the medial thalami with negative CT angiogram and venogram findings, while MRI showed bilateral hemorrhagic rims in the thalami, sub-insular regions, and medial temporal lobes. ANE usually presents a bilateral distribution, with predominance of lesions in the thalami, brainstem, cerebral white matter and cerebellum, which is consistent with the cerebral insults observed in COVID-19 (62). Studies have concluded that men and women might show different responses to COVID-19. Women seem to be less susceptible to viral infections than men overall. The presence of two X chromosomes influences immune regulatory genes to blunt the inflammatory response and increase levels of antibodies and cluster of differentiation (CD)4^+T-cells, and consequently, promoting the expression of cytokines. Moreover, the X chromosome acts on other proteins and genes, including forkhead box (FOX)P-3, toll like receptor (TLR)-8, CD40L, and chemokine receptor (CXCR)3. Nevertheless, the increased susceptibility of women to autoimmune and auto-inflammatory disorders has to be taken into account (64). Coronavirus infection of the CNS has long provided a model for studying demyelinating diseases such as multiple sclerosis, vaccine design, and novel immunotherapeutic to limit virus spread (58). Hemophagocytic lymphohistiocytosis (HLH) is characterized by a severe dysregulation of T-lymphocytes, natural killer cells, and macrophages within the contest of cytokine storm and multiorgan failure, and represents a clear link between hyperinflammation and hypercoagulability (65). This condition has been described in patients with SARS-CoV-2 (1). HLH patients present with pancytopenia, coagulopathy, hepatic dysfunction, hypertriglyceridemia, and high ferritin levels (66).

Coagulopathy

Neurological damage in COVID-19 patients may also be associated with coagulopathy. In a recent meta-analysis, Lippi et al. showed that low platelet counts are associated with poor prognosis in COVID-19 (67). As reported by Yang et al. (54), hematological changes were common in patients with SARS, most notably including lymphopenia and thrombocytopenia, through different potential mechanisms. Preliminary data from COVID-19 cohorts described a major impairment of blood coagulation and derangement of hemostasis in a large number of patients. Han et al. (68) studied alterations in blood coagulation parameters of patients with SARS-CoV-2 infection, observing lower antithrombin values and higher D-dimer, fibrin/fibrinogen degradation products, and fibrinogen levels. Tang et al. (56) observed high levels of D-dimer and fibrin/fibrinogen degradation products in all non-survivors, confirming activation of coagulation cascade and secondary hyperfibrinolysis. Within this context, the neurological manifestations associated with SARS-CoV-2 may be determined by a hypercoagulable state with high D-dimer levels. The association between ischemic stroke and high D-dimer levels has been previously described in the literature (69, 70). D-dimer elevation reflects ongoing thrombus formation, although it is also an acute-phase reactant that enhances the inflammatory process itself by stimulating monocyte synthesis and release of proinflammatory cytokines (e.g., IL-6), thus contributing to stroke occurrence and progression (71). Coagulopathy and antiphospholipid antibodies were found in patients affected by COVID-19. These findings were associated with both arterial and venous thrombotic events, including cerebral infarcts and limb ischemia. Patients presented with prolonged activated partial thromboplastin and prothrombin times, while two of three patients showed thrombocytopenia (72). Fourteen cases of stroke have been reported out of 214 patients in China (9). Likewise, MRI and CT scans revealed a high prevalence of

stroke in COVID-19 patients (49, 73–75), including in patients younger than 50 years (76). The association between stroke and COVID-19 could be explained also by the fact that both diseases share the same risk factors such as hypertension and diabetes (77, 78), and by the pathological hypercoagulability state that characterize COVID-19. An association between high levels of D-dimer and intracerebral hemorrhage (ICH) was described in a prospective study carried out by Di Castelnuovo et al. (79), although a previous meta-analysis did not show a causal relationship (80). A recent meta-analysis by Zhou et al. (81), which included 13 studies on 891 patients with ICH, concluded that high levels of D-dimer were associated with an elevated risk of ICH. In fact, high D-dimer levels stimulate fibrinolysis with subsequent plasmin generation and microvascular lesions, which might cause the inhibition of hemostasis and a hypo-coagulable state, thus triggering cerebral hemorrhage (79). Moreover, an association between elevated D-dimer levels and large hematoma volume, intraventricular and subarachnoid blood extension, and early mortality has been reported in ICH (82). In summary, although literature is inconclusive concerning the relationship between COVID-19-related hypercoagulability and neurological complications, a possible correlation should be taken into account. Possible mechanisms for activation of intrinsic and extrinsic coagulation pathways, followed by inflammation by SARS-CoV-2 infection are proposed in **Figure 2**.

BRAIN–LUNG CROSSTALK IN COVID-19: AN UNDERESTIMATED MECHANISM

Pathogenesis

Brain–lung crosstalk and its implications for ventilator management are illustrated in **Figure 3**. The respiratory management of COVID-19 shares some characteristics with that of the acute respiratory distress syndrome (ARDS) (83), but different hallmarks must be considered and discussed. COVID-19 pneumonia is as a typical "pulmonary" ARDS (84). In experimental settings (85), "pulmonary" as compared to "extrapulmonary" ARDS is distinguished by increased alveolar–epithelial damage, more neutrophil cell infiltration and fibrinous exudate, increased collagen fibers in the alveoli and interstitium. In clinical studies, different radiological patterns have been identified, with different characteristics and responses to alveolar recruitment. In non-COVID patients, ARDS is characterized by interstitial and alveolar edema homogeneously distributed along the vertical gradient (86, 87), leading to collapse of the most dependent alveoli in the supine position. Regional perfusion follows a gravitational gradient (more perfusion in dependent lung regions), and severe hypoxemia is explained mainly by increased "true shunt" in atelectatic, dependent lung regions. Application of higher levels of positive end-expiratory pressure (PEEP) is associated with alveolar recruitment, improving respiratory mechanics and gas exchange. Thus, in classical ARDS patients, therapeutic maneuvers leading to improvement in gas exchange are associated with better lung aeration. Conversely, COVID-19 pneumonia is characterized by minimal interstitial and alveolar edema, alveolar cellular infiltration and necrosis, with alveolar consolidation and pneumolysis. Regional perfusion follows a non-gravitational gradient (more perfusion in non-dependent lung regions), with hyperperfusion of normally aerated and poorly aerated ("ground glass") tissue, leading to major changes in ventilation-perfusion ratio. Additionally, perfusion in consolidated, dependent lung regions contributes to "true" shunt. Application of higher levels of PEEP does not recruit alveoli; instead, it leads to deterioration of respiratory mechanics, gas exchange, and hemodynamics. Thus, in COVID-19 patients, therapeutic maneuvers leading to improvement in gas-exchange are not associated with improved lung aeration, but rather with redistribution of regional perfusion (88). Interestingly, areas of hypoperfusion may occur in poorly aerated ground-glass areas as well as in non-aerated lung regions. This suggests that some hypoperfusion might be protective against further deterioration of ventilation-perfusion ratio as well as "true" shunt.

Three distinct radiological phenotypes of COVID-19 pneumonia have been described (79). Phenotype 1 is characterized by multiple, focal, overperfused ground-glass opacities, normal or high lung compliance, and severe hypoxemia, probably caused by low ventilation/perfusion and regional shunting. In this case, PEEP should be set according to the lowest driving pressure and/or minimal oxygenation, and inhaled nitric oxide might be useful. Phenotype 2 is characterized by an inhomogeneous and/or asymmetrical distribution of atelectasis, partial alveolar derecruitment, and/or consolidation with peribronchial opacities. In these cases, lateral or prone positioning might be helpful. Finally, phenotype 3 is characterized by patchy, ARDS-like diffuse lung infiltration, with a mixed pattern of overperfused, normally aerated and ground-glass areas as well as hypoperfused, non-aerated lung regions with low compliance. In this setting, mechanical ventilation should follow standard protective ventilatory strategies used for ARDS, with minimal PEEP, prone positioning, and escalation to extracorporeal membrane oxygenation (ECMO) as needed. In all cases, possible microthrombosis and multiorgan failure must be considered.

A correlation between acute lung injury and brain hypoxia has been described by Oddo et al. (89). Reduced systemic oxygenation may affect brain tissue oxygenation, thus leading to secondary brain damage. Measurement of brain tissue oxygenation tension ($PbtO_2$) has confirmed that this parameter is strongly correlated with systemic oxygenation and markers of lung function, including partial pressure of carbon dioxide ($PaCO_2$) and mean arterial pressure. Accordingly, impaired partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio has been associated with lower $PbtO_2$ (89). In another study, patients who underwent an oxygen challenge with 100% FiO_2 showed higher $PbtO_2$ (90). Hypoxic–ischemic damage is also associated with impaired outcome (91). We believe this phenomenon should be considered one of the main mechanisms implicated in neurological dysfunction following SARS-CoV-2 infection. In fact, given these respiratory characteristics, "silent" hypoxia with normal/hypercapnic respiratory failure can occur due to compromised alveolar gas

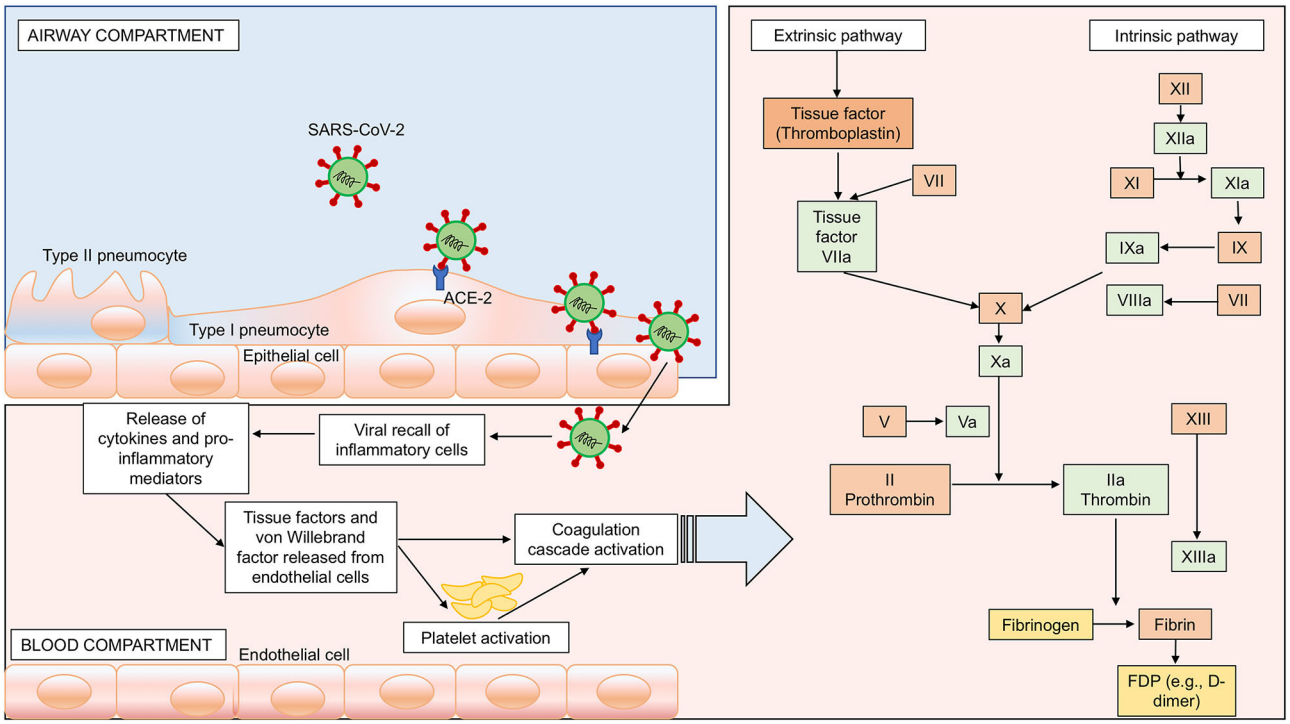


FIGURE 2 | SARS-CoV-2-induced hypercoagulability. Passage of the virus from the airway to the systemic circulation is facilitated by the sluggish movement of blood within the microcirculation and subsequent binding of ACE-2 receptors, expressed on the capillary endothelium, followed by endothelial damage, enhanced inflammation, and hypercoagulability. In this figure, we represent the activation of both intrinsic and extrinsic coagulation pathways as a possible mechanism for hypercoagulability and potential brain damage. Intrinsic pathway: activation of factor (F) XIIa, followed by activation of FXIa and VIII. Extrinsic pathway: activation of FVIIa and tissue factor. Both pathways converge in the common pathway with activation of FXa, FVa, prothrombin into thrombin, fibrinogen into fibrin, and fibrin degradation products (FDP) such as D-dimer.

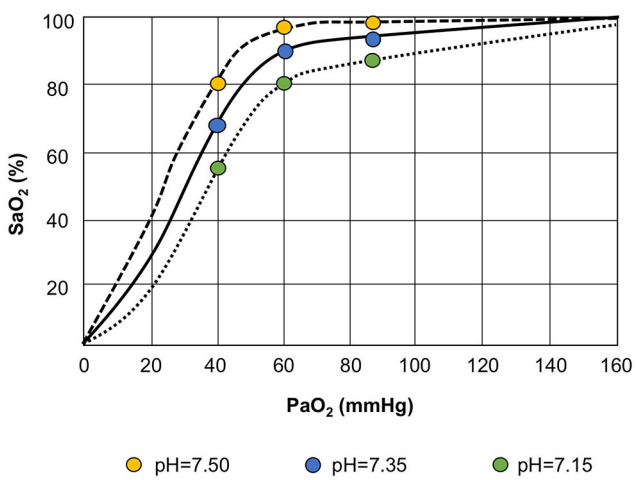


FIGURE 3 | Bohr effect. The oxyhemoglobin dissociation curve is shifted to the left in response to respiratory alkalosis (lower $PaCO_2$ and higher pH), with increased affinity of oxygen for the hemoglobin. Conversely, during respiratory acidosis (higher $PaCO_2$ and lower pH), the alveolar oxygen tension and systemic saturation improve, thus reducing alveolar carbon dioxide tension, as explained by the Bohr effect: the higher the acidity, the more carbon dioxide is eliminated.

exchange (92). Our knowledge concerning hypobaric hypoxia can be derived from aviation medicine (93). High altitude correlates with severe hypoxemia, which triggers the carotid chemoreceptors, activating the respiratory drive; hypocapnia ensues. The oxyhemoglobin dissociation curve shifts to the left in response to respiratory alkalosis and increased affinity of oxygen for hemoglobin, thereby increasing the alveolar oxygen tension and systemic saturation after reducing alveolar carbon dioxide tension, as explained by the Bohr effect—the greater the acidity, the more carbon dioxide is eliminated (94). PaO_2 and oxygen delivery (DO_2) can be optimized by modulating blood pH and $PaCO_2$, hemoglobin concentration, cardiac output, and arterial content of oxygen. These factors mean close attention is warranted when implementing lung-protective strategies, particularly when using low oxygen targets (55–80 mmHg) and permissive hypercapnia. In phenotype 1, characterized by lower potential alveolar recruitability, raising hemoglobin and cardiac output should be considered as a strategy to improve DO_2, as explained in **Figure 4**. One possible side effect of higher hemoglobin is increased blood viscosity, raising the risk of cerebrovascular events (95). In phenotype 3 (ARDS-like COVID), prone positioning, higher PEEP, and RMs should be attempted instead to increase PaO_2 and control $PaCO_2$ levels. At

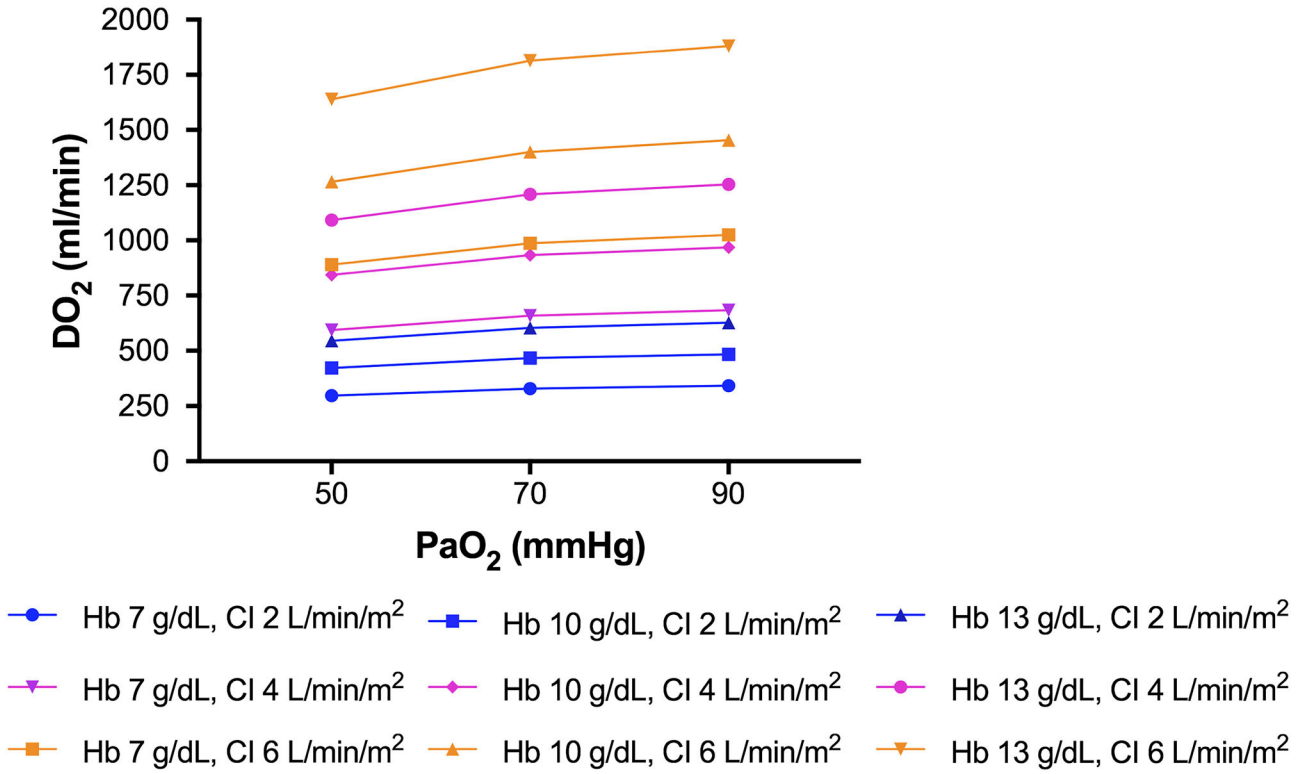


FIGURE 4 | Improving oxygen delivery to the brain. Raising hemoglobin and cardiac output should be considered for improving oxygen delivery, especially in COVID-19 phenotype 1. This figure represents different delivery of oxygen (DO_2) at a fixed cardiac output, by changing hemoglobin, or at fixed hemoglobin, by changing cardiac output.

this point, it is crucial that brain–lung–hemodynamics crosstalk be addressed (**Figures 5A–C**) (96). Current knowledge on the cerebral effects of mechanical ventilation has shifted in favor of moderate-PEEP strategies instead of low- or zero-PEEP strategies, due to possible beneficial effects on brain tissue oxygenation (97–99). Nevertheless, higher PEEP levels may be considered in COVID-19 phenotype 3 to reach acceptable levels of oxygen saturation in the brain (100), thus improving cerebral blood flow and perfusion (101). In this phenotype (but not in phenotypes 1 or 2), lung recruitment maneuvers might also improve oxygenation by improving gas exchange, although their effects on intracranial pressure (ICP) could be detrimental due to impaired jugular venous outflow and venous return (102).

According to the "blast injury theory," the sympathetic storm, cytokine storm, and hyperinflammatory state caused by infection can induce a transient increase in intravascular pressure, with endothelial damage, raised pulmonary vascular hydrostatic pressure, and increased capillary permeability, thus promoting lung derangement and a secondary brain insult (103). This could explain, at least in part, why patients with severe COVID-19 have worse neurological outcomes (104). Both oxygen and carbon dioxide have been considered important determinants of cerebral homeostasis, due to their effects on cerebral blood flow (105). Low cerebral blood flow due to low $PaCO_2$ is associated with cerebral ischemia, while high cerebral blood flow results in cerebral hyperemia and higher ICP (105). A rise in ICP may also be achieved by increasing $PaCO_2$ if intracranial compliance is reduced. In patients not amenable to alveolar recruitment maneuvers, such as those with COVID-19 phenotype 1, overdistension of alveolar areas contributes to a rise in $PaCO_2$ due to the increase in dead space, followed by cerebral vasodilatation. Conversely, in patients responsive to recruitment maneuvers (COVID-19 phenotype 3), shunt is reduced, oxygenation improves, and the $PaCO_2$ is decreased, with lower dead space and less changes in ICP and cerebral perfusion (83, 106). PaO_2, $PaCO_2$, pH, hemoglobin, and DO_2 might all be considered as clinical targets for bedside monitoring where available, to protect both the brain and the lung.

Experimental and Clinical Evidence

The first report of brain autopsies in COVID-19 patients was published on June 12, 2020. Impressively, the authors reported that, at histologic analysis, all 18 examined patients (100%) had evidence of acute hypoxic ischemic damage to the cerebrum and cerebellum. Neither encephalitis nor any evidence of specific viral invasion was identified (107). The neuroimaging features of 108 hospitalized COVID-19 patients demonstrated a non-specific pattern, with predominance of acute

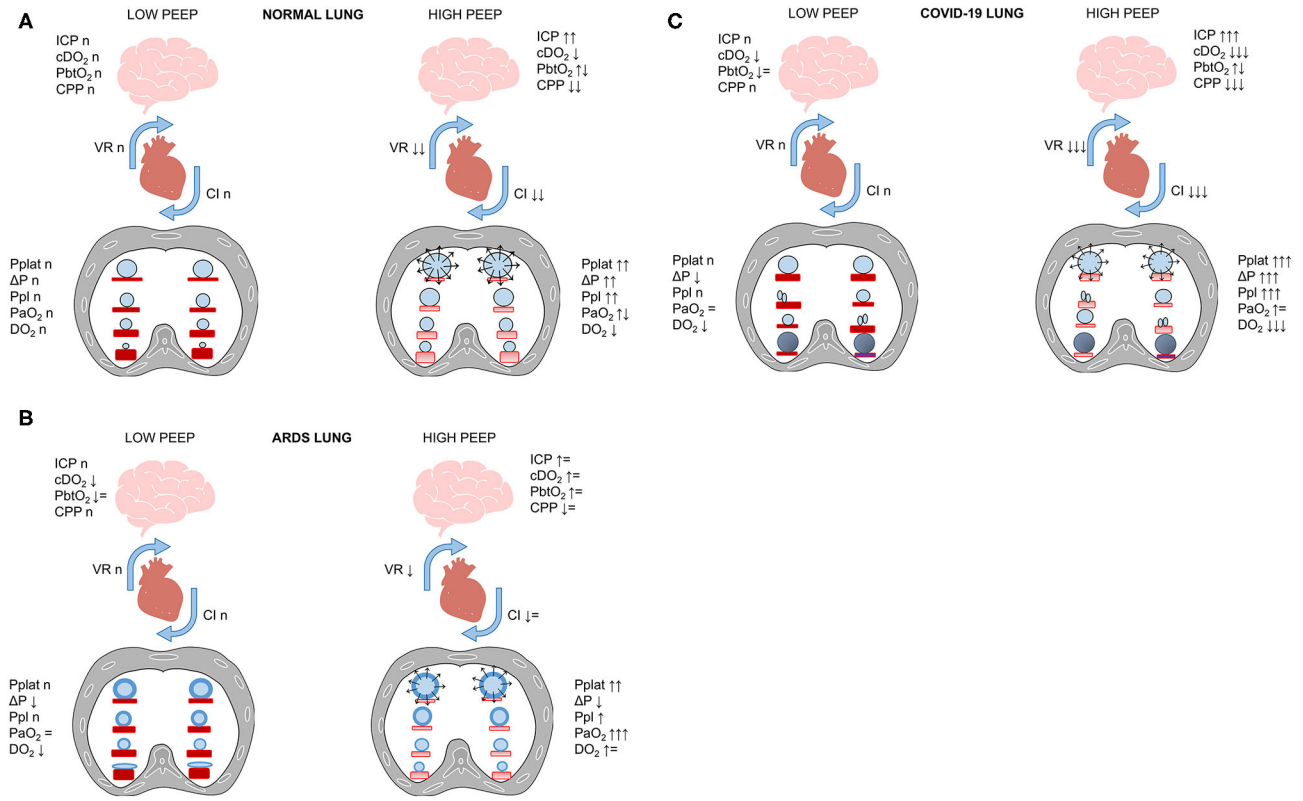


FIGURE 5 | (A–C) Brain–lung–heart cross talk. SARS-CoV-2 lung infection can require mechanical ventilation, which heightens the pro-inflammatory cascade. In this figure, we propose the effect of increased PEEP on the cardiovascular system and CNS in healthy subjects **(A)**, ARDS **(B)**, and COVID-19 **(C)**. In normal lungs **(A)**, high PEEP and alveolar hyperdistention cause increased plateau pressure (Pplat), driving pressure (ΔP), and pleural pressure (Ppl), with consequent reduction of venous return (VR) and cardiac index (CI) and reduced cerebral perfusion pressure (CPP) and increased intracranial pressure (ICP). This can be partially offset by the presence of preserved gas exchange. In ARDS patients **(B)**, the increase in PEEP with recruitment of collapsed areas does not cause significant changes in hemodynamics or cerebral function, and can increase oxygen delivery (cDO_2). Conversely, in COVID-19 patients **(C)** who do not respond to recruitment, the concomitance of alveolar hyperdistention after PEEP increase and hypoxemia can cause serious impairment of cerebral dynamics and cerebral hypoxemia (low $PbtO_2$).

ischemic infarcts and intracranial hemorrhage. MRI findings included the posterior reversible encephalopathy syndrome (PRES), hypoxic–ischemic encephalopathy, and exacerbation of preexisting demyelinating disease, corroborating the role of a hyperinflammatory/hypercoagulable state and brain–lung crosstalk as major mechanisms potentially underpinning neurological complications in COVID-19 (108). Further evidence of neurological involvement is the higher incidence of ICU delirium in COVID-19 patients when compared to non-COVID patients (26.8 vs. 7.7%, $p = 0.003$) (109). This may be explained by the fact that profound hypoxia is known to predispose to long-term cognitive impairment and hypoxic delirium phenotypes, whether caused by BBB dysfunction, inflammation, hypoperfusion, hypoxemia, or a combination thereof (110–112).

In summary, encephalopathy and cerebrovascular disease are the main neurological features identified in severe COVID-19 (73, 113). Despite compelling evidence of viral neurotropism, we believe this is not the primary causative factor of neurological involvement. Instead, in most cases it is likely due to impairment of the delicate equilibrium between the brain and the lung and to the hyperinflammatory, pro-coagulative state that is characteristic of SARS-CoV-2 infection.

CONCLUSIONS

In COVID-19 patients, central and peripheral nervous system changes may be caused by viral neurotropism (such as impairment of olfaction and taste), by a hyperinflammatory and hypercoagulative state, or even by mechanical ventilation-associated impairment. Three distinct phenotypes of pulmonary injury have been identified in association with COVID-19 pneumonia, each requiring individualized respiratory support strategies to minimize lung injury and optimize oxygen delivery to different organs—including the brain. Data from prospective observational studies, randomized clinical trials, and autopsies are urgently needed to confirm the latest findings concerning the causal roles of hypoxic–ischemic brain damage, inflammation, and hypercoagulability in the neurological manifestations of COVID-19.

AUTHOR CONTRIBUTIONS

DB: design and conceptualization, drafting, and revising the manuscript for intellectual content. PA, PF, and PP: drafting and revising the manuscript for intellectual content. IB, GZ, LB, NP, DG, AV, MB, and AS: revising the manuscript for intellectual content. PP, PR, and CR: design and conceptualization and revising the manuscript for intellectual content. All authors: read and approved the final version of the manuscript.

FUNDING

This study was supported by Brazilian Council for Scientific and Technological Development (CNPq), and Carlos Chagas Filho Rio de Janeiro State Research Foundation (FAPERJ).

ACKNOWLEDGMENTS

We express our gratitude to Mrs. Moira Elizabeth Schottler and Mr. Filippe Vasconcellos for their assistance in editing the manuscript.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
2. *Naming the Coronavirus Disease (COVID-19) and the Virus that Causes It*. Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (accessed March 31, 2020).
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *NEJM.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
4. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol.* (2020) 92:418–23. doi: 10.1002/jmv.25681
5. Choi WJ, Lee KN, Kang EJ, Lee H. Middle east respiratory syndrome-coronavirus infection: a case report of serial computed tomographic findings in a young male patient. *Korean J Radiol.* (2016) 17:166–70. doi: 10.3348/kjr.2016.17.1.166
6. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveil.* (2020) 25:2000045. doi: 10.2807/1560-7917.ES.2020.25.3.2000045
7. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. *Viruses.* (2020) 12:135. doi: 10.3390/v12020135
8. The Lancet. Emerging understandings of 2019-nCoV. *Lancet.* (2020) 395:311. doi: 10.1016/S0140-6736(20)30186-0
9. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *JAMA Neurol.* (2020) 77:1–9. doi: 10.2139/ssrn.3544840
10. McGrath BA, Brenner MJ, Warrillow SJ, Pandian V, Arora A, Cameron TS, et al. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. *Lancet Resp Med.* (2020) 8:717–25. doi: 10.1016/S2213-2600(20)30230-7
11. Robba C, Battaglini D, Pelosi P, Rocco RMP. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. *Exp Rev Respir Med.* (2020) 22:1–4. doi: 10.1080/17476348.2020.1778470
12. Pinzon RT, Wijaya VO, Buana RB, Al Jody A, Nunsio PN. Neurologic characteristics in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Front Neurol.* (2020) 11:565. doi: 10.3389/fneur.2020.00565
13. Ferrarese C, Silani V, Priori A, Galimberti S, Agostoni E, Monaco S, et al. An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEUROCOVID). *Neurol Sci.* (2020) 41:1–5. doi: 10.1007/s10072-020-04450-1
14. Pelosi P, Rocco PRM. The lung and the brain: a dangerous cross-talk. *Crit Care.* (2011) 15:168. doi: 10.1186/cc10259
15. Corman VM, Muth D, Niemeyer D, Drosten C. Hosts and sources of endemic human coronaviruses. *Adv Virus Res.* (2018) 100:163–88. doi: 10.1016/bs.aivir.2018.01.001
16. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. *J Pathol.* (2015) 235:185–95. doi: 10.1002/path.4454
17. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* (2004) 203:631–7. doi: 10.1002/path.1570
18. Mattern T, Scholtz W, Feller AC, Flad HD, Ulmer AJ. Expression of CD26 (Dipeptidyl Peptidase IV) on resting and activated human T-lymphocytes. *Scand J Immunol.* (1991) 33:737–48. doi: 10.1111/j.1365-3083.1991.tb02548.x
19. Chan PKS, To KF, Lo AWI, Cheung JLK, Chu I, Au FWL, et al. Persistent infection of SARS coronavirus in colonic cells *in vitro*. *J Med Virol.* (2004) 74:1–7. doi: 10.1002/jmv.20138
20. Lu C-W, Liu X-F, Jia Z-F. 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet.* (2020) 395:e39. doi: 10.1016/S0140-6736(20)30313-5
21. Koester V. Coronavirus entering and replicating in a host cell. *ChemViews.* (2020) 5:e1000428. doi: 10.1002/chemv.202000018
22. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* (2020) doi: 10.1001/jamaneurol.2020.2065. [Epub ahead of print].
23. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* (2020) 11:995–8. doi: 10.1021/acschemneuro.0c00122
24. Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, et al. Neurological manifestations of COVID-19 (SARS-CoV-2): a review. *Front Neurol.* (2020) 11:518. doi: 10.3389/fneur.2020.00518
25. Trojanowicz B, Ulrich C, Kohler F, Bode V, Seibert E, Fiedler R, et al. Monocytic angiotensin-converting enzyme 2 relates to atherosclerosis in patients with chronic kidney disease. *Nephrol Dial Transplantat.* (2017) 32:287–98. doi: 10.1093/ndt/gfw206
26. Spiegel M, Schneider K, Weber F, Weidmann M, Hufert FT. Interaction of severe acute respiratory syndrome-associated coronavirus with dendritic cells. *J Gen Virol.* (2006) 87:1953–60. doi: 10.1099/vir.0.81624-0
27. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. *Transl Stroke Res.* (2020) 11:322–5. doi: 10.1007/s12975-020-00818-9
28. Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis virus transmission pathways. *J Pathol.* (2004) 203:622–30. doi: 10.1002/path.1560
29. McCray PB, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L, et al. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *J Virol.* (2007) 81:813–21. doi: 10.1128/JVI.02012-06
30. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol.* (2018) 95:e00404–18. doi: 10.1128/JVI.00404-18
31. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med.* (2005) 202:415–24. doi: 10.1084/jem.20050828

32. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:552–5. doi: 10.1002/jmv.25728
33. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol.* (2008) 82:7264–75. doi: 10.1128/JVI.00737-08
34. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, et al. Acute-onset smell and taste disorders in the context of Covid-19: a pilot multicenter PCR-based case-control study. *Eur J Neurol.* (2020) 2020:14273. doi: 10.1111/ene.14273
35. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis.* (2020) 2020:ciaa330. doi: 10.1093/cid/ciaa330
36. Yan CH, Faraji F, Prajapati DP, Boone CE, deConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol.* (2020) 10:807–13. doi: 10.1002/alr.22579
37. Lechien JR, Chiesa-Estomba CM, de Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* (2020) 277:2251–61. doi: 10.1007/s00405-020-05965-1
38. Politi LS, Salsano E, Grimaldi M. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and Anosmia. *JAMA Neurol.* (2020) 2020:2125. doi: 10.1001/jamaneurol.2020.2125
39. Coolen T, Lolli V, Sadeghi N, Rovai A, Trotta N, Taccone FS, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. *Neurology.* (2020). doi: 10.1212/WNL.0000000000010116. [Epub ahead of print].
40. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* (2020) 395:1417–18. doi: 10.1016/S0140-6736(20)30937-5
41. von Weyhern CH, Kaufmann I, Neff F, Kremer M. Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *Lancet.* (2020) 395:e109. doi: 10.1016/S0140-6736(20)31282-4
42. Jacomy H, Fragoso G, Almazan G, Mushynski WE, Talbot PJ. Human coronavirus OC43 infection induces chronic encephalitis leading to disabilities in BALB/C mice. *Virology.* (2006) 349:335–46. doi: 10.1016/j.virol.2006.01.049
43. Lee S, Nedumaran B, Hypolite J, Caldwell B, Rudolph MC, Malykhina AP. Differential neurodegenerative phenotypes are associated with heterogeneous voiding dysfunction in a coronavirus-induced model of multiple sclerosis. *Sci Rep.* (2019) 9:10869. doi: 10.1038/s41598-019-47407-x
44. Mecha M, Carrillo-Salinas FJ, Mestre L, Feliú A, Guaza C. Viral models of multiple sclerosis: neurodegeneration and demyelination in mice infected with Theiler's virus. *Prog Neurobiol.* (2013) 101–102:46–64. doi: 10.1016/j.pneurobio.2012.11.003
45. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory Coronaviruses. *J Virol.* (2000) 74:8913–21. doi: 10.1128/JVI.74.19.8913-8921.2000
46. Boucher A, Desforges M, Duquette P, Talbot PJ. Long-term human coronavirus-myelin cross-reactive T-cell clones derived from multiple sclerosis patients. *Clin Immunol.* (2007) 123:258–67. doi: 10.1016/j.clim.2007.02.002
47. Talbot PJ, Paquette JS, Ciurli C, Antel JP, Ouellet F. Myelin basic protein and human coronavirus 229E cross-reactive T cells in multiple sclerosis. *Ann Neurol.* (1996) 39:233–40. doi: 10.1002/ana.410390213
48. Zanin L, Saraceno G, Panciani PP, Renisi G, Signorini L, Migliorati K, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. *Acta Neurochirur.* (2020) 162:1491–4. doi: 10.1007/s00701-020-04374-x
49. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *New Engl J Med.* (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
50. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T, et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *J Neurol Neurosurg Psychiatry.* (2020) 91:846–8. doi: 10.1136/jnnp-2020-323522
51. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. *J Med Virol.* (2020) 92:424–32. doi: 10.1002/jmv.25685
52. Heuer JF, Selke M, Crozier TA, Pelosi P, Herrmann P, Perske C, et al. Effects of acute intracranial hypertension on extracerebral organs: a randomized experimental study in pigs. *J Neurol Surg A Cent Eur Neurosurg.* (2012) 73:289–95. doi: 10.1055/s-0032-1304813
53. Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit care.* (2020) 24:353. doi: 10.1186/s13054-020-03062-7
54. Yang M, Ng MHL, Chi KL. Thrombocytopenia in patients with severe acute respiratory syndrome (review). *Hematology.* (2005) 10:101–5. doi: 10.1080/10245330400026170
55. González-Duarte A, García-Ramos GS, Valdés-Ferrer SI, Cantú-Brito C. Clinical description of intracranial hemorrhage associated with bleeding disorders. *J Stroke Cerebrovasc Dis.* (2008) 17:204–7. doi: 10.1016/j.jstrokecerebrovasdis.2008.02.008
56. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* (2020) 18:844–7. doi: 10.1111/jth.14768
57. Kitchens CS. Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). *Hematol Am Soc Hematol Educ Progr.* (2009) 2009:240–6. doi: 10.1182/asheducation-2009.1.240
58. Bergmann CC, Lane TE, Stohlman SA. Coronavirus infection of the central nervous system: host-virus stand-off. *Nat Rev Microbiol.* (2006) 4:121–32. doi: 10.1038/nrmicro1343
59. Lavi E, Cong L. Type I astrocytes and microglia induce a cytokine response in an encephalitic murine coronavirus infection. *Exp Mol Pathol.* (2020) 115:104474. doi: 10.1016/j.yexmp.2020.104474
60. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Inf Dis.* (2005) 41:1089–96. doi: 10.1086/444461
61. Ray P, Wangzhou A, Ghneim N, Yousuf M, Paige C, Tavares-Ferreira D, et al. A Pharmacological interactome between COVID-19 patient samples and human sensory neurons reveals potential drivers of neurogenic pulmonary dysfunction. *Brain Behav Immun.* (2020). doi: 10.1016/j.bbi.2020.05.078. [Epub ahead of print].
62. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19–volume, page range.associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology.* (2020) 2020:201187. doi: 10.1148/radiol.2020201187
63. Dixon L, Varley J, Gontsarova A, Mallon D, Tona F, Muir D, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. *Neurol Neuroimmunol Neuroinflammation.* (2020) 7:e789. doi: 10.1212/NXI.0000000000000789
64. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *J Biol Regul Homeost Agents.* (2020). doi: 10.23812/Editorial-Conti-3. [Epub ahead of print].
65. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* (2020) 395:1033–4. doi: 10.1016/S0140-6736(20)30628-0
66. Skinner J, Yankey B, Shelton BK. Hemophagocytic lymphohistiocytosis. *AACN Adv Crit Care.* (2019) 30:151–64. doi: 10.4037/aacnacc2019463
67. Lippi G, Plebani M, Michael Henry B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta.* (2020) 506:145–8. doi: 10.1016/j.cca.2020.03.022
68. Han H, Yang L, Liu R, Liu F, Wu K-L, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med.* (2020) 58:1116–20. doi: 10.1515/cclm-2020-0188
69. Yao T, Tian BL, Li G, Cui Q, Wang CF, Zhang Q, et al. Elevated plasma D-dimer levels are associated with short-term poor outcome in patients with acute ischemic stroke: a prospective, observational study. *BMC Neurol.* (2019) 19:175. doi: 10.1186/s12883-019-1386-3
70. Koch HJ, Horn M, Bogdahn U, Ickenstein GW. The relationship between plasma D-dimer concentrations and acute ischemic stroke subtypes. *J Stroke Cerebrovas Dis.* (2005) 14:75–9. doi: 10.1016/j.jstrokecerebrovasdis.2004.12.002

71. Zi W-J, Shuai J. Plasma D-dimer levels are associated with stroke subtypes and infarction volume in patients with acute ischemic stroke. *PLoS ONE.* (2014) 9:e86465. doi: 10.1371/journal.pone.0086465
72. Goldberg MF, Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular disease in COVID-19. *AJNR Am J Neuroradiol.* (2020) 41:1170–2. doi: 10.3174/ajnr.A6588
73. Scullen T, Keen J, Mathkour M, Dumont AS, Kahn L. COVID-19 associated encephalopathies and cerebrovascular disease: the New Orleans experience. *World Neurosurg.* (2020). doi: 10.1016/j.wneu.2020.05.192. [Epub ahead of print].
74. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol.* (2020) 267:2185–92. doi: 10.1007/s00415-020-09885-2
75. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thromb Haemost.* (2020) 2020:jth.14938. doi: 10.1111/jth.14938
76. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787
77. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg.* (2020) 194:105921. doi: 10.1016/j.clineuro.2020.105921
78. Battaglini D, Robba C, Lopes da Silva A, dos Santos Samary C, Leme Silva P, Dal Pizzol F, et al. Brain–heart interaction after acute ischemic stroke. *Crit Care.* (2020) 24:163. doi: 10.1186/s13054-020-02885-8
79. Di Castelnuovo A, Agnoli C, de Curtis A, Giurdanella MC, Sieri S, Mattiello A, et al. Elevated levels of D-dimers increase the risk of ischaemic and haemorrhagic stroke: findings from the EPICOR study. *Thromb Haemost.* (2014) 112:941–6. doi: 10.1160/th14-04-0297
80. Zhang J, Song Y, Shan B, He M, Ren Q, Zeng Y, et al. Elevated level of D-dimer increases the risk of stroke. *Oncotarget.* (2018) 9:2208–19. doi: 10.18632/oncotarget.23367
81. Zhou Z, Liang Y, Zhang X, Xu J, Kang K, Qu H, et al. Plasma D-dimer concentrations and risk of intracerebral hemorrhage: a systematic review and meta-analysis. *Front Neurol.* (2018) 9:1114. doi: 10.3389/fneur.2018.01114
82. Cheng X, Zhang L, Xie NC, Ma YQ, Lian YJ. High plasma levels of d-Dimer are independently associated with a heightened risk of deep vein thrombosis in patients with intracerebral hemorrhage. *Mol Neurobiol.* (2016) 53:5671–8. doi: 10.1007/s12035-015-9487-5
83. Robba C, Battaglini D, Ball L, Patroniti N, Loconte M, Brunetti I, et al. Distinct phenotypes require distinct respiratory management strategies in severe COVID-19. *Respir Physiol Neurobiol.* (2020) 279:103455. doi: 10.1016/j.resp.2020.103455
84. Pelosi P, Caironi P, Gattinoni L. Pulmonary and extrapulmonary forms of acute respiratory distress syndrome. *Semin Respir Crit Care Med.* (2001) 22:259–68. doi: 10.1055/s-2001-15783
85. Leite-Junior JHP, Garcia CSNB, Souza-Fernandes AB, Silva PL, Ornellas DS, Larangeira AP, et al. Methylprednisolone improves lung mechanics and reduces the inflammatory response in pulmonary but not in extrapulmonary mild acute lung injury in mice. *Crit Care Med.* (2008) 36:2621–8. doi: 10.1097/CCM.0b013e3181847b43
86. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med.* (1994) 149:8–13. doi: 10.1164/ajrccm.149.1.8111603
87. Goodman LR, Fumagalli R, Tagliabue P, Tagliabue M, Ferrario M, Gattinoni L, et al. Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. *Radiology.* (1999) 213:545–52. doi: 10.1148/radiology.213.2.r99nv42545
88. Gattinoni L, D'andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA.* (1993) 269:2122–7. doi: 10.1001/jama.269.16.2122
89. Oddo M, Nduom E, Frangos S, MacKenzie L, Chen I, Maloney-Wilensky E, et al. Acute lung injury is an independent risk factor for brain hypoxia after severe traumatic brain injury. *Neurosurgery.* (2010) 67:338–44. doi: 10.1227/01.NEU.0000371979.48809.D9
90. Rosenthal G, Hemphill JC, Sorani M, Martin C, Morabito D, Meeker M, et al. The role of lung function in brain tissue oxygenation following traumatic brain injury. *J Neurosurg.* (2008) 108:59–65. doi: 10.3171/JNS/2008/108/01/0059
91. Van Santbrink H, Vd Brink WA, Steyerberg EW, Suazo JAC, Avezaat CJJ, Maas AIR, et al. Brain tissue oxygen response in severe traumatic brain injury. *Acta Neurochirur.* (2003) 145:429–38. doi: 10.1007/s00701-003-0032-3
92. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis Dis.* (2020). doi: 10.1016/S1473-3099(20)30367-4. [Epub ahead of print].
93. Ottestad W, Søvik S. COVID-19 patients with respiratory failure: what can we learn from aviation medicine? *Br J Anaesth.* (2020). doi: 10.1016/j.bja.2020.04.012. [Epub ahead of print].
94. Teboul JL, Scheeren T. Understanding the Haldane effect. *Intensive Care Med.* (2017) 43:91–3. doi: 10.1007/s00134-016-4261-3
95. Sekhon MS, Griesdale DE, Czosnyka M, Donnelly J, Liu X, Aries MJ, et al. The effect of red blood cell transfusion on cerebral autoregulation in patients with severe traumatic brain injury. *Neurocrit Care.* (2015) 23:210–6. doi: 10.1007/s12028-015-0141-x
96. Iadecola C, Anrather J. The immunology of stroke: rom mechanisms to translation. *Nat Med.* (2011) 17:796–808. doi: 10.1038/nm.2399
97. Nemer SN, Caldeira JB, Santos RG, Guimarães BL, Garcia JM, Prado D, et al. Effects of positive end-expiratory pressure on brain tissue oxygen pressure of severe traumatic brain injury patients with acute respiratory distress syndrome: a pilot study. *J Crit Care.* (2015) 30:1263–6. doi: 10.1016/j.jcrc.2015.07.019
98. Pelosi P, Ferguson ND, Frutos-Vivar F, Anzueto A, Putensen C, Raymondos K, et al. Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med.* (2011) 39:1482–92. doi: 10.1097/CCM.0b013e31821209a8
99. Boone MD, Jinadasa SP, Mueller A, Shaefi S, Kasper EM, Hanafy KA, et al. The effect of positive end-expiratory pressure on intracranial pressure and cerebral hemodynamics. *Neurocrit Care.* (2017) 26:174–81. doi: 10.1007/s12028-016-0328-9
100. Alhazzani W, Hylander Møller M, Arabi YM, Loeb M, Ng Gong M, Fan E, et al. Surviving sepsis campaign: guidelines on the management of critically Ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med.* (2020) 48:e440–69. doi: 10.1097/CCM.0000000000004363
101. Huynh T, Messer M, Sing RF, Miles W, Jacobs DG, Thomason MH, et al. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. *J Trauma.* (2002) 53:488–93. doi: 10.1097/00005373-200209000-00016
102. Robba C, Bonatti G, Battaglini D, Rocco PRM, Pelosi P. Mechanical ventilation in patients with acute ischaemic stroke: from pathophysiology to clinical practice. *Crit Care.* (2019) 23:388. doi: 10.1186/s13054-019-2662-8
103. Mascia L. Acute lung injury in patients with severe brain injury: a double hit model. *Neurocrit Care.* (2009) 11:417–26. doi: 10.1007/s12028-009-9242-8
104. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med.* (2020). doi: 10.1056/NEJMcp2009575. [Epub ahead of print].
105. Bouma GJ, Muizelaar JP. Cerebral blood flow in severe clinical head injury. *New Horiz.* (1995) 3:384–94.
106. Mascia L, Grasso S, Fiore T, Bruno F, Berardino M, Ducati A. Cerebro-pulmonary interactions during the application of low levels of positive end-expiratory pressure. *Intensive Care Med.* (2005) 31:373–9. doi: 10.1007/s00134-004-2491-2
107. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. *N Engl J Med.* (2020) 2020:NEJMc2019373. doi: 10.1056/NEJMc2019373
108. Mahammedi A, Saba L, Vagal A, Leali M, Rossi A, Gaskill M, et al. Imaging in neurological disease of hospitalized COVID-19 patients: an Italian multicenter retrospective observational study. *Radiology.* (2020) 2020:201933. doi: 10.1148/radiol.2020201933
109. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic

disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology.* (2020). doi: 10.1212/WNL.0000000000009848. [Epub ahead of print].

110. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med.* (2012) 185:1307–15. doi: 10.1164/rccm.201111-2025OC
111. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir Med.* (2018) 6:213–22. doi: 10.1016/S2213-2600(18)30062-6
112. Sasannejad C, Ely EW, Lahiri S. Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care.* (2019) 23:352. doi: 10.1186/s13054-019-2626-z
113. Deliwala S, Abdulhamid S, Abusalih MF, Al-Qasmi MM, Bachuwa G. Encephalopathy as the sentinel sign of a cortical stroke in a patient infected with coronavirus disease-19 (COVID-19). *Cureus.* (2020) 12:e8121. doi: 10.7759/cureus.8121

Conflict of Interest: Outside the submitted work DG reports honoraria from Stepstone Pharma GmbH and unconditional grants from MSD Italia and Correvio Italia. Outside the submitted work, MB has received funding for scientific advisory boards, travel, and speaker honoraria from Angelini, Astellas, AstraZeneca, Basilea, Bayer, BioMerieux, Cidara, Correvio, Cubist, Menarini, Molteni, MSD, Nabriva, Paratek, Pfizer, Roche, Shionogi, Tetraphase, Thermo Fisher, and The Medicine Company.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 14 August 2020
doi: 10.3389/fneur.2020.00850

Impact of COVID-19 on Acute Stroke Presentation at a Comprehensive Stroke Center

*Masaki Nagamine[1], Daniel S. Chow[2,3], Peter D. Chang[2,3], Bernadette Boden-Albala[4], Wengui Yu[1] and Jennifer E. Soun[2]**

[1] Department of Neurology, University of California, Irvine Medical Center, Orange, CA, United States, [2] Department of Radiological Sciences, University of California, Irvine Medical Center, Orange, CA, United States, [3] Center for Artificial Intelligence in Diagnostic Medicine, University of California, Irvine, Irvine, CA, United States, [4] Department of Population Health and Disease Prevention, Department of Epidemiology, University of California, Irvine, Irvine, CA, United States

Background: COVID-19 has impacted healthcare in many ways, including presentation of acute stroke. Since time-sensitive thrombolysis is essential for reducing morbidity and mortality in acute stroke, any delays due to the pandemic can have serious consequences.

Methods: We retrospectively reviewed the electronic medical records for patients presenting with acute ischemic stroke at a comprehensive stroke center in March–April 2020 (the early months of COVID-19) and compared to the same time period in 2019. Stroke metrics such as incidence, time to arrival, and immediate outcomes were assessed.

Results: There were 48 acute ischemic strokes (of which 7 were transfers) in March–April 2020 compared to 64 (of which 12 were transfers) in 2019. The average last known well to arrival time (±SD) for stroke codes was 1,041 (±1682.1) min in 2020 and 554 (±604.9) min in 2019. Of the patients presenting directly to the ED with a known last known well time, 27.8% (10/36) presented in the first 4.5 h in 2020, in contrast to 40.5% (15/37) in 2019. Patients who died comprised 10.4% of the stroke cohort in 2020 (5/48) compared to 6.3% in 2019 (4/64).

Conclusions: During the first 2 months of COVID-19, there were fewer overall stroke cases who presented to our hospital, and of these cases, there was delayed presentation in comparison to the same time period in 2019. Recognizing how stroke presentation may be affected by COVID-19 would allow for optimization of established stroke triage algorithms in order to ensure safe and timely delivery of stroke care during a pandemic.

Keywords: stroke, COVID-19, public health, thrombolytics, stroke triage

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu, Servicio de Neurología, Hospital Clínico San Carlos, Spain

Reviewed by:
Jose M. Trejo, Burgos University Hospital, Spain
Carlos Tejero-Juste, Lozano Blesa University Clinical Hospital, Spain

***Correspondence:**
Jennifer E. Soun
jesoun@hs.uci.edu

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *29 May 2020*
Accepted: *07 July 2020*
Published: *14 August 2020*

Citation:
Nagamine M, Chow DS, Chang PD, Boden-Albala B, Yu W and Soun JE (2020) Impact of COVID-19 on Acute Stroke Presentation at a Comprehensive Stroke Center. Front. Neurol. 11:850. doi: 10.3389/fneur.2020.00850

INTRODUCTION

The overwhelming burden of the current COVID-19 pandemic on the healthcare system has produced unintended consequences on acute stroke care. COVID-19 which was first diagnosed in Wuhan, China, and spread rapidly worldwide, has affected over 4.5 million individuals worldwide and over 1.4 million in the U.S. as of May 15, 2020 (1). While the number of COVID-19 cases presenting to hospitals has risen exponentially, there are reports of precipitous declines in the

number of patients presenting with acute stroke in many countries, including China, Italy and the U.S. (2–5). Reports suggest a global increase in treatment delays for life threatening and disabling conditions and at worst, an increase in the number of patients presenting outside of time sensitive treatment windows (6–9). The impact of COVID-19 on outcomes of stroke patients who may be delaying or foregoing presentation to hospitals is consequential since early interventions are potentially life-saving. Time-sensitive thrombolysis for qualifying ischemic stroke patients is a critical component of the stroke treatment paradigm. Tissue plasminogen activator (tPA) up to 3 to 4.5 h and thrombectomy up to 24 h have been established as the standard of care and have shown therapeutic benefit in large randomized clinical trials (10–12). The purpose of this study is to evaluate our institution's experience with patients presenting with acute stroke symptoms during the early months of the COVID-19 pandemic.

METHODS

We retrospectively reviewed patients who presented with acute stroke symptoms to University of California Irvine Medical Center (UCI) during the time period of March 1–April 30, 2020. This period was chosen to coincide with our hospital's initial experience with COVID-19. UCI is a 411-bed comprehensive stroke center serving Orange County, CA, with 317 acute ischemic stroke cases who presented in 2019. We analyzed the incidence, time to arrival, severity, administered therapies, and immediate outcomes of stroke cases during the early months of COVID-19 and compared to the same time period (March 1–April 30, 2019) 1 year prior. All data was obtained through UCI's stroke database and electronic medical record, and the study was performed in accordance with IRB guidelines.

RESULTS

A total of 48 patients presented with acute stroke symptoms during March 1-April 30, 2020, in comparison to 64 patients from March 1–April 30, 2019 (**Table 1**). This included 1 patient with COVID-19 diagnosed by nucleic acid detection test. Mean age was 65.25 ± 16.1 years in 2020 compared to 69 ± 14.9 years in 2019. There were 7 interfacility transfers (IFT) and 3 inpatient strokes in 2020 and 12 IFTs and 3 inpatient strokes in 2019. The mean time from last known well (LKW) to arrival for stroke code patients was 1,041 ± 1682.1 min in 2020 and 554 ± 604.9 min in 2019. Of the patients presenting directly to the ED with a known last known well time, 27.8% (10/36) presented in the first 4.5 h in 2020, in contrast to 40.5% (15/37) in 2019. The mean presenting NIH Stroke Scale (NIHSS) score was 10.29 ± 8.5 and discharge NIHSS if the patient survived was 5.86 ± 5.2 in 2020 in comparison to 9.52 ± 9.8 and 7.05 ± 8.4, respectively, in 2019. Five patients each received tPA in 2020 and 2019, and 9 patients underwent thrombectomy in 2020 in contrast to 4 patients in 2019. Patients who died comprised 10.4% of the stroke cohort in 2020 (5/48) compared to 6.3% in 2019 (4/64). Mean time from patient arrival to administration of tPA (door to needle) in minutes was 49.6 (±37.2) in 2020 compared to 50 (±20.1) in 2019. Mean time from patient arrival to vessel puncture for endovascular therapy (door to puncture) in minutes was 109 (±32.4) in 2020 compared to 132 (±22.6) in 2019.

TABLE 1 | Demographics, time metrics, and early clinical outcomes of acute ischemic stroke patients in March–April 2020 (COVID-19 pandemic) in comparison to March–April 2019.

	March–April 2020 (*n* = 48)	March–April 2019 (*n* = 64)
Age, y, mean ± SD	65.25 ± 16.1	69 ± 14.9
Female, *n* (%)	12/48 (25%)	25/64 (39%)
Race		
Hispanic	20	11
Black/African-American	0	3
Non-Hispanic White	12	42
Asian	14	8
Stroke presentation, *n*		
Stroke code or consult	36	37
Inpatient stroke	3	3
Interfacility Transfer	7	12
Unknown LKW	2	12
LKW to Arrival in minutes, mean ± SD*	1,041 ± 1682.1	554 ± 604.9
Presentation < 4.5Hr in minutes, *n* (%)	10/36 (27.8%)	15/37 (40.5%)
Door to imaging in minutes, mean ± SD	25.35 ± 32.8	18 ± 11.6
Door to needle in minutes, mean ± SD	49.6 ± 37.2	50 ± 20.1
Door to puncture in minutes, mean ± SD	109 ± 32.4	132 ± 22.6
NIHSS at presentation, mean ± SD	10.29 ± 8.5	9.52 ± 9.8
NIHSS at discharge if patient survived, mean ± SD	5.86 ± 5.2	7.05 ± 8.4
Thrombolysis, *n*		
tPA	5	5
Thrombectomy	9	4
TICI, *n*		
0, 1, or 2a	1	1
2b, 2c, or 3	8	3
Deaths, *n* (%)	5 (10%)	4 (6%)

**Excludes inpatient strokes, IFT's, and unknown LKW.*
LKW, last known well; IFT, interfacility transfer; NIHSS, NIH Stroke Scale; tPA, tissue plasminogen activator; TICI, thrombolysis in cerebral infarction.

DISCUSSION

The COVID-19 pandemic has affected the presentation of acute stroke cases in our single-center experience during the early months of the pandemic. We found a decreased number of stroke cases and a delayed presentation to the hospital in 2020 in comparison to 2019. In addition, fewer cases were presenting in the acute time window when tPA could be administered for qualifying patients, although more patients underwent thrombectomy which suggests increased numbers of stroke cases from large vessel occlusion. Despite additional regulations instated for donning personal protective equipment during stroke code presentations in 2020, the

door-to-needle and door-to-puncture times were similar between the 2 years. Interestingly, the initial NIHSS was similar between the two time periods, and the discharge NIHSS was actually better in 2020. These findings warrant further investigation, but improved discharge NIHSS may be related to higher rate of thrombectomy. However, a greater percentage of patients died from stroke in 2020 in comparison to 2019.

Changes in stroke presentation due to COVID-19 may be a result of several factors. Patients may be reluctant to seek healthcare for fear of being exposed to the virus and presenting only when strokes are severe. In addition, due to restrictions in public gatherings and social distancing measures, patients who have incapacitating strokes tend to be found by others in a delayed fashion prior to presentation. Delays in presentation prevent patients from meeting criteria for life-saving therapies and may cause increased morbidity and mortality given the time-sensitivity of treatments. Patients with milder strokes or transient ischemic attacks could be avoiding the healthcare system altogether, which could be dangerous since these patients are at increased risk of a recurrent ischemic stroke and warrant secondary prevention (13).

In order to ensure continued safe and timely acute stroke management during COVID-19, updated stroke algorithms have been proposed that address all steps of the stroke management pathway, including pre-hospitalization and interfacility transfer, hospitalization and treatment, and discharge and rehabilitation (14–16). These guidelines have introduced measures such as COVID-19 screening and personal protective equipment into stroke triage to ensure the safety of patients and the stroke team while emphasizing the importance of preventing delays in care. The optimization of telemedicine and other virtual clinician guidance tools has become essential to triage patients appropriately and provide education and prevention (17).

Limitations of this study include a retrospective single-center experience, which may not be generalizable to other stroke centers. Patient presentation to surrounding stroke centers are not accounted for in this study. Additionally, the patient number is low, allowing for only descriptive analysis of the statistics. Only immediate clinical status has been reported, and long-term clinical outcomes remain to be seen. The effect of COVID-19 on delays once the patient reaches the hospital also needs to be assessed to see if current protocols need further optimization.

In conclusion, this study highlights how stroke presentation has been impacted by COVID-19, with fewer overall cases, delays in presentation, and increased mortality. To address these potential issues, updated stroke guidelines which incorporate adherence to COVID-19 precautions into triage and treatment algorithms will allow patients to continue to receive optimal stroke care. Furthermore, more public outreach focusing on awareness of time-sensitive treatment windows for cerebral reperfusion may help prevent delays in presentation and irreversible brain injury during COVID-19 and future pandemics.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board, Human Research Protections at the Office of Research, University of California, Irvine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MN collected, analyzed, interpreted the data, and helped to write the manuscript. JS wrote the manuscript. DC, PC, WY, BB-A, and MN were major contributors in the study design and editing of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track covid-19 in real time. *Lancet Infect Dis.* (2020) 20:533–4. doi: 10.1016/S1473-3099(20)30120-1
2. Zhao J, Rudd A, Liu R. Challenges and potential solutions of stroke care during the coronavirus disease 2019 (covid-19) outbreak. *Stroke.* (2020). 51:1356–7. doi: 10.1161/STROKEAHA.120.029701
3. Morelli N, Rota E, Terracciano C, Immovilli P, Spallazzi M, Colombi D, et al. The baffling case of ischemic stroke disappearance from the casualty department in the covid-19 era. *Eur Neurol.* (2020) 83:213–15. doi: 10.1159/000507666
4. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral effect of covid-19 on stroke evaluation in the united states. *N Engl J Med.* (2020) 383:400–1. doi: 10.1056/NEJMc2014816
5. Baracchini C, Pieroni A, Viaro F, Cianci V, Cattelan AM, Tiberio I, et al. Acute stroke management pathway during coronavirus-19 pandemic. *Neurol Sci.* (2020) 41:1003–5. doi: 10.1007/s10072-020-04375-9
6. Markus HS, Brainin M. Covid-19 and stroke—a global world stroke organization perspective. *Int J Stroke.* (2020) 2020:1747493020923472. doi: 10.1177/1747493020923472
7. Feral-Pierssens AL, Claret PG, Chouihed T. Collateral damage of the covid-19 outbreak: expression of concern. *Eur J Emerg Med.* (2020) 27:233–4. doi: 10.1097/MEJ.0000000000000717
8. Hecht N, Wessels L, Werft F-O, Schneider UC, Czabanka M, Vajkoczy P. Need for ensuring care for neuro-emergencies—lessons learned from the covid-19 pandemic. *Acta Neurochir.* (2020) 162:1795–801. doi: 10.2139/ssrn.3605279
9. Montaner J, Barragán-Prieto A, Pérez-Sánchez S, Escudero-Martínez I, Moniche F, Sánchez-Miura JA, et al. Break in the stroke chain of survival due to covid-19. *Stroke.* (2020) 51:2307–14. doi: 10.1161/STROKEAHA.120.030106
10. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* (2008) 359:1317–29. doi: 10.1056/NEJMoa0804656
11. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973

12. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. (2017) 378:11–21. doi: 10.1056/NEJMoa1706442
13. Amarenco P. Five-year risk of stroke after tia or minor ischemic stroke. *N Engl J Med*. (2018) 379:1580–81. doi: 10.1056/NEJMc1808913
14. Dafer RM, Osteraas ND, Biller J. Acute stroke care in the coronavirus disease 2019 pandemic. *J Stroke Cerebrovasc Dis*. (2020) 29:104881. doi: 10.1016/j.jstrokecerebrovasdis.2020.104881
15. Fraser JF, Arthur AS, Chen M, Levitt M, Mocco J, Albuquerque FC, et al. Society of neurointerventional surgery recommendations for the care of emergent neurointerventional patients in the setting of covid-19. *J NeuroInterv Surg*. (2020) 12:539–41. doi: 10.1136/neurintsurg-2020-016098
16. Khosravani H, Rajendram P, Notario L, Chapman Martin G, Menon Bijoy K. Protected code stroke. *Stroke*. (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.029838
17. Sheth Sunil A, Wu T-C, Sharrief A, Ankrom C, Grotta James C, Fisher M, et al. Early lessons from world war covid. *Stroke*. (2020) 51:2268–72. doi: 10.1161/STROKEAHA.120.030154

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 19 August 2020
doi: 10.3389/fneur.2020.00870

Glimpsing the Impact of COVID19 Lock-Down on People With Epilepsy: A Text Mining Approach

Jacopo Lanzone[1], Cristina Cenci[2], Mario Tombini[1], Lorenzo Ricci[1], Tommaso Tufo[3], Marta Piccioli[4], Alfonso Marrelli[5], Oriano Mecarelli[6] and Giovanni Assenza[1]*

[1] Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, University Campus Bio-Medico of Rome, Rome, Italy, [2] DNM-Digital Narrative Medicine, Rome, Italy, [3] Policlinico Gemelli Foundation University Hospital IRCSS, Rome, Italy, [4] Unit of Neurology, AO S. Filippo Neri, Rome, Italy, [5] Unit of Neurology, AO S. Salvatore, L'Aquila, Italy, [6] Department of Neurology and Psychiatry, "Sapienza" University of Rome, Rome, Italy

Objectives: To describe how the recent lock-down, related to SARS-COV-II outbreak in Italy, affected People With Epilepsy (PwE), we designed a survey focused on subjective reactions. Using Natural Language Processing (NLP), we analyzed words PwE and People without Epilepsy (PwoE) chose to express their reactions.

Methods: As a subset of a larger survey, we collected from both PwE (427) and PwoE (452) single words (one per subject) associated to the period of lock down. The survey was spread thanks to the efforts of Italian league against epilepsy Foundation during the days of maximum raise of the pandemic. Data were analyzed via bag of word and sentiment analysis techniques in R.

Results: PwoE and PwE showed significantly different distribution in word choice (X^2, $p = 4.904e{-}13$). A subset of subject used positive words to describe this period, subjects with positive feelings about the lock down were more represented in the PwE group (X^2, $p = 0.045$).

Conclusion: PwoE developed reactive stress response to the restrictions enacted during lock-down. PwE, instead, chose words expressing sadness and concern with their disease. PwE appear to internalize more the trauma of lock down. Interestingly PwE also expressed positive feelings about this period of isolation more frequently than PwoE. Our study gives interesting insights on how People with Epilepsy react to traumatic events, using methods that evidence features that do not emerge with psychometric scales.

Keywords: COVID-19, epilepsy, text-mining, neuropsychology, natural-language processing

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu, Servicio de Neurología, Hospital Clínico San Carlos, Spain

Reviewed by:
Milena Gandy, Macquarie University, Australia
Alessandro Principe, Hospital del Mar, Spain

****Correspondence:***
Jacopo Lanzone
jacopo.lanzone@gmail.com

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: *23 May 2020*
Accepted: *08 July 2020*
Published: *19 August 2020*

Citation:
Lanzone J, Cenci C, Tombini M, Ricci L, Tufo T, Piccioli M, Marrelli A, Mecarelli O and Assenza G (2020) Glimpsing the Impact of COVID19 Lock-Down on People With Epilepsy: A Text Mining Approach. Front. Neurol. 11:870. doi: 10.3389/fneur.2020.00870

INTRODUCTION

In order to describe the impact of epileptic disorders on People With Epilepsy (PwE) we often take advantage of quantitative scores such as psychometric scales targeting depressive symptoms, emotion dysregulation, anxiety and stigma perception (1). Scores do not take into consideration qualitative and more subjective facets of epilepsy. In this brief communication we report how we used Natural Language Processing (NLP) to better describe differences between People With-out Epilepsy (PwoE) and PwE in coping with the recent SARS-CoV-2 pandemic.

NLP methods are widely used in marketing and social sciences but they are under-represented in the study of chronic medical conditions such epilepsy (2–4). We think that language processing can be useful in describing interesting aspects of coping with chronic diseases such as epilepsy (4, 5).

METHODS

We collected word clusters as a subset of a broader online survey on COVID-19 and epilepsy (6, 7). The survey was spread thanks to the efforts of LICE [Lega Italiana Contro l'Epilessia, the Italian chapter of the International League Against Epilepsy (ILAE)] Foundation and included clinical data and psychometric scales.

Respondents were asked to type a single simple word they came across when thinking about how the lock-down caused by COVID19 pandemic affected their life.

Data, consisting in a single word for each response, was imported in R as a commas separated vector (csv) file and processed with text mining libraries (Tidytext), using a "bag of words" approach (8).

Answers were stemmed, transformed to upper-case and collected in a digital corpus that was then subset among PwE and PwoE groups. Single words were translated in English using Google cloud^{TM} translations and were manually controlled by the authors. Translation was considered to be robust since terms used were simple and generally non-metaphorical. Singletons (single occurring words) were eliminated, since they do not bear interesting information. To evidence differences in occurrence of the most used terms we considered terms with at least three recurrences in one of the groups (PwoE and PwE) and created a difference matrix of words occurrence in the two groups.

Differences were thus calculated on a reduced dataset (excluding single occurring word and words with frequency <3). Moreover, we calculated polarization score using the "Affin" lexicon (9). Polarization is a technique used in sentiment analysis that leverages lexicons: large libraries of words assigned with positive or negative value depending on the polarity of the term.

Differences in word frequency distribution and difference in distribution of positive and negative words were tested with Chi^2 Difference in polarity were tested with Mann-Whitney test.

Alpha level was set as $p = 0.05$ for statistical significance.

RESULTS

Our survey opened on April 11, 2020 and closed at 11.59 p.m. of April 16, 2020. The survey was completed by 879 subjects:427 PwE (327 females, 38.6 ± 11.8 years) and 452 PwoE (331 females, 43.89 ± 12.25 years). Difference in age and sex between the two groups was not significant, women were more represented than men [as is described that they tend to be more keen to answering online surveys (10)]. Data on psychometric scales and in-depth clinical data was published elsewhere (7). Among PwE 49.6% (212/427) were seizure free and 15.7% (67/427) reported seizure worsening during the lockdown period (7), these categories were too unbalanced and we did not find significant difference in word choice distribution among them.

After eliminating singletons and words with <3 occurrences our corpus consisted of 605 entries: 46.6% PwE (282/605), 53.4% PwoE (323/605).

Chi^2 test showed significant difference in the frequency distribution between the word used by the two groups ($X^2 = 159.06$, df = 51, $p = 4.904e{-}13$).

Chi^2 test showed increased frequency in the occurrence of words with positive "Affin" score in the PwE group compared to the PwoE ($X^2 = 5.3953$, df = 1, $p = 0.045$, PwE = 10.2%, 29/282; PwoE = 5.2%, 17/323).

We analyzed polarization scores among the two datasets, finding no significant differences and an average polarization value of −1.28 in PwE and −1.39 in PwoE (polarization range −5, 5).

Using the word corpus, we created (**Figure 1A**) that is a "mind-map" of feelings and emotions related to the lock down in both groups. In **Figure 1B**, we show the difference in word frequency between the two groups, highlighting terms that are over expressed and under expressed in the PwoE and PwE groups.

DISCUSSION

Textual analysis helps to evidence interesting patterns in word choice. PwE and PwoE tend to use different words to describe the lockdown period. While the most expressed words are the same (**Figure 1A**), words that are over expressed in the PwE, and in PwoE point out how the two groups cope differently with the same stressful event.

PwoE consistently over-report many terms that express anxiety as a reactive response to the stressful event; words like "prison," "distance," "loneliness," "anguish," "stress," "change" are frequently used. In our interpretation, PwoE develop anxiety since they are concerned with practical issues and limitations of lock down.

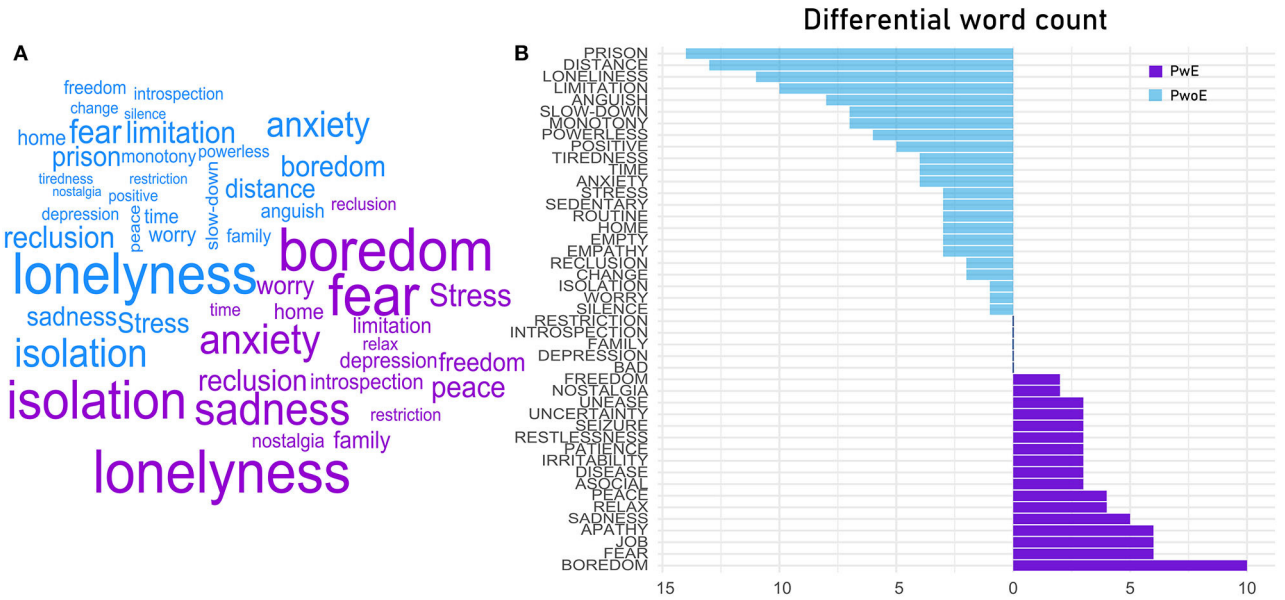
On the other hand, PwE tend to over-report terms like "fear" "boredom" "sadness" "apathy" "asocial" "disease" "seizure"; these terms are related to something more than reactive stress. PwE during lockdown do not just feel isolated, limited and anxious in their day-to-day life; they also worry about their disease and tend to develop depressive thoughts.

This could be partly related to the well-known fact that PwE tend to be more depressed than PwoE (11–13), but could also relate to the heavy burden of stigma in PwE.

Our hypothesis is that while PwoE tend to react to isolation as expected with anxiety, PwE already feel as they live in a condition of relative stigma and isolation (14) and thus tend to give a more negative interpretation to the lock down, developing feelings in the depression sphere (15, 16).

Moreover, it is interesting to note that both in PwoE and PwE there is a subgroup of people expressing positive feelings about the lock down. This occurs more frequently in PwE as is shown by less negative scores in average polarization of the terms used and significant Chi2.

Apparently, some see the lockdown as a chance to "relax" and find "peace." In our interpretation PwE express more this feeling



	COUNT	PwE	PwoE		COUNT	PwE	PwoE		COUNT	PwE	PwoE		COUNT	PwE	PwoE		COUNT	PwE	PwoE
LONELINESS	61	25	36	FREEDOM	17	10	7	RESTRICTION	8	4	4	TIREDNESS	4	0	4	CHANGE	3	3	0
ISOLATION	45	22	23	PEACE	16	11	5	NOSTALGIA	8	5	3	SILENCE	4	0	4	UNEASE	3	3	0
FEAR	42	24	18	HOME	15	6	9	POSITIVE	8	3	5	RECLUSION	4	4	0	UNCERTAINTY	3	3	0
BOREDOM	40	25	15	PRISON	14	0	14	MONOTONY	7	0	7	SEIZURE	3	3	0	RESTLESSNESS	3	3	0
ANXIETY	36	16	20	FAMILY	14	7	7	SLOW-DOWN	7	0	7	PATIENCE	3	3	0	DISEASE	3	3	0
SADNESS	31	18	13	DEPRESSION	14	8	6	POWERLESS	6	0	6	SILENCE	3	3	0	IRRITABILITY	3	3	0
RECLUSION	26	10	16	DISTANCE	13	0	13	BAD	6	3	3	APATHY	3	3	0	ROUTINE	3	0	3
STRESS	25	11	14	TIME	12	4	8	JOB	6	6	0	EMPATHY	3	0	3	SEDENTARY	3	0	3
LIMITATION	22	6	16	INTROSPECTION	12	6	6	CHANGE	5	0	5	APATHY	3	3	0	EMPTY	3	0	3
WORRY	17	8	9	ANGUISH	8	0	8	RELAX	5	5	0	ASOCIAL	3	3	0				

FIGURE 1 | Depicts a word-cloud based on word counts in the two groups PwE (purple) and PwoE (blue) **(A)**. Segment **(B)** shows the differential frequency of word counts between the two groups, thus evidencing terms that are over-expressed in PwoE (blue) or in PwE (purple). The table shows absolute and group word frequency. PwoE in blue (People without Epilepsy), PwE in purple (People with Epilepsy).

since isolation reliefs many of them from the social burden of their disease. This condition of forced isolation (lock-down) can be interpreted by some as a form of leveling of the stigma and pressure usually perceived by epileptic people in their ordinary life. Therefore, PwE report more frequently relief during this moment of temporary interruption.

CONCLUSION

We report results from an exploratory text mining study on how PwE and PwoE cope with the lock-down related to SARS-CoV-2. PwoE respond to the lock-down developing reactive anxiety while PwE seem to internalize this stressful event, developing feelings that lay in the depressive sphere. Moreover, some individuals reported relief in this period of isolation, these subjects are more represented in the PwE group.

LIMITATIONS

Due to privacy regulation we could not control the exact provenience of each answer, this could be a source of selection bias. Due to the nature of NLP our study is more descriptive than inferential thus is more helpful in making hypothesis from large set of data.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and

institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JL analyzed data and wrote the full manuscript. GA, OM, and CC helped in developing the surveys and interpreting the results and supervised the analysis process. MT, LR, TT, MP, and AM helped developing the surveys and greatly helped in spreading the survey among patients and controls. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We sincerely thank the President of Fondazione-Epilessia LICE, Amedeo Bianchi and all the members of the administration board for aiding the distribution of our survey through their social channels.

REFERENCES

1. Vogt VL, Äikiä M, Barrio del A, Boon P, Borbély C, Bran E, et al. Current standards of neuropsychological assessment in epilepsy surgery centers across Europe. *Epilepsia*. (2017) 58:343–55. doi: 10.1111/epi.13646
2. Sheikhalishahi S, Miotto R, Dudley JT, Lavelli A, Rinaldi F, Osmani V. Natural language processing of clinical notes on chronic diseases: systematic review. *JMIR Med Inform*. (2019) 7:e12239. doi: 10.2196/12239
3. Hripcsak G, Friedman C, Alderson PO, DuMouchel W, Johnson SB, Clayton PD. Unlocking clinical data from narrative reports: a study of natural language processing. *Ann Internal Med*. (1995) 122:681–8. doi: 10.7326/0003-4819-122-9-199505010-00007
4. Cenci C, Mecarelli O. Digital narrative medicine for the personalization of epilepsy care pathways. *Epilep Behav*. (2020) 111:107143. doi: 10.1016/j.yebeh.2020.107143
5. Falcone T, Dagar A, Castilla-Puentes RC, Anand A, Brethenoux C, Valleta LG, et al. Digital conversations about suicide among teenagers and adults with epilepsy: a big-data, machine learning analysis. *Epilepsia*. (2020) 61:951–8. doi: 10.1111/epi.16507
6. Assenza G, Lanzone J, Ricci L, Boscarino M, Tombini M, Galimberti CA, et al. Electroencephalography at the time of Covid-19 pandemic in Italy. *Neurol Sci*. (2020) 41:1999–2004. doi: 10.1007/s10072-020-04546-8
7. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care at the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol*. (2020) 11:737. doi: 10.3389/fneur.2020.00737
8. Zhang Y, Jin R, Zhou Z-H. Understanding bag-of-words model: a statistical framework. *Int J Mach Learn & Cyber*. (2010) 1:43–52. doi: 10.1007/s13042-010-0001-0
9. Naldi M. *A Review of Sentiment Computation Methods With R Packages. arXiv:190108319 [cs]*. (2019). Available online at: http://arxiv.org/abs/1901.08319 (accessed May 10, 2020).
10. Smith WG. *Does Gender Influence Online Survey Participation? A Record-Linkage Analysis of University Faculty Online Survey Response Behavior*. (2008) Available online at: https://eric.ed.gov/?id=ED501717 (accessed May 10, 2020).
11. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry*. (2003) 54:388–98. doi: 10.1016/s0006-3223(03)00469-4
12. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology*. (2013) 80:590–9. doi: 10.1212/WNL.0b013e31827b1ae0
13. Agrawal N, Bird JS, von Oertzen TJ, Cock H, Mitchell AJ, Mula M. Depression correlates with quality of life in people with epilepsy independent of the measures used. *Epilepsy Behav*. (2016) 62:246–50. doi: 10.1016/j.yebeh.2016.07.020
14. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, De Mojà R, et al. Epilepsy-associated stigma from the perspective of people with epilepsy and the community in Italy. *Epilepsy Behav*. (2019) 98:66–72. doi: 10.1016/j.yebeh.2019.06.026
15. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, Ulivi M, et al. Depressive symptoms and difficulties in emotion regulation in adult patients with epilepsy: association with quality of life and stigma. *Epilep Behav*. (2020) 107:107073. doi: 10.1016/j.yebeh.2020.107073
16. Oosterhuis A. Coping with epilepsy: the effect of coping styles on self-perceived seizure severity and psychological complaints. *Seizure*. (1999) 8:93–96. doi: 10.1053/seiz.1998.0255

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 20 August 2020
doi: 10.3389/fneur.2020.00910

Acute Ischemic Stroke and COVID-19: Experience From a Comprehensive Stroke Center in Midwest US

Parneet Grewal[*†], *Pranusha Pinna*[†], *Julianne P. Hall, Rima M. Dafer, Tachira Tavarez, Danielle R. Pellack, Rajeev Garg, Nicholas D. Osteraas, Alejandro Vargas, Sayona John, Ivan Da Silva*[‡] *and James J. Conners*[‡]

Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, United States

OPEN ACCESS

Edited by:
Tomohisa Nezu, Hiroshima University, Japan

Reviewed by:
Anna M. Planas, Consejo Superior de Investigaciones Científicas (CSIC), Spain
Lina Palaiodimou, University General Hospital Attikon, Greece

***Correspondence:**
Parneet Grewal
parneetgrewal298@yahoo.com

[†]*These authors have contributed equally to this work and share first authorship*

[‡]*These authors have contributed equally to this work and share senior authorship*

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *17 June 2020*
Accepted: *15 July 2020*
Published: *20 August 2020*

Citation:
Grewal P, Pinna P, Hall JP, Dafer RM, Tavarez T, Pellack DR, Garg R, Osteraas ND, Vargas A, John S, Da Silva I and Conners JJ (2020) Acute Ischemic Stroke and COVID-19: Experience From a Comprehensive Stroke Center in Midwest US. Front. Neurol. 11:910. doi: 10.3389/fneur.2020.00910

Background: COVID-19 has been associated with increased risk of venous and arterial thromboembolism including ischemic stroke. We report on patients with acute ischemic stroke and concomitant COVID-19 in a diverse patient population.

Methods: This is a retrospective analysis of patients hospitalized with acute ischemic stroke (AIS) and COVID-19 to our comprehensive stroke center in Chicago, IL, between March 1, 2020, and April 30, 2020. We reviewed stroke characteristics, etiologies, and composite outcomes. We then compared our cohort with historic patients with AIS without COVID-19 admitted in the same time frame in 2019 and 2020.

Results: Out of 13 patients with AIS and COVID-19, Latinos and African-Americans compromised the majority of our cohort (76.8%), with age ranging from 31–80 years. Most strokes were cortical (84.6%) and more than 50% of patients had no identifiable source, and were categorized as embolic stroke of unknown source (ESUS). A trend toward less alteplase administration was noted in the COVID-19 stroke patients compared to the non-COVID group from 2020 and 2019 (7.1 vs. 20.7% p 0.435 and 7.1 vs. 27.2% p 0.178). Endovascular thrombectomy was performed in 3 (23%) patients. Systemic thrombotic complications occurred in 3 (23%) COVID-19 AIS patients. Median National Institutes of Health Stroke Scale and modified Rankin Scale at discharge were 11 (IQR 4–23) and 4 (IQR 3–4), respectively. In the logistic regression model corrected for age and sex, COVID-19 was associated with discharge to mRS > 2 (p 0.046, OR 3.82, CI 1.02–14.3). Eight patients (63.8%) were discharged home or to acute rehabilitation, and two deceased from COVID-19 complications.

Conclusion: AIS in the setting of COVID-19 is associated with worse outcomes, especially among African-American and Latino populations. Large vessel disease with ESUS was common suggesting an increased risk of coagulopathy and endothelial dysfunction as a potential etiology.

Keywords: acute ischemic stroke, COVID-19, racial disparity, coronavirus, stroke care

INTRODUCTION

The severe acute respiratory distress syndrome virus (SARS-CoV-2) causing the coronavirus disease 2019 (COVID-19) was first identified in Wuhan, China, and has since spread throughout the world at an alarming rate, affecting over 7 million people as of June 7, 2020 (1). Neurologic involvement including stroke has been reported (2, 3). Ischemic strokes in COVID-19 have been associated with poor outcomes but the data are mainly limited to Asian and white populations. Data on the potential increased risk of stroke in COVID-19 has not yet been reported in racially diverse patient populations such as Latinos and African-Americans (4, 5).

In this manuscript, we report clinical and laboratory characteristics along with outcomes of patients with COVID-19 and acute ischemic stroke (AIS) who presented to our comprehensive stroke center in Chicago, IL, between March 1, 2020 and April 30, 2020. Our tertiary care center has been in the epicenter of the outbreak in Chicago in the Midwest US and regularly cares for an underserved and diverse patient population with lower health literacy. To validate our findings, to further identify mechanisms of stroke and outcome variables, we compared our cohort with stroke patients from the same time frame in 2020 along with historical cohort from 2019.

METHODS

We conducted a retrospective observational analysis of the medical records of all patients admitted to Rush University Medical Center in Chicago, Illinois, United States, between March 1, 2020 and April 30, 2020, with the diagnosis of AIS, confirmed on magnetic resonance imaging (MRI) or computed tomography (CT) and who were positive for COVID-19 with real-time reverse transcriptase polymerase-chain-reaction assay from a nasopharyngeal swab. To compensate for any seasonal or monthly variation in incidence and mortality from AIS, we compared the cohort with a control group of non-COVID-19 AIS patients hospitalized within the matched time frame in 2020. We also compared with a historical cohort from 2019 to control for any changes in the patient population over time. Two different cohorts were used as control to avoid random variation in demographics between pre-COVID and COVID-era.

Demographics and clinical and laboratory data were collected via a review of the electronic medical record system. These included age, gender, ethnicity, pre-existing vascular risk factors, admission vital signs, laboratory values, and National Institutes of Health Stroke Scale (NIHSS) score on admission and at discharge (or at the time of data collection for patients still hospitalized). We divided the patients with COVID-19 AIS into the "COVID" group, defined as patients admitted initially with COVID-19 symptoms then subsequently developing AIS, and the "neuro" group, with patients admitted for AIS as initial symptoms, and tested positive for COVID-19. "COVID" group had more extensive inflammatory and coagulopathy workup. All patients received acute stroke care per the American Heart Association and American Stroke Association guidelines (6).

We used the (TOAST) classification to determine stroke etiology (7). All AIS patients received extensive evaluation including advanced cardiac imaging, hypercoagulability panel, and prolonged cardiac monitoring while admitted inpatient. We further evaluated cryptogenic stroke patients to identify embolic stroke of unknown source (ESUS) etiology according to the published criteria (8). Patients with potential stroke mechanisms thought to be due to hypercoagulable state due to COVID-19 were placed under cryptogenic and/or ESUS mechanisms.

Outcome measures were based on discharge disposition and modified Rankin Scale (mRS) (9). COVID-19 severity was defined as mild, regular, or severe/critical based on the 7th edition of "Novel Coronavirus Pneumonia Diagnosis and Treatment Plan," with the description as follows: mild, defined as minor clinical symptoms and lack of lung inflammation on imaging; regular, with fever and respiratory tract symptoms, and evidence of visible lung inflammation on imaging; severe, with either shortness of breath, RR more than 30 breaths per minute, or SpO2 <93% at rest on pulse oximetry; and critical, with the need for mechanical ventilation or the presence of shock or combined failure of other organs requiring ICU monitoring (10).

Statistical testing was used to detect in-between group differences and association of individual variables to the pre-selected outcomes. The cohort groups were compared using Student's *t*-test for parametric continuous variables, MannWhitney U test for non-parametric continuous variables, and Fisher's exact test for dichotomous variables. Logistic regression was used to analyze selected variables (either clinically relevant or with statistical association in the first analysis) in regards to the pre-selected outcome measurements, correcting for confounding factors. All analyses were performed using commercially available SPSS (v. 21, Chicago IL, USA) statistical software. Significance was set at $p < 0.05$. Data were collected using REDCap, an electronic data capture tool hosted at our institution (11). This research protocol was approved by the Rush University institutional review board.

RESULTS

Demographics and Clinical Characteristics

Between March 1, 2020 and April 30, 2020, ∼650 patients were hospitalized with COVID-19, of whom 13 patients had AIS (estimated percentage of 2.0%). The COVID-19 AIS cohort was mostly comprised of Latino (46.1%) and African-American (30.7%) individuals, ages ranging from 31 to 80 years (mean 61.6 years). There were 6 patients in the "COVID" group (47%) and 7 in the "Neuro" group (53%). The average time for diagnosis of AIS in the "COVID" group after the hospitalization was 7.1 ± 5.1 days. Conventional vascular risk factors were common in both with no specific predilection for either the "COVID" or the "Neuro" groups. The three most common risk factors in the COVID-19 AIS cohort were hypertension (69.2%), type 2 diabetes mellitus (DM) (69.2%), and hyperlipidemia (30.7%). The COVID-19 was considered severe or critical in 61.5% ($n = 8$)

Abbreviations: SARS-CoV-2, severe acute respiratory distress syndrome virus; COVID-19, coronavirus disease 19; NIHSS, National Institutes of Health Stroke Scale.

TABLE 1 | Demographics and clinical features of 13 consecutive acute ischemic stroke patients with COVID-19 infection.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Presenting symptoms (COVID vs. Neuro)	COVID	COVID	COVID	COVID	COVID	COVID	Neuro	Neuro	Neuro	Neuro	Neuro	Neuro	Neuro
Time of onset of neuro symptoms	(2 days)	(15 days)	(3 days)	(11 days)	(4 days)	(8 days)							
Age range	55–60	70–75	55–60	75–80	60–65	70–74	35–40	65–70	80–85	60–65	45–50	80–85	30–35
Race/Ethnicity	AA	Other	Latino	Other	AA	AA	White	Latino	Latino	AA	Latino	Latino	Latino
Vascular risk factors	None	HTN, DM2, CAD	HTN, HLD, DM2	HTN, Afib	HTN, Obesity	HTN, DM2	DM2	HTN, DM2 Obesity	DM2	HTN, HLD, DM2, CAD	HTN, HLD, DM2	HTN, HLD	None
Severity of COVID-19*	Regular	Severe/ critical	Severe/critical	Severe/ critical	Mild	Mild	Mild	Severe/ critical	Severe/ critical	Severe/ critical	Severe/critical	Regular	Severe/critical
Admission GCS	15	15	13	12	14	11	15	13	14	6	5	15	14
NIHSS on admission	2	2	23	6	3	23	4	26	4	28	22	13	11
NIHSS on discharge or last NIHSS on exam	2	4	13	14	2	18	6	3	28	19	35	0	16
mRS on discharge or last mRS on exam	2	3	4	5	2	3	4	3	6	4	6	0	4
Stroke etiology	Cryptogenic	SW disease	Cryptogenic	Cardio-embolism (Afib)	Cardio-embolism (MI < 4 weeks)	Large artery atherosclerosis (ICA)	Cryptogenic	Cryptogenic	Cryptogenic	Cardio-embolism (PFO with *in situ* DVT)	Large artery atherosclerosis (ICA)	Cryptogenic	Cryptogenic
	ESUS		ESUS				ESUS	ESUS	ESUS			ESUS	ESUS
Stroke location	Cortical	Subcortical	Cortical	Cortical	Cortical	Cortical	Cortical	Cortical	Cortical	Cortical	Cortical	Cortical	Brainstem and cerebellum
	Bilateral, multifocal	Left MCA	Left MCA	Right MCA	Right MCA	Right MCA	Left MCA	Left PCA	Left PCA, right MCA	Left PCA left MCA	Left MCA	Right MCA	
Large vessel occlusion	No	No	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No	No
Acute intervention	No	No	Thrombectomy/ TICI2B	No	No	No	Thrombectomy/ TICI2B	No	No	No	IV-tPA thrombectomy/ TICI3	IV-tPA	No
Systemic arterial or venous thrombosis	No	No	Arterial	No	No	No	No	No	No	Deep venous	No	No	Arterial
Disseminated intravascular coagulopathy	No	No	No	Yes	No	No	No	No	No	No	No	No	No
Therapeutic anticoagulation	None	None	Enoxaparin	Apixaban	None	None	Apixaban	None	None	Rivaroxaban	None	Coumadin	Enoxaparin
Antiplatelets	None	Aspirin	None	Aspirin	Ticagrelor aspirin	Aspirin	None	Aspirin	Aspirin	None	None	Clopidogrel	None
Discharge disposition	Home	Acute rehab	Acute rehab	LTAC	Home	Acute rehab	Acute rehab	Acute rehab	Expired	LTAC	Expired	Home	-

**Severity of COVID-19 infection was based on the 7th edition of "Novel Coronavirus pneumonia diagnosis and treatment plan" and the patients were divided into mild form (clinical symptoms are minor and imaging does not show any lung inflammation), regular (has fever and respiratory tract symptoms, imaging shows visible lung inflammation), severe (adults who have either shortness of breath, RR>30 breaths/min, SpO2 < 93% at rest) and critical form (mechanical ventilation required or shock or combined failure of other organs that requires ICU monitoring) (10).*

COVID-19, Coronavirus disease 19; F, Female; M(Male; AA, African-American; HTN, Hypertension; HLD, Hyperlipidemia; DM2, Diabetes mellitus type 2; CAD, coronary artery disease; GCS, Glasgow comma scale; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; ESUS, Embolic stroke of unknown source; SW dis., Small vessel disease; MI, Myocardial infarction; ICA, Internal carotid artery; DVT, deep venous thrombosis; PFO, patent foramen ovale; MCA, middle cerebral artery; PCA, posterior cerebral artery; TICI, Thrombolysis in cerebral ischemia score; IV-tPA, intravenous-alteplase; LTAC, long-term acute care facility.

TABLE 2 | Admission vitals and admission laboratory values for acute ischemic stroke patients with COVID-19.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	Mean admission values
Presenting symptoms (COVID vs. Neuro)	COVID	COVID	COVID	COVID	COVID	COVID	Neuro	Neuro	Neuro	Neuro	Neuro	Neuro	Neuro	
Temp. (F)	102.5	100.2	99.2	95.4	97.3	97.4	98.0	99.2	98.1	101.7	97.8	98.4	98.7	99.5
MAP (mmHg)	82	75	111	96	61	107	91	113	104	111	01	6	116	82.6
HR (per minute)	128	85	118	151	49	93	68	80	87	101	76	48	94	90.6
RR (per minute)	20	36	23	10	18	20	18	24	18	38	28	13	19	21.9
SpO2 (%)	99	95	94	97	98	95	97	76	89	78	97	100	99	93.3
WBC (K/uL) (range)	0.21 (0.24–12.57)	5 (5–15.12)	19.53 (7.23–21.9)	7.82 (5.65–10.92	20.95 (11.52–24.19)	6.51 (5.80–10.19)	15.15 (6.85–15.15)	11.74 (5.86–11.91)	5.39 (5.00–11.23)	7.74 (7.74–15.05)	7.5 (7.5–22.4)	4.45 (2.49–5.21)	6.23 (6.23–15.53)	9.09
Lymphocyte count (K/uL) (range)	0.59 (0.21–0.98)	0.58 (0.53–2.62)	0.97 (0.76–1.55)	0.67 (0.54–2.17)	0.98 (0.98–1.82)	–	4.22 (4.22–3.25)	0.50 (0.58–1.58)	0.87 (0.82–0.97)	1.81 (0.59–2.6)	02.2 (0.52–2.2)	0.67 (0.44–1.16)	1.24 (1.22–1.52)	1.27
Platelet count (K/uL) (range)	4 (4–46)	187 (110–243)	468 (355–868)	83 (30–204)	277 (277–486)	309 (263–357)	348 (228–348)	219 (214–477)	293 (265–364)	284 (153–318)	173 (140–200)	224 (158–235)	292 (172–399)	243.15
AST (U/L) (range)	6 (5–152)	77 (22–113)	186 (18–256)	1023 (32–1626)	89 (19–89)	24 (24–55)	16 (12–30)	376 (24–395)	19	64 (18–78)	15 (15–162)	32 (32–129)	96 (25–96)	155.6
ALT (U/L) (range)	20 (8–262)	65 (16–96)	130 (10–144)	360 (24–649)	15 (13–17)	26 (26–68)	29 (19–31)	364 (24–364)	13	34 (25–57)	12 (8–24)	22 (22–62)	195 (105–195)	98.8
Creatinine (mg/dL) (range)	0.62 (0.49–0.67)	2.97 (1.78–4.6)	1.07 (0.77–1.12)	5.46 (1.16–5.46)	3.13 (2.16–3.29)	2.39 (2.39–2.81)	0.71 (0.51–0.71)	2.11 (0.67–2.38)	2.48 (2.05–2.48)	1.9 (0.83–3.84	3.24 (2.3–10.01)	3.05 (3.05 – 8.0)	0.66 (0.57–0.72)	2.29
D-dimer (mg/L FEU) (range)	>27.5	>27.5 (6.07–>22.50)	14.78 (2.04–14.78)	>27.50	3.79 (3.13–3.79)	3.79	0.32 (0.30–0.32)	2.92	3.99 (2.65– 3.99)	<0.10 (<0.10–7.4)	17.76 (1.15–374)	–	7.5 (2.58–7.51)	>11.4
CRP (mg/dL) (range)	211.2 (146.3–367.3)	229.7 (16.5–501.8)	84.2 (84.2–364.5)	49.1 (29.8–148.1)	313.1 (131.7–313.1)	41.6	10.8 (10.8–28.6)	304 (67–387.8)	200.4 (200.4–309.9)	10 (7.7–374.3)	15.1 (15.1–384)	19.5 (14.0–19.5)	<5.0 (<5.0–226.8)	114.9
Ferritin (ng/mL) (range)	6,037	2,241 (1,884–5,176)	671 (503–790)	681 (257–791)	3,038	771	27 (27–34)	1,396 (341–1,396)	372 (349–372)	624 (423–1,749)	361 (36–4,942)	2,810	1,732 (931–1,732)	1,597
LDH (U/L) (range)	124 (124–228)	532 (478–678)	678 (272–678)	891 (320–1351)	928	413	193 (193–198)	511 (435–523)	407 (307–407)	907 (418–907)	356 (356–1,063)	371 (371 –446)	548 (246–548)	527.6
Fibrinogen (mg/dL) (range)	436	311 (253–311)	702 (676–702)	90 (65–436)	783	715	489 (489–599)	813	813	–	507 (507–785)	239	–	536.18
CK (U/L) (range)	12	637 (87–1,246)	19,247 (72–19,247)	52 (15–129)	765 (146–765)	168	42.0 (21.0–53.0)	177 (74–511)	48	1,018 (400–3,475)	1,925 (1891–3,226)	163 (76–163)	9	1,866.3

COVID-19, coronavirus disease 2019; Temp., Temperature; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate; SpO2, pulse oximetry; WBC, white blood cells; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; LDH, lactate dehydrogenase; CK, creatinine kinase.

divided between the "COVID" (50%) and the "Neuro" (71.4%) groups, and mild and/or regular in 38.5% ($n = 5$) of patients. Out of the 13 patients, 30.7% ($n = 4$) patients also had superimposed bacterial infection. Median admission NIHSS was 16 (IQR 4–23) in all the COVID-AIS patients, with higher score of 13 in the "Neuro" group compared to 4.5 in the "COVID" group (**Table 1**).

Laboratory Characteristics

Initial vitals and laboratory values are demonstrated in detail in **Table 2**. Average temperature was 99.6 ± 1.8 degree F, mean arterial pressure was 82.6 ± 38.7 mmHg, heart rate was 90.6 ± 29.4 beats per minute, respiratory rate was 22 ± 8 breaths per minute, and oxygen saturation was 93.3 ± 7.8%. Patients in the "COVID" group were more likely to have multiorgan failure and elevated inflammatory and coagulopathy markers (**Table 2**).

Outcome Measures

Ischemic strokes were predominantly cortical (84.6%), in the distribution of the middle cerebral artery (76.9%), followed by the posterior cerebral artery (23%). Stroke etiology was classified as cryptogenic and/or ESUS in 53.8% ($n = 7$), cardioembolic in 23% ($n = 3$), large artery atherosclerosis in 15.3% (n = 2), and small vessel disease in 7% ($n = 1$). ESUS was suspected in 71.4% of "Neuro" compared to 33.3% of "COVID." Overall, 60% ($n = 3$) of patients with evidence of large vessel occlusion (LVO) underwent endovascular thrombectomy. While the "COVID" group had more LVO (50%), more patient in the "Neuro" group (42.8 vs. 16.6%) received acute stroke interventions, with delays in identification of AIS symptoms in the "COVID" group attributed to masking of symptoms by the COVID-19 systemic manifestations. Therapeutic anticoagulation was initiated in 38.4% ($n = 5$) patients due to concerns of hypercoagulable state and in 7% ($n = 1$) due to atrial fibrillation. The median NIHSS at discharge for the COVID AIS cohort was 11 (IQR 4–23), with median mRS of 4 (IQR 3–4). Favorable outcome with discharges to home or to acute rehabilitation facilities was seen in 61.5% ($n = 3$) Two patients (15.3%) expired from COVID-19 complications, and two (15.3%) required long term facility care. One patient remains hospitalized (**Table 1**).

Univariate and Logistic Regression Analysis

Except for DM type 2 which was more prevalent in the COVID-19 AIS group (64.2 vs. 24.5%, p 0.008), patients were overall

TABLE 3 | Comparison of acute ischemic stroke patients with COVID-19 infection with acute ischemic stroke patients without COVID-19 infection admitted in the same time frame of March 1, 2020–April 30, 2020, and March 1, 2019–April 30, 2019.

	1. COVID-AIS group (*N* = 13)	2. AIS group 2020 (*N* = 53)	3. AIS group 2019 (*N* = 88)	*p*-value 1 vs. 2	*p*-value 1 vs. 3
Age (mean)	61.6	63	68	0.935	0.096
Male Sex (%)	46.1	52.8	51.1	0.569	0.597
Race/Ethnicity (%)					
Latino	46	9.5	9	**0.0075**	**0.0036**
African American	31	32	36	0.989	0.766
Comorbidities (%)					
CAD	15.3	15	19.3	0.664	0.738
DM	69.2	24.5	38.6	**0.006**	0.069
HTN	69.2	52.8	75	0.549	0.522
HLD	30.7	39.6	42	0.548	0.397
CHF	7.6	3.7	13.6	0.992	0.689
Prior ischemic stroke	0	13.2	17	–	–
PAD	15.2	0	7.9	–	0.603
Alcohol/drug abuse	0	11.3	6.8	–	–
Tobacco abuse	0	22.6	22.7	–	–
Obesity (BMI > 30)	15.2	28.3	32.9	0.496	0.219
Admission NIHSS (median) (IQR)	16 (4–23)	8 (3–19)	7 (2–16)	0.081	0.089
Discharge NIHSS (median) (IQR)	11 (4–23)	3 (2–13)	4 (1–11)	**0.036**	**0.042**
Stroke Etiology (%)					
Cryptogenic and/or ESUS	53.8	47.1	30.6	0.763	0.121
Cryptogenic and/or ESUS + cardio-embolism	76.9	67.9	61.3	0.519	0.244
IV-tPA (%)	15.3	20.7	27.2	0.435	0.178
EVT (%)	23	20.75	26.1	0.999	0.507
Discharge mRS (median) (IQR)	4 (3–4)	3 (1–4)	3 (1–4)	0.050	0.063
Discharge mRS >2 (%)	76.9%	47.16	40.9	**0.047**	**0.010**

COVID-19, coronavirus disease 2019; AIS, Acute ischemic stroke; CAD, coronary artery disease; DM, Diabetes mellitus type 2; HTN, Hypertension; HLD, Hyperlipidemia; CHF, congestive heart failure; PAD, peripheral artery disease; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; ESUS, Embolic stroke of unknown source; IV-tPA, intravenous-tissue plasminogen activator; EVT, Endovascular thrombectomy; mRS, modified Rankin Scale. The bold numerical values indicates statistically significant.

equally balanced for age, sex and comorbidities with the non-COVID stroke cohorts from 2019 and 2020. The COVID-19 AIS group had more Latinos compared to both historical 2019 and 2020 cohorts (46.1 vs. 9%, p 0.0036 and 46.1 vs. 9.5%, p 0.0075). The percentage of African-American patients in all groups was similar (31 vs. 32%, p 0.989 and 31 vs. 36%, p 0.766). While the median admission NIHSS was not different among the COVID-19 AIS and the non-COVID-19 stroke patients in 2020 and 2019, the discharge NIHSS was significantly higher [11 (IQR 4–23) vs. 3 (IQR 2–13), p 0.036 and 11 (IQR 4–23) vs. 4 (IQR 1–11), p 0.042]. There was a trend toward less alteplase administration in the COVID-19 AIS patients though no statistically significant (7.1 vs. 20.7%, p 0.435 and 7.1 vs. 27.2%, p 0.178). COVID-19 AIS cohort had worse mRS > 2 at discharge (78.5 vs. 47.16%, p 0.047 and 78.5 vs. 40.9%, p 0.010) (**Table 3**), even after correction for age and sex in a logistic regression model [p 0.046, OR 3.82, (CI 1.02–14.3)].

DISCUSSION

In this single-center retrospective observational study, we identified 13 patients with AIS and concomitant COVID-19. Approximately 2.0% of all COVID-19 patients at our institution were diagnosed with AIS, a percentage higher than previously reported in the literature from the USA (12) but similar to that from Wuhan, China (5). The mean age of patients with AIS and COVID-19 was 61.6, without significant sex predilection. Unlike the data emerging out of New York (12), there was a higher percentage of Latinos and African Americans in our cohort (76.8%), highlighting the racial disparity of COVID-19 in our Metropolitan city. Several studies have highlighted the disproportionate burden of this disease on these communities. Social and economic disparities, less access to healthcare along with genetic factors associated with more potent thrombo-inflammatory response may have contributed to higher infection rate and worse outcome in Latinos and African-Americans (13, 14). The majority of our patients had the severe or critical form of COVID-19, which re-iterates the prior published findings of high prevalence of neurological complications seen in this group (2). Also, the trend toward cortical strokes with etiological classification as ESUS reflects the coagulopathy and potential causal link between COVID-19 and stroke (12).

The delay in conventional stroke interventions especially amongst patients who developed AIS while receiving treatment for COVID-19 may be explained by the masking of acute stroke symptoms by the viral illness, delay in stroke symptoms recognition, and/or use of anticoagulation at the time of evaluation.

Several potential mechanisms can lead to a stroke in the setting of COVID-19. Angiotensin-converting enzyme which is the target site of SARS-CoV2 is expressed by cells of the nervous system. This renders the brain at risk of direct endothelial cell infection and diffuse endothelial inflammation (15). COVID-associated coagulopathy which is likely the result of intense inflammatory response, can lead to increased thrombotic complications including ischemic stroke (16). Cardiac involvement is also a prominent feature of COVID-19, leading to stress cardiomyopathy, direct myocardial injury, and arrhythmias with potential increased risk of ischemic stroke (17). Lastly, prolonged hospitalization and dysautonomia may lead to ischemic stroke especially in the setting of septic shock and hypotension (18).

STRENGTHS AND LIMITATIONS

Our study provides a detailed description of patients with COVID-19 and AIS and highlights the racial disparity and poor outcomes associated with this highly contagious viral infection. This study also highlights that despite COVID-19 affecting elderly patients more severely, increased risk of AIS in COVID-19 is independent of age. Comparison with current and historical cohorts suggests a direct causal link of COVID-19 and AIS highlighting the importance of checking for COVID-19 in patients with ESUS and/or cryptogenic stroke mechanisms.

Our study has several limitations with its small size, retrospective approach, and lack of long term follow up and outcome. We also suspect that the incidence of AIS is much higher as many patients with the infection may have succumbed to the disease before identification of the stroke symptoms, or may not have been evaluated by the neurology service, and thus the neurological symptoms may not have been captured.

CONCLUSION

In summary, ischemic stroke in COVID-19- tend to be more severe, mainly cortical, may occur independent of common vascular risk factors, does not have sex predilection and can affect younger population also. AIS in COVID-19 was more commonly seen in Latino and African American communities by our group, a reflection of the health care disparity and limited access to care among the minority population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Rush University Institutional review board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PG and PP contributed equally as first authors in the acquisition of data, interpretation of data, and manuscript writing. ID and JC contributed equally as last authors in the interpretation of data

and critical revision of the manuscript for intellectual content. JH, RD, TT, DP, RG, NO, AV, and SJ contributed in design and acquisition of data. All authors take full responsibility for the credibility of the data and results of the manuscript.

ACKNOWLEDGMENTS

We would like to acknowledge our data coordinators, Anjali Asthana MPH, MS, Kelsey Fegan BS, Vikram Patel MSN, RN.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in china, 2019. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, china. *JAMA Neurol.* (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
3. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe sars-cov-2 infection. *N Engl J Med.* (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
4. Escalard S, Maïer B, Redjem H, Delvoye F, Hébert S, Smajda S, et al. Treatment of acute ischemic stroke due to large vessel occlusion with covid-19: experience from paris. *Stroke.* (2020) 51:2540–3. doi: 10.1161/STROKEAHA.120.030574
5. Qin C, Zhou L, Hu Z, Yang S, Zhang S, Chen M, et al. Clinical characteristics and outcomes of covid-19 patients with a history of stroke in Wuhan, China. *Stroke.* (2020) 51:2219–23. doi: 10.1161/STROKEAHA.120.030365
6. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2019) 50:e344–418. doi: 10.1161/STR.0000000000000211
7. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke.* (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
8. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol.* (2014) 13:429–38. doi: 10.1016/S1474-4422(13)70310-7
9. Broderick JP, Adeoye O, Elm J. Evolution of the modified rankin scale and its use in future stroke trials. *Stroke.* (2017) 48:2007–12. doi: 10.1161/STROKEAHA.117.017866
10. *Novel Coronavirus Pneumonia Diagnosis and Treatment Plan* (Provisional 7th ed.). Available online at: https://www.chinalawtranslate.com/en/coronavirus-treatment-plan-7/ (accessed April 30, 2020).
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (redcap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* (2009) 42:377–81 doi: 10.1016/j.jbi.2008.08.010
12. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. Sars2-cov-2 and stroke in a new york healthcare system. *Stroke.* (2020). 51:2002–11. doi: 10.1161/STROKEAHA.120.030335
13. Yancy CW. COVID-19 and African Americans. *JAMA.* (2020) 323:1891–2. doi: 10.1001/jama.2020.6548
14. Vepa A, Bae JP, Ahmed F, Pareek M, Khunti K. COVID-19 and ethnicity: a novel pathophysiological role for inflammation. *Diabetes Metab Syndr.* (2020) 14:1043–51. doi: 10.1016/j.dsx.2020.06.056
15. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in covid-19. *Lancet.* (2020) 395:1417–8 doi: 10.1016/S0140-6736(20)30937-5
16. Connors JM, Levy JH. Covid-19 and its implications for thrombosis and anticoagulation. *Blood.* (2020) 135:2033–40. doi: 10.1182/blood.2020006000
17. Akhmerov A, Marbán E. Covid-19 and the heart. *Circ Res.* (2020) 126:1443–55. doi: 10.1161/CIRCRESAHA.120.317055
18. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with covid-19: the albacovid registry. *Neurology.* (2020). doi: 10.1212/WNL.0000000000009937

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 25 August 2020
doi: 10.3389/fneur.2020.00928

MENA-SINO Consensus Statement on Implementing Care Pathways for Acute Neurovascular Emergencies During the COVID-19 Pandemic

Hosam Al-Jehani[1,2†], Seby John[3†], Syed Irteza Hussain[3], Amal Al Hashmi[4], May Adel Alhamid[5], Dareen Amr[6], Atilla Ozcan Ozdemir[7,8], Ashfaq Shuaib[9], Adel Alhazzani[10], Mohammad Ghorbani[11], Ossama Mansour[6] and Maher Saqqur[9,12] on behalf of the MENA-SINO group*

[1] Department of Neurosurgery and Interventional Radiology, King Fahad Hospital of the University, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, [2] Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada, [3] Neurological Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates, [4] Central Stroke Unit, Ministry of Health of Oman, Khoula Hospital, Muscat, Oman, [5] Department of Neurology and Interventional Radiology, King Fahad Hospital of the University, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, [6] Stroke and Neurointervention Unit, Neurology Department, Alexandria University School of Medicine, Alexandria, Egypt, [7] Department of Neurology, Neurocritical Care, Eskisehir Osmangazi University, Eskişehir, Turkey, [8] Department of Neurology, Stroke Center, Eskişehir, Turkey, [9] Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada, [10] Neurology Division, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia, [11] Division of Vascular and Endovascular Neurosurgery, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran, [12] Trillium Hospital, University of Toronto at Mississauga, Mississauga, ON, Canada

OPEN ACCESS

Edited by:
Beom Joon Kim, Seoul National University Bundang Hospital, South Korea

Reviewed by:
Yang-Ha Hwang, Kyungpook National University, South Korea
Luis Rafael Moscote-Salazar, University of Cartagena, Colombia

***Correspondence:**
Hosam Al-Jehani
hjehani@iau.edu.sa

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *14 June 2020*
Accepted: *17 July 2020*
Published: *25 August 2020*

Citation:
Al-Jehani H, John S, Hussain SI, Al Hashim A, Alhamid MA, Amr D, Ozdemir AO, Shuaib A, Alhazzani A, Ghorbani M, Mansour O and Saqqur M (2020) MENA-SINO Consensus Statement on Implementing Care Pathways for Acute Neurovascular Emergencies During the COVID-19 Pandemic. Front. Neurol. 11:928. doi: 10.3389/fneur.2020.00928

In the unprecedented current era of the COVID-19 pandemic, challenges have arisen in the management and interventional care of patients with acute stroke and large vessel occlusion, aneurysmal subarachnoid hemorrhage, and ruptured vascular malformations. There are several challenges facing endovascular therapy for stroke, including shortages of medical staff who may be deployed for COVID-19 coverage or who may have contracted the infection and are thus quarantined, patients avoiding early medical care, a lack of personal protective equipment, delays in door-to-puncture time, anesthesia challenges, and a lack of high-intensity intensive care unit and stroke ward beds. As a leading regional neurovascular organization, the Middle East North Africa Stroke and Interventional Neurotherapies Organization (MENA-SINO) has established a task force composed of medical staff and physicians from different disciplines to establish guiding recommendations for the implementation of acute care pathways for various neurovascular emergencies during the current COVID-19 pandemic. This consensus recommendation was achieved through a series of meetings to finalize the recommendation.

Keywords: COVID, endovascular therapy, recommendation, MENA, acute ischemic stroke, subarachnoid hemorrhage

BACKGROUND

The novel coronavirus disease (COVID-19) was first identified in the Wuhan province of China in late December 2019 and spread rapidly around the globe. Consequently, a pandemic characterized by a rapid spread through respiratory droplets with human-to-human contact was declared by the World Health Organization on March 11, 2020 (1–4).

COVID-19 in the Middle East

COVID-19 is the second coronavirus outbreak to affect the Middle East, following the MERS-CoV reported in Saudi Arabia in 2012. The United Arab Emirates (UAE) was the first Middle East country to report a coronavirus-positive case, following the Wuhan coronavirus outbreak in China (4).

COVID-19 and Stroke

COVID-19 is increasingly being recognized as a cause of thromboembolic phenomena, such as acute ischemic strokes and cerebral venous sinus thrombosis (5).

CHALLENGES OF INTRAVENOUS THROMBOLYSIS AND ENDOVASCULAR THERAPY (EVT) INTERVENTIONS

Patient Avoidance of Seeking Medical Attention

Published and anecdotal reports suggest that during the pandemic, there has been a drastic reduction in the number of stroke patients being evaluated in the emergency room (ER) or being admitted to hospitals worldwide (6). It is highly unlikely that the incidence of stroke has suddenly changed or reduced. This could be explained by the inability to seek medical care due to the extreme restrictions established to limit virus transmission or fear of contracting the virus upon visiting the hospital. In addition tertiary care hospitals may be inundated with COVID-19 patients, and as such, patients with stroke are being treated at secondary-care facilities or may not be transferred to comprehensive stroke centers at all. Clearly, strokes remain an emergency, and patients should seek immediate care despite the current pandemic.

Healthcare Personnel Shortages

Healthcare personnel have a high risk of becoming infected during this novel pandemic, particularly before transmission dynamics are fully characterized. Of the COVID-19 cases reported to the Centers for Disease Control from February 12 to April 9, a proportion included data on whether the patient was a healthcare worker (HCW) in the USA, with up to 19% of cases identified as healthcare personnel (7). Quarantines for HCWs who have tested positive and for those with high-risk exposures could severely impact the smooth functioning of stroke units and may even jeopardize an entire department if it involves small numbers (e.g., a neurointerventional team). In addition, many hospitals are redeploying clinicians of all specialties to the care of COVID-19 patients, thereby draining resources of care for other medical conditions. Both of the above factors present a substantial challenge, even for well-established stroke centers, and stroke teams will likely experience staff shortages.

Hospital Beds for Stroke

It is likely that hospitals will be inundated with COVID-19 patients. Specifically, these patients will include individuals who are critically ill from a respiratory viewpoint; these patients will require intensive care unit (ICU) hospitalization, and many will require ventilators. Thus, disruptions in standard protocols such as post-thrombolysis and post-thrombectomy care should be expected, and variations in protocol or abbreviated protocols will be needed to efficiently utilize staffing and bed space while maintaining the best possible patient care. Repatriation from a comprehensive stroke center to lower levels of care following a period of stability after critical procedures, such as mechanical thrombectomy, aneurysm occlusion, or hematoma evacuation, may be reasonable (8).

Shortage of Personal Protective Equipment

The provision of adequate personal protective equipment (PPE) and clear guidelines on its application are imperative to protect healthcare personnel and to prevent viral spread among HCWs. Given that community transmission of COVID-19 is well-established in most areas, all stroke alerts presenting to the ER should ideally be treated as a potentially infected patient. While the use of PPE for maximum protection, as dictated by international and institutional bodies, is ideal, this practice may not be possible given the PPE shortages that are being encountered in many countries (9). Thus, responses to code stroke may be delayed due to PPE unavailability.

Anesthesia Challenges

Known or suspected COVID-19 patients as well as carriers will likely require mechanical thrombectomy for large vessel occlusion. This situation poses challenges regarding anesthetic management, given the urgent nature of the procedure and an "unknown" COVID-19 status. COVID-19 has a high risk of spreading through droplets and aerosols (1, 10). Bag-mask ventilation, intubation, extubation, and airway suctioning are aerosol-generating procedures, and any disconnection of the circuit risks further aerosolizing secretions. In theory, monitored anesthesia care (MAC) may prevent intense aerosolization; however, stroke patients undergoing MAC sedation may require supplemental oxygen via a nasal cannula mask or other methods, such as chin-lift or jaw thrust maneuvers, to improve oxygenation, which may increase the degree of airborne exposure to the anesthesia provider and other involved HCWs. Another consideration is the need to convert from MAC to general anesthesia (GA) in a minority of patients. Urgent intubation in a non-negative pressure room introduces an exposure risk to all team members within the room. In addition, workflows with regard to dedicated space for intubation pose additional challenges.

Delay in Treatment Timelines

While prehospital delays are expected, given travel, and transfer logistics amidst ongoing community lock-downs in many

countries, several challenges remain once the patient arrives at the ER. Protocols for protected stroke alerts have been published. Limited neurology personnel, PPE shortages, transfer times through designated corridors/elevators from the ER to imaging with appropriate PPE, unavailability of computerized tomography (CT) scanners during disinfection periods, and time for donning/doffing PPE are all potential factors that may increase door-to-needle times when treating patients with intravenous thrombolysis as well as door-to-puncture for thrombectomy.

Angiography Suite

To minimize exposure, staffing within the room should be kept to a minimum; however, some patients may be technically challenging, and an additional hand may be extremely helpful. Challenges while operating with multiple layers of PPE are foreseeable. The physical and psychological burden of neurointerventional stroke calls, particularly during the current pandemic, is likely substantial, especially given the small size of these teams. As reported by a recent survey of neurointerventional nurses and radiology technologists from 20 stroke centers in the USA, only 9 centers (45%) had more than 6 nurses or technologists in their call pools for stroke (11). Many institutions with multiple angiography suites are reserving one dedicated suite for suspected COVID-19 strokes or other emergencies.

MENA-SINO GUIDING RECOMMENDATIONS FOR EVT

As a leading regional neurovascular organization, MENA-SINO has established a task force comprised of physicians, nurses, and medical staff from different disciplines (neurology, neurosurgery, interventional neuroradiology, and neurocritical care) to establish guiding recommendations for the implementation of acute care pathways for various neurovascular emergencies during the current COVID-19 pandemic. These recommendations can be greatly enhanced by telemedicine options to minimize patient–physician interactions, as dictated by clinical needs. Other international entities have also published different guidelines, all aiming at achieving "protected code stroke protocol" (12–14).

We describe the following guiding recommendations to be implemented in the MENA region to facilitate care for patients and to provide optimal protection for HCWs.

1. Patients must be properly triaged to guide the safety of their clinical encounter (**Figure 1**).
2. A clear standardized list of priorities for treatment must be established across the different neurovascular pathologies (**Table 1**). This standardization will render treatments more efficient and will allow for optimal healthcare delivery, by establishing proper operational policies.
3. Outpatient and office visits should be conducted virtually to avoid unnecessary contact between patients and physicians.
4. Each patient should be transferred to another institution if required, as soon as he/she is sufficiently stable to receive the required intervention (**Table 1**).
5. COVID and non-COVID regions should be designated within the hospital to guide the safety and reciprocity of patient transfers between institutions.

The following process is recommended for the referring hospital:

Prehospital Stage

For all stroke patients presenting directly to the ER or being transferred, the following measures should be taken.

1. Infection control screening: Symptoms or signs of COVID-19, history of infection, contact with infected persons, and travel history should be obtained by emergency medical services (EMS) personnel evaluating the patient at the first encounter.
2. All patients should wear a surgical mask when able, irrespective of the screening outcome.
3. Pre-notification: Hospitals should be pre-notified regarding stroke specifics, COVID screening results, and suspicious cases, if any.
4. When available, telemedicine should be utilized for triage in the prehospital phase. If telemedicine is not available, off-label use of social messaging applications for remote medical consultation can be used, although caution is needed to respect patient data confidentiality.

Hospital Stage

Emergency Room

1. The ER should be divided such that separate spaces and corridors are available for COVID and non-COVID patients.
2. To screen for symptoms of COVID-19 in expedited manner to conform to the time-critical nature of stroke care (**Figure 1**).
3. All patients should wear a surgical mask.
4. Patients with a positive infection screen or those highly suspected, as reported by emergency medical services (EMS) or ER personnel should be roomed in a dedicated COVID area or negative-pressure room if available.
5. Telemedicine (telestroke) should be utilized when available to obtain history and to perform a neurological examination in order to limit direct contact between medical staff and patients.
6. A protective code stroke protocol should be established for patients with a positive COVID screen. One member of the stroke team should perform the evaluation and provide therapy donning full PPEs.
7. A scoring system should be established for risk stratification of HCW exposure and risk of COIVD-19 infection (**Table 2**).

Acute Imaging

1. Standard hospital imaging protocols should be followed for acute stroke treatments.
2. If multiple CT rooms are available, a dedicated CT scan room for COVID-19 patients should be established, provided that the addition of the chest CT does not incur a treatment delay of more than 5 min.
3. If positive pulmonary symptoms are present, consider performing low-dose chest CT simultaneously with head CT

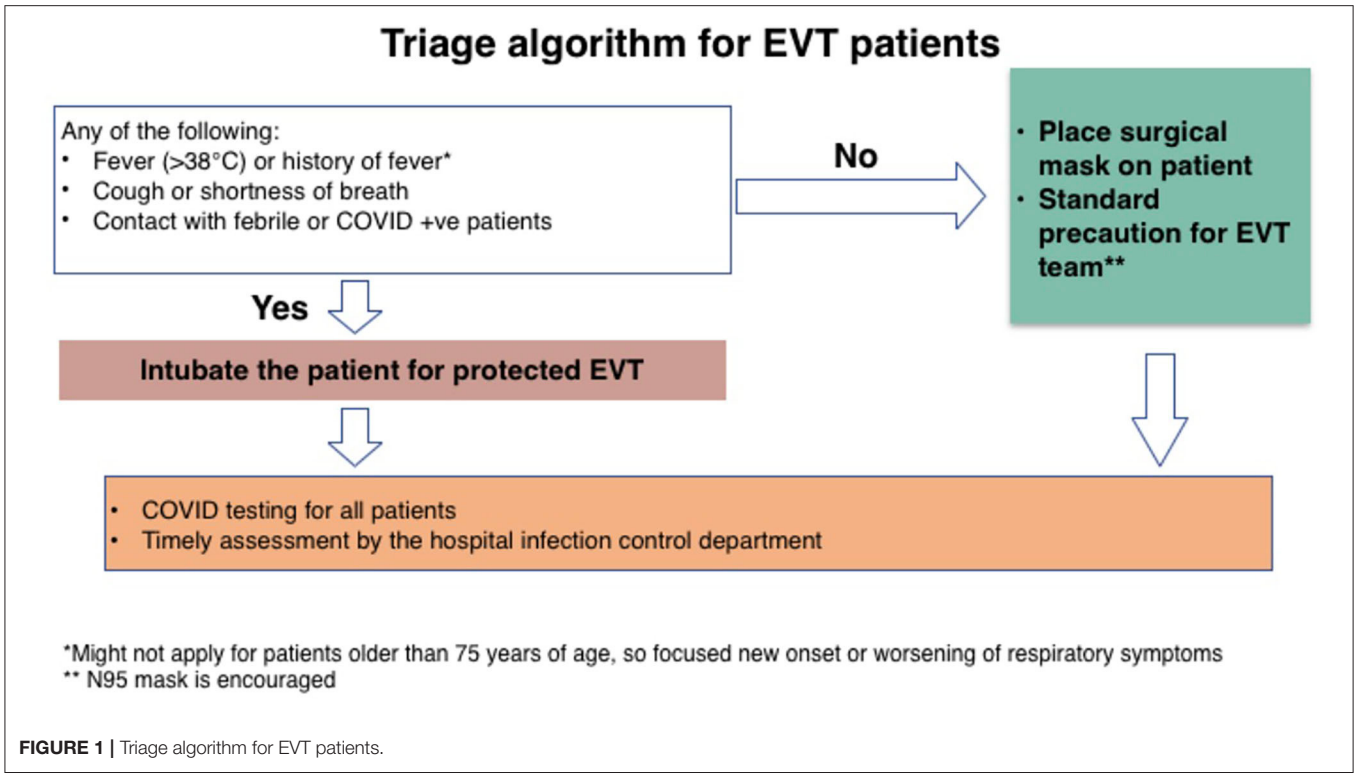


FIGURE 1 | Triage algorithm for EVT patients.

TABLE 1 | EVT priority of transfer based on disease entity.

Category	Timeline	Disease entity
Priority 1	Immediate: Acute life- threatening condition or acute transfer within 6 h	Acute ischemic stroke (AIS)
Priority 2	Within 24 h: Loss of life or significant function that can be saved	Coiling or clipping of a ruptured saccular aneurysm with SAH Craniotomy or embolization of a ruptured AVM with prenidal/nidal aneurysms Decompressive craniectomy or hematoma evacuation*
1. If there is not a high risk for in-hospital mortality (inferred from mortality and prognosis assessment scales such as SOFA)		
Priority 3	Within 1 week: Life or significant functional loss that can be saved by intervention within 1 week	Complex ruptured intracranial aneurysm requiring special preparation or equipment
Priority 4	Within 1 month: Life or significant functional loss that can be saved by intervention within 1 month	1. Ruptured AVM with no nidal aneurysms 2. High-grade dural AV fistulae with ICH 3. Carotid revascularization (endarterectomy or stenting) for symptomatic carotid stenosis
Priority 5	After the COVID-19 pandemic	Any other pathology with non-hemorrhagic or ischemic presentation, with a strong recommendation to address risk factors and provide continuous surveillance

using head and neck CT angiography (CTA). It is also wise to include chest CT in the stroke protocol, as PCR tests and the absence of pulmonary symptoms do not exclude the possibility of COVID-19 infection.

4. Avoid multiple visits to the CT room to minimize exposure.
5. For acute imaging, magnetic resonance imaging (MRI) should be avoided if possible. The use of MRI should be restricted to absolute necessities, following the guidance provided by the American College of Radiology on the use of MRI (15).

Acute Stroke Treatment: Intravenous Thrombolysis and Endovascular Thrombectomy

1. Patients should continue to be treated according to current standard guidelines for intravenous thrombolysis and endovascular mechanical thrombectomy, with the best adherence possible (16).
2. Although there are some situations for which the current guidelines have no clear answers or strong recommendations,

TABLE 2 | Healthcare worker exposure risk stratification.

Risk attribute for contact with COVID-19 patient	Score 1	Contact duration	Score 2	Distance	Score 3	Total score	Risk stratification
Health worker wearing proper protective gear	0	Less than 20 min	1	More than 1.5 m (6 feet)	1	_____	Score 2–3: Low risk
		More than 20 min	2	Less than 1.5 m (6 feet)	2		
Health worker NOT wearing proper protective gear	1	Less than 20 min	1	More than 1.5 m (6 feet)	1		Score 4–5: High risk
		More than 20 min	2	Less than 1.5 m (6 feet)	2		

Adopted from the MOH, Saudi Arabia.

the decision to treat a patient should take into account the seriousness of the COVID-19 disease and prognosis, particularly with regard to endovascular thrombectomy. For patients with evidence of multi-organ dysfunction or critical illness, outcomes of endovascular intervention may be suboptimal, and the risks and benefits of such procedures must be weighed against the consumption of resources and potential exposure to caregivers. A multidisciplinary discussion among the treating physicians should be held to make the most appropriate treatment decision.

Airway Management

1. The anesthesia team should be notified as soon as possible regarding potential endovascular procedures.
2. Conscious sedation should be considered as first-line treatment for patients with acute stroke interventions, if the patient is stable. However, a low threshold should be maintained for intubation in patients with respiratory distress, inability to protect the airway, posterior circulation stroke, vomiting, or agitation and for those who are uncooperative.
3. Intubation should be performed in a negative-pressure room separate from the angiography suite or in a dedicated angiography suite with negative pressure capabilities. In the absence of negative pressure, an aerosol box can be a good substitute in special situations (17).
4. Extubation should be avoided in the angiography suite and instead be performed in a negative-pressure room.
5. Transfers should avoid breaking the initial ventilator circuit, bagging, or reconnection to a new ventilator.

The following process is recommended for the referring hospital:

1. Acute ischemic stroke
   a) All patients must be screened for COVID-19. The use of telecommunication is recommended if available.
   b) Any patient with fever or respiratory symptoms should be disclosed upon the referral request to ensure proper precautions [as a COVID-19-positive individual or person under investigation [PUI]] and to ensure that trends of vital signs are properly recorded.
   c) The National institute of health stroke scale (NIHSS) must be documented, and the score must exceed 5 for a transfer to be considered.
   d) Perform brain non-contrast CT (NCCT) to rule out hemorrhage or the presence of an established infarction (Alberta stroke program early CT score (ASPECTS) above 6).
   e) Perform CTA to confirm the occurrence of large vessel occlusion and CT perfusion to identify a mismatch. A higher large vessel occlusion (LVO) score may be acceptable for transfer, depending on local logistic preparedness.
   f) Patients with a high risk of COVID-19 should wear a surgical mask.
   g) Obtain chest CT at the time of the initial CT (ground-glass appearance).
   h) If the patient presents with an unknown time of onset or a delayed onset, the option of obtaining a CT perfusion or a brain MRI should be offered in the receiving hospital to assess any mismatch prior to a consideration of transfer. If this procedure is not feasible, the ASPECTS should guide the transfer, with tissue imaging performed in the receiving stroke center.

   ** Intravenous tissue plasminogen activator (IV-tPA) eligible patients should receive thrombolysis based on the protocol in the referring hospital (telestroke managed or guided by stroke neurology).
2. Aneurysmal subarachnoid hemorrhage (aSAH)
   a) All patients must be screened for COVID-19, as described above.
   b) Any patient with fever or respiratory symptoms should be disclosed upon the referral request to ensure proper precautions (as a COVID-19-positive individual or PUI) and to ensure that the trends of vital signs are properly recorded.
   c) Glasgow coma scale (GCS) and World federation of neurosurgical societies (WFNS) grades must be documented (consideration for transfer: GCS > 9 and WFNS grade 1–3).
   d) Perform brain NCCT to document the SAH and to exclude intraventricular hemorrhage or intracerebral hemorrhage (IVH-ICH) and hydrocephalus requiring an external ventricular drain (EVD).
   e) Perform CTA to confirm the presence of intracranial aneurysm and to rule out any other vascular pathology.

f) Obtain chest CT at the time of the initial CT (ground-glass appearance) for the above-mentioned reasons.
g) If the CTA is negative for aneurysm, the transfer should be aborted, and repeat vascular imaging (CTA or digital subtraction angiography [DSA]) should obtained within 7 days.

** In the case of a high-grade SAH, improvement after the EVD insertion should warrant a referral request.

3. After the need for an interventional procedure has been confirmed, the following steps should be taken:

a) The patient should be intubated in the referring hospital, and a closed circuit should be ensured throughout the process of transferring from and to the referring hospital.
b) The patient must be accompanied by a medical transfer team that follows strict PPE precautions. This team should be equipped to offer hemodynamic and ventilatory support during the transfer.
c) The patient should be connected to a portable ventilator that will be used throughout the transfer process, including the angiographic procedure, to ensure that the closed ventilatory circuit is not interrupted.

Precautions during the endovascular procedure

All patients should be treated as though there is a high suspicion of the patient being COVID-19-positive. Accordingly, the following precautions should be implemented:

1. PPE for all staff coming in contact with the patient

- Lead apron and a yellow gown
- Head cover
- N-95 mask covered by a regular mask
- Goggles
- Face shield
- Sterile gown and gloves

2. Strict and supervised movement between different zones in the angiography suite

- Cold zone outside the angiography suite (green zone: control room)
- Intermediate zone (yellow zone: scrubbing area)
- Hot zone (red zone: inside the angiography suite)

3. The angiogram set, pressure bags, and basic access catheters should be prepared for use before the patient enters the angiogram suite. Ready-to-use verapamil and heparin syringes should be included in the angiogram set, and a vial of actylase (IV tPA) should be available in the cold zone. Other antiplatelet agents can be added based on local protocols.
4. A high-efficiency particulate air (HEPA) filter should be placed by the door of the angiogram suite.
5. All closets and cabinets should be closed during the angiography procedure.
6. The room should be labeled as COVID-19-POSITIVE, with no entry other than the angiography team.
7. Intervention technicians should remain in the cold zone to limit exposure and to facilitate material handling.
8. The circulating nurse should remain in the cold zone, supervising the movement of personnel and the donning/doffing of PPE upon entry and exit of any angiography team member.
9. The angiography team in the hot zone should consist of

- One scrub nurse
- Up to two interventionists
- One anesthesia physician, with strict control on the airway to avoid suctioning and aerosol leaks

10. All interventional material should remain outside the angiography suite (in the cold zone) and should be handed to the scrub nurse upon request.
11. The arterial access sheath should be removed at the end of the angiographic procedure. Manual compression or a closure device should be utilized for hemostasis.

** Depending on the policy implemented, the patient can either remain in the treating hospital or be transferred back to their referring hospital.

F. Teamwork during the pandemic

F.1. In any given region, neurovascular centers are advised to reduce the number of healthcare staff on clinical duty during the pandemic. We emphasize that all HCWs should continue to take universal precautions and utilize PPE as guided by the Ministries of Health and/or local institutional infection control protocols.

F.2. Cross-privileging of neurointerventionalists during the pandemic should be implemented if the need arises. This approach will allow for continuous care of patients needing these interventions.

Psychological Support for Healthcare Workers

A recent study assessing the magnitude of mental health outcomes and associated factors among HCWs treating patients exposed to COVID-19 in China reported symptoms of depression (634; 50.4%), anxiety (560; 44.6%), insomnia (427; 34.0%), and distress (899; 71.5%) (18).

Healthcare providers may benefit from following the measures listed below.

- ► Self-monitor and pace.
- ► Regularly check in with colleagues, family, and friends (check-ins may need to be virtual).
- ► Take brief relaxation/stress management breaks.
- ► Establish a COVID-free discussion zone.
- ► Seek reliable information and proper expert assessments to assist in making informed decisions if needed.
- ► Focus efforts on what is within your power.
- ► Check in with other colleagues to discuss work experiences.
- ► Provide consultations and collegial support (remotely).
- ► Allow for "hot debriefs," e.g., following the STOP-5 approach (Summarize, Things that went well, Opportunities to improve, Point to action and responsibility) adapted from the Edinburgh emergency medicine model developed by (19).

- Schedule time off from work for gradual reintegration into personal life.
- Prepare for worldview changes in one's life that may not be mirrored by others.

CLOSING REMARKS

Despite the current challenges encountered in the EVT treatment of acute stroke and neurointervention, there remain opportunities to learn from the current pandemic experience, with applications for future disasters.

In summary, our main recommendations are the following:

1- The risk of COVID-19 (**Figure 1**) should be stratified in order to prioritize and optimize (**Table 1**) the utilization of available resources during the COVID-19 pandemic in the MENA region, where resources are limited.
2- The role of telestroke in acute and clinical settings is critical for avoiding unnecessary contact between patients and physicians during the pandemic and to better utilize specialized stroke physicians with limited resources.
3- In an acute ischemic stroke, stringent prescreening criteria should be implemented to distinguish high-risk COVID-19 patients from low-risk patients, with subsequent stroke protocols based on the COVID-19 risk.
4- In aSAH patients, prescreening should be performed before admission and intervention, and a stringent high-risk protocol should be followed in the Neuro-ICU and during intervention based on prescreening results.

In conclusion, the MENA-SINO statement provides guidance to interventionalists and hospitals for prioritizing medical care for neurovascular patients. While these guidelines consider patient safety and infection protective protocols, they do not replace sound clinical judgment, the consideration of patient-specific factors, or institutional policies and procedures.

AUTHOR CONTRIBUTIONS

HA-J and SJ: concept design, writing of the manuscript, provision of protocol sections, and revision of the final document. OM, MS, DA, and MA: writing of the manuscript, provision of protocol sections, and revision of the final document. AO, AS, AA, MG, and AAH: provision of protocol sections and revision of the final document. SH: writing of the manuscript and provision of protocol sections. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in wuhan, china, of novel coronavirus-infected pneumonia. *N Engl J Med.* (2020) 382:1199–207. doi: 10.1056/NEJMoa2001316
2. Wu F, Zhao S,Yu B,Chen YM, Wang W, Song ZG, et al.A new coronavirus associated with human respiratory disease in China. *Nature.* (2020) 579:265–9. doi: 10.1038/s41586-020-2008-3
3. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* (2020) 579:270–3. doi: 10.1038/s41586-020-2012-7
4. World Health Organization. *Coronavirus Disease COVID-19 Data.* (2020). Available online at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
5. Morelli N, Rota E, Terracciano C, Immovilli P, Spallazzi M, Colombi D, et al. The baffling case of ischemic stroke disappearance from the casualty department in the COVID-19 Era. *Eur Neurol.* (2020) 83:1–3. doi: 10.1159/000507666
6. Parag G, Justin JC, Laura CP, Edward JS, Ruijun C, Assem J, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med.* (2020) 382:2372–4. doi: 10.1056/NEJMc2010419
7. Burrer SL, de Perio MA, Hughes MM, Kuhar DT, Luckhaupt SE, McDaniel CJ, et al. Characteristics of health care personnel with COVID-19—United States, February 12–April 9 (2020).
8. Griffin E, Murphy S, Sheehan M, Power S, Brennan P, O'Hare A, et al. Early repatriation post-thrombectomy: a model of care which maximises the capacity of a stroke network to treat patients with large vessel ischaemic stroke. *J NeuroInterven Surg.* (2020). doi: 10.1136/neurintsurg-2019-015667
9. Bauchner H, Fontanarosa PB, Livingston EH. Conserving Supply of personal protective equipment—a call for ideas. *Jama.* (2020). doi: 10.1001/jama.2020.4770. [Epub ahead of print].
10. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
11. Fargen KM, Ansari SA, Spiotta A, Dabus G, Mokin M, Brown P, et al. Influence of thrombectomy volume on non-physician staff burnout and attrition in neurointerventional teams. *J NeuroInterven Surg.* (2020). doi: 10.1136/neurintsurg-2020-SNIS.10. [Epub ahead of print].
12. Aggour M, White P, Kulcsar Z, Fiehler J, Brouwer P. European society of minimally invasive neurological therapy (ESMINT) recommendations for optimal interventional neurovascular management in the COVID-19 Era. *J Neurointerv Surg.* (2020). 12:542–4. doi: 10.1136/neurintsurg-2020-016137
13. Bajunaid K, Sabbagh AJ, Ajlan A, Al-Jehani H, Alnaami I, Khormi YH, et al. Consensus statement of the saudi association of neurological surgery (SANS) on triage of neurosurgery patients during COVID-19 pandemic in Saudi Arabia. *Neurosciences.* (2020) 25:148–51 doi: 10.17712/nsj.2020.2.20200054
14. Khosravani H, Rajendram P, Notario L, Chapman M, Menon B. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) pandemic. *Stroke.* (2020) 51:e156–7. doi: 10.1161/STROKEAHA.120.030243
15. ACR. *Guidance on COVID-19 and MR Use.* Available online at: https://www.acr.org/Clinical-Resources/Radiology-Safety/MR-Safety/COVID-19-and-MR-Use
16. Powers W, Rabinstein A, Ackerson T, Adeoye O, Bambakidis N, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke

association. *Stroke.* (2019) 50:e344–e418. doi: 10.1161/STR.0000000000000211
17. Canelli R, Connor CW, Gonzalez M, Nozari A, Ortega R. Barrier enclosure during endotracheal intubation. *N Engl J Med.* (2020). doi: 10.1056/NEJMc2007589
18. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, Wu J. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw Open*. (2020) 3:e203976. doi: 10.1001/jamanetworkopen.2020.3976
19. Couper K, Perkins G. Debriefing after resuscitation. *Curr Opin Crit Care.* (2013) 19:188–94. doi: 10.1097/MCC.0b013e32835f58aa

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 11 September 2020
doi: 10.3389/fneur.2020.01053

Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes

Antonio E. Camelo-Filho[1†], André M. S. Silva[1†], Eduardo P. Estephan[1,2], Antônio A. Zambon[1], Rodrigo H. Mendonça[1], Paulo V. S. Souza[3], Wladimir B. V. R. Pinto[3], Acary S. B. Oliveira[3], Iron Dangoni-Filho[1], Ana F. P. Pouza[1,4], Berenice C. O. Valerio[5] and Edmar Zanoteli[1]*

[1] Department of Neurology, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil, [2] Department of Neurology, Faculdade de Medicina Santa Marcelina, São Paulo, Brazil, [3] Department of Neurology and Neurosurgery, Universidade Federal de São Paulo, São Paulo, Brazil, [4] Department of Neurology, Instituto de Assistência Médica ao Servidor Público Estadual, São Paulo, Brazil, [5] Department of Internal Medicine, Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, Brazil

OPEN ACCESS

Edited by:
Jesús Porta-Etessam,
Hospital Clínico San Carlos, Spain

Reviewed by:
Lucia Galan,
Hospital Clínico San Carlos, Spain
Lorenzo Silva,
Hospital Universitario Puerta de Hierro Majadahonda, Spain

***Correspondence:**
Edmar Zanoteli
edmar.zanoteli@usp.br

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Neuromuscular Diseases, a section of the journal Frontiers in Neurology

Received: 25 June 2020
Accepted: 11 August 2020
Published: 11 September 2020

Citation:
Camelo-Filho AE, Silva AMS, Estephan EP, Zambon AA, Mendonça RH, Souza PVS, Pinto WBVR, Oliveira ASB, Dangoni-Filho I, Pouza AFP, Valerio BCO and Zanoteli E (2020) Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes. Front. Neurol. 11:1053. doi: 10.3389/fneur.2020.01053

Myasthenia gravis (MG), an autoimmune neuromuscular disorder, may be a risk factor for severe COVID-19. We conducted an observational retrospective study with 15 consecutive adult MG patients admitted with COVID-19 at four hospitals in São Paulo, Brazil. Most patients with MG hospitalized for COVID-19 had severe courses of the disease: 87% were admitted in the intensive care unit, 73% needed mechanical ventilation, and 30% died. Immunoglobulin use and the plasma exchange procedure were safe. Immunosuppressive therapy seems to be associated with better outcomes, as it might play a protective role.

Keywords: Myasthenia Gravis, COVID-19, SARS-CoV-2, neuromuscular disorders, immunosuppression

INTRODUCTION

Since the first outbreak description of coronavirus disease 2019 (COVID-19) (1), there has been growing evidence of potential neurological complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). On the other hand, the current COVID-19 pandemic may impact specific neurological populations, such as neuromuscular and autoimmune disease patients, raising concerns regarding best practices in these groups.

Myasthenia gravis (MG), an autoimmune neuromuscular disorder, may be a risk factor for severe COVID-19 due to multiple issues, such as immunosuppressive therapy, baseline respiratory weakness, and exacerbation from a viral infection and drug exposure (3). However, the available information is limited. Only one study (4) describing a series of five patients and two case reports (5), including a myasthenic crisis and a patient with a mild COVID-19 course (6), were reported. Here, we describe characteristics and outcomes of 15 hospitalized patients with MG and COVID-19.

METHOD

We conducted an observational retrospective cross-sectional study including all consecutive adult patients diagnosed with MG (based on antibodies or on electrophysiology) and admitted with COVID-19 at four hospitals in São Paulo, Brazil, from March 15, 2020, to May 31, 2020. All patients had COVID-19 diagnoses based on respiratory symptoms and on positive nasopharyngeal swab polymerase-chain-reaction (RT-PCR) testing for SARS-CoV-2. Informed consent was waived

because of the retrospective observational nature of the study and the analysis used anonymous clinical data.

All patients underwent detailed clinical examinations, and neuromuscular specialists in each hospital collected the medical chart reviews. The MGFA (Myasthenia Gravis Foundation of America) scores (7) were defined based on the clinical descriptions one month prior to hospitalizations. MG exacerbation was defined as a MGFA score worsening from the baseline or a respiratory insufficiency needing mechanical ventilation (MV). We considered a use of at least 40 mg prednisone per day or an association of prednisone plus a second immunosuppressant drug as a high level of immunosuppressive treatment.

RESULTS

Fifteen patients with MG and COVID-19 were identified, including 10 patients with the anti-acetylcholine receptor (AChR) antibody, one patient with the anti-muscle-specific tyrosine kinase (MuSK) antibody, and four patients without serological definition. **Table 1** summarizes the clinical characteristics, treatments, and outcomes of the patients.

Nine (60%) female patients, with a mean age of 34.5 years, and six (40%) male patients, with a mean age of 61.3 years, were included. Ten patients presented generalized MG manifestations (MGFA score $\geq$ II) in the last month before admission, and the other five had only ocular symptoms (MGFA I). The median disease duration was 9 years. Fourteen (93.3%) patients were using prednisone, nine (60%) patients were taking a second oral immunosuppressant, one patient was receiving rituximab, and another patient was using monthly intravenous immunoglobulin (IVIG). Six (40%) patients were previously thymectomized.

Dyspnea (93.3%), fever (86.7%), cough (66.7%), and myalgia (46.7%) were the most common presenting symptoms. Thirteen (86.7%) patients needed hospitalization in an intensive care unit (ICU), with a median stay of 16 days. Most patients had MG exacerbation or mechanical ventilation needs. Eleven (73.3%) patients required intubation, and the remaining four (26.7%) needed an oxygen nasal cannula. Five patients requiring MV presented mild to moderate pneumonia (<50% pulmonary involvement). Two patients had worsening of MG symptoms without the need for mechanical ventilation support. The median hospitalization stay was 18 days, but two patients remained hospitalized at the time of the manuscript writing. Four patients died.

All patients received antibiotics (11 used a macrolide). Five (33.3%) patients were treated with specific therapies for MG exacerbation: one patient received IVIG, and four patients underwent plasma exchange therapy (PLEX). No complications regarding these therapies were reported. Six (40%) patients underwent continuous neuromuscular blockades (NMBs) for MV, and four of these patients died (#1, 2, 6, and 12) and one was still on mechanical ventilation (#5) for more than 14 days, at the time of the manuscript writing.

Of the four patients who died, all were male, more than 50 years old, did not use high levels of immunosuppressive treatment, and did not receive IVIG nor PLEX during hospitalization. Three of them had MGFA I before admission, and two had no other comorbidities. Otherwise, four (26.7%) patients had better outcomes without the need for MV. They were all young females using prednisone plus a second immunosuppressant drug. Additionally, a thymectomy did not necessarily determine a poor outcome because the disease course was similar between thymectomized and non-thymectomized patients.

DISCUSSION

To our knowledge, this is the largest series of MG and COVID-19 patients. Most patients hospitalized for COVID-19 with previous MG had a severe course of the disease (87% were admitted in ICU, and 73% needed mechanical ventilation). Previous use of prednisone plus immunosuppressive therapies did not seem to determine an additional unfavorable outcome. Lethality could not be completely determined in our study because two patients remained hospitalized at the time of the manuscript writing, but it was at least 30%.

Neurological complications of COVID-19 have been described in several studies and include encephalopathy, myalgia, headache, cerebrovascular disease, immune-mediated neuropathy, and rhabdomyolysis (2, 3, 8). However, the risk of worse outcomes for several groups of patients with autoimmune neurological diseases is still in debate, and few original studies addressed this issue. As long as the knowledge regarding the SARS-CoV-2 infection continues to evolve, several case reports and case series will try to answer whether some neurological or autoimmune conditions determine an unfavorable course of COVID-19 (3–7).

Moreover, using immunosuppressant drugs during the COVID-19 pandemic remains a challenge (9). Immunosuppressed patients could be at a higher risk for a more severe COVID-19 course. However, growing evidence shows that immunosuppression might play a protective role, reducing the immune response that leads to an inflammatory cytokine storm and to clinical deterioration (10, 11). There is a recent report of a multiple sclerosis patient (12) who had a favorable outcome after a COVID-19 infection while using a B cell-depleting drug: ocrelizumab. Our data support this hypothesis because the previous use of prednisone plus immunosuppressive therapies did not seem to cause an additional unfavorable outcome. Of the four patients that died, none used a high level of immunosuppressive treatment. Interestingly, all patients that did not require mechanical ventilation were using prednisone plus a second immunosuppressant drug. Previous small reports of MG and COVID-19 also demonstrated a favorable course in the patients using prednisone plus a second immunosuppressive drug at baseline (4, 6).

Regarding treatment for MG exacerbation, four patients underwent PLEX therapy and one patient received IVIG, and all of them had favorable outcomes. None of the patients that underwent these therapies died or had complications, and all patients, but one, were discharged without worse MGFAs

TABLE 1 | Clinical characteristics, treatments and outcomes of the 15 patients with myasthenia gravis and COVID-19.

#	Age group*	MGFA pre-adm	Years of MG	Antibody	Baseline immuno suppressive treatment	Thymectomy	Commorbidities	MG symptoms exacerbation	Respiratory support	Chest CT >50% involvement	cNMB	COVID19 treatments	MG treatments	days of ICU / total hospital stay	MGFA discharge
1	≥60	I	15	AchR+	Pred 20 qd	No	None	Exacerbation leading to MV	MV	**	Yes	CTX, AZM, OTV, AMK, TEC	Pred continued	12/13	Deceased
2	≥60	I	3	AchR+	Pred 30 qd	No	DM, HTN	Exacerbation leading to MV	MV	Yes	Yes	CTX, AZM, TZP	Pred continued	8/9	Deceased
3	20–39	IIA	13	AchR+	Pred 60 qd + AZA 250 qd + IVIg 1g/kg monthly	Yes	None	Exarcerbation without MV	NC	No	No	CTX	Pred and AZA continued, IVIg 2g/kg added	4/8	IIA
4	40–59	IIA	10	AchR+	Pred 30 qd + MTX 15 mg weekly	Yes	DM	No	NC	No	No	CTX	Pred increased to 40 mg/day, MTX continued	16/18	Remains hospitalized (IIA)
5	20–39	IIA	4	N/A	Pred 5 qd + MTX 20 mg weekly	No	HTN, SLE	Exacerbation leading to MV	MV	No	Yes	CTX, OTV, MEM, CST, LZD	Pred continued, MTX withheld	25/29	Remains hospitalized (V)
6	40–59	IIA	14	N/A	No therapy	Yes	None	Exacerbation leading to MV	MV	Yes	Yes	CLR, CTX, AZM, OTV	None	7/7	Deceased
7	40–59	IIA	9	AchR+	Pred 40 qd + CCP 150 mg qd	Yes	HTN, DM, HCV	Exacerbation leading to MV	MV	No	No	CTX, AZM, TZP, MEM	Pred increased, 5 PLEX sessions added, CCP withheld	25/42	IIA
8	40–59	IIB	22	AchR+	Pred 10 qd + AZA 200 qd	Yes	GAD	Exacerbation leading to MV	MV	No	No	CTX, AZM, TZP	Pred increased, 4 PLEX sessions added, AZA withheld	20/24	IIA

(Continued)

TABLE 1 | Continued

#	Age group*	MGFA pre-adm	Years of MG	Antibody	Baseline immuno suppressive treatment	Thymectomy	Commorbidities	MG symptoms exacerbation	Respiratory support	Chest CT >50% involvement	cNMB	COVID19 treatments	MG treatments	days of ICU / total hospital stay	MGFA discharge
9	20–39	I	5	AchR+	Pred 5 qd + AZA 200 qd	No	DM, Epilepsy	Exacerbation leading to MV	MV	Yes	No	CTX, AZM	Pred continued, 5 PLEX sessions added, AZA withheld	12/20	IIA
10	20–39	IIB	2	Musk+	Pred 60 qd + RTX 375mg/m2	No	None	Exacerbation leading to MV	MV	No	No	CTX, AZM	Pred continued, 5 PLEX sessions added	16/28	IIB
11	20–39	I	11	AchR+	Pred 5 qd + AZA 150 qd	No	None	No	NC	No	No	AZM	Pred increased to 20mg/day, AZA continued	0/3	I
12	≥60	I	5	N/A	Pred 25 qd	No	HTN, asthma	Exacerbation leading to MV	MV	Yes	Yes	CTX, CLR, MEM, VAN	Pred increased	15/16	Deceased
13	20–39	IIB	16	N/A	Pred 30 qd + AZA 250 qd	Yes	None	Exarcerbation without MV	NC	No	No	CTX, AZM	Pred increased to 60 mg/day and AZA withheld	0/8	IIB
14	≥60	III	1	AchR+	Pred 40 qd + IVIg 2g/kg IBW monthly	No	HTN	Exacerbation leading to MV	MV	Yes	No	CTX, AZM, MEM, LZD, AMK, PMB	Pred increased	32/42	III
15	20–39	IIA	4	AchR+	Pred 30 qd	No	None	Exacerbation leading to MV	MV	No	Yes	CTX	Pred increased	17/22	I

*AMK, Amikacin; AZA, Azathyoprine; AZM, Azithromycin; CCP, Cyclosporin; CLR, Clarithromycin; CST, Colistin; CTX, Ceftriaxone; cNMB, continuous neuromuscular blocking; GAD, generalized anxiety disorder; IVIg, Intravenous immunoglobulin; LZD, Linezolid; MEM, Meropenem; MGFA pre-adm, Myasthenia Gravis Foundation of America score at the month before admission; MTX, Methotrexate; MV, mechanical ventilation; OTV, Oseltamivir; PLEX, Plasma exchange; PMB, Polymyxin B; Pred, Prednisone; RTX, Rituximab; TEC, Teicoplanin; TZP, Piperacillin-tazobactam; VAN, Vancomycin. *Written consent for gender and age information could not be obtained due to pandemic. Age presented in the following groups: 20–39 years, 40–59 years, and 60 years and over. **Not performed due to the critical medical condition.*

compared to their admission scores. In other two reports, IVIG therapy was also administered for three MG patients with COVID-19, that evolved with favorable outcomes (4, 5). Furthermore, patients with MG frequently worry about exacerbation after exposure to drugs, such as antibiotics and NMB agents. In our series, the continuous use of NMBs was noted in most ventilated patients, and all of them died or remained hospitalized. This finding may confirm concerns about using these agents in MG patients.

Studies with COVID-19 patients requiring hospitalization revealed ICU admission rates from 14 to 26% and intra-hospital mortality rates from 21 to 28% (13, 14). Data from the Brazilian Ministry of Health shows an ICU admission rate of 32.9% and a mechanical ventilation rate of 18.6% throughout the country (15). Our cohort presents a rate of 86.7% of ICU admission and a lethality rate of 30%, although it could not be completely determined because two patients remained hospitalized. The more severe course in our cohort may relate to complex respiratory failure triggered by viral replication and MG exacerbation. Differentiating these possible causes is difficult, so neurological consultation and possibly early immunotherapy (IVIG and PLEX) for MG patients with severe COVID-19 infections are needed.

Our study has some limitations. First, this observational study included only hospitalized patients. We did not address the impact of MG and COVID-19 in outpatient settings. Second, the unfavorable course may be associated with other variables, such as age, comorbidities or pulmonary impairment. The deceased patients from our cohort had similar risk factors than non-MG fatal patients affected by COVID-19 (they were male, older than 60 years or had comorbidities). Thus, we cannot make assumptions that MG is an independent risk factor for death. The small number of patients and the absence of a control group limited statistical analysis for risk factors establishment.

In conclusion, MG patients hospitalized for COVID-19 may have a more severe course than other hospitalized patients. The baseline immunosuppressive therapy is not necessarily associated with worse outcomes in these patients; thus, its maintenance is advised. Furthermore, immunotherapy for MG exacerbation seems to be safe and must be considered in this context.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AC-F, AS, and EZ contributed to the conception and design of the study. AC-F, AS, EZ, and EE contributed to the drafting of the manuscript and table design. All authors contributed to the acquisition, analysis of data, and critical revision of the manuscript.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. *N Engl J Med*. (2019) 382:727–33. doi: 10.1056/NEJMoa2001017
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
3. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. (2020) 94:959–69. doi: 10.1212/WNL.000000000000956
4. Anand P, Slama MCC, Kaku M, Ong C, Cervantes-Arslanian AM, Zhou L, et al. COVID-19 in patients with myasthenia gravis. *Muscle Nerve*. (2020) 62:254–8. doi: 10.1002/mus.26918
5. Delly F, Syed MJ, Lisak RP, Zutshi D. Myasthenic crisis in COVID-19. *J Neurol Sci*. (2020) 414:116888. doi: 10.1016/j.jns.2020.116888
6. Ramaswamy SB, Govindarajan R. COVID-19 in refractory myasthenia gravis-a case report of successful outcome. *J Neuromuscul Dis*. (2020) 7:361–4. doi: 10.3233/JND-200520
7. Jaretzki A III, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology*. (2000) 55:16–23. doi: 10.1212/wnl.55.1.16
8. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. *Neurology*. (2020) 95:e1060–70. doi: 10.1212/WNL.0000000000009937
9. Valencia-Sanchez C, Wingerchuk DM. A fine balance: Immunosuppression and immunotherapy in a patient with multiple sclerosis and COVID-19. *Mult Scler Relat Disord*. (2020) 42:102182. doi: 10.1016/j.msard.2020.102182
10. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet*. (2020) 395:1517–20. doi: 10.1016/S0140-6736(20)30920-X
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. (2020) 395:1033–4. doi: 10.1016/S0140-6736(20)30628-0
12. Novi G, Mikulska M, Briano F, Toscanini F, Tazza F, Uccelli A, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? *Mult Scler Relat Disord*. (2020) 42:102120. doi: 10.1016/j.msard.2020.102120
13. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. *JAMA*. (2020) 323:2052–9. doi: 10.1001/jama.2020.6775
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
15. Ministério da Saúde, Brazil. *SRAG 2020 - Banco de dados de Síndrome Respiratória Aguda Grave*. (2020). Available online at: https://opendatasus.saude.gov.br/dataset/bd-srag-2020 (accessed July 30, 2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 17 September 2020
doi: 10.3389/fneur.2020.01052

Neuromuscular Complications With SARS-COV-2 Infection: A Review

Nakul Katyal[1], Naureen Narula[2], Sudeep Acharya[3] and Raghav Govindarajan[1]*

[1] Department of Neurology, University of Missouri, Columbia, MO, United States, [2] Department of Pulmonary- Critical Care Medicine, Staten Island University Hospital, New York, NY, United States, [3] Department of Internal Medicine, Staten Island University Hospital, New York, NY, United States

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases were first reported in Wuhan, Hubei province of China in December, 2019. SARS- COV-2 primarily affects the cardio-respiratory system. Over the last few months, several studies have described various neurological sequelae of SARS-COV-2 infection. Neurological complications are more frequent in patients with severe respiratory infections. In this review, we have analyzed the current literature on neuromuscular complications associated with SARS-COV-2 and highlighted possible mechanisms of neuromuscular invasion. We reviewed 11 studies describing 11 cases of Guillain Barre syndrome (GBS), and 1 case each of Miller Fisher syndrome, Polyneuritis Cranialis, Acute myelitis, Oculomotor paralysis and Bell's Palsy associated with SARS-COV-2 infection. Mean age of patients with GBS was 61.54 years, with standard deviation (SD) 14.18 years. Majority patients had fever and cough as the first symptom of SARS COV-2 infection. Mean time for onset of neurological symptoms from initial symptoms in 11 patients was 8.18 days, with SD of 2.86 days. Mean time to performing electrodiagnostic study from onset of neurological symptom was 6 days with standard deviation of 3.25. Six patients had demyelinating pattern, three had acute sensory motor axonal neuropathy, and one had acute motor axonal neuropathy on electrodiagnostic studies.

Keywords: COVID 19, SARS-CoV-2, neuromuscular, neurology, complications, pathophysiology

OPEN ACCESS

Edited by:
Tomohisa Nezu,
Hiroshima University, Japan

Reviewed by:
Kalliopi Pitarokoili,
Ruhr University Bochum, Germany
Christopher Lawrence Kramer,
University of Chicago Medicine,
United States

****Correspondence:***
Nakul Katyal
katyal.nakul@gmail.com

Specialty section:
This article was submitted to Neuromuscular Diseases, a section of the journal Frontiers in Neurology

Received: *19 June 2020*
Accepted: *11 August 2020*
Published: *17 September 2020*

Citation:
Katyal N, Narula N, Acharya S and Govindarajan R (2020) Neuromuscular Complications With SARS-COV-2 Infection: A Review. Front. Neurol. 11:1052. doi: 10.3389/fneur.2020.01052

INTRODUCTION

In December 2019, several reports of patients with severe pneumonia of unknown causes emerged from Wuhan, Hubei province of China (1). In February 2020, the International Committee on Taxonomy of Viruses officially renamed the novel coronavirus responsible for this outbreak as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). The World Health Organization declared SARS- COV-2 as pandemic on March 11, 2020 (3). Since then, the epicenter of the pandemic has moved from China to Europe then to North America and Asia.

The first neurological complication from SARS-CoV-2 was reported as a case of viral encephalitis on March 4, 2020, at Beijing Ditan Hospital (4). In a retrospective case series of 214 patients with SARS-COV-2 infection from Wuhan, neurologic symptoms were seen in 36.4% of patients and were more common in patients with severe respiratory infections; these included acute cerebrovascular events, impaired consciousness, and muscle injury (5).

Neuromuscular complications such as critical illness myopathy, polyneuropathy, and guillain barre syndrome (GBS) have been reported with prior SARS outbreaks of 2003 and Middle East respiratory syndrome (MERS) (6, 7). Over the last few months, several studies have described

numerous neuromuscular complications in patients with SARS-COV-2 infection. This article presents a narrative review of the current literature on neuromuscular complications associated with SARS- COV 2 infection and describes the possible underlying mechanism of neuro-muscular invasion.

METHOD

Search Strategy and Selection Criteria

We searched Medline, Google Scholar, and Pubmed using keywords; "Neurological," "Neurology," "Neuromuscular," "complications," "SARS COV-2," "COVID-19." Search was limited to English language manuscript only. The literature search was last done on 31st May, 2020. At the time of writing this article, we identified 53 research literature describing neurological complications in SARS-COV-2, out of these, 11 described neuromuscular complications in SARS- COV-2 (8–18). Out of these 11, seven studies described 11 cases of GBS, one described Miller Fisher syndrome and Polyneuritis Cranialis, one described Acute myelitis, one described Oculomotor paralysis and 1 described Bell's Palsy (8–18).

Table 1 describes the demographic data, time to onset of neurological symptoms, diagnostic criteria, intervention and outcomes from 11 reported studies with neuromuscular complications associated with SARS- COV-2 infection.

NEUROMUSCULAR COMPLICATIONS WITH SARS-COV-2

Guillain Barre Syndrome (GBS)

Demographics

Seven studies have described a total of 11 cases of GBS (8–14). Out of 11 patients, nine were male, and two was female (8–14). Mean age of these 11 patients was 61.54 years, with standard deviation (SD) 14.18 years. Seven out of 11 patients had fever as the first symptom of SARS COV-2 infection (8–14). Six out of those seven had cough as an accompanying symptom (8–14). Two out of 11 patients had fatigue and myalgia as the first symptom of SARS COV-2 infection (8–14). Remaining two out of 11 patients had cough and anosmia as the first symptom of SARS COV-2 infection (8–14).

Mean time for onset of neurological symptoms from initial symptoms in 11 patients was eight. 18 days, with SD of 2.86 days.

Lumbar Puncture

Out of 11 patients, nine underwent lumbar puncture out of which 8 showed albuminocytological disproportion on cerebrospinal fluid analysis. One showed normal protein and no cells. Lumbar puncture was not performed in two patients.

Imaging

Imaging studies including computed tomography (CT) head scan, Magnetic resonance imaging (MRI) brain and spine were obtained in nine out of 11 patients. Two patients had MRI evidence of caudal nerve root enhancement on MRI spine, one patient had bilateral facial nerve enhancement. In the remaining six patients, imaging studies were unremarkable.

Electrodiagnostic Studies

Electrodiagnostic studies were obtained in 10 out of 11 patients. Mean time to performing electrodiagnostic study from onset of neurological symptom was 6 days with standard deviation of 3.25. Six out of 10 patients had demyelinating patterns (prolonged motor latencies, severe conduction velocity slowing, and conduction blocks) (8–14). Three patients had acute sensory motor axonal neuropathy and remaining one had acute motor axonal neuropathy (8–14). None of the patients had follow up electrodiagnostic study.

Table 2 describes details of electrodiagnostic studies from 10 reported cases of Guillain Barre syndrome associated with SARS-COV-2 infection.

Interventions

All 11 patients received IVIG treatment in combination with various antivirals, antibiotics, and immunosuppressive agents. Majority cases used a standard dose of IVIG; 0.4 mg/kg/day for 5 days. None of the studies mentioned any complications associated with IVIG therapy.

Outcomes

Death was reported as an outcome in one of 11 patients. Final outcomes were unavailable/not reports for three patients. Poor outcome defined as persistent/ worsening of symptoms was reported in two patients. One had complete neurological recovery. Remaining four patients had improvement of symptoms with decreased weakness. Though none of the studies mentioned dysautonomia, one patient had hemodynamic disturbances with severe drug-resistant hypertension, suggesting possible autonomic nervous system involvement (8). Four out of 11 patients developed neuromuscular respiratory failure. One patient developed respiratory failure, 3 days from onset of neurological symptoms, one at 2 weeks days from onset of neurological symptoms and remaining two at a month after onset of neurological symptoms.

Miller Fisher Syndrome

Ortiz et al. reported the first case of Miller fisher syndrome in a 50-year-old man who presented with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, 5 days after developing cough, malaise, headache, low back pain, and fever (15). Workup was remarkable for albuminocytologic dissociation and positive testing for GD1b-IgG antibodies (15). SARS- COV-2 infection was confirmed by qualitative real-time reverse-transcriptase–polymerase-chain-reaction assay utilizing oropharyngeal swab (15). The patient was successfully treated with IVIG and achieved complete neurological recovery after 2 weeks, with exception of residual ageusia and anosmia (15).

Polyneuritis Cranialis

Ortiz et al. also described the first case of polyneuritis cranialis in a 39-year-old male who presented with ageusia, bilateral abducens palsy, areflexia, 3 days after developing diarrhea, a low-grade fever, and a poor general condition (15). Workup was remarkable for albuminocytologic dissociation (15).

TABLE 1 | Description of demographic data, time to onset of neurological symptoms, diagnostic criteria, intervention and outcomes from 11 reported studies with neuromuscular complications associated with SARS-COV-2 infection.

Number of Patients	Sex	Age	Pre- neuro symptoms	Presenting neurological symptoms	Time to onset of neuro- symptoms from initial symptom	Diagnosis	Lumbar Puncture	Radiological findings	Electrodiagnostic studies	Intervention	Outcome	Time to outcome from onset of neurological symptoms	Follow up	References
1	M	71	Low grade fever	Paresthesia, weakness	1 week	GBS	Albumino-cytological disproportion (protein 54 mg/dl, cells: 9 /Ul)	CT head: negative	Decreased to absent SNAP, Markedly increased CMAP distal latency.	Lopinavir ritonavir IVIG (0.4 g/kg/d for 5 days)	Death: Severe respiratory failure.	3 days	NA	(8)
1	M	64	Fever, cough	Paresthesia, tetraparesis	11 days	GBS	Albuminocytologic dissociation (protein 1.66 g/l, Cells: normal)	NA	Decreased velocities, absent F waves	Lopinavir +Ritonavir + IVIG (0.4 g/kg/d for 5 days)	Unavailable	NA	NA	(9)
1	M	70	Myalgia, fatigue, cough	Paresthesia, allodynia, flaccid paralysis	10 days	GBS	Albumino-cytologic dissociation	MRI-ruled out myelopathy	Sensorimotor demyelinating polyneuropathy with sural sparing pattern.	IVIG (0.4 g/kg/d for 5 days)	Rehabilitation	15 days	NA	(10)
1	M	54	Fever, cough	Numbness, weakness lower extremities	10 day	GBS	Not Performed	MRI: Unremarkable	Not Performed	IVIG + Hydroxychloroquine	Rehabilitation	Unavailable	NA	(11)
1	F	61	Fatigue	Bilateral lower extremity weakness	1 day	GBS	Albumino-cytologic dissociation (Protein 124 mg/dl, normal cells)	NA	Delayed distal latencies and absent F waves	Umifenovir+ Lopinavir+ Ritanovir+ IVIG	Complete neurological recovery	30 days	NA	(12)
1	M	65	Fever, cough, dyspnea	Bilateral lower extremity weakness	10 days	GBS	Not obtained	MRI Brain, Spine: Negative	Absent SNAP, Decreased CMAP amplitude	Lopinavir + Ritonavir Hydroxychloroquine IVIG(0.4 g/kg/d for 5 days)	Unavailable	NA	NA	(13)
5	F	77	Fever, cough,	1.Flaccid areflexic tetraplegia ascending to facial weakness and respiratory failure	7 days	GBS	Albumino-cytologic dissociation (protein:101 mg/dl, cells: 4/UL)	MRI head: Normal. MRI Spine: Enhancement of caudal nerve roots	Decreased ulnar SNAP, decreased tibial and ulnar CMAP. Absent ulnar and tibial F waves.	IVIG 2 cycles	Poor Outcome: Persistent severe UE weakness, dysphagia and LE paraparesis, neuromuscular respiratory failure.	2 weeks	NA	(14)
	M	23	Fever, sore throat	2. Facial diplegia, lower limb paresthesia, ataxia	10 days	GBS	Albumino-cytologic dissociation (protein:123 mg/dl, no cell)	MRI head: Enhancement of b/l facial nerves. MRI Spine: normal.	Decreased ulnar SNAP, decreased tibial and ulnar CMAP. Decrease in facial nerve cMAP amplitude. Absent F waves	IVIG	Decreased facial and extremity weakness	Unavailable	NA	(14)
	M	55	Fever, cough	3. Flaccid tetraparesis, facial weakness.	10 days	GBS	Alb minocytologic dissociation (protein: 193 mg/dl, no cells)	MRI head: Normal. MRI Spine: Enhancement of caudal nerve roots	Decreased ulnar and tibial CMAP Absent ulnar and tibial F waves	IVIG 2 cycles	Poor Outcome: Neuromuscular respiratory failure	1 month	NA	(14)
	M	76	Dry cough, anosmia	4. Flaccid tetraparesis and ataxia	5 days	GBS	Normal protein, no cells	MRI head: normal. MRI Spine: normal	Increased tibial latencies, decreased CMAP amplitude, decreased velocities. Decreased ulnar amplitude.	IVIG	Mild Improvement, Unable to stand at 1 month	1 month	NA	(14)
	M	61	Dry cough, Anosmia, ageusia	5. Facial weakness, flaccid paraplegia, respiratory failure	7 days	GBS	Albuminocytologic dissociation (protein: 40 mg/dl, cells: 3/UL)	MRI head: NA. MRI Spine: normal	Increased tibial latencies, decreased CMAP amplitude, decreased velocities. Decreased sural SNAP, absent tibial F waves.	IVIG + PLEX	Tetraplegic, neuromuscular respiratory failure	1 month	NA	(14)
2	M	50	Fever, cough, malaise, headache	Anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia	5 day	Miller Fisher syndrome	Albuminocytologic dissociation, positive GD1b-IgG antibodies.	NA	NA	IVIG	Full neurological recovery, except residual ageusia and anosmia	2 weeks		(15)
	M	39	Fever, diarrhea	Ageusia, bilateral abducens palsy, areflexia	3 day	Polyneuritis cranialis	Albuminocytologic dissociation	NA	NA	Acetaminophen	Full neurological recovery	2weeks	After 2 weeks, complete recovery	(15)

(Continued)

TABLE 1 | Continued

Number of Patients	Sex	Age	Pre- neuro symptoms	Presenting neurological symptoms	Time to onset of neuro- symptoms from initial symptom	Diagnosis	Lumbar Puncture	Radiological findings	Electrodiagnostic studies	Intervention	Outcome	Time to outcome from onset of neurological symptoms	Follow up	References
1	M	64	Fever, fatigue	Flaccid LE paralysis, Urinary and bowel incontinence	7 days	Acute myelitis	NA	NA	NA	Moxifloxacin + tamiflu + Ganciclovir+Lopinavir+ Ritonavir+Dexamethasone+ IVIG	Rehabilitation	14days	NA	(16)
1	M	62	Weakness	Diplopia, left eye ptosis	5 day	Oculomotor Palsy	NA	MRI, MRA negative	NA	Moxifloxacin, Tamiflu, Lopinavir, Ritbavirin, Steroids, IVIG (0.4 g/kg once every day)	Death due to respiratory failure	12 days	NA	(17)
1	F	65	Pain in mastoid region	Left peripheral facial palsy	1 day	Left Bell's Palsy	NA	MRI Brian: Unremarkable	NA	arbidol and ribavirin	Recovery	Unavailable	1month	(18)

SARS- COV-2 infection was confirmed by qualitative real-time reverse-transcriptase–polymerase-chain-reaction assay utilizing oropharyngeal swab (15). The patient had normal respiratory, cardiovascular and abdominal examination and therefore was treated symptomatically with acetaminophen only which resulted in full neurological recovery after 2 weeks (15). This case indicates that patients with normal cardio-respiratory exam may have better neurological outcomes.

Acute Myelitis

Zhao et al. reported the first case of acute myelitis in a 66 year old male who developed flaccid weakness of bilateral lower extremity with bowel and bladder incontinence and sensory level at T 10, 7 days after developing fever (16). SARS- COV-2 infection was confirmed by nucleic testing utilizing nasopharyngeal swab (16). Lumbar puncture and MRI studies were not performed given pandemic related reasons (16). The patient was treated with a combination of moxifloxacin, tamiflu, ganciclovir, lopinavir, ritonavir, dexamethasone, and IVIG (15 g once daily × 7 days) (16). The patient achieved improvement in bilateral upper and lower extremity strength and was eventually discharged to a rehabilitation facility (16).

Oculomotor Paralysis

Wei et al. described the first case of oculomotor paralysis in a 65 year old male who presented with 5 days history of persistent diplopia, and left eyelid droop (17). The patient had complete ptosis of left eye and the left eye was down and out at rest (17). MRI and Magnetic resonance angiography (MRA) were unremarkable however, CT chest showed diffuse ground glass opacities (17). SARS- COV-2 was detected in the throat swab (17). The patient was treated with a combination of moxifloxacin, tamiflu, ribavirin, lopinavir, methylprednisolone, and IVIG (0.4 g/kg once every day). Unfortunately, he developed respiratory failure and died on day 12 of admission (17).

Bell's Palsy

Wan et al. described the first case of Bell's Palsy in a 65 year old female who presented with left lower motor neuron facial paralysis, 2 days after developing pain in the mastoid region (18). Interestingly, this patient had no other symptoms of viral illness. MRI brain showed no abnormality however, computed tomography (CT) chest showed patchy areas of ground-glass shadows in the right lower lung raising suspicion for SARS-COV 2 (18). SARS- COV-2 infection was confirmed by real-time reverse-transcriptase–polymerase-chain-reaction assay utilizing throat swabs (18). The patient was successfully treated with arbidol and ribavirin and achieved resolution of neurological symptoms and lung shadows after 1 month (18).

MECHANISM OF NEUROMUSCULAR INVOLVEMENT IN SARS-COV-2

Angiotensin-Converting Enzyme 2 Mediated Pathway

The first major target of SARS- COV-2 is the ACE-2 receptor located on epithelial cells of the respiratory tract (19). This

TABLE 2 | Description of electrodiagnostic studies from 10 reported cases of Guillain Barre syndrome associated with SARS- COV-2 infection.

Timing of electrodiagnostic studies from onset of neurological symptoms	Electrodiagnostic studies	Interpretation	Follow up electrodiagnostic studies	References
Day 4	1. Absence of both the sural nerve sensory nerve action potential (SNAP) and the tibial nerve compound muscle action potential (CMAP). 2. Markedly increased common peroneal CMAP distal latency, markedly decreased velocity, moderately decreased CMAP amplitude (with spatial and temporal dispersion) for the same nerve. 3. Decreased ulnar SNAP amplitude.	Acute polyradiculoneuritis, confirmed demyelination	None, Patient died unfortunately.	(8)
Day 5	1. Decreased right median, and bilateral ulnar velocities and increased F wave latencies in same nerves 2. Increased distal latencies and decreased velocities along bilateral peroneal and tibial nerves.	Acute inflammatory demyelinating polyneuropathy.	Unavailable	(9)
Day 5	1. Sensorimotor demyelinating polyneuropathy with sural sparing pattern. 2. F wave study showed decreased persistence or absent F-waves in tested nerves.	Acute inflammatory demyelinating polyneuropathy.	Unavailable	(10)
Day 5	1. Increased left median distal latencies. 2. Increased left ulnar distal latencies and absent F waves 3. Increased bilateral tibial distal latencies and absent F waves	Acute inflammatory demyelinating polyneuropathy.	Unavailable	(12)
Day 9	1.Absent SNAP, Decreased CMAP amplitude along bilateral tibial and median nerves	Acute sensory motor axonal neuropathy	Unavailable	(13)
Day 3	1.Decreased ulnar SNAP, decreased tibial and ulnar CMAP. 2. Absent ulnar and tibial F waves.	Acute sensory motor axonal neuropathy	Unavailable	(14)
Day 12	1. Decreased ulnar SNAP, decreased tibial and ulnar CMAP. 2.Decrease in facial nerve cMAP amplitude. 3. Absent tibial F waves	Acute sensory motor axonal neuropathy	Unavailable	(14)
Day 11	1.Decreased ulnar and tibial CMAP 2. Absent ulnar and tibial F waves	Acute motor axonal neuropathy	Unavailable	(14)
Day 2	1. Increased tibial latencies, decreased CMAP amplitude, decreased velocities. 2. Decreased ulnar amplitude.	Acute inflammatory demyelinating polyneuropathy.	Unavailable	(14)
Day 4	1. Increased tibial latencies, decreased CMAP amplitude, decreased velocities, conduction block. 2. Decreased sural SNAP, absent tibial F waves	Acute inflammatory demyelinating polyneuropathy.	Unavailable	(14)

binding results in downregulation of ACE-2 expression as well as the viral entry and replication (20). Loss of ACE-2 expression leads to dysregulation of the renin-angiotensin system which causes an elevated production of angiotensin II (21). The overproduction of angiotensin II results in a cascade of interactions that eventually leads to severe acute lung injury (21).

ACE2 receptors are present widespread throughout the brain, including cardio-respiratory neurons of the brainstem (dorsal vagal complex), endothelial cells, glial cells, basal ganglia, motor cortex, and raphe (21–23). Once in blood circulation, SARS-COV-2 can travel via hematogenous route to infect the endothelial cells of the blood–brain barrier and then accumulate in ACE-2 rich brain regions causing neurological sequelae (21, 24). Respiratory distress experienced during SAR-CoV2 infection may result from compromise of the brainstem's cardiorespiratory center (21, 25, 26).

Olfactory Pathway

The anatomical organization of olfactory nerve and olfactory bulb in the nasal cavity provides a direct portal for entry of SARS-COV-2 from periphery to CNS (21, 27). After infecting nasal cells, COV can reach the brain and cerebrospinal fluid through the olfactory nerve and olfactory bulb within 7 days and cause inflammation and demyelinating reaction (4).

Trans-Synaptic Pathway

The major mechanism by which viruses cause neuromuscular complications involves the entry through peripheral nerve endings located in the skin and mucosa (28, 29). This process is followed by an endogenous neuronal mechanism causing retrograde axonal transport of viruses from the cell periphery to the neuronal cell body (28, 29). Multiple other COV-viruses are known to exhibit transsynaptic transfer properties including HCoV-OC43, HEV 67N (21, 30–32). HEV 67N shares more than 91% homology with the novel SARS-CoV-2 thus further consolidating the hypothesis of retrograde transfer as a possible mechanism of neuro-muscular invasion in SARS-COV-2 (21, 30–32).

Immune Mediated Pathway

Cytokine storm is an immune-mediated life-threatening disease, which is caused by impaired natural killer and cytotoxic T-cell function (33, 34). Viral infection is the most frequent trigger, either as a primary infection in healthy people or after reactivation in immunosuppressed patients (33, 34). Cytokine storm is associated with an exaggerated inflammatory response caused by hypersecretion of proinflammatory cytokines such as interferon γ, tumor necrosis factor α (TNFα), interleukin 1, 4, 6, 8, 10, and 18 which causes tissue damage and progressive systemic organ failure (33–38). Experimental studies infecting *in vitro* cultured glial cells (including microglia, astrocytes and oligodendrocytes) with COV noted enormous production of inflammatory factors such as IL-6, IL-12, IL-15, and TNF-α (4, 39, 40). Interleukin (IL)-6, is positively correlated with the severity of COVID-2019 symptoms (33–40). Exaggerated immune responses with SARS-COV-2 might contribute to development of acute inflammatory demyelinating poly radiculo-neuropathies.

All the above described mechanisms were not based on studies on peripheral neurons or Schwann cells, therefore the exact mechanism remains unknown. Further dedicated studies are required to undermine the exact cause of neuromuscular invasion of SARS-COV 2 virus.

CONCLUSION

Neurological complications with SARS-COV-2 are being reported exponentially. Majority literature is anecdotal and reported in the form of isolated case reports and case series. In order to better understand the causal relationship, and underlying pathophysiology, meta-analysis of these studies is warranted. Physicians must familiarize themselves with the rapidly evolving literature to provide uptodate care to the affected patients.

AUTHOR CONTRIBUTIONS

NK, NN, and SA contributed to literature research, manuscript writing. RG made revisions and helped in editing the manuscript.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
2. Li X, Zai J, Zhao Q, Nie Q, Li Y, Foley B, et al. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. *J Med Virol.* (2020) 92:602–611. doi: 10.1002/jmv.25731
3. WHO Director-General's opening remarks at the media briefing on COVID-19 (2020). Available online at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19 (accessecd March 11, 2020).
4. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* (2020) S0889-1591(20)30357-3.
5. Mao L, Wang MD, Chen SH, He QW, Chang J, Hong CD, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *MedRxiv.* (2020). doi: 10.2139/ssrn.3544840
6. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH et al. Neurological complications during treatment of middle east respiratory syndrome. *J Clin Neurol.* (2017) 13:227–33. doi: 10.3988/jcn.2017.13.3.227
7. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan.* (2005) 14:113—9.
8. Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, et al. Guillain-Barré syndrome related to COVID-19 infection. *Neurol Neuroimmunol Neuroinflamm.* (2020) 7:e741. doi: 10.1212/NXI.0000000000000741
9. Camdessanche JP, Morel J, Pozzetto B, Paul S, Tholance Y, Botelho-Nevers E. COVID-19 may induce Guillain-Barré syndrome. *Rev Neurol (Paris).* (2020) 176:516–518. doi: 10.1016/j.neurol.2020.04.003
10. Coen M, Jeanson G, Culebras Almeida LA, Hubers A, Stierlin F, Najjar I, et al. Guillain-Barré syndrome as a complication of SARS-CoV-2 infection. *Brain Behav Immun.* (2020) 87:111–112. doi: 10.1016/j.bbi.2020.04.074
11. Virani A, Rabold E, Hanson T, Haag A, Elrufay R, Cheema T, et al. Guillain-Barré Syndrome associated with SARS-CoV-2 infection. *IDCases.* (2020) 20:e00771. doi: 10.1016/j.idcr.2020.e00771
12. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence?. *Lancet Neurol.* (2020) 19:383–4. doi: 10.1016/S1474-4422(20)30109-5
13. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: a case report. *J Clin Neurosci.* (2020)76:S0967-5868(20)30882-1. doi: 10.1016/j.jocn.2020.04.062
14. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain–Barré syndrome associated with SARS-CoV-2. *N Engl J Med.* (2020) 382:2574–76 doi: 10.1056/NEJMc2009191
15. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Mañas R, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology.* (2020) 95:e601–5. doi: 10.1212/WNL.0000000000009619
16. Zhao K, Huang J, Dai D, Feng Y, Liu L, Nie S. Acute myelitis after SARS-CoV-2 infection: a case report. *medRxiv.* (2020). doi: 10.1101/2020.03.16.20035105
17. Wei H, Yin H, Huang M, Guo Z. The 2019 novel coronavirus pneumonia with onset of oculomotor nerve palsy: a case study. *J Neurol.* (2020) 267:1550–3. doi: 10.1007/s00415-020-09773-9
18. Wan Y, Cao S, Fang Q, Wang M, Huang Y. Coronavirus disease 2019 complicated with Bell's palsy: a case report. *Neurology.* doi: 10.21203/rs.3.rs-23216/v1
19. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses.* (2020) 12:14. doi: 10.3390/v12010014
20. Kuba K, Imai Y, Rao S, Jiang C, Penninger JM. Lessons from SARS: control of acute lung failure by the SARS receptor ACE2. *J Mol Med.* (2006) 84:814–20. doi: 10.1007/s00109-006-0094-9
21. Iroegbu JD, Ifenatuoha CW, Ijomone OM. Potential neurological impact of coronaviruses: implications for the novel SARS-CoV-2. *Neurol Sci.* (2020) 41:1329–37. doi: 10.1007/s10072-020-04469-4
22. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. *J Neurochem.* (2008) 107:1482–94. doi: 10.1111/j.1471-4159.2008.05723.x
23. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *Am J Physiol - Regul Integr Comp Physiol.* (2007) 292:R373–81. doi: 10.1152/ajpregu.00292.2006
24. Desforges M, Favreau DJ, Brison É, Desjardins J, Meessen-Pinard M, Jacomy H, et al. Human coronaviruses: respiratory pathogens revisited as infectious neuroinvasive, neurotropic, and neurovirulent agents. In: Singh SK, Ruzek D, editors. *Neuroviral Infections*. Boca Raton: CRC Press (2013). p. 93–121. doi: 10.1201/b13908-7

25. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 9:552–5. doi: 10.1002/jmv.25728
26. Li Y, Li H, Fan R, Wen B, Zhang J, Cao X, et al. Coronavirus infections in the central nervous system and respiratory tract show distinct features in hospitalized children. *Intervirology.* (2016) 59:163–9. doi: 10.1159/000453066
27. Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. *Cell Host Microbe.* (2013) 13:379-393. doi: 10.1016/j.chom.2013.03.010
28. Sodeik B. Mechanisms of viral transport in the cytoplasm. *Trends Microbiol.* (2000) 8:465–72. doi: 10.1016/S0966-842X(00)01824-2
29. Berth SH, Leopold PL, Morfini G. Virus-induced neuronal dysfunction and degeneration. *Front Biosci.* (2009) 14:5239–59. doi: 10.2741/3595
30. Dubé M, Le Coupanec A, Wong AH, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol.* (2018) 92:e00404–e00418. doi: 10.1128/JVI.00404-18
31. Li Z, He W, Lan Y, Zhao K, Lv X, Lu H, et al. The evidence of porcine hemagglutinating encephalomyelitis virus induced nonsuppurative encephalitis as the cause of death in piglets. *PeerJ.* (2016) 4:e2443. doi: 10.7717/peerj.2443
32. Gonzalez J, Gomez-Puertas P, Cavanagh D, Gorbalenya A, Enjuanes L. A comparative sequence analysis to revise the current taxonomy of the family Coronaviridae. *Arch Virol.* (2003) 148:2207–35. doi: 10.1007/s00705-003-0162-1
33. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult hemophagocytic syndrome. *Lancet.* (2014) 383:1503–16. doi: 10.1016/S0140-6736(13)61048-X
34. Scott RB, Robb-Smith AH. Histiocytic medullary reticulocytosis. *Lancet.* (1939) 2:194–8. doi: 10.1016/S0140-6736(00)61951-7
35. Sumegi J, Barnes MG, Nestheide SV, Lee SM, Villanueva J, Zhang K et al. Gene expression profiling of peripheral blood mononuclear cells from children with active hemophagocytic lymphohistiocytosis. *Blood.* (2011) 117:E151–60 doi: 10.1182/blood-2010-08-300046
36. Milner JD, Orekov T, Ward JM, Cheng L, Velez FT, Junttila I, et al. Sustained IL-4 exposure leads to a novel pathway for hemophagocytosis, inflammation, and tissue macrophage accumulation. *Blood.* (2010) 116:2476–83. doi: 10.1182/blood-2009-11-255174
37. Chiossone L, Audonnet S, Chetaille B, Chasson L, Farnarier C, Haddad YB, et al. Protection from inflammatory organ damage in a murine model of hemophagocytic lymphohistiocytosis using treatment with IL-18 binding protein. *Front Immunol.* (2012) 3:239 doi: 10.3389/fimmu.2012.00239
38. Wan SX, Yi QJ, Fan SB, Lv JL, Zhang XX, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *MedRxiv.* (2020). doi: 10.1101/2020.02.10.20021832
39. Bohmwald K, Galvez NMS., Rios M, Kalergis AM. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci.* (2018) 12:386. doi: 10.3389/fncel.2018.00386
40. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. *J Clin Neurosci.* (2020). doi: 10.20944/preprints202004.0453.v1. [Epub ahead of print].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 17 September 2020
doi: 10.3389/fneur.2020.01044

The Potential Role of SARS-COV-2 in the Pathogenesis of Parkinson's Disease

Pedro Chaná-Cuevas[1,2]*, *Philippe Salles-Gándara*[1], *Alejandro Rojas-Fernandez*[3], *Constanza Salinas-Rebolledo*[3] *and Anna Milán-Solé*[4]

[1] Movement Disorders Center, CETRAM, Santiago, Chile, [2] Faculty of Medical Science, University of Santiago of Chile, Santiago, Chile, [3] Institute of Medicine & Center for Interdisciplinary Studies on the Nervous System (CISNe), Universidad Austral de Chile, Valdivia, Chile, [4] Liga Chilena Contra la Epilepsia (LICHE), Santiago, Chile

Considering their current burden and epidemiological projections, nowadays Parkinson's disease and the COVID-19 pandemic are two key health problems. There is evidence of the pathogenic role of neurotropic viruses in neurodegenerative diseases and coronaviruses are neurotropic, with some of them selectively targeting the basal ganglia. Moreover, some authors demonstrated the longevity of these viruses in the affected cells of the nervous system for long periods. Coronavirus was detected in brain autopsies and SARS-CoV-2 has been isolated from the CSF of affected patients. The marked inflammatory response in some particular patients with COVID-19 with a consequent increase of pro-inflammatory cytokines is considered a prognostic factor. Immunologic changes are observed in patients with Parkinson's disease, possibly having a role in its pathogenesis. A dynamic pro-inflammatory state accompanies α-synuclein accumulation and the development and progression of neurodegeneration. Also, some viral infectious diseases might have a role as triggers, generating a cross autoimmune reaction against α-synuclein. In the past Coronaviruses have been related to Parkinson's disease, however, until now the causal role of these viruses is unknown. In this paper, our focus is to assess the potential relationship between SARS-CoV-2 infection and Parkinson's disease.

Keywords: coronavirus, SARS virus, nervous system diseases, movement disorders, Parkinson disease, alpha-synuclein, neurodegenerative diseases, pandemics

OPEN ACCESS

Edited by:
Tomohisa Nezu,
Hiroshima University, Japan

Reviewed by:
Micaela Morelli,
University of Cagliari, Italy
Nabin Koirala,
Haskins Laboratories, United States

***Correspondence:**
Pedro Chaná-Cuevas
pedro.chana@usach.cl

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *01 June 2020*
Accepted: *10 August 2020*
Published: *17 September 2020*

Citation:
Chaná-Cuevas P, Salles-Gándara P, Rojas-Fernandez A, Salinas-Rebolledo C and Milán-Solé A (2020) The Potential Role of SARS-COV-2 in the Pathogenesis of Parkinson's Disease. Front. Neurol. 11:1044. doi: 10.3389/fneur.2020.01044

INTRODUCTION

Parkinson's disease (PD) is the second most common and the most rapidly growing neurodegenerative disorder (1). Its pathological hallmarks are loss of dopaminergic neurons in the substantia nigra (SN) pars compacta and accumulation of misfolded α-synuclein, which is found in intracytoplasmic inclusions called Lewy bodies (2).

The current global burden of PD is about 6.2 million cases (3), and it is expected that more than 12 million people worldwide will be affected by the year 2040 (1, 4). This exponential growth worldwide may be attributed to several factors (5), including infectious diseases. A recent analysis suggests that viral and bacterial infections might increase the risk of developing PD (6).

The hypothesis of a viral trigger associated with the pathogenesis of PD emerged more than 100 years ago, due to the relation of lethargic encephalitis (Von Economo disease) and post-encephalitic parkinsonism that occurred after the 1918 type A H1N1 influenza pandemic (7). Until now, influenza remains the main basis of the viral hypothesis, supported by its neurotrophic properties, with preferential targets in the SN and ventral tegmental area (8); and the finding of MxA protein in Lewy bodies, which is implicated in the defense against influenza (9). In the last decades, additional viruses have been associated with both acute and chronic parkinsonism, including Epstein Barr virus, Coxsackie, Japanese encephalitis B, western equine encephalitis, West Nile virus, herpes viruses, and HIV (8, 10, 11).

The contemporary pandemic, starting from December 2019 to date, of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is responsible for coronavirus disease (COVID-19), is now a worldwide health concern (10). With more than 16 million COVID-19 cases globally (July 28, 2020)[1], our attention is now set on the hypothetical relations of this new coronavirus infection on PD pathogenesis, its potential as a trigger for the neurodegenerative process, and its consequent impact on the epidemiology of PD. One of the elements that set off this alarm was the report of anosmia in patients infected by SARS-CoV-2, but also the neuroinvasive potential of coronaviruses (CoVs) and a noticeable inflammatory reaction in severe COVID-19 cases. As we know, immune activation in the peripheral and central nervous system (CNS) is a common finding in cases of PD (12, 13). Moreover, inflammation can trigger α-synuclein misfolding, aggregation, and propagation through the CNS (14–16). α-synuclein aggregation may activate microglia, favoring the pro-inflammatory response and cell damage signals, which ultimately leads to neuronal death. In this hypothetical scenario, older adults may represent a susceptible group to the development of neurodegenerative disorders, as aging might be associated with low-grade and chronic inflammation ("inflammaging") (16), and the inability to control inflammation (17).

Exploring the potential relationship of SARS-CoV-2 and PD is essential because of the epidemiological implications and the understanding of physio pathological aspects of both disorders. Our paper attempts to elucidate some of those hypothetical links and its possible consequences.

The Neuroinvasive Potential of SARS-CoV-2

Most CoVs share a similar viral structure, infection route, and pathogenic mechanism. The penetration of the virus in host cells is mediated by the angiotensin-converting enzyme 2 (ACE2), and dipeptidyl peptidase 4 (DPP4) (18). In addition to the severe acute respiratory syndrome, human CoV infections may manifest severe neurological complications including seizures, refractory status epilepticus, encephalitis, acute disseminated encephalomyelitis, cerebellitis, Guillan-Barré syndrome, leukoencephalopathy, and critical illness neuromyopathy (19).

Not unexpectedly, evidence shows that neuroinvasion and neurotropism is one common feature of CoVs. Such neuroinvasive propensity has been documented for most βCoVs, including SARS-CoV, MERS-CoV, HCoV-229E, HCoV-OC43, mouse hepatitis virus (MHV), and porcine hemagglutinating encephalomyelitis coronavirus (HEV) (18).

As an example of CNS invasion, following intranasal inoculation of susceptible mice, HCoV-OC43 infects the olfactory bulb and disseminates to the hippocampus and cortex, from which it appears to spread by the trans-neuronal route to the brainstem (20). Meanwhile, Fishman et al., observed a strong tropism for the basal ganglia in the region of the subthalamic nucleus and SN in MHV-A59-infected C57BL/6 mice, with fewer signs of infection in other brain regions (21). Alongside, Arbor et al. demonstrated the potential chronic persistence of HCoV-229E and HCoV-OC43 infection in human neuronal cell lines, specially oligodendrocytes, and possibly neurons (22). Further, HCoV-OC43 RNA can be detected for over a year in the CNS of infected mice that survived the acute encephalitis (23).

CNS invasion was also demonstrated in humans. Gu et al. (24) reported a postmortem study of patients who died 14–62 days after the onset of SARS symptoms. Brain edema and scattered red degeneration of neurons affected the brains in 6 of 8 confirmed cases. Moreover, the presence of virus confined to the cytoplasm of numerous neurons in the hypothalamus and cortex was confirmed by light microscopy, electron microscopy, and real-time PCR (24). The average time from symptom onset to hospital admission is 7 days, while the average time of admission to the intensive care unit is 8 days (25). This latency may represent the "window of time" for the virus to enter the CNS (26).

Similar to other CoVs, SARS-CoV-2 infects cells through the interaction between its spike protein (S) and ACE2. For this interaction, protein S must be cleaved by Transmembrane Serine Protease (TMPRSS2) (27, 28). Cells expressing both ACE2 and TMPRSS2 are more susceptible to SARS-CoV-2 infection (29). Recently, Chen et al. investigated ACE2 expression by analyzing data from brain transcriptome databases. The SARS-CoV-2 receptor was highly expressed in the SN and brain ventricles, and distributed in excitatory as well as inhibitory neurons, but also astrocytes and oligodendrocytes (30).

Although there is no evidence of strong co-expression of $ACE2^{+}/TMPRSS2^{+}$ in the brain (29), Brann et al. showed that non-neuronal cells of the sensory olfactory epithelium (sustentacular cells, horizontal basal cells, microvillar cells, and Bowman's gland cells) express both ACE2 and TMPRSS2. Human sustentacular cells express both genes at levels comparable to those observed in lung cells. Thus, these cells could be the first to be infected with SARS-CoV-2 (27). These non-neuronal cells support mature olfactory sensory neurons (OSNs) in the sensory epithelium. Supporting cells infected by SARS-CoV-2 could eventually spread the virus to OSNs through axonal transport (31), later invading neurons within the olfactory bulb and then to the CNS causing inflammation (32). The mechanism of viral penetration through the olfactory bulb into the brain has been previously proposed to play a role in neurodegenerative diseases,

[1] Available online at: https://covid19.who.int

acting as a trigger for the spread of pathologically aggregated proteins in a prion-like manner (33).

In a retrospective analysis of patients hospitalized with COVID-19 in Wuhan, China, the authors found that of 214 cases, 78 had neurologic manifestations, including impaired consciousness and cerebrovascular diseases, with a higher prevalence in more severe cases (34, 35). Also, anosmia and dysgeusia are commonly reported in COVID-19 patients (36). Recently, cerebrospinal fluid (CSF) samples from patients with COVID-19 presenting meningitis and encephalitis were positive for SARS-CoV-2 (37). The nasopharyngeal sample from one patient with meningitis was negative in the RT-PCR test for SARS-CoV-2, but a CSF sample resulted positive for the virus (38). These findings support the hypothesis that SARS-CoV-2 like other CoVs has the potential to infect brain cells (39).

Interestingly, SARS- CoV-2 RNA was also detected in the feces in ∼50% of patients with COVID-19. Moreover, there is evidence of intestinal inflammation in these patients (40). These findings recall the model of gut-driven inflammation in PD pathogenesis. In this model an initial infection, which directly or indirectly affects the GI system, triggers an inflammatory response, increasing the levels of α-synuclein in the gut and brain, which would initiate its aggregation (41).

In our opinion, these findings support the neuroinvasive potential of SARS-CoV-2 similar to other coronaviruses. The ability of CoVs to remain for long periods in the CNS could perpetuate the central inflammatory response and the risk of neurodegeneration. The more or less selective invasion of the SN and basal ganglia could be partially explained by a high local expression of ACE2, resembling pathologically affected areas in PD. Finally, invasion through the olfactory bulb and evidence of intestinal inflammation in COVID-19 patients reflects on the Braak's hypothesis, and the model of gut-origin of PD.

SARS-CoV-2 and the Inflammatory Response

A fast and synchronized innate immune response is the first line of defense against viral infections. On the contrary, dysregulated and exaggerated immune reactions may cause immune damage to the human body (42).

For example, in the SARS-CoV epidemic, cerebral involvement was related to the exaggerated viral immune response. A study reported a high ratio of monokine induced by IFN-γ (Mig), and IFN-γ inducible protein 10 (IP 10) in the blood of patients with SARS, and an increase in Mig but not IP-10 in brain tissue, which in turn seems to attract CD68+ macrophages and CD3+ lymphocytes to the sites of virus infection; contributing to brain damage (43). This effect is mediated by NF-κB. Its pharmacological inhibition markedly decreased Mig in the affected organs (44). Drugs like Bortezomib and other proteasome inhibitors possess this inhibitory potential and could eventually regulate the inflammatory response (45).

In COVID-19, high levels of IL-1B, IFN-γ, IP-10, and monocyte chemoattractant protein 1 (MCP-1) have been detected. These cytokines may activate the T-helper type 1 (Th1) cell response, a key event in the activation of specific immunity. Nevertheless, contrasting to SARS cases, patients with COVID-19 also have elevated levels of Th2 cell-secreted cytokines (such as IL-4 and IL-10), which inhibit the inflammatory response (44, 45).

Current evidence indicates that some of the COVID-19 patients present characteristics similar to secondary adult hemophagocytic syndrome, including cytopenia (46, 47) and cytokine storm syndrome (48, 49). This inflammatory cytokine storm is closely associated with the development of acute respiratory distress syndrome and extrapulmonary multiple-organ failure. Significantly high blood levels of cytokines and chemokines were detected in patients with severe cases of COVID-19 admitted to the intensive care unit, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα which are believed to promote disease severity (47). The cytokine serum levels, specially IL-2R and IL-6 in patients with COVID-19, positively correlate with mortality rate (46). Ruan et al. conducted a retrospective study in 150 laboratory-confirmed Chinese patients with SARS-CoV-2. They observed elevated IL-6 levels in non-survivors compared to those with mild infection (50). Moreover, a case of COVID-19-associated acute necrotizing hemorrhagic encephalopathy (ANE) was recently reported (51). This type of encephalopathy is a rare complication in other viral infections, associated with intracranial cytokine storm and a breakdown of the blood-brain barrier, rather than a direct viral invasion (52). Previous studies showed that an exaggerated and dysregulated cytokine response leads to neuronal death (53).

From our viewpoint, the importance of these findings lies in previous evidence indicating that exaggerated or prolonged systemic inflammation alone is sufficient to pathologically modify α-synuclein in the CNS. Moreover, peripheral inflammation may also increase α-synuclein uptake from the circulation into the brain by promoting disruption of the blood-brain barrier (54); the increased permeability of the blood-brain barrier facilitates lymphocyte infiltration into the CNS, and microglial activation, which is a hallmark in neurodegenerative diseases (55). Also, peripheral inflammation may exacerbate the central brain's ongoing damage in several neurodegenerative diseases (56).

Inmunologic Variations in Parkinson's Disease

Certainly, immune activation is an important piece in the puzzle of PD physiopathology. CNS immune changes are characterized mainly by reactive microgliosis and high concentrations of pro-inflammatory cytokines. Similarly, an imbalance in lymphocyte populations favors a TH1-type peripheral system immune response.

As we pointed out, brain autopsies of PD cases show microglial and oligodendroglial activation and upregulation of major histocompatibility class II (MHCII). Activated microglia in the putamen expressed TNF-alpha and IL-6, remarkably, these inflammatory cytokines may also have a neurotrophic role. The expression of these factors is concomitant with α-synuclein accumulation and loss of dopaminergic cells in the SN (57). Meanwhile, Mogi et al. reported higher concentrations of

IL-1ß, IL-6, epidermal growth factor (EGF), and transforming growth factor-alpha (TGF-alpha) in striatal regions in the brain of PD cases compared with controls. IL-1ß, an immune response-generated cytokine, stimulates astrocyte proliferation, while IL-6 is a B-cell stimulating factor. At the same time, astrocytes as well as microglial cells secrete IL-1ß and IL-6 (58).

Baba et al. analyzed T-lymphocyte populations in patients with PD. They found a characteristic predominant expression of $CD8^+$ T cells, depletion of $CD4^+$ $CD25^{+\ highcells}$, and a shift to a TH1-type peripheral immune system (13). Also, Stevens et al., found a 15–25% reduction in TCRαβ+, CD4+ (T helpers), and CD19+ (B) cells compared to controls (59).

A meta-analysis from 25 studies involving 1,547 patients with PD and 1,107 controls, was consistent with elevated peripheral concentrations of several inflammatory cytokines, including, IL-6, TNF, IL-1β, IL-2, IL-10, CRP, and RANTES in patients with PD (60). These changes might be associated with the inflammatory process in the brain.

Additionally, various genetic loci were identified in genome-wide association studies as risk factors for PD, some within the HLA region, coding for immune genes including MHCII (61, 62), particularly the rs3129882 single nucleotide polymorphism (SNP). The GG homozygosity of this SNP is associated with increased baseline and inducible MHC-II expression in APCs, favoring a more pro-inflammatory CD4+ T cell response (63).

It is not clear if these changes in the immune system are the cause or consequence of an initial trigger for the neurodegenerative process: based on what was previously stated, the inflammatory insult associated with SARS-CoV-2 infection could be a predisposing factor, particularly in susceptible individuals. Moreover, immunologic variations in PD patients may affect their outcome after SARS-CoV-2 infection.

The Neuroinflamatory Response and Synucleinopathy

The normal function of α-synuclein is partially understood. Part of its role involves the recycling of synaptic vesicles and synaptic transmission, as it is abundant in synaptic clefts (64, 65). Consequently, the loss of its normal neuronal function could play a central role in PD pathophysiology.

Current evidence suggests different pathogens as triggers of a cerebral chronic neuroinflammatory response (66, 67); α-synuclein is involved in important aspects of immune activation, specifically with the innate immune response. It may have a regulatory role in the immune response of peripheric and central neurons (68–70) and could be involved in the canonic activation of inflammatory pathways (inflammation), as well as the chronic immune response and neurotoxicity (neurodegeneration) (71). This occurs due to the overexpression of Toll-like receptors (TLR) and Nuclear Factor (NF-κB), activating, in turn, the cytokine response cascade. The presence of extracellular α-synuclein is a marker of molecular damage (72).

There is also evidence to suggest that α-synuclein plays a role in mechanisms of infection responses, with an increased expression of α-synuclein in viral processes such as in Nile Virus encephalitis (73), and worse disease prognosis in α-synuclein knockout mice (74). During viral infections, α-synuclein increases, acting as an inhibitor of viral growth in neurons in the CNS by acting as a restricting factor of viral RNA (75). TLR are a group of transmembrane glycoproteins implicated in pathogen recognition and immune response, which are regulated by α-synuclein, as well as other immune mechanisms (76). α-synuclein can function as an antigen associated with cellular damage and can be recognized by TLR 1 to 4, 7, and 8. The activation and potentiation of inflammatory responses are related to TLR 2 and 3, with a magnifying effect of Interferon γ (IFN-γ) (72, 73, 77), suggesting that the activation of the immune response, could lead to a chronic inflammatory process (76, 77). Finally, one hypothesis debates that infectious processes may generate an autoimmune response against α-synuclein (78) (**Figure 1**).

Evidence of the Relation of SARS-CoV-2 and Parkinson's Disease

As we mentioned previously, proinflammatory events such as viral infections are proposed as predisposing factors for individuals to develop PD and long-term neuronal loss (79). Special consideration regarding SARS-CoV-2 is its capacity to induce a marked systemic pro-inflammatory response. A prospective case-control study showed that men with higher plasma IL-6 concentrations had an increased risk of developing PD (80). As stated above, this interleukin is highly elevated in COVID-19. Therefore, it is necessary to determine the persistence of high IL-6 levels in recovered COVID-19 patients.

As we know, SARS-CoV-2 infects cells through ACE2 and TMPRSS2. Interestingly, Li et al. found that TMPRSS2 is up-regulated in rats treated with 6-hydroxydopamine (6-OHDA), a widely used tool to model PD, compared to control rats. This study showed that genes codifying for this protein are differentially regulated and may play an important role in the development of the disease (81). Surprisingly, in the past CoVs were related to PD patients. Specifically, intrathecal antibodies for CoVs types MHV-JHM and MHV-A59 are elevated in PD patients compared to individuals with other neurological diseases (82). However, the causal role of these viruses in PD is still unknown.

Although we are waiting for a longer follow-up period of recovered COVID-19 patients, some features in the acute phase of the disease are very striking. For example, anosmia and gastrointestinal symptoms are common early findings (34, 83); and a high prevalence of impaired consciousness was observed in more severe cases (34). It was thought that its neurotropic affinity could be related to its ability to produce respiratory symptoms, with over 89% of patients in the intensive care units unable to generate spontaneous ventilation, putatively due to central dysfunction (18). Hyposmia and gastrointestinal manifestations are also common non-motor symptoms in PD during the prodromal phase, a period during which neurodegeneration has begun (84–86). According to Braak's hypothesis, these symptoms represent the first stage of PD which involves the deposition of α-synuclein in the anterior olfactory nucleus and dorsal motor

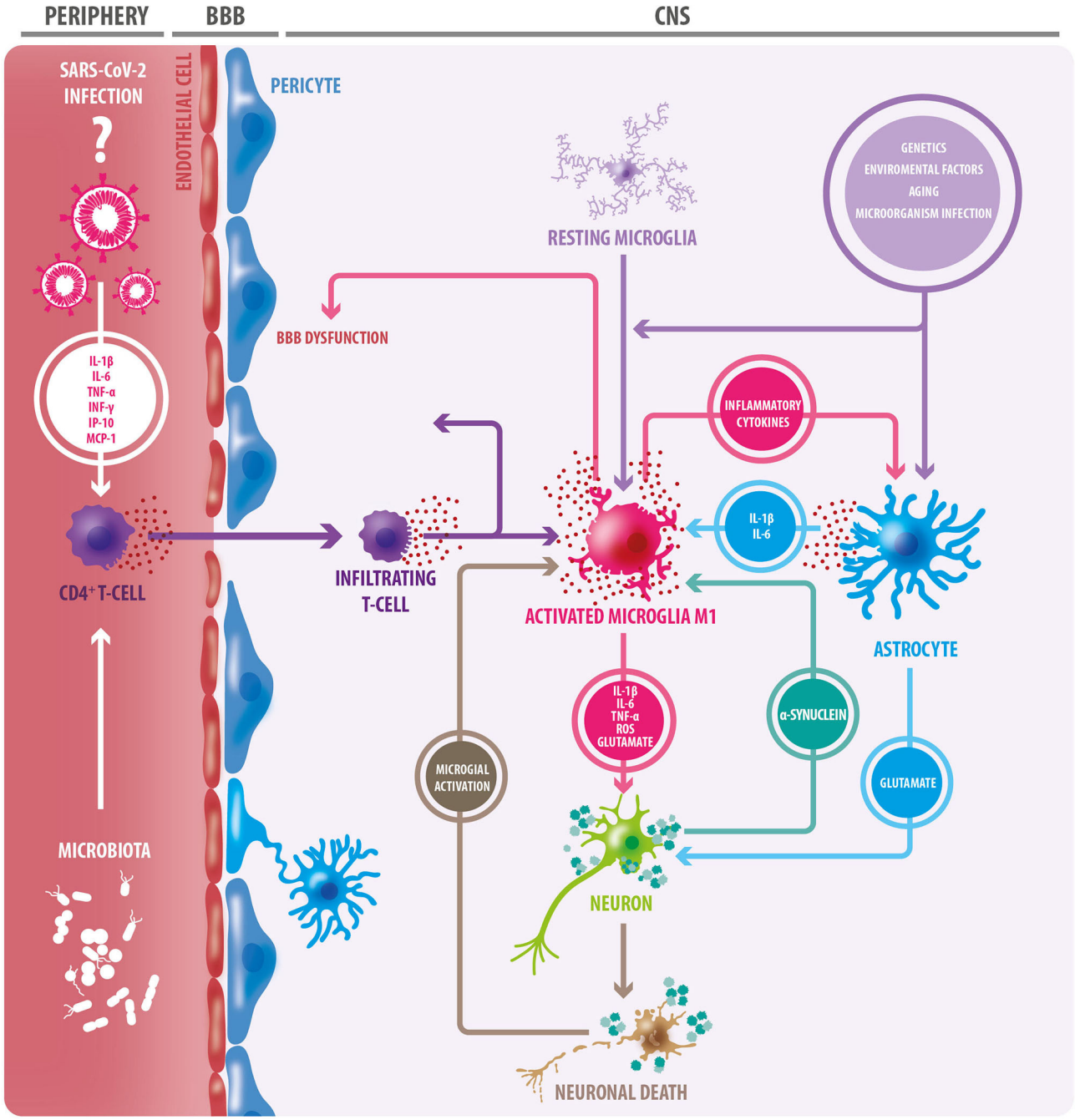


FIGURE 1 | Triggering factors of the neuroinflammatory process. Aging, in addition to genetic and environmental factors, and infections of certain microorganisms, can trigger a neuroinflammatory response through microglial and oligodendroglial activation. Activated microglia adopt an M1 inflammatory phenotype, secreting proinflammatory cytokines, reactive oxygen species (ROS), and glutamate; factors that cause neuronal damage. In this context, astrocytes become reactive, and like microglia, they secrete proinflammatory cytokines. Many of these cytokines act on microglial cells, exacerbating microglial activation, and favoring neuronal damage. The release of TNF-alpha by microglia induces increased glutamate release by astrocytes: a detrimental event for neurons. In this context, degenerating and/or dead neurons are observed, which in turn trigger microglial activation. Protein accumulation (e.g., alpha-synuclein) is another triggering factor for microglial activation. Microglia degrades and presents components of dead cells and protein aggregates to CD4+ T lymphocytes. This, in conjunction with the release of cytokines, results in the infiltration of CD4 + T cells, which release more proinflammatory cytokines, leading to greater neurodegeneration. As a consequence of this neuroinflammation, the blood-brain barrier (BBB) becomes dysfunctional, leading to the entry of peripheral immune cells. In the periphery, gut microbiota can trigger inflammation mediated by innate immune cells. The SARS-CoV-2 virus generates a "cytokine storm" at the peripheral level, therefore, it could have a similar effect. Inflammatory cytokines from peripheral blood circulation could also contribute to BBB permeabilization.

nucleus of the vagus (87). We could then presuppose an overlap in the anatomical distribution of the initial pathological process of both diseases.

CONCLUSION

The ongoing COVID-19 pandemic is expected to affect a large amount of the world's population. Although we have more clarity about its acute behavior, the chronic effects of this virus are yet to be seen, since a comprehensive understanding of SARS-CoV-2 is still lacking. The systemic inflammatory response induced by SARS-CoV-2 seems enough to set off the alarms on its potential relation with neuroinflammation, but also cumulative evidence supports its neurotropic capacity. Neuroinflammation associated with COVID-19 may be involved in subsequent neurodegeneration. Alternative mechanisms by which this virus may putatively generate long term neuronal alterations could be related to an autoimmune response against α-synuclein, which seems to have a role in immune regulation and protection against viral infections. Taking into account all this information, we believe that there is a potential relation between SARS-CoV-2 and the pathogenesis of PD. Thus, a high degree of vigilance should be kept for the hypothetical role of this virus in neurodegenerative processes in recovered COVID-19 patients.

AUTHOR CONTRIBUTIONS

The authors declare contributed conception of the review. PC-C and PS-G wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This work was partial supported by Universidad de Santiago de Chile Dicyt (Grant Código 021601CHC_POSTDOC). This work was funded by FONIS EU-LAC T010047.

ACKNOWLEDGMENTS

We would like to acknowledge the contributions of specific colleagues, institutions, or agencies that aided the efforts of the authors.

REFERENCES

1. Dorsey ER, Sherer T, Okun MS, Bloemd BR. The emerging evidence of the Parkinson pandemic. *J Parkinsons Dis.* (2018) 8:S3–8. doi: 10.3233/JPD-181474
2. Balestrino R, Schapira AHV. Parkinson disease. *Eur J Neurol.* (2020) 27:27–42. doi: 10.1111/ene.14108
3. Ray Dorsey E, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol.* (2018) 17:939–53. doi: 10.1016/S1474-4422(18)30499-X
4. Dorsey ER, Bloem BR. The Parkinson pandemic - a call to action. *JAMA Neurol.* (2018) 75:9–10. doi: 10.1001/jamaneurol.2017.3299
5. Morens DM, Folkers GK, Fauci AS. What is a pandemic? *J Infect Dis.* (2009) 200:1018–21. doi: 10.1086/644537
6. Meng L, Shen L, Ji HF. Impact of infection on risk of Parkinson's disease: a quantitative assessment of case-control and cohort studies. *J Neurovirol.* (2019) 25:221–8. doi: 10.1007/s13365-018-0707-4
7. Jang H, Boltz DA, Webster RG, Smeyne RJ. Viral parkinsonism. *Biochim Biophys Acta Mol Basis Dis.* (2009) 1792:714–21. doi: 10.1016/j.bbadis.2008.08.001
8. Takahashi M, Yamada T, Nakajima S, Nakajima K, Yamamoto T, Okada H. The substantia nigra is a major target for neurovirulent influenza A virus. *J Exp Med.* (1995) 181:2161–9. doi: 10.1084/jem.181.6.2161
9. Yamada T. Viral etiology of parkinson's disease: focus on influenza A virus. *Park Relat Disord.* (1996) 2:113–21. doi: 10.1016/1353-8020(96)00006-5
10. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet.* (2020) 395:470–3. doi: 10.1016/S0140-6736(20)30185-9
11. Limphaibool N, Iwanowski P, Holstad MJV, Kobylarek D, Kozubski W. Infectious etiologies of parkinsonism: pathomechanisms and clinical implications. *Front Neurol.* (2019) 10:1–11. doi: 10.3389/fneur.2019.00652
12. Ransohoff RM, Perry VH. microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol.* (2009) 27:119–45. doi: 10.1146/annurev.immunol.021908.132528
13. Baba Y, Kuroiwa A, Uitti RJ, Wszolek ZK, Yamada T. Alterations of T-lymphocyte populations in Parkinson disease. *Park Relat Disord.* (2005) 11:493–8. doi: 10.1016/j.parkreldis.2005.07.005
14. Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). *Mol Med Rep.* (2016) 13:3391–6. doi: 10.3892/mmr.2016.4948
15. Caggiu E, Arru G, Hosseini S, Niegowska M, Sechi G Pietro, Zarbo IR, et al. Inflammation, infectious triggers, and Parkinson's disease. *Front Neurol.* (2019) 10:1–9. doi: 10.3389/fneur.2019.00122
16. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol.* (2018) 14:576–90. doi: 10.1038/s41574-018-0059-4
17. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and age-related diseases: role of inflammation triggers and cytokines. *Front Immunol.* (2018) 9:586. doi: 10.3389/fimmu.2018.00586
18. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 2:0–2. doi: 10.1002/jmv.25728
19. Robinson CP, Busl KM. Neurologic manifestations of severe respiratory viral contagions. *Crit Care Explor.* (2020) 2:e0107. doi: 10.1097/CCE.0000000000000107
20. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses.* (2019) 12:1–28. doi: 10.3390/v12010014
21. Fishman P, Gass J, Swoveland P, Lavi E, Highkin M, Weiss SR. Infection of the basal ganglia by a murine coronavirus. *Science.* (1985) 229:877–9. doi: 10.1126/science.2992088
22. Arbour N, Côté G, Lachance C, Tardieu M, Cashman NR, Talbot PJ. Acute and persistent infection of human neural cell lines by human coronavirus OC43. *J Virol.* (1999) 73:3338–50. doi: 10.1128/JVI.73.4.3338-3350.1999
23. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res.* (2014) 194:145–58. doi: 10.1016/j.virusres.2014.09.011
24. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med.* (2005) 202:415–24. doi: 10.1084/jem.20050828
25. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019. novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–9. doi: 10.1001/jama.2020.1585

26. Li YC, Bai WZ, Hirano N, Hayashida T, Taniguchi T, Sugita Y, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. *J Comp Neurol.* (2013) 521:203–12. doi: 10.1002/cne.23171
27. Brann DH, Tsukahara T, Weinreb C, Lipovsek M, van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv.* (2020) 6:1–51. doi: 10.1101/2020.03.25.009084
28. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* (2020) 181:271–80.e8. doi: 10.1016/j.cell.2020.02.052
29. Han L, Wei X, Liu C, Volpe G, Wang Z, Pan T, et al. Single-cell atlas of a non-human primate reveals new pathogenic mechanisms of COVID-19. *bioRxiv [Preprint].* (2020). doi: 10.1101/2020.04.10.022103
30. Chen R, Wang K, Yu J, Chen Z, Wen C, Xu Z. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *bioRxiv [Preprint].* (2020). doi: 10.1101/2020.04.07.030650
31. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol.* (2018) 92:e00404-18 doi: 10.1128/JVI.00404-18
32. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci.* (2018) 12:386. doi: 10.3389/fncel.2018.00386
33. Rey NL, Wesson DW, Brundin P. The olfactory bulb as the entry site for prion-like propagation in neurodegenerative diseases. *Neurobiol Dis.* (2018) 109:226–48. doi: 10.1016/j.nbd.2016.12.013
34. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) doi: 10.1001/jamaneurol.2020.1127
35. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *JAMA Neurol.* (2020) 77:1–9. doi: 10.1101/2020.02.22.20026500
36. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clin Infect Dis.* (2020) 53:1689–99. doi: 10.1093/cid/ciaa330
37. Li Y, Bai W-Z, Hashikawa T. Response to commentary on: the neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:707–9. doi: 10.1002/jmv.25824
38. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis.* (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
39. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. *J Neurol Sci.* (2020) 413:116832. doi: 10.1016/j.jns.2020.116832
40. Effenberger M, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, et al. Faecal calprotectin indicates intestinal inflammation in COVID-19. *Gut.* (2020) 69:1543–4. doi: 10.1136/gutjnl-2020-321388
41. Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? *NPJ Park Dis.* (2017) 3:3. doi: 10.1038/s41531-016-0002-0
42. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nat Rev Immunol.* (2013) 13:875–87. doi: 10.1038/nri3547
43. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine Mig in pathogenesis. *Clin Infect Dis.* (2005) 41:1089–96. doi: 10.1086/444461
44. Powell JD, Boodoo S, Horton MR. Identification of the molecular mechanism by which TLR ligation and IFN-g synergize to induce Mig. *Clin Dev Immunol.* (2004) 11:77–85. doi: 10.1080/10446670410001670535
45. Thibaudeau TA, Smith DM. A practical review of proteasome pharmacology. *Pharmacol Rev.* (2019) 71:170–97. doi: 10.1124/pr.117.015370
46. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. *J Infect.* (2020) 80:607–13. doi: 10.1016/j.jinf.2020.03.037
47. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
48. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet.* (2020) 395:1033–4. doi: 10.1016/S0140-6736(20)30628-0
49. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet.* (2014) 383:1503–16. doi: 10.1016/S0140-6736(13)61048-X
50. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* (2020) 46:846–8. doi: 10.1007/s00134-020-05991-x
51. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19–associated acute hemorrhagic necrotizing encephalopathy: CT and MRI Features. *Radiology.* (2020) 296:E119–20. doi: 10.1148/radiol.2020201187
52. Rossi A. Imaging of Acute disseminated encephalomyelitis. *Neuroimaging Clin N Am.* (2008) 18:149–61. doi: 10.1016/j.nic.2007.12.007
53. De Santis G. SARS-CoV-2: a new virus but a familiar inflammation brain pattern. *Brain Behav Immun.* (2020) 87:95–6. doi: 10.1016/j.bbi.2020.04.066
54. Sui Y-T, Bullock KM, Erickson MA, Zhang J, Banks WA. Alpha synuclein is transported into and out of the brain by the blood–brain barrier. *Peptides.* (2014) 62:197–202. doi: 10.1016/j.peptides.2014.09.018
55. Lull ME, Block ML. Microglial activation and chronic neurodegeneration. *Neurotherapeutics.* (2010) 7:354–65. doi: 10.1016/j.nurt.2010.05.014
56. Ferrari CC, Tarelli R. Parkinson's disease and systemic inflammation. *Parkinsons Dis.* (2011) 2011:1–9. doi: 10.4061/2011/436813
57. Imamura K, Hishikawa N, Sawada M, Nagatsu T, Yoshida M, Hashizume Y. Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson's disease brains. *Acta Neuropathol.* (2003) 106:518–\26. doi: 10.1007/s00401-003-0766-2
58. Mogi M, Harada M, Kondo T, Riederer P, Inagaki H, Minami M, et al. Interleukin-1β, interleukin-6, epidermal growth factor and transforming growth factor-α are elevated in the brain from parkinsonian patients. *Neurosci Lett.* (1994) 180:147–50. doi: 10.1016/0304-3940(94)90508-8
59. Stevens CH, Rowe D, Morel-Kopp MC, Orr C, Russell T, Ranola M, et al. Reduced T helper and B lymphocytes in Parkinson's disease. *J Neuroimmunol.* (2012) 252:95–9. doi: 10.1016/j.jneuroim.2012.07.015
60. Qin XY, Zhang SP, Cao C, Loh YP, Cheng Y. Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: a systematic review and meta-analysis. *JAMA Neurol.* (2016) 73:1316–24. doi: 10.1001/jamaneurol.2016.2742
61. Zahoor I, Shafi A, Haq E. Pharmacological treatment of Parkinson's disease. In: Stoker TB, Greenland JC, editors. *Parkinson's Disease: Pathogenesis and Clinical Aspects [Internet]*. Brisbane, QLD: Codon Publications (2018).
62. Misra MK, Damotte V, Hollenbach JA. The immunogenetics of neurological disease. *Immunology.* (2018) 153:399—414. doi: 10.1111/imm.12869
63. Kannarkat GT, Cook DA, Lee JK, Chang J, Chung J, Sandy E, et al. Common genetic variant association with altered HLA expression, synergy with pyrethroid exposure, and risk for Parkinson's disease: an observational and case-control study. *NPJ Parkinsons Dis.* (2015) 1:15002. doi: 10.1038/npjparkd.2015.2
64. Burré J, Sharma M, Südhof TC. Cell biology and pathophysiology of α-synuclein. *Cold Spring Harb Perspect Med.* (2018) 8:a024091. doi: 10.1101/cshperspect.a024091
65. Burré J. The synaptic function of α-synuclein. *J Parkinsons Dis.* (2015) 5:699–713. doi: 10.3233/JPD-150642
66. Olsen LK, Cairns AG, Ådén J, Moriarty N, Cabre S, Alamilla VR, Almqvist F, et al. Viral mimetic priming enhances α-synuclein-induced degeneration: Implications for Parkinson's disease. *Brain Behav Immun.* (2019) 80:525–35. doi: 10.1016/j.bbi.2019.04.036
67. Olsen LK, Dowd E, McKernan DP. A role for viral infections in parkinson's etiology? *Neuronal Signal.* (2018) 2:20170166. doi: 10.1042/NS20170166
68. Stolzenberg E, Berry D, Yang D, Lee EY, Kroemer A, Kaufman S, et al. A role for neuronal alpha-synuclein in gastrointestinal immunity. *J Innate Immun.* (2017) 9:456–63. doi: 10.1159/000477990
69. Ashton NJ, Ide M, Zetterberg H, Blennow K. Salivary biomarkers for Alzheimer's disease and related disorders. *Neurol Ther.* (2019) 8:83–94. doi: 10.1007/s40120-019-00168-1
70. Labrie V, Brundin P. Alpha-Synuclein to the rescue: immune cell recruitment by alpha-synuclein during gastrointestinal infection. *J Innate Immun.* (2017) 9:437–40. doi: 10.1159/000479653

71. Kuhbandner K, Hoffmann A, González Alvarado MN, Seyler L, Bäuerle T, Winkler J, et al. alpha-Synuclein: a modulator during inflammatory CNS demyelination. *J Mol Neurosci*. (2020) doi: 10.1007/s12031-020-01498-8
72. Wang J, Chen Z, Walston JD, Gao P, Gao M, Leng SX. Interferon-γ potentiates α-synuclein-induced neurotoxicity linked to toll-like receptors 2 and 3 and tumor necrosis factor-α in murine astrocytes. *Mol Neurobiol.* (2019) 56:7664–79. doi: 10.1007/s12035-019-1567-5
73. Lesteberg KE, Beckham JD. Immunology of west nile virus infection and the role of alpha-synuclein as a viral restriction factor. *Viral Immunol.* (2018) 32:38–47. doi: 10.1089/vim.2018.0075
74. Massey AR, Beckham JD. Alpha-synuclein, a novel viral restriction factor hiding in plain sight. *DNA Cell Biol.* (2016) 35:643–5. doi: 10.1089/dna.2016.3488
75. Beatman EL, Massey A, Shives KD, Burrack KS, Chamanian M, Morrison TE, et al. Alpha-synuclein expression restricts RNA viral infections in the brain. *J Virol.* (2016) 90:2767–82. doi: 10.1128/JVI.02949-15
76. Pei Y, Maitta RW. Alpha synuclein in hematopoiesis and immunity. *Heliyon.* (2019) 5:e02590. doi: 10.1016/j.heliyon.2019.e02590
77. La Vitola P, Balducci C, Cerovic M, Santamaria G, Brandi E, Grandi F, et al. Alpha-synuclein oligomers impair memory through glial cell activation and via Toll-like receptor 2. *Brain Behav Immun.* (2018) 69:591–602. doi: 10.1016/j.bbi.2018.02.012
78. Caggiu E, Paulus K, Arru G, Piredda R, Sechi G Pietro, Sechi LA. Humoral cross reactivity between α-synuclein and herpes simplex-1 epitope in Parkinson's disease, a triggering role in the disease? *J Neuroimmunol.* (2016) 291:110–4. doi: 10.1016/j.jneuroim.2016.01.007
79. Ringheim GE, Conant K. Neurodegenerative disease and the neuroimmune axis (Alzheimer's and Parkinson's disease, and viral infections). *J Neuroimmunol.* (2004) 147:43–9. doi: 10.1016/j.jneuroim.2003.10.013
80. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. *Am J Epidemiol.* (2008) 167:90–5. doi: 10.1093/aje/kwm260
81. Li J, Sun Y, Chen J. Transcriptome sequencing in a 6-hydroxydopamine rat model of Parkinson's disease. *Genes Genet Syst.* (2019) 94:61–9. doi: 10.1266/ggs.18-00036
82. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov Disord.* (1992) 7:153–8. doi: 10.1002/mds.870070210
83. Lüers J-C, Klußmann JP, Guntinas-Lichius O. [The covid-19 pandemic and otolaryngology: what it comes down to?]. *Laryngorhinootologie*. (2020) 99:287–91. doi: 10.1055/a-1095-2344
84. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. *Gastroenterology.* (2020) 158:1518–9. doi: 10.1053/j.gastro.2020.02.054
85. Scheperjans F, Aho V, Pereira PAB, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord.* (2015) 30:350–8. doi: 10.1002/mds.26069
86. Tarakad A, Jankovic J. Anosmia and ageusia in Parkinson's disease. *Int Rev Neurobiol.* (2017) 133:541–56. doi: 10.1016/bs.irn.2017.05.028
87. Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, et al. Identifying prodromal parkinson's disease: pre-motor disorders in Parkinson's disease. *Mov Disord.* (2012) 27:617–26. doi: 10.1002/mds.24996

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 17 September 2020
doi: 10.3389/fneur.2020.01004

Etiologic Subtypes of Ischemic Stroke in SARS-CoV-2 Patients in a Cohort of New York City Hospitals

Ambooj Tiwari[1,2,3,4], Ketevan Berekashvili[1,2,3,4], Volodomyr Vulkanov[4], Shashank Agarwal[2], Amit Khaneja[3], David Turkel-Parella[1,2,3,4], Jeremy Liff[1,2,3,4], Jeffrey Farkas[1,2,3,4], Thambirajah Nandakumar[3], Ting Zhou[2], Jennnifer Frontera[2], David E. Kahn[2], Sun Kim[2], Kelly A. Humbert[2], Matthew D. Sanger[2], Shadi Yaghi[2], Aaron Lord[2], Karthikeyan Arcot[1,2,3,4] and Adam A. Dmytriw[5]*

[1] Interventional Neuro Associates, Greenvale, NY, United States, [2] Langone Medical Center, New York University, New York, NY, United States, [3] Jamaica Hospital Medical Center, Richmond Hill, NY, United States, [4] Brookdale University Hospital and Medical Center, Brooklyn, NY, United States, [5] Neuroradiology & Neurointervention Service, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Nai-Fang Chi,
Taipei Veterans General Hospital, Taiwan
I-Hsiao Yang,
Kaohsiung Medical University Hospital, Taiwan

***Correspondence:**
Ambooj Tiwari
amboojtiwari@gmail.com

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 28 April 2020
Accepted: 30 July 2020
Published: 17 September 2020

Citation:
Tiwari A, Berekashvili K, Vulkanov V, Agarwal S, Khaneja A, Turkel-Parella D, Liff J, Farkas J, Nandakumar T, Zhou T, Frontera J, Kahn DE, Kim S, Humbert KA, Sanger MD, Yaghi S, Lord A, Arcot K and Dmytriw AA (2020) Etiologic Subtypes of Ischemic Stroke in SARS-CoV-2 Patients in a Cohort of New York City Hospitals. Front. Neurol. 11:1004. doi: 10.3389/fneur.2020.01004

Objective: To describe the ischemic stroke subtypes related to coronavirus disease 2019 (COVID-19) in a cohort of New York City hospitals and explore their etiopathogenesis.

Background: Most neurological manifestations are non-focal, but few have reported the characteristics of ischemic strokes or investigated its pathophysiology.

Methods: Data were collected prospectively April 1-April 15, 2020 from two centers in New York City to review possible ischemic stroke types seen in COVID-19-positive patients. Patient presentation, demographics, related vascular risk factors, associated laboratory markers, as well as imaging and outcomes were collected.

Results: The age of patients ranged between 27 and 82 years. Approximately 81% of patients had known vascular risk factors, the commonest being hypertension (75%) followed by diabetes (50%) coronary disease or atrial fibrillation. Eight patients presented with large vessel occlusion (LVO) with median age 55 years (27-82) and all were male. Eight patients presented with non-LVO syndromes, with median age 65.5 years (59–82) and most were female (62.5%). Both groups were 50% African Americans and 37.5% South Asian. Both groups had similar D-dimer levels although other acute phase reactants/disease severity markers (Ferritin, CRP, procalcitonin) were higher in the LVO group. The LVO group also had a significantly higher mortality compared to the non-LVO group. The most common etiology was cryptogenic (6 patients) followed by small vessel occlusion (3 patients) and undetermined-unclassified (3 patients). For the remaining 4 patients, 2 were identified as cardioembolic and 2 with large artery atherosclerosis.

Conclusion: COVID-19-related ischemic events can present as small vessel occlusions, branch emboli or large vessel occlusions. The most common etiology is cryptogenic. Patients with LVO syndromes tend to be younger, male and may have elevated acute inflammatory markers.

Keywords: COVID-19, acute ischemic strokes, emergent large vessel occlusion, mechanical thrombectomy, ischemic stroke

INTRODUCTION

The novel Coronavirus outbreak came to the fore in December 2019 (1). Several features have been common manifestations of this disease: a primarily lower respiratory tract illness, a severe form that is more common in people with underlying diseases and higher mortality/case fatality in older populations (1–4). Multiple population health studies have also shown that the pandemic has impacted poorer communities with more severity than those with higher socio-economic status (5, 6). A particularly virulent form of immunological response, the cytokine storm syndrome especially seems to affect these vulnerable subgroups (4, 7, 8). This syndrome is also often associated with extrapulmonary complications of coronavirus disease 2019 (COVID-19) (7, 9).

In the last 3 months, multiple case reports have highlighted the extra-pulmonary complications of the disease (9–12). A prominent subgroup of these include thromboembolic complications (11–13). They have also been often associated with lab markers suggesting an underlying inflammatory and hypercoagulable condition (11, 13, 14). To this end, the specter of a COVID-19-specific coagulopathy has been raised, which is both inflammatory and consumptive, different from traditional disseminated intravascular coagulopathy (9).

Most neurological complications have focused on non-focal presentations like headaches, encephalopathy and skeletal muscle injury (10, 15). While some authors have mentioned the possibility of a form of meningoencephalitis, viral causation of neurological diseases have been mentioned less often (16, 17). Reports of patients presenting with focal signs secondary to ischemic strokes have been scant (10, 18). Several studies have recently shown the neurovascular effects of the virus on intracranial circulation as well as its overall prevalence in hospitalized patients (19, 20). Both have reported independently on outcomes of large vessel occlusion (LVO) as well as non-LVO patients though none have compared the two populations. Previous stroke research has shown that LVO patients tend to have worse presentations as well as outcomes than non-LVO patients (21).

The objective of this study was to study the characteristics of ischemic strokes in COVID-19 patients in two NYC hospital systems serving some of the most affected zip codes of Brooklyn and Queens (22). These centers are safety net hospitals which provide care to a high proportion of the underserved and vulnerable populations of eastern Queens as well as Central and Eastern Brooklyn. We also sought to compare the imaging, laboratory and presentation markers of different ischemic stroke subtypes seen in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection over a concentrated continuous 15-day period from April 1 to April 15th. We further sought to compare these variables between LVO and non LVO cases to determine if there were any factors that differentiated COVID-related strokes in these groups.

METHODS

Institutional Review Board approval as well as waiver for informed consent for the study was obtained independently from the IRBs at Brookdale Hospital University Medical Center and Jamaica Medical Center, respectively. A retrospective analysis of prospectively-maintained stroke databases was performed.

Study Population

The period between April 1st through 15th was chosen for analysis due to universal implementation of SARS-CoV-2 screening policy for every admitted patient and peak admission rate and census for COVID-19 at these centers. Furthermore, 75% of all COVID-19 related neurovascular events for the period of March-May happened in this short 15-day window. This sample, thus, approximated with the full spectrum of disease manifestation and variability in these centers. This was also the most comprehensive and complete data we were able to collect at the time of writing this paper. All consecutive patients with ischemic stroke were chosen and results from both NYC hospitals were pooled for this analysis.

Case Selection, Disease Definitions, and Classification

Only patients who tested positive for SARS-CoV-2 were included for this study. We excluded any cases that were thought to be COVID-19 positive based only on clinical or radiological suspicion. Tests which were administered at these organizations to confirm SARS-CoV-2 infections included: Cobas SARS-CoV-2 real time RT-PCR (Roche Holding AG, Basel, Switzerland), Xpert® Xpress SARS-CoV-2 (Cepheid Inc., Sunnyvale, CA) and Abbott Real-time SARS-CoV-2 PCR assay (Abbott Laboratories, Chicago, IL).

Acute onset of a focal neurological deficit was used as a clinical identification criterion for a neurovascular event. All patients underwent parenchymal imaging with non-contrast computed tomography (NCCT) and/or magnetic resonance imaging (MRI) of the brain to confirm evidence of an acute stroke. Vascular imaging with CT angiography (CTA) or MR angiography (MRA) was performed whenever feasible to define different types of vascular lesions. Using the aforementioned clinical definition, we identified 23 patients who sustained acute neurovascular events. We first excluded non-ischemic neurovascular events based on the initial NCCT imaging. This excluded 4 patients, two with subarachnoid hemorrhage and two with intracerebral hemorrhage, one of which was associated with venous thrombosis. Thus, there were 19 primary ischemic events detected. Based on further imaging with MRI and/or follow -up NCCT we excluded three more patients who were deemed to have transient ischemic attacks (TIA). In the period from April 1st−15th, 3,488 patients tested positive and a total of 207 patients were admitted with stroke or TIA. Of these, 27 (13.0%) were COVID positive. This yielded 16 patients eligible for final analysis comprising a pooled analysis of nine patients from Jamaica Hospital Medical Center and seven from Brookdale Hospital Medical Center.

We recorded ASPECTS (Alberta Stroke Program Early CT Score) for all patients with anterior circulation LVOs in our stroke database. Our institutional protocol is to perform mechanical thrombectomy only on patients with ASPECTS of 6 or greater. This is done in order to avoid malignant hyper-perfusion injury or for reasons of futility. However, all patients

were included in the LVO category irrespective of therapy offered. Follow-up parenchymal imaging with NCCT or MRI was typically performed 2–5 days after initial presentation to define the full extent of infarcted tissue.

For the purpose of etiological classification, we utilized the SSS-TOAST classification system in order to best capture the cryptogenic etiology as well as approximate causative etiology for therapeutic reasons (23). Lesion location on CT and/or MRI was used as the criterion to define cortical vs. subcortical and/or lacunar infarctions and select small vessel occlusion etiology whenever applicable. Next, vascular imaging was used to define large artery atherosclerosis, intracranial or extracranial. Echocardiography and electrocardiogram (EKG) were used to define cardioembolic sources. When none of these were present, laboratory data was evaluated to screen for known hypercoagulable conditions. If all were negative, when patients had more than one putative mechanism or if patients had repeat infarctions despite appropriate maximal therapy (dual antiplatelet or Glycoprotein IIb/IIIa inhibitor therapy for large artery atherosclerosis and anticoagulation for cardioembolism), they were assigned the "undetermined" etiology. In all these cases, a stroke neurologist assigned the value of evident, probable or possible to the etiologic mechanism based on algorithms provided by Ay et al. (23).

Variables Collected

Demographics including age, sex, race were collected. Past medical history, especially pertaining to vascular risk factors like diabetes, hypertension, smoking, stroke or chronic kidney disease (CKD) was also collected. COVID-19-related variables that were collected were as follows: type of symptoms, timeline from first symptoms to ischemic event, antibiotic/antiviral treatment protocol and extra-pulmonary and extra-neurological diseases. Stroke-related variables included time of onset (or last known well) and presentation time to a healthcare facility, acute parenchymal (CT or MRI) and vascular imaging (CTA or MRA), acute treatment (tPA and/or endovascular thrombectomy), pre- or post- stroke prophylaxis (anticoagulation vs. antiplatelet therapy) as well as post-stroke follow up imaging with MRI or CT. Relevant laboratory information was collected and included stroke work-up related data like routine blood counts, basic metabolic panel, coagulation profile (PT/PTT/INR), hemoglobin A1c (HbA1c), LDL, triglycerides and troponin values as well as COVID-related laboratory markers such as neutrophil-lymphocyte ratio, D-dimer, c-reactive protein (CRP), procalcitonin, ferritin, and lactate dehydrogenase. Non-neurological imaging information included chest x-ray findings, transthoracic echocardiography and deep venous thrombosis ultrasonography when available.

Statistical Analysis

Univariable analysis of all 16 patients was performed using descriptive statistics. This included mean, standard deviation (SD), median and interquartile range (IQR) for variables with continuous distribution. Percentages were calculated for dichotomous or categorical variables. Following this, the groups were divided into LVO and non-LVO patients. Univariable analysis of intra-group variables were reported using descriptive statistics. Finally, a bivariable analysis to evaluate inter-group differences between LVO and non-LVO groups was performed. We used the Mann Whitney U-Test for continuous variables due to non-parametric distribution of both groups. Analysis was performed using the "SciPy" data science library in Python (version 3.7) and two-sided $p < 0.05$ was considered significant.

RESULTS

During the month of March, testing kits were limited, and universal testing had not been implemented. Also, many patients who had a terminal event within 24 h of arrival were not tested. Therefore, while 16 COVID-positive strokes were identified, the true incidence of stroke in this population remains unknown.

Characteristics of the Study Population

The age of patients ranged between 27 and 82 years. There was an overall male preponderance 68.8% Racial distribution in descending order was as follows: African American (50%), South Asian (37.5%) and one each of Hispanic (6.3%) and Caucasian (6.3%). Approximately 81% of the patients had known vascular risk factors, the most common being hypertension (75%) followed by diabetes (50%). The majority (62.5%) of diabetics were in poor long-term control. The most common prodromal symptoms were fever and cough. Median time from first COVID symptom onset to stroke was 4 days (IQR: 7 days). The majority of our patients (75%) presented to the emergency room (ER) from the community. Four patients were admitted with respiratory symptoms and developed stroke during the hospital course. Only two patients (12.5%) presented within the window to receive intravenous thrombolytic therapy. Median time from last known well to symptom recognition was 9 h and 45 min. Median time from symptom recognition to seeking neurological care was 2 h and 16 min. Nearly a third of the patients (31%) were put on anticoagulation therapy for COVID. However, only one of them (6.3%) was on anticoagulation prophylactically secondary to elevated D-dimer levels. This patient developed a stroke in spite of full dose anticoagulation. Common laboratory derangements in our series included: elevated neutrophil-lymphocyte ratio (median, 7.2 and mean, 9.4), elevated D-dimer (median, 5,554, mean, 4,898), increased CRP (median, 14.7 mean, 24.5) and high ferritin values (median, 442.5, mean, 811.7). Involvement in other systems besides the lungs and brain was seen in 60%. Death during hospitalization occurred in 37.5%. A third of those deaths could be attributed to respiratory disease from COVID-19. No deep venous thrombosis or pulmonary embolism was detected in our series.

Patients With Large Vessel Occlusions (LVO)

The patients with large vessel occlusion (LVO) had a median age of 55 years old (age range: 27–82 years, IQR: 23) and all were male. Vascular risk factors were present in 75% of patients, the commonest being hypertension (62.5%) and diabetes (50%) albeit with no know coronary or cerebrovascular disease. The median NIHSS for this group was 22 (IQR: 5). Only one

TABLE 1 | Patient with large vessel occlusion (LVO) syndromes.

Characteristics of patients with LVO								
Patient ID	1	2	3	4	5	6	7	8
Demographics and vascular history								
Age	67	69	40	46	27	55	55	73
Sex	Male	Male	Male	Male	Male	Male	Male	Male
Race	South Asian	Caucasian	African American	African American	South Asian	South Asian	African American	African American
Vascular risk factors	DM, HTN	HTN, Smoking	DM, HTN	None	None	DM, HTN, Smoking	DM	HTN, CVA
COVID history								
COVID symptoms	Fever, Dyspnea	Fever, Cough, Dyspnea	None	Shock, Hypoxia	Fever, Cough	Fever, Cough, Chills, Dyspnea	None	None
COVID Treatment	HCQ*, AZT; Doxycycline	HCQ, Doxycycline	AZT,HCQ*	HCQ, AZT	N/A	Ceftriaxone, AZT	HCQ, AZT	None
Other Systemic Disease	AKI, NSTEMI	AKI	N/A	N/A	N/A	N/A	N/A	AKI
Stroke history and acute imaging								
LKW-symptom detection (mins)	780	360	0	1,320	30	240	1,320	540
Symptoms detection -Door (mins)	0	40	905	66	97	0	200	200
NIHSS (admission)	21	21	26	32	18	23	25	6
CT ASPECTS	4	5	7	N/A	9	4	4	7
CTA/MRA lesion	Left ICA	Left M1/MCA	Left M1/MCA	Proximal Basilar	Left M1/MCA	Right ICA-T	Left ICA+MCA	Left ICA non occlusive mural thrombus without atherosclerosis f/b complete ICA-MCA occlusion
Stroke therapy and prophylaxis								
EVT	N	N	Y	N	Y	N	N	N
No EVT reason	Low ASPECTS	Low ASPECTS	N/A	Medically Unstable	N/A	Low ASPECTS	Low ASPECTS	Rapid infarct progression
IV tPA	N	N	N	N	Y	N	N	N
TICI	N/A	N/A	2b	N/A	2b	N/A	N/A	N/A
Stroke prophylaxis agent	Clopidogrel	UFH	ASA f/b DOAC	UFH	DAPT f/b LMWH	UFH	ASA	Eptifibatide f/b DAPT
Imaging (non-acute)								
CXR	B/L patchy infiltrates	interstitial opacities bilateral	Left lower field hazy opacity	B/L atelectasis	B/L patchy infiltrates	B/L patchy opacities	B/L ground glass opacities	B/L upper ground glass opacities
Ejection fraction	N/A	60%	26%	60%	75%	60%	60%	N/A
Other echo abnormalities	N/A	Mild Left Atrial dilatation	global LV hypokinesis	N/A	N/A	N/A	N/A	None

(Continued)

TABLE 1 | Continued

MRI brain (Follow-up infarcts)	N/A	Left MCA partial (deep + parietal)	Left Basal Ganglia, temporal gyri, frontal	N/A	N/A	N/A	N/A	Complete infarction of Left MCA territory
CT head (Follow-up)	B/L MCA territories' infarction	Left MCA deep	N/A	Right pontine/left cerebellar stroke	N/A	Right hemispheric infarction and Occipital ICH	Left hemispheric infarction	Mild early changes in left parieto-occipital areas
Outcome and etiology								
Etiology	Cardio: Prob	Undetermined: Crypto	Cardio: Poss	Undetermined: Crypto	Undetermined: Crypto	Undetermined: Crypto	Undetermined: Crypto	Undetermined: Unclassified*
mRS at discharge	6	4	3	6	3	6	6	6

LVO, Large Vessel Occlusion; DM, diabetes mellitus; HTN, hypertension; CVA, cerebrovascular accident; Y, Yes; N, No; HCQ, hydroxychloroquine; AZT, azathioprine; AKI, Acute Kidney Injury; NSTEMI, Non ST Elevation Myocardial Infarction; N/A, Not Applicable/Available; LKW, last known well; mins, minutes; NIHSS, National Institutes of Health Stroke Score; CT, computed tomography; ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT Angiography; MRA, Magnetic Resonance Angiography; ICA, internal carotid artery; MCA, middle cerebral artery; M1, M1 segment of Middle Cerebral Artery; ICA-T, ICA Terminus; f/b, followed by; EVT, endovascular therapy; tPA, tissue plasminogen activator; TICI, thrombolysis in cerebral infarction; AP, antiplatelet; AC, anticoagulation; UFH, unfractionated heparin; ASA, acetylsalicylic acid; DOAC, Direct Oral Anticoagulants; DAPT, Dual Anti-platelet Agents; LMWH, low molecular weight heparin; NLR, neutrophil-lymphocyte ratio; WBC, white blood cell count; INR, international normalized ratio; PTT, partial thromboplastin time; CRP, c-reactive protein; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; LDL, low-density lipoprotein; CXR, chest x-ray; B/L, Bilateral; LV, Left Ventricle; ICH, intracranial hemorrhage; Prob, Probable; Poss, Possible; Crypto, Cryptogenic; mRS, modified Rankin scale.

**Patient considered to have mural thrombus of unknown etiology (no dissection flaps or underlying atherosclerotic plaque visualized on angiographic modality) with possible progression to further thrombosis and/or embolization of the entire vascular tree.*

patient was aware of being COVID-positive prior to arrival to the hospital. Three patients were admitted for pulmonary worsening and developed strokes while they were inpatients. All of them were in isolation contributing to delays in recognition of stroke. All others presented to the ER as a stroke and were found to be COVID-positive during work up of their stroke. Six patients had an echocardiogram and one (12.5%) was found to have a low ejection fraction. Three patients (37.5%) were put on anticoagulation for poststroke prophylaxis based on D-dimer levels. Another three patients were on antiplatelet agents including both patients with large artery atherosclerosis who were on dual therapy with aspirin and clopidogrel. Mortality was seen in 62.5% cases and correlated with severity of neurovascular morbidity. The mean mRS and standard deviation at discharge for this group was 5 and 1.4, respectively, while the median mRS and IQR at discharge was 6 and 2.25, respectively (**Table 1**).

Only two patients were able to undergo mechanical thrombectomy. One of these patients (Patient #5) both received IV tPA and underwent mechanical thrombectomy. The details of the case are discussed in **Figure 1**. Both patients who underwent thrombectomy were young (<45 years of age) and were initially placed on antiplatelet therapy. However, based on sustained D-dimer elevation they were later transitioned to anticoagulation. One of these patients had an EF < 30%. Both were discharged to acute rehabilitation units and were able to ambulate with help at the time of discharge (mRS, 3). Of the other six, four had low ASPECTS (<6) making them poor candidates for thrombectomy. Median ASPECTS was 5 reflecting the advanced state of tissue infarction the majority of patients experienced by the time of stroke evaluation. Finally, two patients were too medically unstable for mechanical thrombectomy. One of them (Patient # 8) was initially admitted for mild stroke symptoms secondary to a partially-occlusive mural thrombus extending from the carotid bifurcation to distal cervical segment. There was no underlying atherosclerotic plaque visualized. The patient was put on IV Integrilin, however 2 h later he developed sudden pulmonary worsening leading to endotracheal intubation. Subsequent emergent neurological imaging (obtained within 3 h of initial imaging) revealed complete occlusion of the internal carotid artery (ICA) and middle cerebral artery (MCA) as well as infarction of an entire hemispheric territory.

Non-large Vessel Occlusions (Non-LVO) Patients

Eight patients presented with non-LVO syndromes. The median age was 65.5 (range: 59–82, IQR: 14) and most of the patients were female (62.5%). Median NIHSS was 9.5 (IQR: 5.75). All had multiple vascular risk factors except one albeit with no known coronary disease or atrial fibrillation. This latter patient (Patient #8) was however morbidly obese. Only one patient (12.5%) presented early enough for IV thrombolysis. Based on parenchymal and vascular imaging, four patients were classified as small vessel disease, two with large artery atherosclerosis and two were classified as cardioembolic or cryptogenic. The latter were treated with anticoagulation while the others were treated with antiplatelet therapy. Only one patient had an EF < 30%

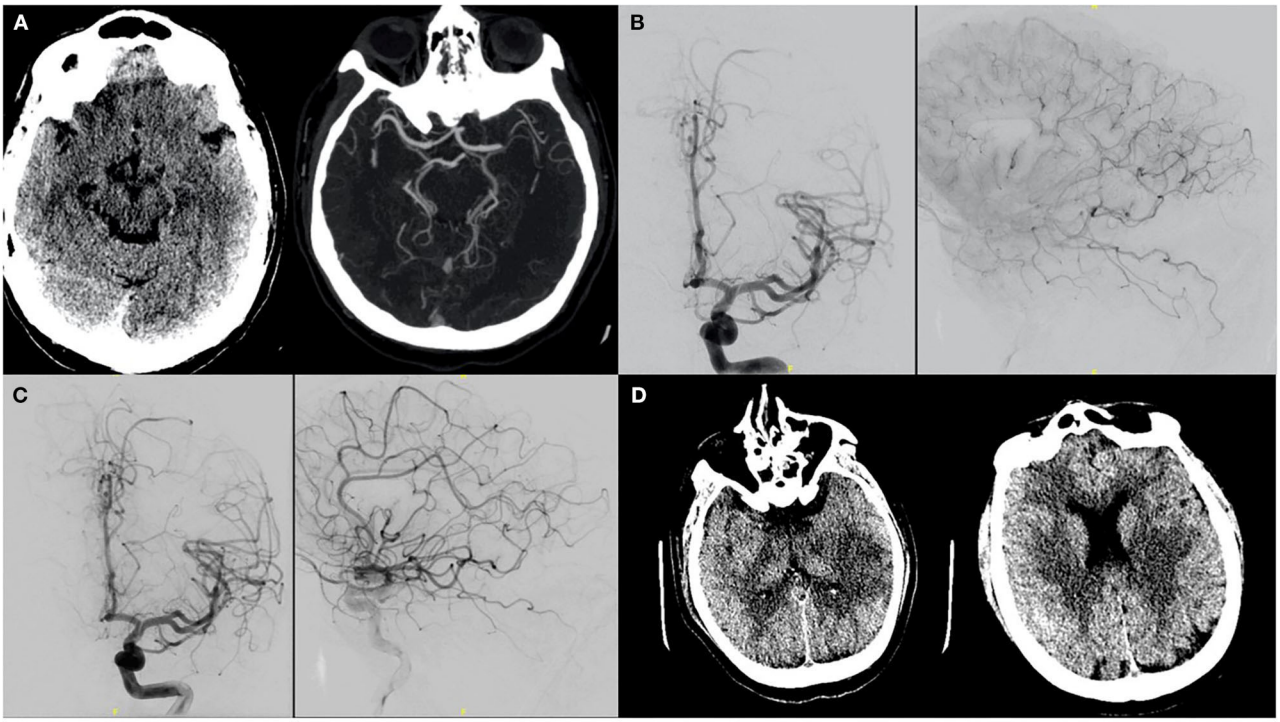


FIGURE 1 | A patient with no significant past medical history presented to the ER after 8 days of viral illness and was on Azithromycin therapy after testing positive on day 3. NIHSS was 18 on presentation secondary to a left MCA syndrome. **(A)** CT/CTA confirmed a left M1 thrombus. As presentation was within 4.5 h of symptoms onset, IV tPA was administered. **(B)** The patient was taken for mechanical thrombectomy and on initial cerebral angiography showed partial recanalization post-TPA and migration of the clot to distal MCA branches. **(C)** The patient was thus given intra-arterial tPA in these branches. **(D)** Post procedurally, infarcts in the left putamen as well as temporal and parietal regions were seen. On last follow-up patient's mRS was 3.

but the presentation as well as imaging was most consistent with small vessel occlusion. The median mRS at discharge was 3.5 (IQR: 1.25) (**Table 2**).

Patient #10 was the youngest patient in this second group. This patient had no known vascular risk factors except for morbid obesity. Reason for admission was pulmonary worsening and was being treated with ceftriaxone, azithromycin and remdesivir. This was the only case started preemptively on anticoagulation with low molecular weight heparin (LMWH) based on D-Dimer elevation, with agent being enoxaparin in all cases. Due to respiratory distress, the patient has to be intubated and 27 h post-intubation developed a seizure. This prompted further imaging with MRI which revealed multiple small embolic infarcts in all three main territories with normal-appearing vasculature on MRA. This was the only inpatient stroke in this group as well as its only mortality. The latter was secondary to septic shock.

Comparison of LVO and Non-LVO Patients

When comparing both groups, we found that both had similar racial makeup with 50% African American and 37.5% South Asian. The LVO group identified their stroke symptoms earlier and sought emergency medical care earlier than their non-LVO counterparts. Only one patient in each group presented early enough to receive thrombolysis. More patients in the LVO group were started on anticoagulation. Both groups had similar D-dimers although other acute phase reactants/disease severity markers (Ferritin, CRP, Procalcitonin) were higher in the LVO group. Counterintuitively, the neutrophil-lymphocyte ratio (NLR) was higher in the non-LVO group. Both groups also had similar levels of pre-admission diabetic control (HbA1c) as well as median number of vascular risk factors per patient. The results of analysis between both groups are summarized in **Table 3**.

On further interrogation with bivariate analysis, we found both groups were significantly different in terms of age, gender and severity of presentation. Patients with LVO were younger, belonged to the male gender and had a higher NIHSS at presentation. The LVO group also had a significantly higher mortality. While most of the laboratory markers were not significantly different, ferritin value was significantly higher in the LVO group as compared to the non-LVO group. There was insufficient power with this sample size for determination beyond the aforementioned variables. These results are summarized in **Table 4**.

Etiologic Classification

We used the SSS-TOAST criteria to define the etiologies of stroke encountered. We used parenchymal, vascular as well as cardiac monitoring and imaging to arrive at these diagnoses. The most common etiology was undetermined-cryptogenic (6 patients) followed by small vessel occlusion (3 patients) and undetermined-unclassified category (3 patients). For the

TABLE 2 | Patients with non large vessel occlusion (LVO) syndromes.

Characteristics of patients with non-LVO syndromes								
Patient ID	9	10	11	12	13	14	15	16
Demographics and vascular history								
Age	82	59	80	74	60	62	64	67
Sex	Male	Female	Female	Female	Female	Male	Female	Male
Race	African American	Hispanic	African American	African American	African American	South Asian	South Asian	South Asian
Vascular risk factors (description)	DM, HTN, CVA, CKD	None*	DM, HTN	DM, HTN	DM, HTN, CVA, CKD	HTN, CAD, CHF	HTN	HTN
COVID history								
COVID symptoms	Cough	Fever, Cough, Chills	Hypoxia	Cough, Chills	Cough, Chills	Fever, Cough, Dyspnea	Fever, Cough, Chills	Fever, Cough
COVID treatment	Ceftriaxone, AZT	Ceftriaxone, AZT, Remdesivir	HCQ, Ceftriaxone	HCQ, AZT	None	Ribavirin	HCQ, AZT	Ceftriaxone, AZT
Other systemic disease	AKI	Septic shock	AKI			NSTEMI		
Stroke history and acute imaging								
LKW—symptom detection (mins)	1,500	1,635	630	2,325	630	120	0	480
Symptom detection -Door (mins)	60	0	240	2,340	213	480	175	50
NIHSS (admission)	7	10	23	9	6	14	5	12
CTA/MRA lesion Location	N/A	N/A	N/A	N/A	N/A	N/A	Right M1-M2/MCA stenosis	Cervical LICA Occlusion
Stroke therapy and prophylaxis								
IV tPA	N	N	N	N	N	N	Y	N
Stroke Prophylaxis type	AC	AC	AP	AP	AP	AP	AP	AP
Stroke Prophylaxis medication	UFH	LMWH	ASA	ASA	ASA	DAPT	DAPT	Eptifibatide f/b DAPT
Imaging and other diagnostic work Up (non-acute)								
CXR	Right Lower Lobe infiltrates	B/L diffuse patchy opacities	B/L diffuse infiltrates	Right Lung infiltrates	Clear	Clear	B/L diffuse opacities	B/L patchy infiltrates
Ejection fraction	60%	N/A	N/A	N/A	N/A	10–15%	N/A	N/A
Other echo abnormalities	Moderate LV Wall thickening	N/A	N/A	N/A	Hyper-dynamic LV	Global LV hypokinesis/ dilatation	N/A	N/A
MRI brain (Follow-up infarcts)	Embolic post left frontal cortex	Multiple vascular territory embolic infarcts	N/A	Thalamo-capsular	Negative	Left Putamen, small right subcortical	N/A	Left Parieto-occipital watershed
CT head (Follow-up infarcts)	N/A	N/A	Internal capsule and Ganglionic infarction	N/A	Right internal capsule infarction	N/A	Right hemispheric infarction	N/A
Outcome and etiology								
Etiology	Undetermined: Crypto	Undetermined: Unclassified**	SVO: Evident	SVO: Evident	SVO: Evident	Undetermined: Unclassified***	LAA: Prob	LAA: Prob
mRS at discharge	3	6	4	3	2	3	5	4

n, number of; DM, diabetes mellitus; HTN, hypertension; CKD, Chronic Kidney Disease (Stages 4-5); CVA, cerebrovascular accident; CAD, Coronary Artery Disease; CHF, Congestive Heart Failure; d, days; Y, Yes; N, No; HCQ, hydroxychloroquine; AZT, azathioprine; AKI, Acute Kidney Injury; NSTEMI, Non ST Elevation Myocardial Infarction; N/A, Not Applicable/Available; LKW, last known well; mins, minutes; NIHSS, National Institutes of Health Stroke Score; CT, computed tomography; ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT Angiography; MRA, Magnetic Resonance Angiography; M1, M1 segment of Middle Cerebral Artery; M2, M2 segment of Middle Cerebral Artery; MCA, middle cerebral artery; ICA, internal carotid artery; tPA, tissue plasminogen activator; AP, antiplatelet; AC, anticoagulation; UFH, unfractionated heparin; LMWH, low molecular weight heparin; ASA, acetylsalicylic acid; DAPT, Dual Anti-platelet Agents; f/b, followed by; NLR, neutrophil-lymphocyte ratio; WBC, white blood cell count; INR, international normalized ratio; PTT, partial thromboplastin time; CRP, c-reactive protein; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; LDL, low-density lipoprotein; CXR, chest x-ray; B/L, Bilateral; LV, Left Ventricle; Crypto, Cryptogenic; SVO, Small Vessel Occlusion; LAA, Large Artery Atherosclerosis; Prob, Probable; mRS, modified Rankin scale.

***Patient had multi-territorial infarcts in spite of full dose anticoagulation as well as elevated D-dimer (admission). Also, no echocardiography available. Therefore, unclassified due to incomplete work up as well as possible multiple etiologic mechanisms present.*

****Infarct patterns suggested SVO etiology but given presence of bilateral territory involvement and low EF, cardioembolism couldn't be ruled out completely. Since there were two putative mechanisms involved, based on the algorithm it was defined as unclassified. *Patient was obese but without documented morbidity.*

TABLE 3 | Comparison between LVO vs. non-LVO (Descriptive).

LVO vs. non-LVO groups (Descriptive analysis)										
	Patients with LVO syndromes					Patients with non-LVO syndromes				
Statistical measure	**Percentage**	**Mean**	**SD**	**Median**	**IQR**	**Percentage**	**Mean**	**SD**	**Median**	**IQR**
Demographics and vascular history										
Age		54	15.79	55	23		68.5	9.04	65.5	14
Sex	100.00%					37.50%				
Race	50.00%					50.00%				
Vascular risk factors (n)		1.5	1.07	2	1.25		2.13	1.46	2	2.25
COVID history										
Symptom duration (d)		5.75		1.5	9.5		3.33	2		
COVID awareness (Yes)	37.50%					12.50%				
Other systemic involved (Yes)	37.50%					50.00%				
Stroke history and acute imaging										
Location at time of CVA (Inpatient)	37.50%					12.50%				
LKW-symptom detection (mins)		573.75	526.36	450	727.5		915	816.76	630	1,143.75
Symptoms detection-door (mins)		188.5	300.03	81.5	170		444.75	780.41	194	242.5
NIHSS (admission)		21.5	7.54	22	5		10.75	5.8	9.5	5.75
Door-CT (mins)		45.67	52.49	26	42		18.67	10.78	16	11.75
Stroke therapy and prophylaxis										
IV tPA	12.50%					87.50%				
Stroke prophylaxis with anticoagulation	37.50%					25.00%				
Pre vs. post anticoagulation prophylaxis (Post)	100.00%					87.50%				
Laboratory results										
NLR		7.61	5.67	6.56	6.59		9.36	7.22	6.43	6.88
WBC (×1,000/μL)		11.1	11.2	7.5	2.25		9.03	3.45	7.85	6.1
Platelets		263.75	69.32	251	93.5		270.25	110.16	215.5	128.5
D-dimer (ng/dL)		5,323.17	4,099.19	5,727.00	6,780.50		4,473.00	3,760.67	4,134.50	6,423.50
INR		1.26	0.23	1.21	0.1		1.15	0.11	1.15	0.11
PTT (s)		29.83	4.81	29.75	1.9		36.65	16.47	30.3	3.35
Procalcitonin (ng/mL)		4.47	8.49	0.32	4.61		0.43	0.66	0.13	0.44
CRP (mg/dL)		34.78	52.42	15.15	12.33		14.33	9.96	14.7	14.65
Ferritin (ng/mL)		1,181.88	1,116.01	1,033.50	792.25		318.17	110.86	312	121
Creatinine (mg/dL)		2.57	3.08	1.5	0.97		1.29	1.01	1.05	0.78
LDH (U/L)		1,226.60	1,200.15	857	209		1,482.33	896.76	1,109.50	817
Troponin (ng/mL)		0.07	0.05	0.05	0.07		0.22	0.42	0.03	0.04
CPK (U/L)		6,909.00	16,213.29	202.5	513		616.2	591.5	267	849
LDL (mg/dL)		107.67	30.74	112	47.5		90.75	50.08	88	78.75
Triglycerides (ng/mL)		192.14	116.33	169	47.5		153	29.53	160	33
Hemoglobin A1C (%)		8.1	3.27	7.2	3.05		8.24	3	6.6	2.4
Imaging (non-acute)										
Ejection fraction (<30%)	12.50%					12.50%				
Etiology (Cryptogenic)	62.50%					12.50%				
mRS at discharge		5	1.41	6	2.25		3.75	1.28	3.5	1.25

LVO, Large Vessel Occlusion; SD, Standard Deviation; IQR, Interquartile Range; n, number of; d, days; CVA, cerebrovascular accident; LKW, last known well; mins, minutes; NIHSS, National Institutes of Health Stroke Score; CT, computed tomography; ASPECTS, Alberta Stroke Program Early CT Score; CTA, tPA, tissue plasminogen activator; NLR, neutrophil-lymphocyte ratio; WBC, white blood cell count; INR, international normalized ratio; PTT, partial thromboplastin time; CRP, c-reactive protein; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; LDL, low-density lipoprotein; mRS, modified Rankin scale.

TABLE 4 | Comparison between LVO vs. non-LVO (Mann Whitney U-test).

LVO vs. non-LVO groups (Mann Whitney U Test)			
Variable	***p*-value**	**Median (LVO)**	**Median (non-LVO)**
Age	0.04	55	65.5
NLR	0.32	6.5625	6.4278845
WBC	0.44	7.5	7.85
INR	0.08	1.21	1.15
PTT	0.17	29.75	30.3
Procalcitonin	0.44	0.32	0.13
CRP	0.41	15.15	14.7
Ferritin	0.02	1033.5	312
Creatinine	0.13	1.5	1.05
LDL	0.23	112	88
Triglycerides	0.46	169	160
LKW-symptom detection (mins)	0.20	450	630
Symptoms detection-door (mins)	0.19	81.5	194
NIHSS (admission)	0.01	22	9.5

NLR, neutrophil-lymphocyte ratio; WBC, white blood cell count; INR, international normalized ratio; PTT, partial thromboplastin time; CRP, c-reactive protein; LDL, low-density lipoprotein; LKW, last known well; NIHSS, National Institutes of Health Stroke Score.

remaining 4 patients, two were identified as cardioembolic and two as large artery atherosclerosis.

The undetermined-unclassified category included three patients. One patient (Patient #14) had infarcts in two separate vascular territories, both consistent with small-vessel occlusion as well as a putative cardioembolic source. Another patient (Patient #8) was brought in symptoms of right sided weakness with unknown time of onset and he was last known normal about 9 h ago. His symptoms were recognized in the morning, but he was brought in 3 h later to the Emergency Department of the receiving hospital. On arrival, his imaging revealed no evidence of intracranial occlusion but a partial occlusion of the left cervical ICA secondary to a mural thrombus. Three hours later while the patient was admitted to the ICU, he deteriorated secondary to his respiratory status and required intubation. We proceeded to perform an emergent MRI, post intubation, that revealed the mural thrombosis had deteriorated into complete ICA-MCA occlusion and complete infarction of the left anterior hemisphere. The third patient to be categorized as such had multi-territorial infarction in spite of anticoagulation, pre-stroke elevation of inflammatory and coagulation pathway markers as well as evidence of septic shock.

In nearly half (n, 8) of our cases, no echocardiogram was available making it difficult to objectively exclude cardioembolic etiology. In three of these cases we used parenchymal distribution to determine etiology (small vessel occlusions). Two were defined as large artery atherosclerosis based on vascular findings while one was cardioembolic due to presence of bilateral anterior circulation LVOs. Two were assigned to the undetermined-unclassified category based on reasons mentioned above (Patients #8 and #14).

DISCUSSION

COVID-19 patients may have an asymptomatic, moderate or a severe course of illness (12). The severe form usually requires intensive care and tends to affect patients who are older, have underlying conditions and are those who develop acute respiratory distress syndrome (24). The most severe form can also affect the heart, liver, kidneys and be associated with sepsis or septic shock (9, 12).

Several case reports have also suggested the possibility of a hypercoagulable condition caused by SARS-CoV-2 (11, 13, 25, 26). This is specifically seen in cases with higher incidence of venous thromboembolism (VTE) or pulmonary embolism (PE). Although initially thought to be secondary to poor deep venous thrombosis (DVT) prophylaxis, recent reports suggest systemic hypercoagulability at play (25, 26). This is further supported by reports of autopsies which found clots in the lung, liver as well as kidneys (12, 27). Lab markers often associated with inflammatory conditions and consumptive coagulopathies are often elevated in these cases and include elevation of D-dimer, fibrin/fibrinogen degradation products (FDP) and fibrinogen (11, 13, 14). D-dimers thresholds have indeed been used by some groups to guide prophylactic systemic anticoagulation in COVID-19 cases (28).

Most neurological manifestations of COVID-19 have been non-focal presentations such as headaches, encephalopathy, long tract cortical signs or seizures (10, 15, 16). Li et al. described the possibility of the neuro-invasiveness of SARS-CoV-2 being similar to other coronaviridae. They distinctly point out the possibility of a synaptic, but non-vascular, transmission of the virus to the brain (16, 29). However more severe forms of COVID-19 cases have been shown to present with strokes (15). As per Mao et al. the rate of neurovascular events in their series was about 5.7% of which 4.9% were ischemic strokes (10). However, direct endothelial damage mediated by the emerging role of the angiotensin converting enzyme 2 (ACE2) receptor has neither precedent in previous coronavirus epidemics nor in sepsis-induced stroke. In addition to vascular endothelial damage, acute cardiac injury and development of antiphospholipid antibodies are important contributing factors (9). In several non-US COVID-19 series, infarcts typically followed a subcortical or distal cortical distribution (10, 15). These reports also pointed at the possibility of several mechanisms for stroke that may be directly related to the infection or its complications (10, 30). These include either the causation of acute cardiac injury, creation of antiphospholipid antibodies or even the result of a severe hypercoagulable condition caused due to D-dimer or fibrinogen abnormalities.

Recently data from several institutions in the US have been published on COVID-strokes (19, 20, 31, 32). Oxley et al. reported an overall higher incidence of large vessel occlusions in COVID-19 patients who were younger than 50-years of age (19). Vascular risk factors appeared to be present in 60% of their patients and cardioembolic sources were not always ruled out. Yaghi et al. in their contemporaneous work in New York delineated a higher incidence of cryptogenic stroke, especially in those who met the criteria of embolic source of undetermined origin (20). They found this to be higher than in patients who did not have COVID-19 in both historic as well as concurrent

control populations. However, the overall incidence was lower than the numbers seen in Mao et al. study from Wuhan (10, 20). They also corroborated that COVID-19 patients were younger, had higher D-dimer levels, a higher NIHSS, as well as a higher rate of large vessel occlusion. Work by Beyrouti et al. further discussed the laboratory findings and radiological features of six patients with COVID-19 (32). All of their patients presented with large vessel occlusions. They all also exhibited higher than normal values for lactate dehydrogenase (LDH), D-dimer, fibrinogen and CRP. Positivity for Lupus anticoagulant was seen in 80% of their patients though only one had a concomitant PTT elevation, something typically found associated COVID-19 hypercoagulability and antiphospholipid syndrome (33, 34).

In our series, we differentiated our population into LVO and non-LVO groups. This was done as the former is historically known to have a higher NIHSS and worse outcome neurologically when not treated (21). Our youngest patient was 27 while our oldest was 82. While the non-LVO group was older, the median ages of both groups are lower than would be expected for the general population (20). In the case of LVO, a median age of 55 is expressly unusual and was also seen in series published by other authors (19, 32). Case were 69% male and the LVO group was uniformly male which is consistent with the high male preponderance seen in COVID cases (35). Also, we had a higher representation of African American and non-white patients in our study than other investigations to-date. This may have to do with the demographic distribution of our participating institutions and further investigation is needed. These data are however instructive of how presentation may be similar in two distinct non-white populations- South-Asian and African-American.

Nearly 70% of our patients had pre-existing conditions, similar to other studies (19, 20, 32). However a higher percentage in the LVO group had no baseline risk factors, and there were no instances of known coronary disease or atrial fibrillation. We also noted a more variable time from COVID-related viral symptom onset to stroke presentation when compared to other studies with the range extending from 0 to 21 days, although the median time to presentation was 4 days. We had a higher percentage of inpatient strokes in our LVO population than our non-LVO population. Interestingly, our LVO populations were both identified earlier and sought care earlier than non-LVO populations as shown by the last known well symptom detection and symptom-detection-door time. Both of these time metrics could have been influenced by the presence of more inpatients in the LVO group. However, the arrival time for early intervention was similar in both populations as shown by rates of thrombolysis. Like Beyrouti et al. and Wang et al., we had a high rate of inflammatory markers in our stroke population (31, 32). These included NLR, ferritin, D-dimer, procalcitonin, CRP, Ferritin and LDH. However, we did not find any inter-group differences between LVO and non-LVO groups for any of these markers except ferritin. The LVO group had significantly higher levels of ferritin than non-LVO patients. Ferritin is known to be a marker for severity of COVID-19, although its significance with regards to neurovascular events has not been clearly delineated (12).

In terms of etiological distributions, we encountered the gamut of small vessel occlusions, cardiogenic emboli, large artery atherosclerosis as well as stroke of undetermined etiology. The most common were the cryptogenic category (6 patients) followed by small vessel occlusions and unclassified-undetermined etiologic category (3 patients). Our results were thus similar to Yaghi et al. with undetermined being the most common etiology in our analysis (50%) of which cryptogenic predominated (20). However, we often found it difficult to ascribe causative mechanisms in our series; at times due to incomplete testing and other times due to multifactorial pathogenesis of stroke in these cases. This is illustrated particularly by cases which were difficult to ascribe to a single etiology or developed strokes in spite of aggressive medical therapy (Patients #8, #10, and # 14). All of them exhibited elevations of inflammatory markers. Thus, it is possible that COVID-19 related thromboembolism may follow multiple separate pathogenetic pathways. In patients with pre-existing vascular risk factors, it may predispose to an ischemic event earlier than if purely driven by those underlying conditions. This could explain why some younger patients in the 20–55 age range presented with stroke. In these situations, it may follow the paradigm seen in other hypercoagulable conditions where two or more factors act synergistically to increase risk of stroke (14). It is also possible that in some cases this hypercoagulable condition by itself is enough to cause an embolic stroke. This may be correlated with elevated lab markers like D-Dimer or NLR or presence of antiphospholipid antibodies (10, 30). A third pathway may be related to its effect on the heart when it causes cardiomyopathy or myocarditis which in turn may predispose to cardioembolism (18, 36). This mechanism may be mediated by ACE2 targeting which could affect the vascular endothelium or the heart directly. Finally, since the incidence of VTE is higher in these cases, the possibility of paradoxical emboli cannot be ignored (14). To our knowledge, this is the first study that attempts to differentiate between the LVO and non-LVO phenotypes of ischemic strokes associated with COVID-19 and discuss their presentation, diagnostic data, etiology and outcome within that context.

Limitations

Our study has several limitations. This is an inherently small analysis of neurovascular cases presenting to two hospitals. As the number of cases in our hospitals often overwhelmed the capacity for testing or intensive care during the initial surge, many were not tested. Thus, we cannot determine the true incidence rate of neurovascular events in COVID patients. Due to the stress on the resources created by COVID-19 some of the patients did not receive advanced imaging such as MRI to confirm whether unknown infarcts may have occurred. Additionally, many cases had other risk factors and the embolic events may have been related to the underlying risk factor rather than the viral infection, or simply exacerbated by it. Finally, the type of strokes caused by the disease fit into several etiologic pathways rendering it difficult to delineate an appropriate treatment or prevention strategy.

CONCLUSION

Stroke in the setting of COVID-19 has an unusual presentation including atypical demographics and delayed time windows. COVID-19 related ischemic events can present as small vessel occlusions, multi-territorial embolic infarcts or large vessel occlusions. The most common etiology is cryptogenic followed by undetermined secondary to multiple mechanisms. Ischemic stroke can be a presenting symptom of COVID-19 and may not always be associated with severe disease markers including in the young, minorities and frontline workers.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

Study regarding human participants were reviewed and approved by the IRB committees at Brookdale Hospital University Medical Center & Jamaica Medical Center, respectively. Written informed consent from the patients/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AT was responsible for concept, data collection, review as well as writing the manuscript. AD and KA were responsible for concept, review as well as editing the final manuscript. SK, KH, MS, AL, TN, TZ, and DK were responsible for clinical care and review of the manuscript. JFr and SY were responsible for clinical care, editing, restructuring, and review of the manuscript. DT-P, JL, and JFa were responsible for the cases and review of the manuscript. VV, SA, and AK were responsible for data collection and review of the manuscript. KB was responsible for data collection, review as well as writing the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.01004/full#supplementary-material

REFERENCES

1. Paules CI, Marston HD, Fauci AS. Coronavirus infections-more than just the common cold. *JAMA*. (2020) 323:707–8. doi: 10.1001/jama.2020.0757
2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. (2020) 395:470–3. doi: 10.1016/S0140-6736(20)30185-9
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–503. doi: 10.1016/S0140-6736(20)30183-5
4. van Kan GA, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. *Clin Geriatr Med*. (2010) 26:275–86. doi: 10.1016/j.cger.2010.02.002
5. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Erratum: hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 states, march 1-30, 2020. *MMWR Morb Mortal Wkly Rep*. (2020) 69:458–64. doi: 10.15585/mmwr.mm6915e3
6. Yancy CW. COVID-19 and African Americans. *JAMA*. (2020) 323:1891–2. doi: 10.1001/jama.2020.6548
7. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. (2020) 395:1033–4. doi: 10.1016/S0140-6736(20)30628-0
8. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. (2020) 71:762–8. doi: 10.2139/ssrn.3541136
9. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. (2020) 46:846–8. doi: 10.1007/s00134-020-05991-x
10. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
11. Han H, Yang L, Liu R, Liu F, Wu K-L, Li J, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. (2020) 58:1116–20. doi: 10.1515/cclm-2020-0188
12. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
13. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis*. (2020) 3:1–4. doi: 10.1007/s11239-020-02105-8
14. Senst B, Tadi P, Goyal A, Jan A. *Hypercoagulability*. Treasure Island, FL: StatPearls Publishing (2020).
15. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
16. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. *J Med Virol*. (2020) 92:552–5. doi: 10.1002/jmv.25728
17. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
18. Zhai P, Ding Y, Li Y. The impact of COVID-19 on ischemic stroke: a case report. *Res Square*. (2020) 15:78. doi: 10.1186/s13000-020-00994-0
19. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. (2020) 382:e60. doi: 10.1056/NEJMc2009787
20. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS2-CoV-2 and stroke in a New York healthcare system. *Stroke*. (2020) 51:e179. doi: 10.1161/STROKEAHA.120.030335
21. Smith WS, Lev MH, English JD, Camargo EC, Chou M, Johnston SC, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. *Stroke*. (2009) 40:3834–40. doi: 10.1161/STROKEAHA.109.561787
22. *COVID-19: Data by Borough*. NYC Health. Available online at: https://www1.nyc.gov/site/doh/covid/covid-19-data-boroughs.page (accessed August 15, 2020).
23. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke:

the causative classification of stroke system. *Stroke*. (2007) 38:2979–84. doi: 10.1161/STROKEAHA.107.490896
24. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. *JAMA*. (2020) 323:1499–500. doi: 10.1001/jama.2020.3633
25. Wang T, Chen R, Liu C, Liang W, Guan W, Tang R, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol*. (2020) 2019:2019–20. doi: 10.1016/S2352-3026(20)30109-5
26. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. (2020) 18:1094–99. doi: 10.1111/jth.14817
27. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in Covid-19: the first autopsy series from New Orleans. *Lancet Respir Med*. (2020) 8:681–6. doi: 10.1101/2020.04.06.20050575
28. Hunt BRA, McClintock C. *Practical Guidance for the Prevention of Thrombosis and Management of Coagulopathy and Disseminated Intravascular Coagulation of Patients Infected With COVID-19* (2020). Available online at: https://thrombosisuk.org/covid-19-thrombosis.php (accessed April, 26 2020).
29. Fraser JF, Arthur AS, Chen M, Levitt M, Mocco J, Albuquerque FC, et al. Society of NeuroInterventional Surgery recommendations for the care of emergent neurointerventional patients in the setting of COVID-19. *J Neurointerv Surg*. (2020) 12:539–41. doi: 10.1136/neurintsurg-2020-016098
30. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. (2020) 382:e38. doi: 10.1056/NEJMc2007575
31. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg*. (2020) 12:648–53. doi: 10.1136/neurintsurg-2020-016220
32. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586
33. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. (2020) 18:1233–4. doi: 10.1111/jth.14768
34. Ortel TL. Antiphospholipid syndrome: laboratory testing and diagnostic strategies. *Am J Hematol*. (2012) 87(Suppl. 1):S75–81. doi: 10.1002/ajh.23196
35. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. (2020) 23:2052–9. doi: 10.1001/jama.2020.6775
36. AHA/ASA Stroke Council Leadership. Temporary emergency guidance to us stroke centers during the COVID-19 pandemic. *Stroke*. (2020) 51:1910–2. doi: 10.1161/STROKEAHA.120.030023

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 18 September 2020
doi: 10.3389/fneur.2020.584522

Negative Impact of the COVID-19 Pandemic on Admissions for Intracranial Hemorrhage

*Amr Abdulazim[1], Anne Ebert[2], Nima Etminan[1], Kristina Szabo[2] and Angelika Alonso[2]**

[1] Department of Neurosurgery, Medical Faculty Mannheim, Mannheim Center for Translational Neurosciences, Heidelberg University, Heidelberg, Germany, [2] Department of Neurology, Medical Faculty Mannheim, Mannheim Center for Translational Neurosciences, Heidelberg University, Heidelberg, Germany

OPEN ACCESS

Edited by:
Sheng-Feng Sung,
Ditmanson Medical Foundation
Chia-Yi Christian Hospital, Taiwan

Reviewed by:
Patricio Sandoval,
Pontificia Universidad Católica de Chile, Chile
Carmen Serna-Candel,
Klinikum Stuttgart, Germany

***Correspondence:**
Angelika Alonso
angelika.alonso@umm.de

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care,
a section of the journal Frontiers in Neurology

Received: 17 July 2020
Accepted: 18 August 2020
Published: 18 September 2020

Citation:
Abdulazim A, Ebert A, Etminan N, Szabo K and Alonso A (2020) Negative Impact of the COVID-19 Pandemic on Admissions for Intracranial Hemorrhage. Front. Neurol. 11:584522. doi: 10.3389/fneur.2020.584522

Background: The COVID-19 pandemic has seriously impacted healthcare systems worldwide. Admissions for various non-COVID-19 emergencies have significantly decreased. We sought to determine the impact of COVID-19 on admissions for intracranial hemorrhage to a German University Hospital emergency department.

Methods: In a retrospective analysis of admissions to the emergency department of the University Hospital Mannheim from January to June 2020 and the corresponding time period in 2019, all patients admitted for either traumatic or non-traumatic intracranial hemorrhage were evaluated. Poisson regression was performed to analyze changes in admission rates as a function of year, epoch (COVID-19-epoch, March to April 2020 and corresponding months 2019; non-COVID-19-epoch, January to February and May to June 2019/2020) and the interaction of year and epoch (reflecting the impact of the pandemic and subsequent lockdown measures).

Results: Overall, 320 patients were included in the study. During the COVID-19-epoch, admission rates for spontaneous intracranial hemorrhage decreased significantly by 42.1% (RR 0.579, $p = 0.002$, 95% confidence interval 0.410–0.818). Likewise, admission rates for traumatic intracranial hemorrhage decreased significantly by 53.7% [RR = 0.463, $p < 0.001$, 95% confidence interval (CI) 0.358–0.599].

Conclusion: The decrease of spontaneous intracranial hemorrhages may be a consequence of underutilization of the healthcare system whereas decreasing rates of traumatic intracranial hemorrhage admissions may predominantly reflect a decrease in true incidence rates due to lockdown measures with restricted mobility. Raising patient awareness to seek emergency healthcare for acute neurological deficits during lockdown measures is important to ensure appropriate emergency care for patients with intracranial hemorrhage.

Keywords: COVID-19, pandemic, intracranial hemorrhage, intracerebral hemorrhage, traumatic brain bleeding

INTRODUCTION

The COVID-19 pandemic has a deep impact on healthcare systems worldwide. Analysis of emergency calls and admissions to emergency departments have recorded a pronounced increment (1, 2). In countries heavily stricken by COVID-19, rapidly rising patient numbers continue to exceed healthcare resources (2, 3) with dramatic consequences (4). At the same time, reports on decreasing admissions for non-COVID-19 conditions are becoming more frequent. While especially cerebrovascular and cardiovascular emergencies seem to be affected (5–7), reductions of trauma admissions have also been reported (8).

Intracranial hemorrhage is a heterogeneous condition, comprising both traumatic and non-traumatic disease patterns. Intracerebral hemorrhage, the leading syndrome in non-traumatic hemorrhage, is characterized by a high case fatality and a high disease burden in survivors, mostly causing a life in functional dependence (9). Whereas the risk of both spontaneous and traumatic intracranial hemorrhage increases with age, traumatic brain injury with intracranial bleeding complications also affects the younger (10) with substantial loss of disability-adjusted life-years. In both cases, an optimal emergency care is of utmost importance to attenuate a potentially fatal course of disease.

We sought to determine the impact of the COVID-19 pandemic and subsequent lockdown measures on admission rates for intracranial hemorrhage during the weeks of the initial spreading of COVID-19 and after stabilization of infection rates in a University Hospital in Germany.

METHODS

The local ethics committee (Ethikkommission II der Medizinischen Fakultät Mannheim, Universität Heidelberg) approved this retrospective study. Patient consent was waived due to the retrospective character of the study and the lack of patient interaction.

The study comprises two observation periods, January to June 2020 and the corresponding period in 2019. The months March and April 2020 were defined as the lockdown period: daily infection rates with SARS-CoV-2 were recorded by the Robert Koch Institute from March 2nd on, and partial lockdown measures were implemented on March 9th. Emergency and pandemic plans in the University Hospital Mannheim were updated on February 28th, and a partial ban of visitors was realized on March 5th.

March and April 2019 and 2020 were termed epoch 1, the remaining months of the years 2019 and 2020 were termed epoch 2. All patients admitted to the emergency department with a diagnosis of intracranial hemorrhage were identified by a retrospective chart review of the admissions to our interdisciplinary emergency department. In detail, all emergency department charts with an ICD-10 admission diagnosis of I60ff, I61ff, I62ff, and S06ff were screened. Inclusion criterion was admission for spontaneous or traumatic intracranial hemorrhage, comprising intracerebral, subdural, epidural, intraventricular and/or subarachnoid hemorrhage. Traumatic hemorrhages affecting more than one intracranial compartment were categorized as complex traumatic brain injury. Patients with intracranial hemorrhage due to arteriovenous malformation or fistula, cerebral venous thrombosis, underlying cavernoma or intracranial aneurysms and patients with hemorrhagic intracerebral malignoma were excluded. The rationale for exclusion of these patient groups is the significant heterogeneity in terms of epidemiology, risk factors, treatment options and prognosis together with low absolute numbers, thus precluding a statistically appropriate evaluation.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 25. Poisson regression was used to test if the rate of admissions changed as a function of year, epoch (epoch 1, March–April; epoch 2, January–February + May–June) and year-by-epoch interaction (reflecting the impact of the pandemic and subsequent lockdown measures), expressed as rate ratio (RR) along with its 95% confidence interval. A p-value <0.05 was

TABLE 1 | Characteristics of patients admitted for intracranial hemorrhage between January and June in 2019 and 2020, as well as in March/April in 2019 and 2020.

	Total Jan–June 2019 + Jan–June 2020	**March/April 2019**	**Lockdown 2020**
	***n* = 320**	***n* = 54**	***n* = 33**
Sex (male, *n*; %)	191 (59.7)	33 (61.1)	21 (63.6)
Age (mean, range)	69.4 (18–101)	69.2 (30–96)	68.4 (18–101)
Non-traumatic intracranial hemorrhage (*n*, %)	138 (43.1)	19 (35.2)	11 (33.3)
ICH	129	18	9
IVH	3	1	1
SAH	6	0	1
Traumatic intracranial hemorrhage (*n*, %)	182 (56.9)	35 (64.8)	22 (66.7)
cTBI	35	4	8
tICH	36	8	4
tSDH	74	13	8
tSAH	31	7	2
EDH	6	3	0
Anticoagulation (*n*, %)	130 (40.6)	19 (35.2)	14 (42.4)
NOAC	40	5	5
Phenprocoumon	16	3	2
PAI	64	9	7
Dual PAI	5	0	0
Other*	5	2	0

*Enoxaparin, 3; Nadroparin, 1; Fondaparinux, 1.

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SDH, subdural hematoma; SAH, non-aneurysmatic subarachnoid hemorrhage; cTBI, complex traumatic brain injury; tICH, traumatic intracerebral hemorrhage; tSDH, traumatic subdural hematoma; tSAH, traumatic subarachnoid hemorrhage; EDH, epidural hematoma; NOAC, non-vitamin K antagonist oral anticoagulants; PAI, platelet aggregation inhibitors.

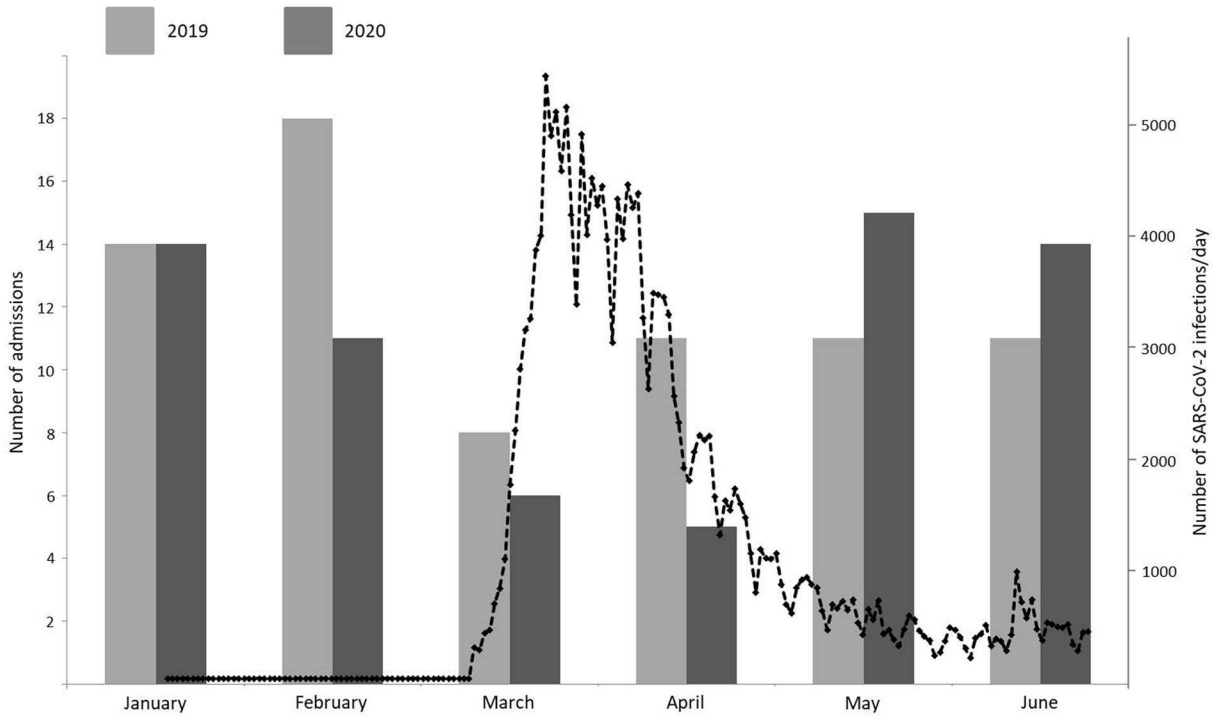


FIGURE 1 | Monthly admission rates for spontaneous intracranial hemorrhage between January and June 2019 (light gray) and January and June 2020 (dark gray) and daily new infections in Germany with SARS-CoV-2 from March 2nd to June 30th (black dotted line).

considered as statistically significant. For group comparisons between the lockdown period (March-April 2020) and the corresponding period in 2019 Chi-square test was used.

RESULTS

Over the cumulative observation periods 01-06/2019 and 01-06/2020, 320 patients were admitted with the diagnosis of either spontaneous or traumatic intracranial hemorrhage (mean age 69.4 years, 59.7% male; see **Table 1**) with a mean monthly admission rate of 26.67 cases [standard deviation (SD) ± 6.050]. Non-traumatic intracranial hemorrhages, predominantly spontaneous intracerebral hemorrhages, comprised 43.1% of the cases, and 40.6% of patients were on some form of anticoagulant medication at the time of admission (**Table 1**).

During the lockdown period (03-04/2020), admission rates for spontaneous intracranial hemorrhage decreased significantly by 42.1%, as found in a significant year-by-epoch interaction [RR = 0.579, $p = 0.002$, 95% confidence interval (CI) 0.410–0.818; see **Figure 1**]. Likewise, admission rates for traumatic intracranial hemorrhage decreased significantly by 53.7%, as found in a significant year-by epoch interaction [RR = 0.463, $p < 0.001$, 95% confidence interval (CI) 0.358–0.599; see **Figure 2**].

The treatment rate with any anticoagulant did not vary between the two observation periods, neither for spontaneous ($p = 0.91$) nor for traumatic intracranial hemorrhage ($p = 0.42$).

In 2020 admission rates increased after the lockdown period for both spontaneous and traumatic intracranial hemorrhage. For traumatic hemorrhages, there was a significant effect for "year" in the Poisson regression (RR = 1.358, $p = 0.007$, CI 1.089–1.695). As reflected in **Figure 2**, this effect is mainly driven by the excess admission rates in June.

DISCUSSION

Our data illustrate the significant impact of the COVID-19 pandemic and associated lockdown measures on admission rates for non-traumatic and traumatic intracranial hemorrhage, with a 42.1% decrease and 53.7% decrease, respectively, in March and April 2020. The referenced period is characterized by the peak of SARS-CoV-2 infection rates in Germany, exceeding 1,000 infections per day on March 8th for the first time, rising to a peak of nearly 5,500/day on March 16th, and stable infection rates of <1,000/day since May 1st. The year-by-epoch interaction resulting from Poisson regression is a good index of a causal relationship with the COVID-19 pandemic.

Two factors may have caused the pronounced decrease observed: a decrease in true incidence rates of intracranial hemorrhages, or a decrease in utilization of the health care system. For spontaneous intracranial hemorrhage, a COVID-19-related decrease in incidence rates is highly unlikely. However, similarly, a significant decrease in admission rates has also been reported for other cerebro- and cardiovascular emergencies, such as ischemic stroke (5, 6, 11), transient ischemic attack (12) or acute coronary syndrome (7) in several countries. Various patient-centered factors may contribute to this phenomenon.

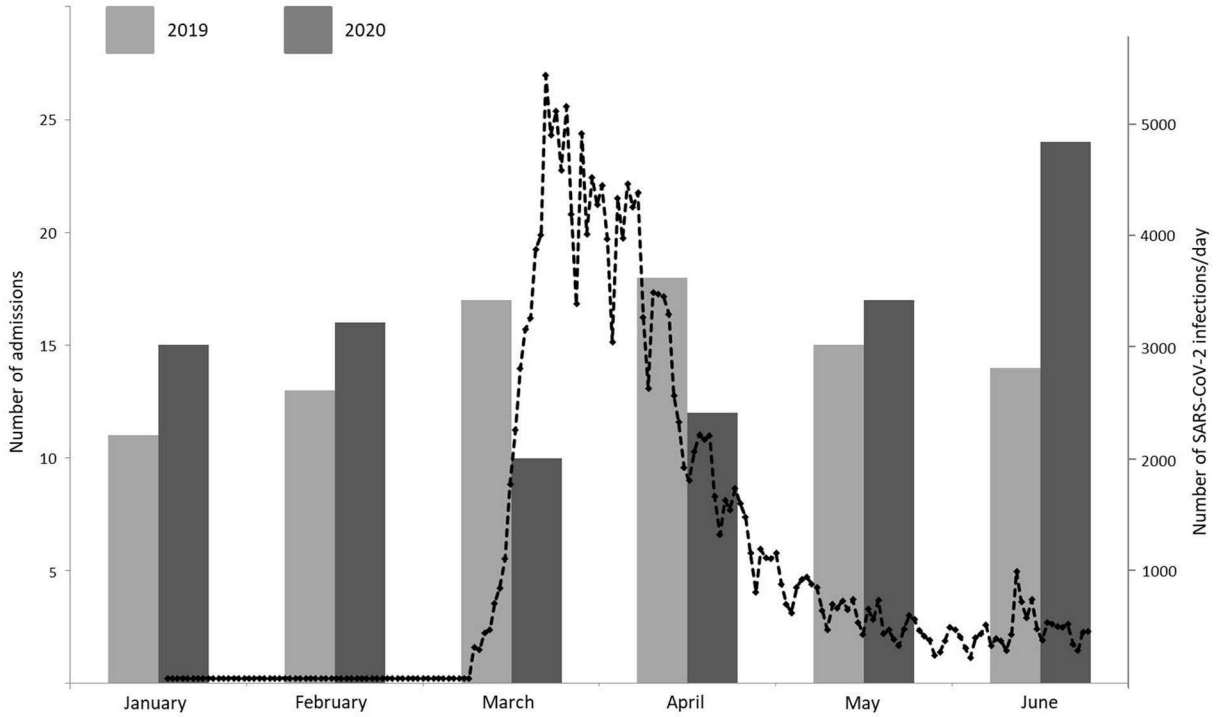


FIGURE 2 | Monthly admission rates for traumatic intracranial hemorrhage between January and June 2019 (light gray) and January and June 2020 (dark gray) and daily new infections in Germany with SARS-CoV-2 from March 2nd to June 30th (black dotted line).

Insistent stay-at-home campaigns and public discussions about imminent intensive care bottlenecks may have unsettled patients whether to present to hospital. In addition, a reluctance to seek medical, especially hospital care, may result from a fear of infection, together with concerns of being isolated due to a strict ban of visitors since the midst of March.

In case of traumatic intracranial hemorrhages, the lockdown status may well have contributed to a decrease in true incidence rates. The observation period March–April 2020 coincides with nation-wide partial lockdown measures in Germany, including social distancing, self-isolation, quarantining, but also a travel ban, closing of schools/daycare and public facilities, such as fitness centers. These measures correspond with a significant decrease in mobility as reflected in freely available online mobility data[1] As a consequence, admissions for extracranial trauma have equally dropped in a significant manner (8, 13). Of interest, our study identified a significant increase in admissions for traumatic intracranial hemorrhage in 2020 compared to the preceding year when excluding the COVID-periods March–April 2020 and the corresponding months in 2019. The increase is mainly driven by excess admission rates during June 2020, possibly attributable to a catch-up effect after a relaxation of lockdown measures.

Overall, the significant increase in admissions for traumatic intracranial hemorrhage in the post-lockdown months May and June 2020 suggests rather a shift of admissions than missed admissions during the lockdown period. However, the decrease of admissions in non-traumatic intracerebral hemorrhage needs to be regarded with concern. Timely diagnosis and treatment of intracranial hemorrhage is indispensable to keep morbidity and mortality low. Although actual mortality rates in Germany do not show an excess mortality since the beginning of the COVID-19 pandemic, the sequelae of missed admissions for cerebro- and cardiovascular emergencies may still lie ahead. A *de novo* absence of patients with intracranial hemorrhages in case of a second wave of infections has to be prevented by all means. This issue has been addressed by the German Society for Neurology demanding campaigns to inform the public about the priority of stroke care in times of the pandemic in order to avoid serious healthcare consequences[2].

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission II der Medizinischen Fakultät Mannheim, Universität Heidelberg. Written informed consent

[1]https://www.covid-19-mobility.org/

[2]https://www.dgn.org/rubrik-dgn/stellungnahmen-der-dgn/3919-auswirkungen-der-sars-cov-2-pandemie-auf-die-versorgung-zerebrovaskulaerer-erkrankungen

for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AAb: data analysis and interpretation, drafting manuscript, and final approval. AE: statistical analysis, critical revision of manuscript, and final approval. NE and KS: data analysis and interpretation, critical revision of manuscript, and final approval. AAl: concept and design, data acquisition, data analysis and interpretation, drafting manuscript, and final approval. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Rudilosso S, Laredo C, Vera V, Vargas M, Renu A, Llull L, et al. Acute stroke care is at risk in the era of COVID-19: experience at a comprehensive stroke center in Barcelona. *Stroke.* (2020) 51:1991–5. doi: 10.1161/STROKEAHA.120.030329
2. Comelli I, Scioscioli F, Cervellin G. Impact of the COVID-19 epidemic on census, organization and activity of a large urban Emergency Department. *Acta Biomed.* (2020) 91:45–9. doi: 10.23750/abm.v91i2.9565
3. Senni M. COVID-19 experience in Bergamo, Italy. *Eur Heart J.* (2020) 41:1783–4. doi: 10.1093/eurheartj/ehaa279
4. Tambone V, Boudreau D, Ciccozzi M, Sanders K, Campanozzi LL, Wathuta J, et al. Ethical criteria for the admission and management of patients in the ICU under conditions of limited medical resources: a shared international proposal in view of the COVID-19 pandemic. *Front Public Health.* (2020) 8:284. doi: 10.3389/fpubh.2020.00284
5. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmunzer B, Barlinn K, et al. Acute stroke in times of the COVID-19 pandemic: a multicenter study. *Stroke.* (2020) 51:2224–7. doi: 10.1161/STROKEAHA.120.030395
6. Bersano A, Kraemer M, Touze E, Weber R, Alamowitch S, Sibon I, et al. Stroke care during the COVID-19 pandemic: experience from three large European countries. *Eur J Neurol.* (2020). doi: 10.1111/ene.14375. [Epub ahead of print].
7. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. *Eur Heart J.* (2020) 41:1852–3. doi: 10.1093/eurheartj/ehaa314
8. Stoker S, McDaniel D, Crean T, Maddox J, Jawanda G, Krentz N, et al. Effect of shelter-in-place orders and the COVID-19 pandemic on orthopaedic trauma at a community level II trauma center. *J Orthop Trauma.* (2020). 34:e336–42. doi: 10.1097/BOT.0000000000001860
9. An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. *J Stroke.* (2017) 19:3–10. doi: 10.5853/jos.2016.00864
10. Powers AY, Pinto MB, Tang OY, Chen JS, Doberstein C, Asaad WF. Predicting mortality in traumatic intracranial hemorrhage. *J Neurosurg.* (2019) 132:552–9. doi: 10.3171/2018.11.JNS182199
11. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center. *J Stroke Cerebrovasc Dis.* (2020) 29:104953. doi: 10.1016/j.jstrokecerebrovasdis.2020.104953
12. Diegoli H, Magalhaes PSC, Martins SCO, Moro CHC, Franca PHC, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke.* (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
13. Forrester JD, Liou R, Knowlton LM, Jou RM, Spain DA. Impact of shelter-in-place order for COVID-19 on trauma activations: Santa Clara County, California, March 2020. *Trauma Surg Acute Care Open.* (2020) 5:e000505. doi: 10.1136/tsaco-2020-000505

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 25 September 2020
doi: 10.3389/fneur.2020.573356

Unfractionated Heparin in SARS-CoV-2 Pneumonia: Ischemic Stroke Case Report

Aslan Efendizade[1], Adam A. Dmytriw[2,3], Kevin Hewitt[1] and Gwynivere A. Davies[4]*

[1] Department of Diagnostic Radiology, State University of New York (SUNY) Downstate Medical Center, University Hospital Brooklyn, Brooklyn, NY, United States, [2] Department of Medical Imaging, University of Toronto, Toronto, ON, Canada, [3] Department of Neuroradiology & Neurointervention, Brigham and Women's Hospital, Boston, MA, United States, [4] Department of Oncology, Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada

OPEN ACCESS

Edited by:
Tomohisa Nezu,
Hiroshima University, Japan

Reviewed by:
Siyuan Fan,
Peking Union Medical College Hospital (CAMS), China
David García-Azorín,
Hospital Clínico Universitario de Valladolid, Spain
Sean Ruland,
Loyola University Medical Center, United States

***Correspondence:**
Aslan Efendizade
Aslan.efendizade@downstate.edu

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 16 June 2020
Accepted: 20 August 2020
Published: 25 September 2020

Citation:
Efendizade A, Dmytriw AA, Hewitt K and Davies GA (2020) Unfractionated Heparin in SARS-CoV-2 Pneumonia: Ischemic Stroke Case Report. Front. Neurol. 11:573356. doi: 10.3389/fneur.2020.573356

Thromboembolism is a known phenomenon in patients with Coronavirus disease 2019 (COVID-19). Recent investigations have revealed that a significant proportion of those hospitalized with severe COVID-19 demonstrate clinical and laboratory markers compatible with hypercoagulability, which is differentiated from disseminated intravascular coagulation (DIC), termed COVID-associated coagulopathy. Additionally, there is increasing concern for development of acute ischemic stroke because of this hypercoagulable state. We present a patient with COVID-19 pneumonia who was managed with unfractionated heparin (UFH) infusion and developed a large ischemic infarct shortly after cessation of the infusion. In retrospect, the patient's coagulation parameters were consistent with overt DIC, although some of these parameters are easily masked by the effects of UFH. These findings emphasize the importance of anticoagulation as well as its careful discontinuation, as failure to do so may result in a significant thromboembolic event.

Keywords: COVID-19, stroke, anticoagulation, heparin, thromboembolism

INTRODUCTION

Preliminary observations of Coronavirus disease 2019 (COVID-19) were consistent with hypoxemic respiratory failure from acute respiratory distress syndrome (ARDS) (1, 2). However, recent investigations have led researchers to question whether the predominant cause of respiratory failure is vascular, with development of microthrombi and pulmonary vasodilatation (3). This is especially relevant given the incidence of venous thromboembolism (VTE) and risk of disseminated intravascular coagulation (DIC) in patients with COVID-19 (2, 4, 5).

An analysis of 1,026 admitted Chinese patients demonstrated that 40% were considered high risk of developing VTE, with many at high risk for bleeding and death, suggesting the need for careful prophylaxis (6). Cui et al. (7) reported a single-center experience of 81 patients in ICU with severe COVID-19 infection who demonstrated a 25% VTE rate [though these patients did not receive prophylactic anticoagulation (7)]. Patients with VTE were older, had significantly lower lymphocyte counts, higher D-dimer values, and prolonged activated partial thromboplastin times (aPTT).

Many patients with sepsis demonstrate deranged coagulation factors. DIC is characterized by dysregulation of coagulation and fibrinolysis, resulting in widespread thrombosis and hemorrhage. Several societies have formulated diagnostic criteria for DIC, such as the International Society of Thrombosis and Hemostasis (ISTH), which tends to classify cases into overt or non-overt DIC. The classification system assigns points (0–3) based on values associated with each parameter—platelet count, fibrin-related markers, prothrombin time (PT), and fibrinogen—and a score ≥5 is compatible with overt DIC (8). One study of 183 hospitalized patients with COVID-19 found that 71.4% of non-survivors (and 0.6% of survivors) met the criteria for overt DIC according to ISTH criteria (9). Subgroup analysis of 99 patients (with high sepsis-induced coagulopathy scores or D-dimer values) who received prophylactic anticoagulation demonstrated significantly reduced mortality, which led some institutions to adopt intermediate or therapeutic anticoagulation for severe cases of COVID-19. How best to dose, time, and discontinue anticoagulation remains to be determined.

CASE DESCRIPTION

A 56-year-old Haitian man with past medical history significant for hypertension, diabetes mellitus, seizure disorder, and prior cerebrovascular accident (CVA) (**Figure 1**) of unknown etiology with residual dysarthria and gait abnormality presented with worsening dry cough and dyspnea on exertion. He denied other respiratory symptoms, fevers, myalgia, sick contacts, and recent travel, as well as novel neurological symptoms. Home medications included amlodipine, aspirin, clopidogrel, atorvastatin, metformin, and levetiracetam.

In the emergency department, the patient was afebrile with an oxygen saturation of 50% on room air, improving to 91% on bilevel positive airway pressure. Physical examination revealed crackles within the lung bases, and the patient was unable to speak in full sentences. Additionally, it was noted that he was not oriented to time or person, nor was he cooperative with a neurological exam, although novel focal neurological deficits were not observed. Relevant admission laboratory markers are summarized (**Table 1**). Electrocardiogram was unremarkable, and chest radiography revealed bilateral multifocal airspace opacities. SARS-CoV-2 polymerase chain reaction by nasopharyngeal sampling was positive, and the patient was started on hydroxychloroquine, ceftriaxone, and azithromycin in addition to standard supportive care.

On the second day of admission, the patient's hypoxemia worsened, requiring intubation and mechanical ventilation with a fraction of inspired oxygen of 0.50. Further D-Dimer elevation (>4,000 ng/ml FEU) led to initiation of therapeutic unfractionated heparin (UFH). Based on management criteria (10), UFH was selected for concomitant acute renal failure (ARF).

On day 5, UFH was held secondary to elevation of aPTT (**Table 2**). Approximately 2 h after, the patient developed a non-reactive left pupil followed by myoclonic head movements 6 h after that. Given that the patient was intubated and under sedation, neurological examination was limited, and this was initially managed as seizure activity given the patient's history. However, he was non-responsive to antiseizure medications. Subsequent neurological evaluation revealed a left fixed pupil (4 mm), absent corneal and vestibulo-ocular reflexes, and no response to painful stimulation. The patient then underwent computed tomography (CT) of the head, which revealed infarcts within the parasagittal left occipital lobe and brainstem (**Figure 2**). Although advanced imaging was not performed, on coronal and sagittal reconstructions of the non-contrast head CT, a dense vessel sign was observed extending from the mid basilar into the left posterior cerebral artery. It should be noted

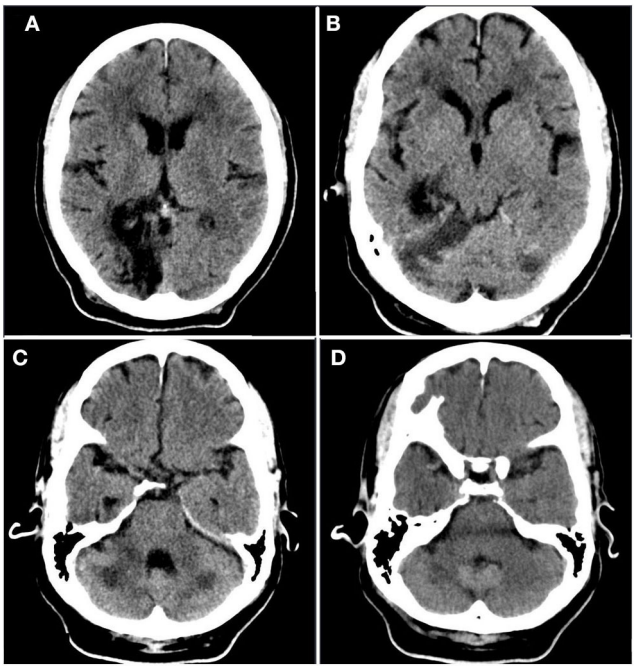


FIGURE 1 | Prior infarct. Rostral to caudal **(A–D)** non-contrast computed tomographic axial slices of the head performed 2 years prior to current admission demonstrates hypoattenuation and parenchymal volume loss in the right parasagittal occipital lobe compatible with an old posterior cerebral artery territory infarct, as well as acute infarct in the territory of the bilateral superior cerebellar arteries.

TABLE 1 | Relevant admission laboratory markers.

Marker	Value	Reference range
Lymphocyte count ($\times 10^3/\mu$l)	0.5	0.9–2.9
Creatinine (mg/dl)	2.0	0.7–1.3
AST (U/L)	153	13–19
ALT (U/L)	81	7–52
CRP (mg/L)	304	0–8
Ferritin (μg/L)	2,495	16–294
LDH (U/L)	1,046	140–271
Procalcitonin (ng/ml)	0.58	0.00–0.10

*Additional labs seen in "Day 1" of **Table 2**. AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein; LDH, lactate dehydrogenase.*

TABLE 2 | Timeline of coagulation parameters.

Marker	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Anticoagulation	SubQ heparin	SubQ heparin	Heparin drip	Heparin drip	Drip held <8 A.M	–	–
D-Dimer[a] (ng/ml FEU)	1,704	–	>4,000	–	–	–	–
PT (s)	–	–	13.7	–	–	13.5	16.3
aPTT (s)	40	–	–	90.3	86.9	27.8	37.5
Platelets ($\times 10^3/\mu l$)	169	200	219	238	220—Large	248—Large	219—Large

On days 1 to 3, the patient received prophylactic subcutaneous heparin 5,000 units every 8 h. On day 3, the patient was transitioned to heparin drip at 1,000 units/h with target aPTT of 60–80 s. On the night of day 4, the patient had equal and reactive pupils. Heparin drip was held before 8 A.M on day 5, and (at 10 A.M) the patient's left pupil became non-reactive and at ∼4 P.M displayed myoclonic head movements. PT, prothrombin time; aPTT, activated partial thromboplastin time; Large, large platelets seen on smear.
[a]D-Dimer reference level 500 ng/ml or less of fibrinogen equivalent units (FEU).

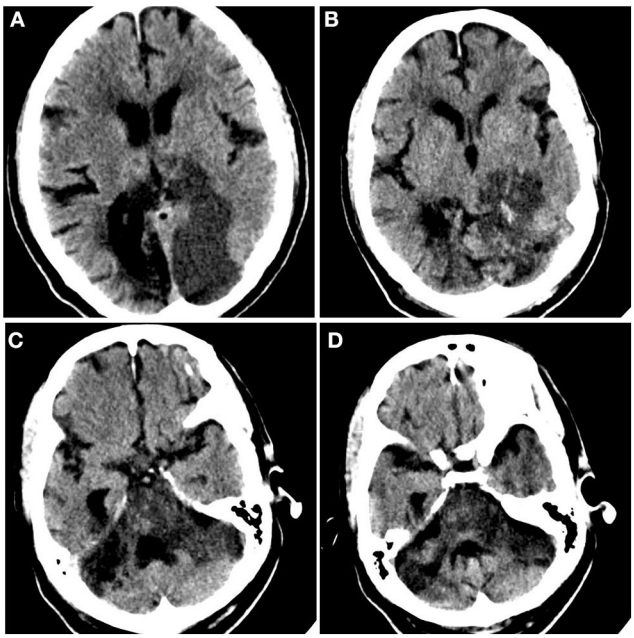


FIGURE 2 | Acute ischemic infarct. Rostral to caudal **(A–D)** non-contrast computed tomographic axial slices of the head performed on this admission demonstrates loss of gray–white differentiation in the parasagittal left occipital lobe and sulcal effacement compatible with recent ischemia, as well as diffuse brainstem edema. Additional surrounding punctate foci of hyperattenuation suggest petechial hemorrhage.

that on the day prior, a bedside transthoracic echocardiogram was unremarkable, and electrocardiogram did not reveal an arrhythmia. Unfortunately, despite supportive care, the patient passed away.

DISCUSSION

Disseminated Intravascular Coagulation

Suggested management of COVID-19 involves monitoring D-Dimer, prothrombin time (PT), international normalized ratio, aPTT, fibrinogen, and platelet counts (11), consistent with sepsis guidelines. The incidence of DIC in COVID-19 patients varies widely by severity of presentation but can be seen in >2/3 of patients who die from severe disease (5). Non-survivors also had significantly higher fibrin degradation product levels and prolonged PT and aPTT values at admission. Interestingly, a meta-analysis of nine studies investigating COVID-19 demonstrated significantly higher values of PT and D-dimer for severe vs. mild cases, but no difference in aPTT or platelet count was observed (12). Relatively mild thrombocytopenia and the disproportionate increase in PT vs. aPTT has led to adoption of the term COVID-associated coagulopathy (CAC).

Typical management strategy for sepsis-associated DIC involves treatment of the underlying infection. Unfortunately, there is no known effective treatment for COVID-19 infection. In DIC with a thrombotic phenotype, therapeutic doses of heparin have been suggested with one randomized controlled trial (RCT) demonstrating superior efficacy of LMWH compared to UFH (13). However, prophylaxis using LMWH, UFH, or mechanical thromboprophylaxis remains the standard of care in most patients with DIC.

Anticoagulation

Several medical centers have published guidelines on prophylactic or therapeutic anticoagulation for COVID-19 patients based on D-Dimer levels and VTE occurrence (10, 11). At our Brooklyn center, both prophylactic and therapeutic anticoagulation is often achieved with apixaban or enoxaparin. UFH infusion is reserved for those with ARF. The Journal of the American College of Cardiology released guidelines addressing the management of COVID-19 associated thromboembolic events (4), identifying additional risk factors including critical illness, prolonged hospitalization and intubation, immobility, and use of investigational therapies. Troponin elevations in COVID-19 patients may therefore not be a direct result of infection but rather inflammation leading to plaque rupture or microthrombi from cytokine storm. For anticoagulation, they recommend prophylactic dosing, with an emphasis on LMWH to reduce health care worker exposure from blood draws or medication management.

Potential Role of UFH in DIC and COVID-19

If the decision is made to initiate UFH, the subsequent diagnosis of DIC may be delayed for various reasons including reduced platelet consumption, attribution of PT elevation to UFH (14),

reduced D-Dimer, and fibrinogen variability (an acute phase reactant). Therefore, use of UFH may lead to delayed recognition of progressive coagulopathy, potentially increasing their risk for adverse consequences. Utilizing the ISTH criteria for DIC, we can retrospectively calculate a score of 5 based on PT and D-Dimer values on the third day of admission (**Table 2**), which is compatible with overt DIC.

Additionally, precautions must be used for timing of medications as previous studies have shown rebound coagulopathy with discontinuation of both UFH and LMWH. In one RCT of patients with acute coronary syndrome, plasma prothrombin fragment and thrombin–antithrombin levels post-discontinuation exceeded levels both during and prior to treatment (15). While this change occurred faster in UFH, the peak levels after LMWH discontinuation were higher, suggesting that both can result in reactivation of the coagulation system, causing thrombus growth, and platelet recruitment. Given the long clinical course of COVID-19 and lack of definitive treatment, patients are thus at higher risk of thrombosis with sudden discontinuation of anticoagulation, which should be discouraged except in the case of clinically relevant bleeding. UFH nomograms should be re-evaluated considering this specific CAC phenotype, whereby preserved platelet counts may predispose to thrombotic events. In contrast, though a study of 221 patients with COVID-19 demonstrated 13 cases of cerebrovascular events, none of these are reported to have occurred in the setting of anticoagulation discontinuation or adjustment (16).

Once a thrombus has formed, the use of thrombolytics, such as tissue plasminogen activator (tPA), may be warranted if timely revascularization would relay a mortality benefit (with massive pulmonary embolism or ischemic stroke). Addressing this, a case series from Poor et al. in which five critically ill COVID-19 patients with ventilator-dependent respiratory failure demonstrated improvement with systemic tPA (3), suggested the presence of microvascular thrombi that did not respond to prophylactic or therapeutic anticoagulation. In our case, given the delay in symptom recognition and diagnosis of ischemic infarct, the patient was not a candidate for administration of thrombolytics. Furthermore, the extent of edema seen on non-contrast head CT suggests that the majority (if not entirety) of the involved vascular territory was infarcted, precluding endovascular thrombectomy.

The relationship between COVID-19 and ischemic stroke is still under investigation. Recently, two multi-center studies have been conducted to investigate the incidence and shed light on the possible etiology. In one study comparing the incidence of stroke in hospitalized or emergency department visits, the authors report an incidence of 1.6% in COVID-19 vs. 0.2% in patients with influenza (17). Another study performed in close geographic proximity to our institution demonstrated 0.9% incidence of imaging proven stroke in patients hospitalized with COVID-19 (18). Of those cases, the authors report that a majority (65.6%) were cryptogenic in etiology and that the observed cases were more likely to be in younger men as compared to historical controls.

LIMITATIONS

Given the tumultuous and resource-strained context during this incident case, there are several limitations. No advanced neuroimaging or Doppler studies were performed as part of the stroke workup. Given the territory of involved brain parenchyma, the location of prior CVA, and the dense vessel seen on head CT, thromboembolism is a possible etiology. However, it should be noted that prior imaging (**Figure 1**) demonstrates the presence of a remote and acute infarct, suggesting that the new infarct (**Figure 2**) likely occurred in the setting of vertebrobasilar disease. With respect to underlying vertebrobasilar disease, blood pressure monitoring in the days leading up to the stroke suggests that a hypotensive episode in the setting of vertebrobasilar disease is less likely as the patient's lowest recorded mean arterial pressure was 78 mmHg.

The period during this admission was quite worrisome for our hospital, such that presence in the patients' rooms and high-risk interactions were limited and may have contributed to a delay in timely and thorough neurological investigation. Furthermore, in the days leading up to the stroke, the patient was intubated and under sedation such that typical manifestations of an acute stroke were not displayed. Thus, it may be the case that the ischemic event occurred before interruption of UFH. Furthermore, additional laboratory investigations were not performed to exclude other etiologies of coagulopathy, such as antiphospholipid antibodies. Finally, venous duplex studies of the extremities or CT pulmonary angiography were not performed to suggest concomitant thromboembolic events.

CONCLUSION

In conclusion, we present a patient with COVID-19 pneumonia who was initiated on UFH for elevated coagulation parameters and subsequently developed neurological symptoms after 2-h UFH interruption, which may have been a sequela of acute ischemic infarct. Additionally, the patient's retrospective ISTH score was compatible with overt DIC, although diagnosis may have been delayed due to UFH effects. This supports the finding of increasing thrombotic risk with COVID-19 that can occur concurrently with an unusual DIC phenotype, outlining the importance of prophylaxis and careful discontinuation of therapeutic anticoagulation.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by SUNY Downstate School of Medicine Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained

from the legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AE: case investigation, manuscript draft, and manuscript revisions. AD and KH: case discussion and manuscript revisions. GD: case discussion manuscript draft and manuscript revisions. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.573356/full#supplementary-material

REFERENCES

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. *JAMA*. (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
3. Poor HD, Ventetuolo CE, Tolbert T, Chun G, Serrao G, Zeidman A, et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. *Clin Transl Med*. (2020) 10:e44. doi: 10.1002/ctm2.44
4. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. (2020) 75:2950–73. doi: 10.1016/j.jacc.2020.04.031
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. (2020) 18:844–7. doi: 10.1111/jth.14768
6. Wang T, Chen R, Liu C, Liang W, Guan W, Tang R, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol*. (2020) 7:e362–3. doi: 10.1016/S2352-3026(20)30109-5
7. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. (2020) 18:1421–4. doi: 10.1111/jth.14830
8. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *J Thromb Haemost*. (2001) 86:1327–30. doi: 10.1055/s-0037-1616068
9. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. (2020) 18:1094–9. doi: 10.1111/jth.14817
10. Yale. *COVID-19 Treatment Adult Algorithm*. (2020). Available online at: https://medicine.yale.edu/intmed/COVID-19%20TREATMENT%20ADULT%20Algorithm%2004272020_382832_5_v4.pdf (accessed April 29, 2020).
11. MGH. *COVID-19 Treatment Guidance*. (2020). Available online at: https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/mass-general-COVID-19-treatment-guidance.pdf (accessed April 29, 2020)
12. Xiong M, Liang X, Wei YD. Changes in blood coagulation in patients with severe coronavirus disease 2019. (COVID-19): a meta-analysis. *Br J Haematol*. (2020) 189:1050–2. doi: 10.1111/bjh.16725
13. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. *J Intensive Care*. (2014) 2:15. doi: 10.1186/2052-0492-2-15
14. Schultz NJ, Slaker RA, Rosborough TK. The influence of heparin on the prothrombin time. *Pharmacotherapy*. (1991) 11:312–6.
15. Bijsterveld NR, Moons AH, Meijers JC, Tijssen JG, Buller HR, Levi M, et al. Rebound thrombin generation after heparin therapy in unstable angina. A randomized comparison between unfractionated and low-molecular-weight heparin. *J Am Coll Cardiol*. (2002) 39:811–7. doi: 10.1016/S0735-1097(01)01825-3
16. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute cerebrovascular disease following covid-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. (2020) 2020. doi: 10.2139/ssrn.3550025. [Epub ahead of print].
17. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol*. (2020) 2020:e202730. doi: 10.1001/jamaneurol.2020.2730
18. Yaghi S, Ishida K, Torres J, Grory BM, Raz E, Humbert K, et al. SARS-CoV-2 and stroke in a new york healthcare system. *Stroke*. (2020) 51:2002–11. doi: 10.1161/STROKEAHA.120.030335

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 06 October 2020
doi: 10.3389/fneur.2020.579070

Stroke and Novel Coronavirus Infection in Humans: A Systematic Review and Meta-Analysis

Kai Wei Lee[1], Abdul Hanif Khan Yusof Khan[2,3], Siew Mooi Ching[1,3], Peck Kee Chia[2], Wei Chao Loh[2], Anna Misya'il Abdul Rashid[2], Janudin Baharin[2], Liyana Najwa Inche Mat[2], Wan Aliaa Wan Sulaiman[2], Navin Kumar Devaraj[1,3], Dhashani Sivaratnam[4], Hamidon Basri[2] and Fan Kee Hoo[2]*

[1] Department of Family Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia, [2] Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia, [3] Malaysian Research Institute on Ageing, Universiti Putra Malaysia, Serdang, Malaysia, [4] Department of Ophthalmology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Malaysia

OPEN ACCESS

Edited by:
Beom Joon Kim,
Seoul National University Bundang Hospital, South Korea

Reviewed by:
Bin Jiang,
Capital Medical University, China
Craig S. Anderson,
University of New South Wales, Australia
Myzoon Ali,
University of Glasgow, United Kingdom

***Correspondence:**
Abdul Hanif Khan Yusof Khan
ahanifkhan@upm.edu.my

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 01 July 2020
Accepted: 03 September 2020
Published: 06 October 2020

Citation:
Lee KW, Yusof Khan AHK, Ching SM, Chia PK, Loh WC, Abdul Rashid AM, Baharin J, Inche Mat LN, Wan Sulaiman WA, Devaraj NK, Sivaratnam D, Basri H and Hoo FK (2020) Stroke and Novel Coronavirus Infection in Humans: A Systematic Review and Meta-Analysis. Front. Neurol. 11:579070. doi: 10.3389/fneur.2020.579070

Background: As the world witnessed the devastation caused by the coronavirus disease 2019 (COVID-19) outbreak, a growing body of literature on COVID-19 is also becoming increasingly available. Stroke has increasingly been reported as a complication of COVID-19 infection. However, a systematic synthesis of the available data has not been conducted. Therefore, we performed a systematic review and meta-analysis of currently available epidemiological, clinical, and laboratory data related to both stroke and COVID-19 infection.

Methods: We systematically searched Medline, Cinahl, and PubMed for studies related to stroke and COVID-19 from inception up to June 4, 2020. We selected cohort studies, case series, and case reports that reported the occurrence of stroke in COVID-19 patients. A fixed-effects model was used to estimate the pooled frequency of stroke in COVID-19 patients with a 95% confidence interval (CI).

Results: Twenty-eight studies were included in the systematic review and seven studies for the meta-analysis. The pooled frequency of stroke in COVID-19 patients was 1.1% (95% CI: 0.8, 1.3). The heterogeneity was low ($I^2 = 0.0\%$). Even though the frequency of stroke among patients having COVID-19 infection was low, those with concomitant COVID-19 infection and stroke suffered from a more severe infection and eventually had a poorer prognosis with a higher mortality rate (46.7%) than COVID-19 alone. Many COVID-19 patients shared the common traditional risk factors for stroke. We noted that ischemic stroke involving the anterior circulation with large vessels occlusion is the most common type of stroke with more strokes seen in multi-territorial regions, suggesting systemic thromboembolism. An elevated level of D-dimers, C-reactive protein, ferritin, lactic acid dehydrogenase, troponin, ESR, fibrinogen, and a positive antiphospholipid antibody were also noted in this review.

Conclusions: The occurrence of stroke in patients with COVID-19 infection is uncommon, but it may pose as an important prognostic marker and indicator of severity of infection, by causing large vessels occlusion and exhibiting a thrombo-inflammatory

vascular picture. Physicians should be made aware and remain vigilant on the possible two-way relationship between stroke and COVID-19 infection. The rate of stroke among patients with COVID-19 infection may increase in the future as they share the common risk factors.

Keywords: stroke, cerebrovascular disease, COVID-19, coronavirus (2019-nCoV), systematic review, meta-analysis, SARS-CoV-2

INTRODUCTION

In December 2019, an outbreak of a novel respiratory infection was first detected in Wuhan, China, linked to three cases of patients presenting with pneumonia (1, 2). The cause of the pneumonia was found to be a viral infection known as novel coronavirus disease (COVID-19), and by March 2020, the World Health Organization (WHO) declared this disease as a pandemic caused by a virus known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) (3, 4). The WHO stated in its report on the state of the world's health that humans are now facing a serious threat from COVID-19 (4, 5), and it was now necessary to declare COVID-19 as a public health emergency (6).

COVID-19's main presentation relates to the infection of the upper respiratory system, with clinical features such as fever, dry cough, myalgia, and malaise, and in more severe cases, patients may develop pneumonia that may proceed to the life-threatening acute respiratory distress syndrome (ARDS) (7). Patients infected with COVID-19 will also experience several mild neurological symptoms such as headache, dizziness and anosmia, to severe symptoms like altered level of consciousness, acute cerebrovascular events, seizures, and ataxia (8, 9). In addition, COVID-19 could also cause viral encephalitis and hemorrhagic necrosis in the mesial temporal lobes and thalamus (10–12). Stroke is one of the more disabling neurological complications being reported, where the first retrospective cohort of COVID-19 showed stroke occurrence in around 2% of the patients (13). The American Stroke Association indicated that the risk of stroke doubled every 10 years after the age of 55, and therefore, stroke affects more older adults than younger ones (14, 15). However, due to COVID-19, literature has reported an increasing number of premature strokes in the younger generation (16).

The pathophysiology for the development of stroke in patients with COVID-19 is multifactorial. Infection, in general, may increase the odds of stroke 1.4-fold, particularly in the early convalescence phase, and this association may also be similarly expected among COVID-19 patients (17). Secondly, SARS-CoV-2 may potentially predispose to thrombogenesis and increase the risk of stroke by infecting the myocardium cells via ACE2 (angiotensin-converting enzyme II) receptor and causing vascular injury and inflammation (18). COVID-19 has been shown to create a prothrombotic state as evidenced by high D-dimer titres that further propagate the risk of thrombosis (19). Moreover, COVID-19 patients appear to be in a hyper inflammation state or cytokine storm like condition, which resulted in secretion of high interleukin-6 (IL-6) levels, which in turn translates to hyperviscosity and increases the risk for stroke propensity (20). Apart from the increased thrombotic potential in large vessels in patients with COVID-19, the patient may also be susceptible to spontaneous intracerebral hemorrhage and micro thrombosis of small penetrating vessels owing to the potential risk of vascular endothelial damage (21). There is growing evidence of the development of thromboembolic complications among patients with COVID-19, the occurrence of stroke. Several case studies have also shown that patients with pre-existing cerebrovascular disease may be at a higher risk for a poor outcome if they become infected with COVID-19 (22–24). Given the worldwide COVID-19 cases are now over nine million as updated on June 26, 2020, and still rising in an exponential manner (25), the understanding of the association between stroke and COVID-19 is essential in order to prevent debilitating sequelae associated with stroke and to aid in the prevention and management in these groups of patients.

Significance of the Study

Due to the novelty of the virus and the relatively short duration of the current COVID-19 outbreak, only a limited and scattered body of scientific evidence on the neurological complications of COVID-19 is currently available. Furthermore, the possible two-way association between COVID-19 and stroke has not yet been elucidated, and currently there are only limited data available on stroke co-occurrence and characterization in patients with COVID-19, which urgently needs further investigation and analysis to ensure a better outcome for this group of patients. Therefore, it is vital to perform this review in order to determine the frequency of stroke among COVID-19 patients and stroke characterization, as this may impact future management.

We, therefore, performed a systematic review and meta-analysis involving the epidemiological, clinical presentation, imaging characteristics, and laboratory finding related to both stroke and COVID-19 infection.

METHODS

This systematic review study was registered with the Medical Research and Ethics Committee, Ministry of Health Malaysia (registration number: NMRR-20-1200-55395) and was

Abbreviations: ACA, Anterior cerebral artery; ACE-2, Angiotensin-converting enzyme type 2 receptor; ARDS, Acute respiratory distress syndrome; CI, Confidence interval; CR, Case report; CRP, C-reactive protein; CS, Case series; ESR, Erythrocyte sedimentation rate; IL-6, Interleukin 6; LDH, Lactic acid dehydrogenase; LVO, Large vessels occlusion; MCA, Middle cerebral artery; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PT, Prothrombin time; RC, Retrospective cohort; TIA, Transient ischemic attack; TOAST, Trial of ORG 10172 in acute stroke treatment; WHO, World Health Organization.

conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (26) (**Appendix 1**).

Literature Search

Two investigators (AHKYK and JB) independently searched the Medline, Cinahl, and PubMed databases for potential studies that were published in peer-reviewed journals from inception to June 4, 2020. We used the following search terms: (Cerebrovascular Accident OR CVA OR Stroke) AND (COVID-19 OR CORONAVIRUS OR 2019-NCOV) with limiters of ENGLISH and HUMAN. The search strategies with the Boolean or phrase operators are shown in **Appendix 2**. Subsequently, we removed duplications using Endnote® before the next process of screening the title and abstracts for suitability. Finally, the selected articles with their full text were assessed for their eligibility to be recruited into this systematic review and meta-analysis.

Study Selection

All relevant articles identified through the above comprehensive databases were imported into the Endnote® programme version X5. Initially, we performed de-duplication. Title and abstracts were then reviewed for their relevance and articles highlighting cases of COVID-19 and its relevance to stroke were reviewed in full text by four investigators (AHKYK, JB, PKC, and WCL) who are clinical neurologists with not <5 years of experience in the field of clinical neurology. Studies were selected based on inclusion criteria that these studies have data on the frequency of stroke in cases of COVID-19 or possess any data relevant to the relative risk of COVID-19 and stroke. Studies were excluded if they are a review paper, or there is no required data for both these conditions. We also excluded any study with patients who developed stroke prior to COVID-19 infection. Any disagreements between the investigators were resolved through discussions and consultations with another two senior investigators (SMC and FKH) before the final consensus for quantitative analysis was reached.

PICO (Participants/Population, Intervention/Exposure, Comparator/Control, Outcomes)

The participants should be those (age >18 years) with or without a confirmed diagnosis of stroke. Exposure was referred to as exposure to COVID-19 disease, whereby there were no limitations in severity criteria. Comparator was referred to as non-COVID-19 disease and COVID-19 patients without stroke. The main outcomes we examined in this review were percentage or frequency of stroke that occurs after COVID-19 infection, whereby the stroke incidence could be an ischemic and hemorrhagic stroke, venous stroke due to venous sinus thrombosis, or transient ischemic attack. The secondary outcomes were clinical presentation, the subtype of stroke, imaging characteristics, and laboratory finding related to both stroke and COVID-19 infection.

Data Extraction

Four investigators were paired into two groups (group 1: AHKYK and JB; group 2: PKC and WCL) to perform the data extraction independently. The following data were extracted from every study: the last name of the first author, year of publication, country, severity status, study design, patient characteristics (ethnicity composition, gender, and mean age), comorbidities (diabetes, hyperlipidemia, hypertension, ischemic heart disease, heart failure, previous stroke, chronic kidney disease/end-stage renal disease, number of stroke patients per overall participants, any information relevant to strokes such as the location of stroke [arterial or venous]), types of stroke (ischemic or haemorrhagic), classification of stroke, mortality rate, and blood parameters. Another two investigators (AMAR and LNIM) performed proofreading to ensure no errors and bias in the data extraction.

Strategy for Data Synthesis

Pooled frequency of stroke among COVID-19 patients was estimated using meta-analysis, and the data required for this was the number of patients with stroke and COVID-19 infection (nominator) divided by the total number of patients with COVID-19 infection (denominator). A synthesis of the findings in the aspect of clinical presentation, imaging characteristics, and laboratory finding extracted from included studies were summarized in tables. Pertaining to clinical presentation, we classified stroke based on vessels occlusion and TOAST, whereby data were presented either in N value or ultimate decision-maker (Yes/No). The ultimate decision, either Yes or No, was used because the particular study had only one patient with stroke. Classification of stroke was based on imaging finding such as arterial vs. venous; ischemic vs. hemorrhagic; location of stroke (anterior circulation, posterior circulation, or multiple territories), whereby data were presented either in *N* value or ultimate decision-maker (Yes/No). Laboratory findings with clinical importance to inflammation due to stroke or viral infection were also examined, which include erythrocyte sedimentation rate, C-reactive protein, ferritin, D-dimer, lactic acid dehydrogenase, fibrinogen, antiphospholipid, procalcitonin, interleukin6, troponin, platelet, and prothrombin time. Blood parameters were presented in mean ± standard deviation or range.

Quality Assessment

The quality of the individual studies pertaining to cohort studies was determined using the checklist Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), which has 22 items that assess components in observational studies (27). A "0" was given if that item was not reported; "1" was awarded if that item was sufficiently shown in the article. Each article's quality was graded as "good" if STROBE scores ≥14/22 or graded as "poor" if strobe score <14/22 (27). Nevertheless, studies would have been included in this review regardless of the STROBE grading.

We used a quality appraisal checklist for case series studies developed by the Institute of Health Economics, which appraises over 20 items. This is a three-options checklist

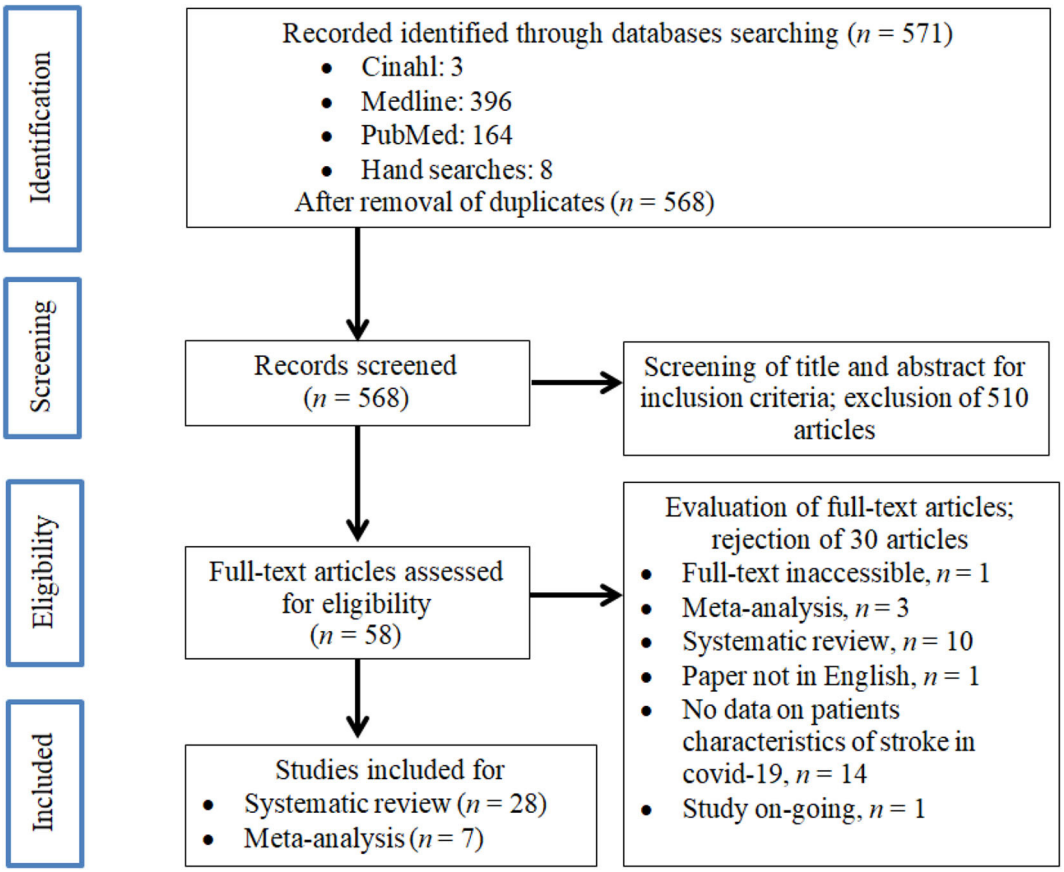


FIGURE 1 | PRISMA flow diagram of the literature screening process.

with Yes/Partial/Unclear/No depending on the clarity of items presented in case series (28) (**Appendix 3**).

Statistical Analysis

A fixed-effect (DerSimonian and Laird method) meta-analysis method was employed to calculate the pooled frequency from these related studies, and it was reported with a 95% confidence interval (CI). I^2 index was used to assess the study's heterogeneity (i.e., low is <25%, moderate 25–50%, and high >50%) that indicated the total percent of discrepancy due to variation in the included studies (29). We also examined publication bias by Begg's test and Egger's test for studies which entered meta-analysis (30). A sensitivity analysis was conducted using leave-one-out meta-analysis to examine how individual studies affect the overall estimation of the rest of the studies. For statistical analysis, Open Meta(Analyst)® software was used, and this software can be accessed and downloaded from http://www.cebm.brown.edu/openmeta/index.html (31).

RESULTS

Description of Included Studies

We identified 571 manuscripts in the initial screening, as shown in **Figure 1**. After removal of duplicate articles ($n = 3$), a total of 568 studies were retrieved for further assessment. After screening for its suitability through the individual title and abstract, 58 studies fulfilled both our inclusion and exclusion criteria. After careful evaluation, 28 articles were finally included for the systematic review and seven studies for the meta-analysis.

Characteristics of Included Studies

The main characteristics of the included studies are shown in **Table 1**. A total sample of 8,771 participants was included in the systematic review. These studies were conducted in many countries worldwide including in China (13, 40, 43), France (37, 39, 48, 50), India (42), Iran (51), Italy (32, 33, 46), the Netherlands (34), Philippines (52), Spain (44, 53), Turkey (58), UK (41, 55), and the USA (21, 35, 36, 45, 47, 49, 54, 56, 57). Out of 27 studies, eight studies were of retrospective cohort study design, 11 were case series, and nine were case reports. The mean age of the participants ranged from 36 to 81 years old, giving a grand mean age of participants from the included studies of 62.9 ± 12.2 years, with more than half of them being males (64.1%). The overall mortality rate among stroke patients ranged from 22.2 to 43.0%; the average mortality rate for stroke patients with COVID-19 and non-COVID-19 infection were 46.7 and 8.7%, respectively. A majority of the respondents

TABLE 1 | Characteristics of the included studies.

References	Year	Country	Study design	Quality assessment	Study period	Patient characteristics (%)		Frequency of stroke		Number of mortality among stroke patients (rate, %)	Number of mortality among stroke patients with COVID+ (%)	Number of mortality among non-COVID stroke patients (%)
						Gender, %	Age was presented either in mean ± standard deviation or median (Interquartile range)	No. patients with stroke	Total no. of participants			
Lodgiani et al.* (32)	2020	Italy	RC	Good	13 Feb−10 April	Male (68); Female (32)	66 (range 5–75)	9	388	2 (22.2)	Unclear	Unclear
Benussi et al. (33)	2020	Italy	RC	Good	21 Feb−5 April	Male (51.2); Female (48.8)	76.9 (range 66.8–85.2)	43	56	19 (17.1)	15 (34.9)	4 (5.9)
Klok et al.* (34)	2020	Netherland	RC	Poor	7 Mar−15 April	Male (76); Female (24)	64 ± 15.5	3	184	N/A	N/A	N/A
Jain et al.* (35)	2020	USA	RC	Good	1 Mar−13 April	Male (60.7); Female (39.3)	64 (range 2 weeks−105)	35	3218	15 (43.0)	Unclear	Unclear
Yaghi et al. (36)	2020	USA	RC	Good	15 April−19 April	Male (71.9); Female (28.1)	63 (IQR 17)	32	3556	18 (27.7)	14 (63.6)	4 (9.3)
Escalard et al. (37)	2020	France	RC	Poor	1 Mar−15 April	Male (80); Female (20)	59.5 (IQR54–71.5)	10	37	9 (24.3)	6 (38)	3 (11)
Helms et al.* (39)	2020	France	PC	Good	4 Mar−31 Mar	Male (81.3); Female (18.7)	63 (1QR 53–71)	2	150	N/A	N/A	N/A
Xiong et al.* (40)	2020	China	RC	Good	18 Jan−20 Mar	Male (55); Female (45)	48.7 ± 17.1	10	917	3 (33.3)	N/A	N/A
Mao et al.* (13)	2020	China	CS	Appendix 3	16 Jan−19 Feb	Male (40.7); Female (59.3)	52.7 ± 15.5	6	214	N/A	N/A	N/A
Beyrouti et al. (41)	2020	UK	CS	Appendix 3	1 April−16 April	Male (83.3); Female (16.7)	69.8 ± 12.7	6	N/A	N/A	1 (16.6)	N/A
Avula et al. (42)	2020	India	CS	Appendix 3	N/A	Male (25); Female (75)	81 ± 5.4	4	N/A	N/A	3 (75.0)	N/A
Zhang et al. (43)	2020	China	CS	Appendix 3	N/A	Male (66.7); Female (33.3)	68 ± 2.7	3	N/A	N/A	N/A	N/A
Barios Lopez et al. (44)	2020	Spain	CS	Appendix 3	25 Mar−17 April	Male (50); Female (50)	71.5 ± 15.3	4	N/A	N/A	2 (50.0)	N/A
Oxley et al. (45)	2020	USA	CS	Appendix 3	23 Mar−7 April	Male (80); Female (20)	40.4 ± 6.2	5	N/A	N/A	N/A	N/A
Tunc et al. (Tunç et al., 2020)	2020	Turkey	CS	Appendix 3	1 April−14 April	Male (50); Female (50)	65.3 ± 12.2	4	N/A	N/A	0 (0.0)	N/A
Morassi et al. (46)	2020	Italy	CS	Appendix 3	16 Mar−5 April	Male (83.3); Female (16.7)	68.5 ± 10.6	6	N/A	N/A	5 (83.0)	N/A
Wang et al. (47)	2020	USA	CS	Appendix 3	N/A	Male (80); Female (20)	46 ± 10.2	5	N/A	N/A	3 (60.0)	N/A
Zayet et al. (48)	2020	France	CS	Appendix 3	25 Mar−3 April	Male (100)	79 ± 5	2	N/A	N/A	1 (50.0)	N/A
Fara et al. (49)	2020	USA	CS	Appendix 3	20 April	Male (20); Female (80)	55 ± 22	3	N/A	N/A	0 (0.0)	N/A

(Continued)

TABLE 1 | Continued

References	Year	Country	Study design	Quality assessment	Study period	Patient characteristics (%)			Frequency of stroke		Number of mortality among stroke patients (rate, %)	Number of mortality among stroke patients with COVID+ (%)	Number of mortality among non-COVID stroke patients (%)
						Gender, %	Age was presented either in mean ± standard deviation or median (Interquartile range)		No. patients with stroke	Total no. of participants			
Valderrama et al. (21)	2020	USA	CR	Appendix 3	N/A	Male	52		1	N/A	N/A	Discharged	N/A
Viguier et al. (50)	2020	France	CR	Appendix 3	25 March	Male	73		1	N/A	N/A	Discharged	N/A
Sharafi Razavi et al. (51)	2020	Iran	CR	Appendix 3	N/A	Male	79		1	N/A	N/A	N/A	N/A
Christian Oliver et al. (52)	2020	Philippines	CR	Appendix 3	N/A	Female	62		1	N/A	N/A	N/A	N/A
Gonzalez-Pinto et al. (53)	2020	Spain	CR	Appendix 3	N/A	Female	36		1	N/A	N/A	Died	N/A
Moshayedi et al. (54)	2020	USA	CR	Appendix 3	N/A	Male	80		1	N/A	N/A	Died	N/A
Hughes et al. (55)	2020	UK	CR	Appendix 3	N/A	Male	59		1	N/A	N/A	Discharged	N/A
Gunasekaran et al. (56)	2020	USA	CR	Appendix 3	N/A	Female	40		1	N/A	N/A	Died	N/A
Goldberg et al. (57)	2020	USA	CR	Appendix 3	N/A	Male	64		1	N/A	N/A	N/A	N/A

RC, Retrospective cohort; PC, Prospective cohort; CS, Case series; CR, Case report; N/A, Not applicable.

**Denotes study with characteristics all COVID-19 patients and not specific to stroke patients.*

were diagnosed with COVID-19 using the reverse transcriptase-polymerase chain reaction (RT-PCR) tests conducted on samples collected either from the nasopharyngeal or oropharyngeal swab, and some also had concurrent confirmation by the antibody serology test.

Frequency of Stroke Among COVID-19 Patients

Eight studies had reported data eligible for the estimation of the pooled frequency of stroke among patients with COVID-19, and therefore the pooled frequency using the fixed-effect model is presented below in **Figure 2**. However, we decided to exclude the article by Benussi et al. in the final analysis due to its high heterogeneity. The pooled frequency of stroke among patients with COVID-19 as derived from the final seven studies was 1.1% (95% CI: 0.8, 1.3) and had a low degree of heterogeneity ($I^2 = 0.0\%$, $p = 0.359$) if the article by Benussi et al. (33) was excluded from the meta-analysis. The pooled frequency increased to 2.7% and heterogeneity was also extremely high ($I^2 = 96.3$, $p < 0.001$) if the article by Benussi et al. (33) was included in the meta-analysis. Egger's test and Begg's test ($p < 0.05$) suggested that there was publication bias; sensitivity analysis also identified all seven studies in the meta-analysis had substantial influences on the pooled frequency of stroke among COVID-19 patients, which cause variation in a pooled frequency ranging from 1.0 to 1.2.

Data on Stroke Patients and Classification of Severity

The data on stroke patients in different groups of severe vs. non-severe COVID-19 infection and stroke patients with and without COVID-19 infection is shown in **Table 2**. Among the seven retrospective studies, two studies provided the number of patients having a stroke in the different groups of severe and non-severe COVID-19 infection (13, 32). One study reported the number of patients having a stroke in the different groups of with or without COVID-19 infection (33). Among patients who suffered from a stroke and classified according to the severity of the infection, the majority were placed in the severe COVID-19 infection group, whereby 60 patients were classified as severe compared to 29 in the non-severe group. Among patients who suffered from a stroke, 150 patients had COVID-19 infection, whereas 141 patients had no COVID-19 infection. The average days to develop stroke among patients after the onset of COVID-19 infection was 6.9 ± 4.5 days.

Regarding the severity stratification for COVID-19 infection, we observed that multiple stratification approaches were used across studies such as severe and non-severe infections that were based on admission to intensive care unit vs. general ward, the presentation of respiratory failure warranting intubation and ventilation, ARDS criteria, and according to guidelines from American Thoracic Society for community-acquired pneumonia as per **Table 2**.

Classification of Stroke Based on Imaging Findings in COVID-19 Patients

The imaging findings in COVID-19 patients are summarized in **Table 3**. Majority of strokes seen among COVID-19 patients were arterial stroke (98.5%) while venous stroke was seen only in three patients (1.5%). Ischemic stroke was the predominant stroke, and

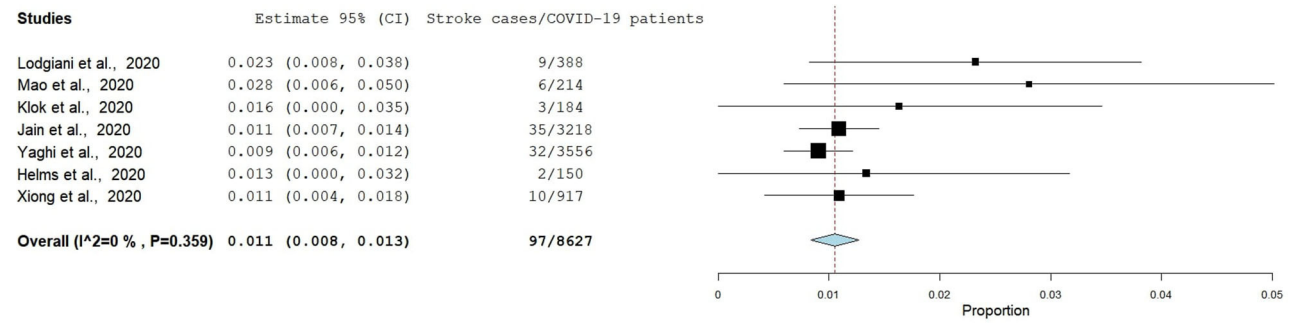


FIGURE 2 | The forest plot of the pooled frequency of stroke among COVID-19 patients.

it was observed in 90.3% of stroke cases as compared to 9.7% patients presenting with hemorrhagic stroke. More than half of stroke happened in anterior circulation (60.0%), followed by the multiple territories (28.0%) and posterior circulation (12.0%). Among the 29 cases of stroke involving the anterior circulation, 28 cases occurred in middle cerebral artery (MCA) region, and only two cases involved the anterior cerebral artery (ACA) region.

Classification of Stroke Based on Vessels Occlusion and TOAST Criteria in COVID-19 Patients

Table 4 summarized the stroke classification based on large vessels occlusion (LVO) and the TOAST (Trial of ORG 10172 in acute stroke treatment) classification (59) in patients with COVID-19. The numbers of stroke were almost equal for LVO (47 stroke cases in 10 studies) and non-LVO (42 cases in 10 studies). Location of LVOs involved were M1 vessels (21, 37, 41, 42, 44, 45, 47, 53, 54), M2 vessel (41, 42, 44, 45, 47, 53), internal carotid (21, 37, 42, 45, 47, 53), multiteritorial (37, 47), posterior cerebral (41, 45), basilar (37), ACA (21, 53), and the vertebral artery (41).

According to the classification of stroke based on the TOAST criteria, we found that large vessels and cryptogenic were the most common type of stroke (28.9%), followed by cardioembolic (15.7%), small vessels (14.0%), and others (12.4%). A majority of the studies did not classify their stroke type with the TOAST classification.

Comorbidities Among Patients in the Study

Table 5 shows the data on comorbidities among participants in the included studies. Hypertension (50.9%) was found to be the highest in percentage among the comorbidities, followed by diabetes (40.0%), atrial fibrillation (23.9%), hyperlipidaemia (17.0%), history of ischemic heart disease (14.8%), smoking (10.5%), previous stroke (6.7%), malignancy (4.5%), chronic kidney disease or end-stage renal disease (2.9%), and finally heart failure (0.4%).

Blood Parameters Among COVID-19 Patients Included in Study

Daa on the blood parameters are shown in **Table 6**. Functions of each of the blood tests and its normal range are summarized in **Appendix 4**. The mean for erythrocyte sedimentation rate (ESR) was in a range of 31–86 mm/1 h. For C-reactive protein (CRP), the mean ranged from 0.101 to 1,920 mg/L, in which majority of studies had a CRP results exceeding the normal range except for the study by Yaghi et al. (36), in which the CRP reading was 0.101 mg/L. We observed that almost all studies had elevated ferritin readings that ranged from 392 to 4609.33 mg/L, except for a study done by Tunc et al. (58), in which the ferritin level was 150.5 mg/L. For lactic acid dehydrogenase (LDH) test, elevated LDH readings across the studies were observed that ranged from 406 to 860.4 IU/L, except for normal levels seen in studies done by Mao et al. (241.5 IU/L) (13) and Benussi et al. (275.7 IU/L) (33).

A majority of the studies included had an elevated mean for the D-dimer test, which ranged from 0.71 to 28.5 mg/L except for the study done by Lodigiani et al. (32), in which the mean of D-dimer was 0.389 on day 4–6 among the survivors, and an elevated D-dimer of 0.943 was reported among the non-survivors.

For the fibrinogen test, a majority of studies reported that the mean for fibrinogen was out of the normal range (200–400 mg/dL), in which they ranged from 462.8 to 6,050 mg/dL, except for the study done by Valderrama et al., which had a normal level (235 mg/dL) (21).

Similarly, a majority of the studies did not capture information on the presence of antiphospholipid, except the studies by Helms et al. (39), Beyrouti et al. (41), Zhang et al. (43), Barios Lopez et al. (44), Zayet et al. (48), Fara et al. (49), and Goldberg et al. (57), in which these studies reported positive findings for the presence of antiphospholipid antibodies. On the other hand, studies by Viguier et al. (50) and Gunasekaran et al. (56) reported the absence of antiphospholipid antibodies. For the procalcitonin titres, three studies had a blood test result of below 1.0 mg/mL, which ranged from 0.23 to 0.8 ng/mL (43, 44, 52), with the highest mean for procalcitonin concentration reported in the study by Avula et al. (4.9 ng/mL) (42). We observed that only three studies captured information on interleukin-6 (IL-6) levels among patients with COVID-19 and stroke, which ranged from 3 to 10.5 pg/mL, which are the studies by Avula et al. (42), Barios Lopez et al. (44), and Yaghi et al. (36). Data of all these studies reported a normal reading for IL-6 levels. For the troponin test, seven studies reported data on the troponin concentration (33, 41–44, 48, 52). Three out of the seven studies reported an

TABLE 2 | Information on the number of stroke patients in groups with and without severe COVID-19 infection as well as with and without COVID-19 infection.

References	No. of patients with stroke in groups with and without severe COVID-19 infection				Severity Stratification	When developed stroke, day in mean (SD, range or IQR)	No. of patients with stroke in groups of with or without COVID-19 infection			
	No. of stroke among patient with severe symptoms re	Total no. of patients with severe symptoms	No. of stroke among patients without severe symptoms	Total no. of patients in non-severe symptoms			No. of stroke among patients with COVID-19	Total no. of patients in COVID-19	No. of stroke among patients without COVID-19	Total no. of patients in non-COVID-19
Lodgiani et al. (32)	3	61	6	327	ICU vs. General ward	N/A	9	388	N/A	N/A
Benussi et al. (33)	N/A	N/A	N/A	N/A	N/A	N/A	43	56	68	117
Klok et al. (34)	N/A	N/A	N/A	N/A	N/A	N/A	3	184	N/A	N/A
Jain et al. (35)	N/A	N/A	N/A	N/A	N/A	N/A	35	3218	N/A	N/A
Yaghi et al. (36)	26	N/A	6	N/A	American Thoracic Society for Community-Acquired Pneumonia	10 (range: 5–16.5)	32	3556	46	N/A
Escalard et al. (37)	N/A	N/A	N/A	N/A	N/A	6 (IQR 2–18)	10	N/A	27	N/A
Helms et al. (39)	N/A	N/A	N/A	N/A	ARDS	NA	2	150	N/A	N/A
Xiong et al. (40)	N/A	319	N/A	598	Republic of China Diagnosis and Treatment Protocol (Trial 6)	Late course (not specified)	10	917	N/A	N/A
Mao et al. (13)	5	88	1	126	American Thoracic Society for Community Acquired Pneumonia	9 (range: 1–18)	6	214	N/A	N/A
Beyrouti et al. (41)	5	Not applicable	1	Not applicable	Respiratory failure requiring ventilation	11.7 ± 7.9	N/A	N/A	N/A	N/A
Avula et al. (42)	3	Not applicable	1	Not applicable	Respiratory failure requiring ventilation	On admission D1	N/A	N/A	N/A	N/A
Zhang et al. (43)	3	Not applicable	0	Not applicable	Respiratory failure requiring ventilation	20. 3 ± 11.7	N/A	N/A	N/A	N/A
Barios Lopez et al. (44)	2	Not applicable	2	Not applicable	ICU admission	7.25 ± 9.9	N/A	N/A	N/A	N/A
Oxley et al. (45)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tunc et al. (Tunç et al., 2020)	0	Not applicable	4	Not applicable	Not applicable (all non-severe)	2 ± 1.2	N/A	N/A	N/A	N/A
Morassi et al. (46)	5	Not applicable	1	Not applicable	ARDS Severity	11.5 ± 0.7	N/A	N/A	N/A	N/A
Wang et al. (47)	3	Not applicable	2	Not applicable	NA	N/A	N/A	N/A	N/A	N/A
Zayet et al. (48)	1	Not applicable	1	Not applicable	Respiratory failure requiring ventilation	N/A	N/A	N/A	N/A	N/A
Fara et al. (49)	0	Not applicable	3	Not applicable	Not applicable (all non-severe)	On admission D1	N/A	N/A	N/A	N/A

(Continued)

TABLE 2 | Continued

References	No. of patients with stroke in groups with and without severe COVID-19 infection				Severity Stratification	When developed stroke, day in mean (SD, range or IQR)	No. of patients with stroke in groups of with or without COVID-19 infection			
	No. of stroke among patient with severe symptoms re	Total no. of patients with severe symptoms	No. of stroke among patients without severe symptoms	Total no. of patients in non-severe symptoms			No. of stroke among patients with COVID-19	Total no. of patients in COVID-19	No. of stroke among patients without COVID-19	Total no. of patients in non-COVID-19
Valderrama et al. (21)	Not applicable	Not applicable	1	N/A	Non-severe patient	7	N/A	N/A	N/A	N/A
Viguier et al. (50)	Not applicable	Not applicable	1	N/A	Non severe patient	7	N/A	N/A	N/A	N/A
Sharafi Razavi et al. (51)	N/A	N/A	N/A	N/A	N/A	3	N/A	N/A	N/A	N/A
Christian Oliver et al. (52)	Not applicable	Not applicable	1	Not applicable	Non-severe patient	14	N/A	N/A	N/A	N/A
Gonzalez-Pinto et al. (53)	1	Not applicable	Not applicable	Not applicable	Respiratory failure requiring ventilation	2	N/A	N/A	N/A	N/A
Moshayedi et al. (54)	1	Not applicable	Not applicable	Not applicable	Respiratory failure requiring ventilation	5	N/A	N/A	N/A	N/A
Hughes et al. (55)	Not applicable	Not applicable	1	Not applicable	Non-severe patient	4	N/A	N/A	N/A	N/A
Gunasekaran et al. (56)	1	Not applicable	Not applicable	Not applicable	Respiratory failure requiring ventilation	7	N/A	N/A	N/A	N/A
Goldberg et al. (57)	1	Not applicable	Not applicable	Not applicable	Respiratory failure requiring ventilation	16	N/A	N/A	N/A	N/A

N/A, Not available.

TABLE 3 | Classification of stroke based on imaging findings in COVID-19 patients.

References	Arterial vs. Venous, *n*		Ischemic vs. Hemorrhagic, *n*			Location of stroke, *n*			
	Arterial	Venous	TIA	Ischemic	Hemorrhagic	Anterior Circulation		Posterior circulation	Multiple territories
						MCA	ACA		
Lodgiani et al. (32)	9	0	0	9	0	N/A	N/A	N/A	N/A
Benussi et al. (33)	43	0	5	35	3	N/A	N/A	N/A	N/A
Klok et al. (34)	3	0	0	3	0	N/A	N/A	N/A	N/A
Jain et al. (35)	35	0	0	26	9	N/A	N/A	N/A	N/A
Yaghi et al. (36)	32	0	0	32	0	N/A	N/A	N/A	N/A
Escalard et al. (37)	10	0	0	10	0	N/A	N/A	N/A	N/A
Helms et al. (39)	2	0	0	2	1	N/A	N/A	N/A	N/A
Xiong et al. (40)	10	0	0	10	3 (complication)	2	0	0	2 (N/A in 6 patients)
Mao et al. (13)	6	0	0	5	1	N/A	N/A	N/A	N/A
Beyrouti et al. (41)	6	2	0	6	0	2	0	1	3
Avula et al. (42)	4	0	0	4	0	4	0	0	0
Zhang et al. (43)	3	0	0	3	0	0	0	0	3
Barios Lopez et al. (44)	4	0	0	4	0	2	1	1	0
Oxley et al. (45)	5	0	0	5	0	4	0	1	0
Tunc et al. (58)	4	0	0	4	0	3	0	1	0
Morassi et al. (46)	6	0	0	5	1	0	1	1	2
Wang et al. (47)	5	0	0	5	0	4	0	1	0
Zayet et al. (48)	2	0	0	2	0	0	0	0	2
Fara et al. (49)	3	0	0	3	0	3	0	0	0
Valderrama et al. (21)	Yes	No	No	Yes	No	Yes	No	No	No
Viguier et al. (50)	Yes	No	No	Yes	No	Yes	No	No	No
Sharafi Razavi et al. (51)	Yes	No	No	No	Yes (LobarandSAH)	Not applicable	Not applicable	Not applicable	Not applicable
Christian Oliver et al. (52)	Yes	No	No	Yes	No	Yes	No	No	No
Gonzalez-Pinto et al. (53)	Yes	No	No	Yes	No	Yes	No	No	No
Moshayedi et al. (54)	Yes	No	No	Yes	Yes (transformation)	No	No	No	Yes (Anterior + posterior)
Hughes et al. (55)	No	Yes	No	Yes	No	N/A	N/A	N/A	N/A
Gunasekaran et al. (56)	Yes	No	No	Yes	No	Yes	No	No	No
Goldberg et al. (57)	Yes	No	No	Yes	No	No	No	No	Yes (MCA + bilateral ACA)

TIA, Transient ischemic attack; MCA, Middle cerebral artery; ACA, Anterior cerebral artery; N/A, Not available; Pertaining to studies with only one patient with stroke, YesYes or No was used instead of n value.

TABLE 4 | Classification of stroke based on vessels occlusion and TOAST in COVID-19 patients.

References	Large vessels occlusion (LVO) vs non-LVO		Location of large vessels, *n*	Classification of stroke based on TOAST, *n*				
	LVO	Non-LVO		Large vessels	Small vessel	Cardioembolic	Cryptogenic	Others
Lodgiani et al. (32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Benussi et al. (33)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Klok et al. (34)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jain et al. (35)	N/A	N/A	N/A	17	9	0	0	0
Yaghi et al. (36)	45.5%	55.50%	N/A	2	0	7	21	2
Escalard et al. (37)	100% (they include only LVO)	0	Carotid terminus (30%); M1 (60%), M2 (0%), Basillar (10%), Multiteritorial (50%)	N/A	N/A	N/A	N/A	N/A
Helms et al. (39)	N/A	N/A	NA	N/A	NA	N/A	N/A	N/A
Xiong et al. (40)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mao et al. (13)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Beyrouti et al. (41)	6	0	M1 (1), M2 (1), Posterior cerebral (2), Vertebral (1), Unknown (1)	NA	NA	NA	NA	NA
Avula et al. (42)	2	2	Internal carotid (1), MCA 1 (not specified M1 or M2)	NA	NA	NA	NA	NA
Zhang et al. (43)	0	3	Not applicable - Non LVO	0	0	0	0	0
Barios Lopez et al. (44)	1	2 (1 not known)	MCA 1 (not specified, M1 or M2)	0	0	2	0	0
Oxley et al. (45)	5	0	Internal Carotid (1), MCA 3 (not specified M1 or M2), Posterior cerebral (1)	NA	NA	NA	NA	NA
Tunc et al. (Tunç et al., 2020)	0	4	Not applicable—Non LVO	2	2	0	0	2
Morassi et al. (46)	0	6	Not applicable—Non LVO	N/A	N/A	N/A	N/A	N/A
Wang et al. (47)	5	0	Internal carotid (2), M1 (1), Tandem carotid+M2 (1), Multiteritorial (1)	NA	NA	NA	NA	NA
Zayet et al. (48)	0	2	Not applicable—Non-LVO	N/A	N/A	N/A	N/A	N/A
Fara et al. (49)	0	3	Not applicable—Non LVO	3	0	0	0	3
Valderrama et al. (21)	Yes	No	Internal carotid + MCA (proximal M1) and ACA	Yes	No	No	No	No
Viguier et al. (50)	No	Yes	Not applicable (non-occlusive ICA thrombus)	Yes (ICA)	No	No	No	No
Sharafi Razavi et al. (51)	Not applicable	Not applicable	Not applicable (because bleeding)	No	No	No	No	No
Christian Oliver et al. (52)	No	Yes	Not applicable (Non-LVO)	Yes (M1)	No	No	No	No

(Continued)

TABLE 4 | Continued

References	Large vessels occlusion (LVO) vs non-LVO		Location of large vessels, *n*	Classification of stroke based on TOAST, *n*				
	LVO	Non-LVO		Large vessels	Small vessel	Cardioembolic	Cryptogenic	Others
Gonzalez-Pinto et al. (53)	Yes	No	Internal carotid + MCA and ACA	Yes	No	No	No	No
Moshayedi et al. (54)	Yes	No	Proximal M1	No	No	Yes	No	No
Hughes et al. (55)	Not applicable	Not applicable	Not applicable (because cerebral venous thrombosis -sigmoid and transverse sinus	N/A	N/A	N/A	N/A	N/A
Gunasekaran et al. (56)	N/A	N/A	NA	N/A	N/A	N/A	N/A	N/A
Goldberg et al. (57)	No	Yes	Not applicable (Non-LVO)	Yes	No	No	No	No

LVO, Large vessels occlusion; MCA, Middle cerebral artery; ACA, Anterior cerebral artery; N/A, Not available; For LVO—cohort % but case series number; Pertaining to studies with only one patient with stroke, Yes or No was used instead of n value.

abnormally elevated troponin concentration, which were 1338.9 pg/mL (43), 791.3 pg/mL (48), and 145 pg/mL, respectively (52). For the prothrombin time, a majority of studies reported levels that fell in the normal range (11–13.5 s) except for the studies by Helmes et al. (39), Zhang et al. (43), Avula et al. (42), and Oxley et al. (45).

For the platelet level, the mean ranged from 112 to 303 $\times 10^9$, and the levels were all within the normal range in the included studies, except for the study done by Christian Oliver et al. (52), which had a slightly elevated level (409 $\times$ 10^9). The normal range for clotting time (prothrombin test) is 11–13.5 s (60). Among the included studies, six studies reported a normal mean for the prothrombin time, and these studies included the studies by Benussi et al. (33), Barios Lopez et al. (44), Zayet et al. (48), Sharafi-Razavi et al. (51), Christian Oliver et al. (52), and Hughes et al. (2020). Five studies reported an abnormal mean for the prothrombin time, with a prothrombin time of 13.8 s for the study by Oxley et al. (45), 15.5 s for Beyrouti et al. (41) and Avula et al. (42), 16.4 seconds for Zhang et al. (43), and up to 84 s for the study by Helms et al. (39).

DISCUSSION

The aim of this current study is to perform a systematic review and meta-analysis concerning the epidemiological, clinical presentation, imaging characteristics, and laboratory findings related to both stroke and COVID-19 infection.

SARS-CoV-2 Features, Epidemiological Findings, and Its Comorbidities in Stroke Patients With COVID-19

Coronaviruses are divided into four genera, in which the new coronavirus (SARS-CoV-2) is classified into the beta genus, which includes viruses causing SARS and MERS (Middle East Respiratory Syndrome) as well (61). There are now at least seven human coronaviruses, including SARS-CoV-1, SARS-CoV-2, MERS-CoV, HCoV-OC43, HCoV-229E, HCoV-NL-63, and HCoV-HKU1 (38). Studies on previous human coronaviruses infections indicated that the virus does not remain confined to the respiratory system and may also disseminate to other organs, including the central nervous system via the angiotensin-converting enzyme type 2 receptor (ACE-2) (62, 63). The possibility of neurological complications may stem from the neurotropic and neurovirulent property of SARS-CoV-2, which are also seen in other human coronaviruses (64).

The association of stroke with viral infection is well-established, albeit uncommon. In general, viral infection, particularly those in the early convalescence phase, increases the odds of stroke by 1.4-folds (17). A previous study amongst SARS-COV-1 patients showed that LVO occurred in a small percentage of patients (2.4%) that were infected in which the two patients had cardiac dysfunction, disseminated intravascular coagulation, and significant hypotension before the onset of stroke (65). A similar trend among MERS patients also showed that only a small number of patients developed stroke associated with

TABLE 5 | Information on comorbidities and smoking habit among patients with COVID-19 infection in the study.

References	Comorbidities, %									
	Diabetes	**Hyperlipidaemia**	**Hypertension**	**Ischemic heart disease**	**Heart Failure**	**Previous stroke**	**Chronic kidney disease/ end-stage renal disease**	**Malignancy**	**Atrial Fibrillation**	**Smoking**
Lodgiani et al.* (32)	32.7	19.6	47.2	13.9	N/A	5.2	15.7	6.4	Unclear	11.6
Benussi et al. (33)	23.3	23.3	60.5	18.6	N/A	N/A	4.7	11.6	N/A	2.3
Klok et al.* (34)	N/A	N/A	N/A	N/A	N/A	N/A	13	2.7	N/A	N/A
Jain et al.* (35)	N/A	N/A	37.9	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yaghi et al. (36)	34.4	56.3	56.6	15.6	6.3	3.1	N/A	N/A	18.8	0
Escalard et al. (37)	40	30	50	N/A	N/A	N/A	N/A	N/A	10	10
Helms et al.* (39)	20	N/A	N/A	48	N/A	4.7	4	6	20	N/A
Xiong et al. (40)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mao et al.* (13)	14	N/A	23.8	7	N/A	N/A	2.8	6.1	N/A	N/A
Beyrouti et al. (41)	33.3	0	66.7	33.3	0	16.7	0	33.3	33.3	16.7
Avula et al. (42)	25	75	100	0	0	0	25	0	0	Not mentioned
Zhang et al. (43)	75	0	100	33.3	0	66.7	0	33.3	0	Not mentioned
Barios Lopez et al. (44)	75	0	50	50	0	0	0	0	25	25
Oxley et al. (45)	20	20	20	0	0	20	0	0	0	0
Tunc et al. (58)	25	0	75	0	0	0	0	0	0	0
Morassi et al. (46)	50	0	66.7	16.7	N/A	16.7	0	0	0	16.7
Wang et al. (47)	20	0	20	40	0	0	0	0	0	0
Zayet et al. (48)	100	0	50	50	0	0	0	0	100	0
Fara et al. (49)	33.3	33.3	33.3	0	0	0	0	0	0	Not mentioned
Valderrama et al. (21)	No	No	Yes	No	No	No	No	No	No	No
Viguier et al. (50)	No	No	No	No	No	No	No	No	No	No
Sharafi Razavi et al. (51)	N/A	N/A	N/A	NA	NA	NA	NA	NA	N/A	N/A
Christian Oliver et al. (52)	Yes	Yes	Yes	No	No	No	No	No	No	No
Gonzalez-Pinto et al. (53)	No	No	No	No	No	No	No	No	No	No
Moshayedi et al. (54)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hughes et al. (55)	Yes	No	Yes	No	No	No	No	No	No	No
Gunasekaran et al. (56)	Yes	No	No	No	No	No	No	No	No	No
Goldberg et al. (57)	No	No	Yes	No	No	No	No	No	No	No

N/A, Not available.

**Denotes study with characteristics all COVID-19 patients and not specific to stroke patients; Pertaining to studies with only one patient with stroke, Yes or No was used instead of n value.*

TABLE 6 | Blood parameters as inflammation markers among COVID-19 patients with stroke.

References	Blood parameters as inflammation markers										Platlet (x10^9)	PT (secs)
	ESR (mm/ 1hr)	CRP (mg/L)	Ferritin (mg/L)	D-dimer (mg/L)	LDH (IU/L)	Fibrinogen (mg/dL)	Antiphospholipids	Procalcitonin, ng/mL	IL-6 (pg/mL)	Troponin (pg/mL)		
Lodgiani et al.* (32)	N/A	N/A	N/A	Day 4–6: Total survivor 0.389 (0.246–0.685) Day 4–6: Total non-survivor 0.943 (0.611–2.618)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Benussi et al. (33)	49 (range 29.3-85)	28 (range 44-71.1)	452.5 (range 268.8-871)	735.5 (range 364.3–2910.8)	277.7 (range 239 - 365)	471 (range 368-545)	N/A	N/A	N/A	27.0 (range 10.0–41.0)	276 (range 197–315) 264.3)	12.8 (range 12.2– 15.6)
Klok et al. (34)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Jain et al. (35)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Yaghi et al. (36)	79 (IQR 53)vs 40 (IQR86)*	0.101 (IQR 0.176)	N/A	3.9 (IQR 7.4)	N/A	N/A	N/A	N/A	Only in 8 patients 10.5 (IQR 96.25) in covid positive	N/A	N/A	N/A
Escalard et al. (37)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Helms et al.* (39)	N/A	N/A	N/A	2.27 (IQR 1.16 - 20)	N/A	699 (IQR 608 - 773)	Positive Lupus anticoagulants in 50 patients	N/A	N/A	N/A	200 (IQR 152–267)	84 (73–91)
Xiong et al. (40)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mao et al.* (13)	N/A	12.2 (range 0.1 - 212)	N/A	0.5 (range 0.1 - 20)	241.5 (range 2.2 - 908)	N/A	N/A	N/A	N/A	N/A	209 (range 18–583)	N/A
Beyrouti et al. (41)	N/A	139.5 ± 108.0	1925.8 ± 1732.9	25.3 ± 28.3	502.5 ± 127.0	628 ± 202	5 patients: Positive lupus anticoagulant and 1 patient: Positive medium titer IgM anti-cardiolipin + low-titer IgG and IgM anti–β2-glycoprotein-1	NA	NA	31.1 ± 21.7 High sensitive pg/mL	290 ± 100.6	15.5 ± 9.3
Avula et al. (42)	N/A	184 ± 57 (in 3 patients)	513.5 (135.9 - 891) ng/L	8.704 ± 5.62 (in 2 patients)	456 ± 256	N/A	N/A	4.9 ± 6.5 (in 2 patients)	8.5 pg/mL (1 patient)	0.065 (< 0.01–0.14) pg/mL	219 ± 94.5	15.5 ± 2.5
Zhang et al. (43)	N/A	97.8 ± 36.8	2207.8 (only in 1 patient)	9.0 ± 10.4	427 ± 199.7	500 ± 120	3 patients: positive for IgA anti-cardiolipin and IgA and IgM anti–β2-glycoprotein-1	0.23 ± 1.6	NA	1338.9 ± 2198.7 pg/mL (troponin I)	112 ± 58.6	16.4 ± 1.2
Barios Lopez et al. (44)	N/A	82.6 ± 115.4	722.6 ± 590.5	28.5 ± 44.3	508.8 ± 283	462.8 ± 113.2	1 patient: positive IgG anti–β2-glycoprotein-1	0.28 ± 0.36	3 pg/mL	17.9 ± 11.8 pg/mL	293 ± 6.9	12.2 ± 0.8
Oxley et al. (45)	N/A	N/A	659 ± 638.2	3.66 ± 5.8	N/A	516.8 ± 138.6	N/A	N/A	N/A	N/A	297 ±112.4	13.8 ± 1.0
Tunc et al. (Tunç et al., 2020)	N/A	N/A	150.5 ± 68.7	0.713 ± 0.24	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Morassi et al. (46)	N/A	93.6 ± 94	N/A	3.9 ± 3.3	860.4 ± 223.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wang et al. (47)	Elevated	Elevated	N/A	Elevated	N/A	N/A	N/A	N/A	Elevated	N/A	N/A	Elevated
Zayet et al. (48)	N/A	69.5 ± 39.5	N/A	10278.5 ± 8092.5 (out of range despite same unit)	505.5 ± 179.5	6,050 ± 550	1 patient: positive IgM anti-cardiolipin	N/A	NA	791.3 ± 744.7	171.5 ± 98.5	12.05 ± 0.25

(Continued)

TABLE 6 | Continued

References	Blood parameters as inflammation markers									Platlet (x10^9)	PT (secs)
	ESR (mm/ 1hr)	CRP (mg/L)	Ferritin (mg/L)	D-dimer (mg/L)	LDH (IU/L)	Fibrinogen (mg/dL)	Antiphospholipids	Procalcitonin, ng/mL	IL-6 (pg/mL)	Troponin (pg/mL)	
Fara et al. (49)	N/A	Elevated in all patients	N/A	Elevated in 1 patient	N/A	NA	1 patient: positive low titer IgM anti-cardiolipin	N/A	N/A	N/A	N/A
Valderrama et al. (21)	37	11	588	>10	N/A	235	NA	N/A	NA	N/A	N/A	N/A
Viguier et al. (50)	N/A	219	1096	2.2	N/A	820	Negative	N/A	N/A	N/A	N/A	N/A
Sharafi Razavi et al. (51)	85	10	NA	NA	N/A	NA	NA	N/A	N/A	N/A	210	12
Christian Oliver et al. (52)	86	1920	4609.33	1.16	406	NA	NA	0.8 ng/mL	NA	145 pg/mL	409	12.9
Gonzalez-Pinto et al. (53)	N/A	N/A	N/A	7.54	N/A	N/A	N/A	N/A	N/A	N/A	NA	N/A
Moshayedi et al. (54)	N/A	N/A	N/A	NA	N/A	N/A	N/A	N/A	N/A	N/A	NA	N/A
Hughes et al. (55)	31	15	N/A	NA	N/A	Unclear	N/A	N/A	N/A	N/A	202	11.1
Gunasekaran et al. (56)	N/A	N/A	3079	28.07 ng/ml	N/A	860	Negative	N/A	N/A	N/A	303	N/A
Goldberg et al. (57)	N/A	N/A	N/A	N/A	N/A	N/A	Positive IgM anti-cardiolipin	N/A	N/A	N/A	N/A	N/A

ESR, erythrocyte sedimentation rate; CRP, C-Reactive Protein; LDH, Lactic Acid Dehydrogenase; IL-6, Interleukin 6; PT, prothrombin time; N/A, Not available.
**Denotes study with characteristics all COVID-19 patients and not specific to stroke patients.*

preceding disseminated intravascular coagulation in one of the patients (66).

In this current review, the pooled frequency of stroke was 1.1%. We decided to remove Benussi et al. (33) in the final result as the study was conducted in a stroke hub for COVID-19 in Italy, which explained the high frequency of stroke (76.8%) among patients with COVID-19. We found that overall, patients with COVID-19 exhibited a lower percentage of stroke, which was 1.1% of patients with COVID-19. This is similar to the worldwide prevalence of stroke (1.12%) (67) but much lower as compared to the prevalence of stroke in the United States (2.5%) and in China (3.1%) (68, 69). The association of stroke seen in patients with COVID-19 may be attributed to the shared traditional risk factors for stroke also seen in COVID-19 patients. Literature reported that the traditional risk factors for stroke are diabetes, hypertension, hyperlipidemia, smoking, atrial fibrillation, previous stroke, ischemic heart disease, and family history of stroke, in which the estimated relative risk for total stroke associated with hypertension was 5.43 (70), 2.28 for diabetes (71), 1.64 for obesity (72), 1.46 for atrial fibrillation (73), and 1.10 for chronic kidney disease (74). Our finding is consistent with the literature that reported that more than half of COVID-19 patients with stroke had comorbidities of hypertension, followed by diabetes, atrial fibrillation, hyperlipidaemia, and/or history of ischemic heart disease.

Imaging Characteristics of Stroke in COVID-19 Infection

Ischemic stroke is the most common type of stroke seen in this review as compared to less frequently occurring haemorrhagic and transient ischemic stroke. Hypertension, diabetes, and cardiovascular disease are known risk factors for ischemic stroke (75). In addition, the risk factors of hemorrhagic and ischemic strokes were also relatively similar (INTERSTROKE study). A recent review showed that all infections increase the risk of acute ischemic stroke, although its pathophysiology is not adequately explained (76).

Anterior circulation is the most common site for stroke, with more than half of the strokes occurring in the middle cerebral artery, followed by the multiple territories. Interestingly in our review, a quarter of the stroke was multi-territorial. This may be due to the propensity of systemic embolisation and microvascular thrombosis that typically occurs in COVID-19 infection due to the excessive production of prothrombotic factors and dysregulation of the anti-thrombotic properties (77), whereas strokes are less commonly seen in the posterior and anterior cerebral arteries (78). This observation is similar to the non-COVID-19 related stroke.

A recent report pointed out the propensity of LVO to occur in patients with COVID-19 and its tendency to occur in the younger age group (45). In our review of the currently available literature, half of the reported stroke cases were due to an LVO as compared to non-large vessel occlusion. This rate is much higher as compared to the general population where LVO usually occurs in around one-third of the patients (79). Furthermore, among studies that used the TOAST classification, one-third reported

stroke types as cryptogenic and others that indicate that there are other underlying pathologies apart from the traditional risk factors that contribute to the occurrence of stroke in patients with COVID-19.

Laboratory Finding and Its Association With the Pathophysiology of Stroke Patients With COVID-19

Apart from the possible neuropathic property of SARS-CoV-2 that causes direct endothelial injury via the ACE-type 2 receptor (80) and sharing of the common traditional risk factors for stroke, the pathophysiology of stroke in COVID-19 patients could also be attributed to the pro-inflammatory and hypercoagulable state predisposing to thrombosis. The thrombo-inflammatory nature of SARS-CoV-2 was noted as to be associated with elevated levels of D-dimer, fibrinogen, platelet, and IL-6 (77). Furthermore, the excessive systemic immune response that may be seen in this novel infection may be due to immunopathogenicity in which the over-stimulation of the immune system by this virus leads to attacks to one's own immune system (81). Cytokine storm may also occur as our immune system goes into an overdrive, leading to a massive influx of SARS-related inflammatory cytokine such as interleukin-1β, IL6, IL12, interferon-γ, inducible protein−10, and monocyte chemoattractant protein-1 (81, 82). These excessive inflammatory cascades may lead to two main sequelae [i.e., production of prothrombotic factors and endothelium damage due to dysregulation of anti-thrombotic properties, subsequently leading to microvascular thrombosis with potential for systemic embolization (77, 83)]. Moreover, inflammatory markers [e.g., C-reactive protein and fibrinogen, are independent risk factors for ischemic stroke and may also predispose to atherosclerosis and endothelial dysfunction that can be further exacerbated by infection (81, 84)].

Hypercoagulable state, on the other hand, as demonstrated by elevated D-dimer levels, abnormality in clotting variables, and hyperferritinemia, not only increases the risk of a thromboembolic event but is also an independent predictor for poor prognosis and mortality (4, 40). The role of other thrombotic markers such as the antiphospholipid antibodies, albeit their role in COVID-19, are also uncertain but may also contribute to the hypercoagulable state (43).

In our review, several markers are commonly used to identify the thrombo-inflammatory nature of COVID-19 (e.g., D-dimers, CRP, ferritin, fibrinogen, antiphospholipid antibodies, LDH, and troponin). Based on our observation, CRP was the most commonly used biomarker, followed by D-dimer, LDH, troponin, and antiphospholipid tests. In this review, stroke patients with COVID-19 consistently presented with an elevated level of D dimers, CRP, ferritin, LDH, troponin, ESR, fibrinogen, and with positive antiphospholipid antibodies reported in some studies. IL-6 and pro-calcitonin were only reported in a few studies and were not found to be elevated.

Subgroup Analysis on Characteristics of Stroke Patients With and Without COVID-19 Infection

Although the mean age of patients with COVID-19 and stroke in our review was 62.9 years, many case series and case reports have shown that those in the younger age group or those with no comorbidities more commonly presented with stroke (42, 43, 49, 50, 53, 56, 58). Furthermore, stroke is shown to occur early in the illness with mean onset at 6.9 days, with reports even showing that patients may present with stroke and at the same time have asymptomatic COVID-19 infection (42, 49). Unfortunately, patients with COVID-19 and stroke had a more severe COVID-19 infection and a poorer prognosis with a higher mortality rate as shown by this current review. The mean mortality rate among stroke patients with COVID-19 infection was 46.7% compared to only 8.7% among those without COVID-19 infection, and this could be attributed to the severity of infections in patients concurrently having neurological complications (13, 53, 54, 56).

A subgroup analysis was done among the population cohorts of the Benussi et al., Yaghi et al., and Escalard et al. studies, which had data on both stroke patients with and without COVID-19 infection (**Table 7**). The cohorts in Yaghi et al. and Escalard et al. studies had more males and younger patients. In contrast, similar age and gender characteristics were seen in the study by Benussi et al. All three cohorts showed the presence of traditional cardio-cerebrovascular comorbidities in patients with COVID-19 infection, which may contribute to the pathophysiology of the stroke. Furthermore, more LVOs were seen in patients with COVID-19 in the study by Yaghi et al. (i.e., 45.5 vs. 27.9%), while the cohort in the study by Escalard et al. only included patients with LVO. In the Yaghi et al. cohort, more cryptogenic strokes were reported among the patients with COVID-19, which required further investigations on its unusual etiology. Interestingly, more hemorrhagic stroke was seen in non-COVID infected patients in the study by Benussi et al., which may suggest the possibility of a thrombotic phenomenon in large vessels that are more predominant in COVID-19 infections rather than the small vessel disease leading to the occurrence of hemorrhage. Mortality was also higher in all three cohorts among patients with COVID-19 infection [i.e., in the studies by Benussi et al. (34.9 vs. 5.9%), Yaghi et al. (63.6 vs. 9.3%), and Escalard et al. (60.0 vs. 11.0%), respectively]. Given the high mortality rates associated with stroke in patients with COVID-19 infection that may cause a more severe stroke with an LVO, future studies are required to investigate the stroke characteristics among patients with COVID-19.

Clinical Implications

Although COVID-19 may predominantly present with respiratory symptoms, this review may create awareness among clinicians on potential presentation of stroke in those having this infection, especially for those with severe infection. As many of the patients share similar traditional risk factors for stroke, the presentation of a patient with stroke to the emergency department in this current pandemic must be

TABLE 7 | Subgroup analysis on characteristics of stroke patients with and without COVID-19 infection.

References	Male,%		Female, %		Age was presented either in mean ± standard deviation or median (interquartile range), or mean (range)		Comorbidities and smoking habit																						Mortality rate, %	
							Diabetes, %		Hyperlipidemia, %		Hypertension, %		Ischemic heart disease, %		Heart failure, %		Previous stroke, %		Chronic kidney disease/ end-stage renal disease, %		Malignancy, %		Atrial fibrillation, %		Smoking, %			
	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-	Stroke C+	Stroke C-
Benussi et al. (33)	51.2	58.8	48.8	41.2	75.9 (range = 66.8–85.2)	74.8 (range = 58.3–80.4)	23.3	20.6	23.3	33.8	60.5	75	18.6	11.8	N/A	N/A	N/A	N/A	4.7	4.4	11.6	27.9	N/A	N/A	2.3	8.8	34.9	5.9
Yaghi et al. (36)	71.9	52.2	28.1	48.8	63 (IQR=17)	70 (IQR = 18)	34.4	28.3	56.3	50	56.6	76.1	15.6	26.1	6.3	10.9	3.1	13.0	N/A	N/A	N/A	N/A	18.8	21.7	0	4.3	63.6	9.3
Escalard et al. (37)	80	48	20	52	59.5 (range = 54)	72 (range = 60–81.5)	40	22	30	37	50	55	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	10	30	10	26	60	11

Stroke C+: Stroke patients with COVID-19 infection; Stroke C-: Stroke patients without COVID-19 infection. N/A: Not available.

reviewed cautiously and treated with high suspicion of the potential presence of SARS-CoV-2 infection in order to prevent further dissemination and deterioration. The role of specific blood tests as a potential thrombo-inflammatory marker can be a guide to predict the possible thromboembolic occurrence and disease severity, hence providing much-needed guidance for physicians in taking necessary preventative measures.

Strength and Limitations

This is the first systematic review summarizing the findings in relation to both COVID-19 and stroke. We found a high incidence of stroke among patients with COVID-19. The majority are ischemic stroke, involve large vessels occlusion, and occurs predominantly in the middle cerebral artery. We also found hypertension as the most common comorbidity among this study participants. Most of the laboratory tests except for IL-6 and procalcitonin appeared to be useful for indicating the presence of inflammation and the prothrombotic state as a predictor for stroke, although results varied between the studies.

This review has several limitations. First, the majority of studies did not provide data based on the severity of the infection, and therefore meta-synthesis for severe cases of COVID-19 and the risk of stroke cannot be performed with the existing studies. Similarly, it is impossible to meta-synthesize the risk of stroke associated with COVID-19 infection for all studies due to the lack of data on stroke characteristics among non-COVID-19 patients. Second, due to the lack of data of comorbidities for participants in the control group, analysis of the associated factors for stroke cannot be performed for this review.

Third, we also found that many varied types of blood tests were used for identifying inflammation and hypercoagulable state; thus, the usefulness of laboratory tests results in identifying patients with high risk for stroke could not be determined with the existing literature. Future research with bigger sample size is needed to rectify these important issues.

CONCLUSION

The occurrence of stroke in patients with COVID-19 infection is uncommon but poses as an important prognostic marker and severity indicator. This brief review suggests that ischemic stroke may occur early in the course of the illness, and may also affect patients in the younger age groups with no comorbidities, causing large vessel occlusion and exhibiting thrombo-inflammatory vascular picture. Given that many patients with COVID-19 share the common traditional risk factors for stroke, physicians must be vigilant in the future for an increase in the number of strokes in patients with COVID-19 as the pandemic continues and to take appropriate preventive measures.

AUTHOR CONTRIBUTIONS

AK, SC, WL, LM, WS, HB, and FH: conceptualization. AK, PC, WL, AR, JB, LM, ND, and DS: data curation. KL, AK, SC, PC, AR, and ND: formal analysis. AK, SC, PC, AR, JB, LM, HB, and

FH: investigation. KL, SC, PC, WL, AR, and JB: methodology. AK and WS: project administration. KL: software. HB and FH: supervision. PC, JB, and DS: validation. DS: visualization. KL, AK, SC, WS, ND, and FH: writing—original draft. KL, AK, SC, PC, WL, AR, JB, LM, WS, ND, HB, and FH: writing—review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This research received its funding from the Universiti Putra Malaysia under Putra Grant initiative (UPM/700-1/3/Geran Putra). The funder had no role in study design, data collection and analysis, preparation of the manuscript, or decision to publish.

ACKNOWLEDGMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.579070/full#supplementary-material

REFERENCES

1. Hui DS, Azhar EI, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—the latest 2019 novel coronavirus outbreak in Wuhan, China. *Int. J. Infect. Dis.* (2020) 91:264. doi: 10.1016/j.ijid.2020.01.009
2. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology*. (2020) 295:210–7. doi: 10.1148/radiol.2020200274
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
4. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. (2020) 579:270–3. doi: 10.1038/s41586-020-2012-7
5. Catharine I, Hilary D, Anthony S. Coronavirus infections-more than just the common cold. *JAMA*. (2020) 323:707–8. doi: 10.1001/jama.2020.0757
6. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. (2020) 76:71–6. doi: 10.1016/j.ijsu.2020.02.034
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
8. Correia AO, Feitosa PWG, de Sousa Moreira JL, Nogueira SÁR, Fonseca RB, Nobre MEP. Neurological manifestations of COVID-19 and other coronaviruses: a systematic review. *Neurol Psychiatr Brain Res*. (2020) 37:27–32. doi: 10.1016/j.npbr.2020.05.008
9. Wilson MP, Jack AS. Coronavirus disease (COVID-19) in neurology and neurosurgery: a scoping review of the early literature. *Clin Neurol Neurosurg*. (2020) 193:105866. doi: 10.1016/j.clineuro.2020.105866
10. Fornell D. *How COVID-19 Affects the Brain in Neuroimaging* (2020). Retrieved from: https://www.itnonline.com/article/how-covid-19-affects-brain-neuroimaging (accessed September 22, 2020).
11. Degeneffe A, Bruneau M, Spitaels J, Gilis N, De Witte O, Lubansu A. Acute hemorrhage after intra-cerebral biopsy in COVID-19 patients: a report of 3 cases. *World Neurosurg*. (2020) 141:157–61. doi: 10.1016/j.wneu.2020.07.045
12. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immunity*. (2020) 88:945–6. doi: 10.1016/j.bbi.2020.04.017
13. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
14. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. (2006) 37:577–617. doi: 10.1161/01.STR.0000199147.30016.74
15. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2011) 42:517–84. doi: 10.1161/STR.0b013e3181fcb238
16. Hurley D. Sharp increase in large-vessel stroke risk seen in young, healthy COVID-19 patients. *Neurol Today*. (2020) 20:36–7. doi: 10.1097/01.NT.0000668912.81159.e3
17. Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MS. Influenza-like illness as a trigger for ischemic stroke. *Ann Clin Transl Neurol*. (2018) 5:456–63. doi: 10.1002/acn3.545
18. Hamming I, Timens W, Bulthuis M, Lely A, Navis Gv, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. (2004) 203:631–7. doi: 10.1002/path.1570
19. Moore HB, Barrett CD, Moore EE, McIntyre RC, Moore PK, Talmor DS, et al. Is there a role for tissue plasminogen activator as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome? *J Trauma Acute Care Surg*. (2020) 88:1. doi: 10.1097/TA.0000000000002694
20. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Investig*. (2020) 130:2620–9. doi: 10.1172/JCI137244
21. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. *Stroke*. (2020) 51:e124–7. doi: 10.1161/STROKEAHA.120.030153
22. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*. (2020) 142:68–78. doi: 10.1161/CIRCULATIONAHA.120.047549
23. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immunity*. (2020) 87:18–22. doi: 10.1016/j.bbi.2020.03.031
24. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. (2020) 17:259–60. doi: 10.1038/s41569-020-0360-5
25. Association AL. *Global COVID-19 Real Time Statistics* (2020). Retrieved from: https://www.worldometers.info/coronavirus/ (accessed September 22, 2020).
26. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. (2015) 4:1. doi: 10.1186/2046-4053-4-1
27. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *PLoS Med*. (2007) 4:e297. doi: 10.1371/journal.pmed.0040297
28. Economics IoH. *Quality Appraisal of Case Series Studies Checklist*. Edmonton, AB: Institute of Health Economics. (2014).
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics Med*. (2002) 21:1539–58. doi: 10.1002/sim.1186

30. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Increase in studies of publication bias coincided with increasing use of meta-analysis. *Br Med J.* (1997) 316:629–34. doi: 10.1136/bmj.315.7109.629
31. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw.* (2012) 49:1–15. doi: 10.18637/jss.v049.i05
32. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* (2020) 191:9–14. doi: 10.1016/j.thromres.2020.04.024
33. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology.* (2020) 95:e910–20. doi: 10.1212/WNL.0000000000009848
34. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.013
35. Jain R, Young M, Dogra S, Kennedy H, Nguyen V, Jones S, et al. COVID-19 related neuroimaging findings: a signal of thromboembolic complications and a strong prognostic marker of poor patient outcome. *J Neurol Sci.* (2020) 414:116923. doi: 10.1016/j.jns.2020.116923
36. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS2-CoV-2 and stroke in a New York Healthcare System. *Stroke.* (2020) 51:30335. doi: 10.1161/STROKEAHA.120.030335
37. Escalard S, Maïer B, Redjem H, Delvoye F, Hébert S, Smajda S, et al. Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19: experience from Paris. *Stroke.* (2020) 51:2540–3. doi: 10.1161/STROKEAHA.120.030574
38. Arabi Y, Harthi A, Hussein J, Bouchama A, Johani S, Hajeer A, et al. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection.* (2015) 43:495–501. doi: 10.1007/s15010-015-0720-y
39. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* (2020) 46:1089–98. doi: 10.1007/s00134-020-06062-x
40. Xiong W, Mu J, Guo J, Lu L, Liu D, Luo J, et al. New onset neurologic events in people with COVID-19 infection in three regions in China. *Neurology.* (2020) 95:10034. doi: 10.1212/WNL.0000000000010034
41. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry.* (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586
42. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain Behav Immun.* (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077
43. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med.* (2020) 382:e38. doi: 10.1056/NEJMc2007575
44. Barrios-López JM, Rego-García I, Muñoz Martínez C, Romero-Fábrega JC, Rivero Rodríguez M, Ruiz Giménez JA, et al. Ischaemic stroke and SARS-CoV-2 infection: a causal or incidental association? *Neurologia.* (2020) 35:295–302. doi: 10.1016/j.nrleng.2020.05.008
45. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. *N Engl J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787
46. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol.* (2020) 267:2185–92. doi: 10.1007/s00415-020-09885
47. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg.* (2020) 12:16220. doi: 10.1136/neurintsurg-2020-016220
48. Zayet S, Klopfenstein T, Kovács R, Stancescu S, Hagenkötter B. Acute cerebral stroke with multiple infarctions and COVID-19, France, 2020. *Emerg Infect Dis.* (2020) 26:201791. doi: 10.3201/eid2609.201791
49. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thrombosis Haemostasis.* (2020). doi: 10.1111/jth.14938
50. Viguier A, Delamarre L, Duplantier J, Olivot JM, Bonneville F. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. *J Neuroradiol.* (2020) 47:393–4. doi: 10.1016/j.neurad.2020.04.003
51. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? *N Microb New Infections.* (2020) 35:100669. doi: 10.1016/j.nmni.2020.100669
52. Christian Oliver C, Yu JRT, Laxamana LC, David-Ona DIA. Intravenous thrombolysis for stroke in a COVID-19 positive Filipino patient. A case report. *J Clin Neurosci.* (2020) 77:234–6. doi: 10.1016/j.jocn.2020.05.006
53. González-Pinto T, Luna-Rodríguez A, Moreno-Estébanez A, Agirre-Beitia G, Rodríguez-Antigüedad A, Ruiz-Lopez M. Emergency room neurology in times of COVID-19: malignant ischaemic stroke and SARS-CoV-2 infection. *Eur J Neurol.* (2020) 27:e35–6. doi: 10.1111/ene.14286
54. Moshayedi P, Ryan TE, Mejia LLP, Nour M, Liebeskind DS. Triage of acute ischemic stroke in confirmed COVID-19: large vessel occlusion associated with coronavirus infection. *Front Neurol.* (2020) 11:353. doi: 10.3389/fneur.2020.00353
55. Hughes C, Nichols T, Pike M, Subbe C, Elghenzai S. Cerebral venous sinus thrombosis as a presentation of COVID-19. *Eur J Case Rep Intern Med.* (2020) 7:001691. doi: 10.12890/2020_001691
56. Gunasekaran K, Amoah K, Rajasurya V, Buscher MG. Stroke in a young COVID-19 patient. *QJM.* (2020) 113:573–4. doi: 10.1093/qjmed/hcaa177
57. Goldberg MF, Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular disease in COVID-19. *Am J Neuroradiol.* (2020) 41:1170–2. doi: 10.3174/ajnr.A6588
58. Tunç A, Ünlübaş Y, Alemdar M, Akyüz E. Coexistence of COVID-19 and acute ischemic stroke report of four cases. *J Clin Neurosci.* (2020) 77:227–9. doi: 10.1016/j.jocn.2020.05.018
59. Chung JW, Park SH, Kim N, Kim WJ, Park JH, Ko Y, et al. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification and vascular territory of ischemic stroke lesions diagnosed by diffusion-weighted imaging. *J Am Heart Assoc.* (2014) 3:e001119. doi: 10.1161/JAHA.114.001119
60. Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. *Mayo Clin Proc.* (2007) 82:864–73. doi: 10.4065/82.7.864
61. Berger JR. COVID-19 and the nervous system. *J Neurovirol.* (2020) 1:5. doi: 10.1007/s13365-020-00840-5
62. Dronkers NF, Baldo JV. Language: aphasia. In: Squire LR, editor. *Encyclopedia of Neuroscience*. Amsterdam: Elsevier (2009). p. 343–8.
63. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* (2020) 395:565–74. doi: 10.1016/S0140-6736(20)30251-8
64. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:552–5. doi: 10.1002/jmv.25728
65. Umapathi T, Kor AC, Venketasubramanian N, Lim CT, Pang BC, Yeo TT, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol.* (2004) 251:1227–31. doi: 10.1007/s00415-004-0519-8
66. Algahtani H, Subahi A, Shirah B. Neurological complications of Middle East respiratory syndrome coronavirus: a report of two cases and review of the literature. *Case Rep Neurol Med.* (2016) 2016:3502683. doi: 10.1155/2016/3502683
67. Lindsay MP, Norrving B, Sacco RL, Brainin M, Hacke W, Martins S, et al. *World Stroke Organization (WSO): Global Stroke Fact Sheet 2019*. London, England: SAGE Publications Sage UK. (2019). doi: 10.1177/1747493019881353
68. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke Statistics-2019 update a report from the American Heart Association. *Circulation.* (2019) 139:659. doi: 10.1161/CIR.0000000000000659
69. Yi X, Luo H, Zhou J, Yu M, Chen X, Tan L, et al. Prevalence of stroke and stroke related risk factors: a population based cross sectional survey in southwestern China. *BMC Neurol.* (2020) 20:5. doi: 10.1186/s12883-019-1592-z

70. He J, Klag MJ, Wu Z, Whelton PK. Stroke in the People's Republic of China: I. Geographic variations in incidence and risk factors. *Stroke.* (1995) 26:2222–7. doi: 10.1161/01.STR.26.12.2222
71. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. *Lancet.* (2014) 383:1973–80. doi: 10.1016/S0140-6736(14)60040-4
72. Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. *Stroke.* (2010) 41:e418–26. doi: 10.1161/STROKEAHA.109.576967
73. Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GY. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: a systematic review and meta-analysis. *Stroke.* (2013) 44:1329–36. doi: 10.1161/STROKEAHA.113.000883
74. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transpl.* (2015) 30:1162–9. doi: 10.1093/ndt/gfv009
75. Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle H, et al. Ischaemic stroke in young adults: predictors of outcome and recurrence. *J Neurol Neurosurg Psychiatry.* (2005) 76:191–5. doi: 10.1136/jnnp.2004.040543
76. Sebastian S, Stein LK, Dhamoon MS. Infection as a stroke trigger: associations between different organ system infection admissions and stroke subtypes. *Stroke.* (2019) 50:2216–8. doi: 10.1161/STROKEAHA.119.025872
77. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thrombosis Haemostasis.* (2020) 18:1559–61. doi: 10.1111/jth.14849
78. Hui C, Tadi P, Patti L. Ischemic stroke. In: *StatPearls* [Internet]. Treasure Island, FL: StatPearls Publishing (2020).
79. Rennert RC, Wali AR, Steinberg JA, Santiago-Dieppa DR, Olson SE, Pannell JS, et al. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. *Neurosurgery.* (2019) 85(Suppl.1):S4–8. doi: 10.1093/neuros/nyz042
80. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5
81. Fan H, Tang X, Song Y, Liu P, Chen Y. Influence of COVID-19 on cerebrovascular disease and its possible mechanism. *Neuropsychiatric Dis Treat.* (2020) 16:1359–67. doi: 10.2147/NDT.S251173
82. Wong C, Lam C, Wu A, Ip W, Lee N, Chan I, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol.* (2004) 136:95–103. doi: 10.1111/j.1365-2249.2004.02415.x
83. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a review. *Acta Neurol Scand.* (2020) 142:14–22. doi: 10.1111/ane.13266
84. Esenwa CC, Elkind MS. Inflammatory risk factors, biomarkers and associated therapy in ischaemic stroke. *Nat Rev Neurol.* (2016) 12:594. doi: 10.1038/nrneurol.2016.125

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 October 2020
doi: 10.3389/fneur.2020.567413

Parkinson's Disease Remote Patient Monitoring During the COVID-19 Lockdown

*Francesco Motolese[1], Alessandro Magliozzi[1], Fiorella Puttini[1], Mariagrazia Rossi[1], Fioravante Capone[1], Keren Karlinski[2], Alit Stark-Inbar[2], Ziv Yekutieli[2], Vincenzo Di Lazzaro[1] and Massimo Marano[1]**

[1] Neurology, Neurophysiology and Neurobiology Unit, Department of Medicine, University Campus Bio-Medico of Rome, Rome, Italy, [2] Montfort Brain Monitor, Binyamina, Israel

OPEN ACCESS

Edited by:
Shen-Yang Lim,
University of Malaya, Malaysia

Reviewed by:
Mariachiara Sensi,
University Hospital of Ferrara, Italy
Lorenzo Chiari,
University of Bologna, Italy

***Correspondence:**
Massimo Marano
m.marano@unicampus.it

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 29 May 2020
Accepted: 02 September 2020
Published: 07 October 2020

Citation:
Motolese F, Magliozzi A, Puttini F, Rossi M, Capone F, Karlinski K, Stark-Inbar A, Yekutieli Z, Di Lazzaro V and Marano M (2020) Parkinson's Disease Remote Patient Monitoring During the COVID-19 Lockdown. Front. Neurol. 11:567413. doi: 10.3389/fneur.2020.567413

Objective: To evaluate the feasibility of a smartphone remote patient monitoring approach in a real-life Parkinson's disease (PD) cohort during the Italian COVID-19 lockdown.

Methods: Fifty-four non-demented PD patients who were supposed to attend the outpatient March clinic were recruited for a prospective study. All patients had a known UPDRS-III and a modified Hoehn and Yahr (H&Y) score and were provided with a smartphone application capable of providing indicators of gait, tapping, tremor, memory and executive functions. Different questionnaires exploring non-motor symptoms and quality of life were administered through phone-calls. Patients were asked to run the app at least twice per week (i.e., full compliance). Subjects were phone-checked weekly throughout a 3-week period for compliance and final satisfaction questionnaires.

Results: Forty-five patients (83.3%) ran the app at least once; Twenty-nine (53.7%) subjects were half-compliant, while 16 (29.6%) were fully compliant. Adherence was hindered by technical issues or digital illiteracy (38.7%), demotivation (24%) and health-related issues (7.4%). Ten patients (18.5%) underwent PD therapy changes. The main factors related to lack of compliance included loss of interest, sadness, anxiety, the absence of a caregiver, the presence of falls and higher H&Y. Gait, tapping, tremor and cognitive application outcomes were correlated to disease duration, UPDRS-III and H&Y.

Discussion: The majority of patients were compliant and satisfied by the provided monitoring program. Some of the application outcomes were statistically correlated to clinical parameters, but further validation is required. Our pilot study suggested that the available technologies could be readily implemented even with the current population's technical and intellectual resources.

Keywords: Parkinson's disease (PD), remote patient monitoring (RPM), telemedicine, smartphone, COVID

INTRODUCTION

On March 9th, 2020 the Italian government imposed a national lockdown, due to Coronavirus disease 2019 (COVID-19) outbreak. Such restriction also aimed to protect fragile people with chronic diseases, a population that is particularly at risk of SARS-CoV-2 complications. However, these patients often needed a tight follow-up and therapies to be tailored from time-to-time. In the last few years, mobile technologies have been extensively explored in patient management. However, this has not changed current clinical practices (1). Herein, we present a prospective study in which we explored the feasibility of remote patient monitoring (RPM) in a real-life cohort of Parkinson's disease (PD) patients. This was performed through a smartphone application designed for monitoring motor and cognitive performances of patients affected by neurological disorders.

PATIENTS AND METHODS

Non-demented PD patients, who were supposed to attend the outpatient clinic in March 2020 for follow-up visits and owned a smartphone, were recruited. All subjects who were enrolled in this observational study received a first phone-call to collect information about their sociodemographic data, their baseline PD motor and non-motor status and quality of life. Accordingly, the following questionnaires were adopted: the Non-Motor Symptoms Questionnaire (NMSQ), the Unified Parkinson's Disease Rating Scale for mentation behavior and mood, activities of daily living and complications of therapy (UPDRS I, II, and IV respectively), the Geriatric Depression Scale short form (GDSsf) and the Parkinson's Disease Questionnaire-8 (PDQ8) (2).

All questionnaires were collected by an experienced clinician (MM) and a trained rater (FP) and the phone-calls were delivered directly to the patient, with or without the involvement of the caregiver.

In the same phone-call, all patients were provided with the instructions to download, run and use the EncephaLog Home™ smartphone application. We provided all the necessary instructions for the use of the app both in written form (i.e., through supportive emails) and a video instruction embedded in the app itself (i.e., only for the TUG test). However, patients were allowed to receive caregivers' help whenever needed.

The app included a starting question with a self-evaluation of the global "Parkinson Status" (0–5), followed by a sequence of cognitive tests exploring reaction time, interference and memory and 10 consecutive tasks exploring motor functions (postural and rest tremor for both arms, timed tapping test for both hands, balance assessment in neutral stance and feet together and two 3-meters Time-Up-and-Go or TUG test). It took ∼15 to 20 min to carry out all the tasks included in the app.

Patients were asked to use the "app" at least twice a week for a 3-week observation period, but they were allowed to use it (as unsolicited) as needed to let the neurologist track their status. Subjects were phone-checked weekly throughout a 3-week period for compliance, upcoming issues and for an evaluation questionnaire at the end of the observation period. The latter was sent to patients by email and mailed back to the physician via e-mail or regular mail. Further details on the final evaluation questionnaires are reported in **Supplementary Materials**.

Data of the last available in-person motor status (i.e., performed in the hospital) was retrospectively collected from medical records. This included the UPDRS-III total score and the modified Hoehn and Yahr scale (H&Y) (3). Both were rated by a single trained physician (MM).

EncephaLog Home™ is a smartphone application, supported both by iOS and Android operating systems, designed by Montfort Brain Monitor LTD (https://www.mon4t.com) - a company providing smartphone-based neurological tests. The English native app was translated in Italian by Montfort (ZY, KK, AS) with medical scientific counseling provided by the Neurology, Neurobiology and Neurophysiology unit of Campus Bio-Medico of Rome University (FM, FP, AM, MM). Further descriptions of the app, its validation stage and details of tests are reported in the **Supplementary Materials**.

All individuals provided informed consent in regards to their participation to the study. The research was performed according to the Declaration of Helsinki and approved by the ethic committee of Campus Bio-Medico of Rome University.

Anonymized app data was prospectively collected and sent from the smartphone in a secured manner (using HTTPS), using Azure for storing and processing the raw data. The latter was accessible along the study but was analyzed only at the end. When the research was conducted, the app data was not meant to be used as an aid to support any kind of intervention (e.g., medication changes).

Descriptive statistics are reported as frequencies (%) or median (quartiles, QI-QIII). Inferential statistics were carried out by the Wilcoxon/Kruskal-Wallis or the Chi-squared test according to data and distributions. The association between variables was investigated by the Spearman test and described as correlation coefficient (p-value). A $p < 0.05$ was adopted as a cut-off to determine statistical significance. Statistics were performed by the JMP-14 software (SAS institute Inc.).

Anonymized data can be made available to qualified investigators.

RESULTS

Fifty-four consecutive PD patients were enrolled, see **Table 1** for socio-demographic and disease feature baseline. Eight patients preferred not to disclose their economic status by phone-calls. Most of them had a caregiver involved in the PD care (46, 85%). Caregivers showed a younger median age (48, 37.5–69.2; $p < 0.001$) and a trend of having a higher formal education level ($p = 0.066$) than patients.

Retrospective UPDRS-III total and H&Y data was traced back no farther than 6 months.

Forty-five (83.3%) patients used the app at least once throughout the entire follow-up period of 3 weeks, with a total number of 313 accesses to tests.

TABLE 1 | Population's socio-demographic and disease feature baseline data.

Age (years)	66.5 (59.7–72.2)
Sex (F), *n* (%)	18 (33)
Education	
Bachelor's degree, *n* (%)	15 (27.7)
High school, *n* (%)	26 (48.1)
Upper secondary school or lower, *n* (%)	13 (22)
Annual family income	
> 55.000 €, *n* (%)	7 (13)
28–55.000 €, *n* (%)	15 (27.5)
<28.000 €, *n* (%)	24 (44)
Not provided	8 (15)
Comorbidities	
3 or more, *n* (%)	17 (31.5)
1 or 2, *n* (%)	21 (38.8)
None, *n* (%)	16 (29.6)
Presence of caregiver	
Close relative (Spouse or son)	43 (79.6)
Other relative or close friends	3 (5.5)
None	8 (14.8)
Caregiver education	
Bachelor's degree, *n* (%)	20 (43.4)
High school, *n* (%)	12 (66)
Upper secondary school or lower, *n* (%)	14 (30)
Disease duration (years)	6.5 (4–11)
Modified Hoehn & Yahr scale	2.5 (2–3)
Patients on Levodopa, *n* (%)	39 (80%)
LEDD (mgs)	547.5 (366.25–1,061.25)
Patients on advanced therapies	
STN DBS, *n* (%)	5 (9.2)
LCIG, *n* (%)	11 (20.3)
UPDRS-III total score	22 (14–32)
UPDRS-I total score	1 (0–2)
UPDRS-II total score	11 (7–16)
UPDRS-IV A & B total score	2 (0–3)
NMSQ total score	9 (5.75–13)
GDSsf total score	3 (1–7)
PDQ8 score (%)	18.8 (9.4–31.3)

Data is reported as median (quartiles, QI-QIII) or frequencies (%). LEDD, Levodopa Equivalency Daily Dose; STN DBS, subthalamic nucleus deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; UPDRS, Unified Parkinson's Disease Rating Scale; NMSQ, Non-Motor Symptoms Questionnaire; GDSsf, Geriatric Depression Scale short form; PDQ8, Parkinson's Disease Questionnaire 8.

In reference to compliance, 29 (53.7%) subjects used the app at least once per week for the 3-week observation period, while 16 (29.6%) were fully compliant (i.e., ran the test at least twice each week for the 3-week observation time) (**Figure 1**). Compliance was hindered by technical issues or digital illiteracy (21, 38.8%), demotivation or non-specific compliance loss (13, 24%) and health-related issues (4, 7.4% with 1 COVID-19 case). In only two cases (3.7%) technical difficulties—i.e., old-generation smartphones—and digital illiteracy impeded the use of the app; all other issues were solved through phone support. Ten patients (18.5%) underwent PD treatment changes, upon request due to clinical reasons. All performed therapeutic interventions were routine modifications of ongoing medications. None was driven by the app outcomes, due to the observational nature of the study at this stage.

Socio-demographic factors did not relate to the compliance, with the exception of caregiver presence. The latter was tendentially associated to a higher rate of full compliance ($p = 0.051$), as well as to a better adherence throughout the program ($p = 0.029$ at the 3rd phone-check)

PD medications, the presence of advanced therapies (i.e., deep brain stimulation or infusional therapies), UPDRS-I and II total scores did not relate to compliance. However, patients undergoing therapy modifications were most likely fully compliant ($p = 0.005$), as well as patients with motor fluctuations (UPDRS-IV, sudden or unpredictable offs, $p = 0.038$). On the other hand, patients with loss of interest on NMSQ were, in the majority of cases, not fully compliant ($p = 0.020$, respectively). Similarly, NMSQ loss of interest ($p = 0.024$), sadness ($p = 0.048$) and anxiety ($p = 0.019$) were related to low adherence on the 1st-check, while lack of motivation (UPDRS-I) related to a later loss of compliance on the 3rd ($p = 0.007$) phone-check. The presence of falls (UPDRS-II; $p = 0.019$) and of a higher H&Y ($p = 0.008$) were related to a lower compliance rate on the 3rd phone-check (**Table 2**).

The analysis of data coming from the final evaluation questionnaire showed that 37 (84%) subjects evaluated their experience as "satisfying" (16, 36.4%) or "very satisfying" (21, 48%) and 21 cases (48%) perceived themselves as "safer" (17, 39.5%) or "much safe" (4, 9.3%) thanks to the RPM. However, 17 (37.2%) required "occasional" support and 9 (21%) "frequent to regular" support by the caregiver. Similarly, a minority (11, 26%) perceived the app as difficult (**Figure 1**, **Supplementary Table**).

An overview of the data collected from the app and the correlation between the app outcomes and disease duration, UPDRS-III total and H&Y are presented in **Supplementary Tables**.

DISCUSSION

This study reported the feasibility of a smartphone-based RPM in a real-life cohort of non-demented PD patients, who were unable to attend the regular follow-up visits due to COVID-19 pandemic.

The "full compliance" (i.e., running the app at least twice per week, for the 3-week period) was an ambitious target to achieve. However, It was encountered in ∼30% and was significantly associated to therapeutic changes and to the presence of motor fluctuations. Although the present RPM study was not designed to perform any medical intervention, such result might suggest that a "patient-demanded" remote monitoring is better suited for "active" follow-ups more than for "passive" at-home monitoring. Nevertheless, more than a half of subjects (∼55%) spontaneously performed the full ∼20-min assessment weekly, providing useful data to track their motor and non-motor performances. This

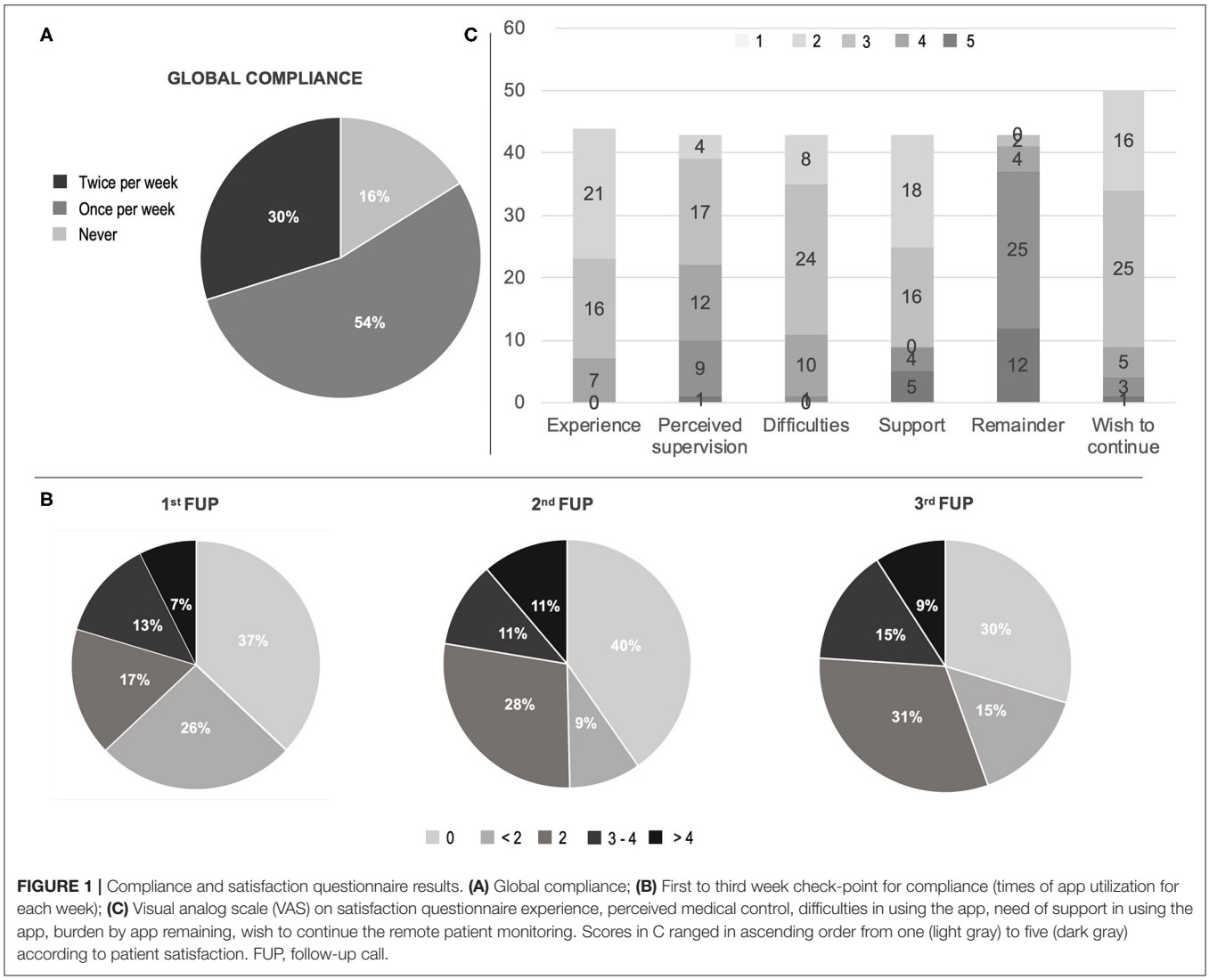


FIGURE 1 | Compliance and satisfaction questionnaire results. **(A)** Global compliance; **(B)** First to third week check-point for compliance (times of app utilization for each week); **(C)** Visual analog scale (VAS) on satisfaction questionnaire experience, perceived medical control, difficulties in using the app, need of support in using the app, burden by app remaining, wish to continue the remote patient monitoring. Scores in C ranged in ascending order from one (light gray) to five (dark gray) according to patient satisfaction. FUP, follow-up call.

result should not be underestimated in light of future potential studies on disease phenotypes and progression tracking.

Our data shares similarities with previous studies. For instance, Arora et al. obtained a 68% adherence by a sample of 10 mild-to-moderate, well-educated, PD patients (vs. 10 controls). All of them received a smartphone with a 5-min/5-task application, to be performed 4 times a day for a month (4). A ∼65% adherence rate was reported also by Horin et al. on a sample of 20 mild-to-moderate PD patients, who were asked to perform a 30-min daily monitoring of three domains on their own smartphone for 90 days (5).

In our study, the majority of patients were compliant and satisfied (**Figure 1**). However, technical difficulties had an incidence close to ∼40%, which is in line with the Italian data on population's problem solving skills in a technological environment (6). Hence, it is reasonable to affirm that, with an adequate in-person training, the program adherence could have been even higher.

Moreover, due to the real-life prospective design, our sample did not exclude patients with a severe involvement (5% had a H&Y of 4) or a lower instruction (22%), being representative of the entire non-demented PD population even on a socio-demographical point-of-view. Additionally, both the contingency of COVID-19 national lockdown and patients' emotional profile might have influenced the adherence. For instance, some non-motor aspects were associated to compliance at the beginning of the RPM (i.e., loss of interest, sadness and anxiety), while others had a prominent role in the full-term program adherence (i.e., lack of motivation, a more severe motor profile). The presence of an educated caregiver is considered essential, nowadays, in the care of PD patients (7). Their role in PD-related device management has been already acknowledged. For instance, the presence of a caregiver in advanced PD patients on device-aided therapies was associated to a better therapeutic outcome overall, despite the relevant burden (8, 9). Our results support the importance of the caregiver in the

TABLE 2 | Motor and non-motor related issues and compliance to the remote patient monitoring prescription.

Full compliance	No	Yes				p-value
Medication changes						
No	33 (64.7)	8 (15.7)				0.005
Yes	2 (3.9)	8 (15.7)				
UPDRS-IV, sudden or unpredictable offs						
No	32 (62.7)	11 (21.6)				0.038
Yes	3 (5.9)	5 (9.8)				
NMSQ, Loss of interest						
No	23 (45)	15 (29)				0.020
Yes	12 (25.5)	1 (2)				
1st compliance check (*n* of app usage)	**0**	**1**	**2**	**3-4**	**>4**	***p*-value**
NMSQ, Loss of interest						
No	14 (27.5)	7 (13.7)	6 (11.7)	7 (13.7)	4 (7.8)	0.024
Yes	3 (5.8)	7 (13.7)	3 (5.8)	0	0	
NMSQ, Sadness						
No	12 (23.5)	6 (11.8)	3 (5.8)	5 (9.8)	4 (7.8)	0.048
Yes	5 (9.8)	8 (15.7)	6 (11.7)	2 (3.9)	0	
NMSQ, Anxiety						
No	10 (19.6)	9 (17.6)	2 (3.9)	6 (11.7)	4 (7.8)	0.193
Yes	7 (13.7)	5 (9.8)	7 (13.7)	1 (1.9)	0	
3rd compliance check (*n* of app usage)	**0**	**1**	**2**	**3–4**	**>4**	***p*-value**
UPDRS-I, lack of motivation						
Normal	12 (23.5)	2 (3.9)	15 (29.4)	7 (13.7)	4 (7.8)	0.007
Less assertive	1 (1.96)	1 (1.96)	2 (3.9)	0	1 (1.96)	
Loss of initiative in elective activities.	0		0	1 (1.96)	0	
Loss of initiative in day to day activities.	0	1 (1.96)	0	0	0	
UPDRS-II, Falling						
None	12 (23.5)	4 (7.8)	14 (27.5)	3 (5.8)	4 (7.8)	0.019
Rare falling	1 (1.9)	4 (7.8)	0	3 (5.8)	1 (1.9)	
Less than once per day	0	0	3 (5.8)	1 (1.9)	0	
Once daily	0	0	0	1 (1.9)	0	
Modified Hoehn & Yahr scale						
1–2	2 (3.9)	4 (7.8)	8 (15.7)	0	5 (9.8)	0.008
2.5	8 (15.7)	1 (1.9)	4 (7.8)	5 (9.8)	0	
3–4	3 (5.8)	3 (5.8)	5 (9.8)	3 (5.8)	0	

UPDRS, Unified Parkinson's Disease Rating Scale; NMSQ, Non-Motor Symptoms Questionnaire; Data is presented as numbers, total frequencies (%). Missing data: there are 3 missing evaluation per compliance check.

device management. The caregiver supported a better patient compliance overall, especially in a later follow-up. Accordingly, the analysis of the final evaluation questionnaire revealed that nearly 20% frequently asked for caregiver's help.

The sample size—which could be appropriated for a pilot study—needs to be improved in a larger prospective study in order to guarantee an adequate representation of the various disease stages and subtypes and to draw more robust conclusions even on app biomarkers. However, this was not a validation study and its primary objective was to evaluate the usability and the compliance of a smartphone app for PD RPM. At the same time, it was possible to associate several quantified motor and cognitive outcomes to available disease severity indexes (disease duration, UPDRS-III total score, H&Y; **Supplementary Materials**), as also previously reported (10–12). Interestingly some of the motor and cognitive parameters—in particular TUG test data—were not associated to age but specific to the PD condition (**Supplementary Table 3**). This observation should be replicated in the presence of a control population, which is currently missing. To this regard, the EncephaLog^{TM} TUG test has been already validated against other medical devices in dedicated laboratories and compared to GAITRite pressure walkaway, Vicon 3D cameras and wearables providing a reliable biomarker in both PD and healthy volunteers (12–14).

Mobile-health is on the rise and demonstrates that, in combination with machine learning protocols, it is able to track some of the complex and fluctuating manifestations of PD (15–17).

According to our results, the presence of fluctuations is associated to a more frequent use of the app. In the presented cohort, motor complications were captured only by the UPDRS-IV questionnaire, which provided a dichotomous outcome about the presence/absence of specific motor fluctuations (e.g., sudden offs, unpredictable offs, dyskinesias). Motor fluctuations would have been better tracked by motor diaries. These were not included in the present study, but we acknowledge their essential role in RPM aimed to address motor fluctuations (16, 17).

In conclusion, our study suggests that available technologies can be used for telemedicine, even in a population with limited skills and in a critical situation like a pandemic—which could considerably affect the health of neurological patients directly or indirectly (i.e., worsening of stressors) (18). Some other limitations, such as the brief protocol duration, the absence of controls and the lack of in-person objective measures to compare, warrant further studies to confirm our preliminary findings.

There is still a long-way ahead of us before in-persons visits could be actually seen as "option-B," since the reliability of new technologies and smartphone apps—released in the most recent years—needs to be proven (19, 20). However, in "emergency conditions", we found that this combined approach—calls and app—can represent a good compromise to follow-up patient care. New studies are warranted on a larger sample size and for longer periods of time to evaluate the effectiveness of mobile health in patients' management.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato etico dell'Università Campus Bio-Medico di Roma. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FM wrote the first draft and managed data collections. AM, FP, and MR collected data. FC and VD reviewed the paper for intellectual content. KK, AS-I, and ZY managed data collection and provided IT assistance. MM wrote the first draft, provided statistical analysis ad reviewed the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We acknowledge all patients and their families that in such harsh period of national quarantine contributed to the research.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.567413/full#supplementary-material

REFERENCES

1. Sim I. Mobile devices and health. *N Engl J Med.* (2019) 381:956–68. doi: 10.1056/NEJMra1806949
2. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, Chaudhuri KR. *Guide to Assessment Scales in Parkinson's Disease*. Tarporley: Springer Healthcare (2014). doi: 10.1007/978-1-907673-88-7_6
3. Fahn S, Elton R. Members of the UPDRS Development Committee. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. *Recent Developments in Parkinson's Disease, Vol 2*. Florham Park, NJ. Macmillan Health Care Information (1987). p. 153–63:293–304.
4. Arora S, Venkataraman V, Zhan A, Donohue S, Biglan KM, Dorsey ER, et al. Detecting and monitoring the symptoms of Parkinson's disease using smartphones: A pilot study. *Park Relat Disord.* (2015) 21:650–3. doi: 10.1016/j.parkreldis.2015.02.026
5. Horin AP, McNeely ME, Harrison EC, Myers PS, Sutter EN, Rawson KS, et al. Usability of a daily mHealth application designed to address mobility, speech and dexterity in Parkinson's disease. *Neurodegener Dis Manag.* (2019) 9:97–105. doi: 10.2217/nmt-2018-0036
6. OECD. *OECD Skills Outlook 2019: Thriving in a Digital World*. Paris: OECD Publishing (2019).
7. Di Stasio E, Di Simone E, Galeti A, Donati D, Guidotti C, Tartaglini D, et al. Stress-related vulnerability and usefulness of healthcare education in Parkinson's disease: the perception of a group of family caregivers, a cross-sectional study. *Appl Nurs Res.* (2020) 51:151186. doi: 10.1016/j.apnr.2019.151186
8. Sensi M, Cossu G, Mancini F, Pilleri M, Zibetti M, Modugno N, et al. Which patients discontinue? Issues on Levodopa/carbidopa intestinal gel treatment: Italian multicentre survey of 905 patients with long-term follow-up. *Park Relat Disord.* (2017) 38:90–2. doi: 10.1016/j.parkreldis.2017.02.020
9. Tessitore A, Marano P, Modugno N, Pontieri FE, Tambasco N, Canesi M, et al. Caregiver burden and its related factors in advanced Parkinson's disease: data from the PREDICT study. *J Neurol.* (2018) 265:1124–37. doi: 10.1007/s00415-018-8816-9
10. Lee W, Evans A, Williams DR. Validation of a smartphone application measuring motor function in Parkinson's Disease. *J Park Dis.* (2016) 6:371–82. doi: 10.3233/JPD-150708
11. Lee W, Williams DR, Evans A. Feasibility of smartphone-based testing of interference in Parkinson's Disease. *Neurodegener Dis.* (2018) 18:133–42. doi: 10.1159/000488593
12. Yahalom G, Yekutieli Z, Israeli-Korn S, Elincx-Benizri S, Livneh V, Fay-Karmon T, et al. Smartphone based timed up and go test can identify postural instability in Parkinson's Disease. *Isr Med Assoc J.* (2020) 22:37—42.
13. Tchelet K, Stark-Inbar A, Yekutieli Z. Pilot study of the EncephaLog smartphone application for gait analysis. *Sensors.* (2019) 19:5179. doi: 10.3390/s19235179
14. Yahalom H, Israeli-Korn S, Linder M, Yekutieli Z, Karlinsky KT, Rubel Y, et al. Psychiatric patients on neuroleptics: evaluation of Parkinsonism and quantified assessment of gait. *Clin Neuropharmacol.* (2020) 43:1–6. doi: 10.1097/WNF.0000000000000371
15. Espay AJ, Hausdorff JM, Sánchez-Ferro Á, Klucken J, Merola A, Bonato P, et al. A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *Mov Disord.* (2019) 34:657–63 doi: 10.1002/mds.27671

16. Zhan A, Mohan S, Tarolli C, Schneider RB, Adams JL, Sharma S, et al. Using smartphones and machine learning to quantify Parkinson disease severity: the mobile Parkinson Disease score. *JAMA Neurol.* (2018) 75:876. doi: 10.1001/jamaneurol.2018.0809
17. Erb MK, Karlin DR, Ho BK, Thomas KC, Parisi F, Vergara-Diaz GP, et al. mHealth and wearable technology should replace motor diaries to track motor fluctuations in Parkinson's disease. *NPJ Digit Med.* (2020) 3:6. doi: 10.1038/s41746-019-0214-x
18. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol.* (2020) 11:737. doi: 10.3389/fneur.2020.00737
19. Duffy S, Lee TH. In-person health care as option B. *N Engl J Med.* (2018) 378:104–6. doi: 10.1056/NEJMp1710735
20. Fasano A, Mancini M. Wearable-based mobility monitoring: the long road ahead. *Lancet Neurol.* (2020) 19:378–9. doi: 10.1016/S1474-4422(20)30033-8

Conflict of Interest: ZY is co-founder and CEO, AS-I is CSO and KK is CTO of Montfort Brain Monitor LTD a company providing smartphone-based neurological tests.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 08 October 2020
doi: 10.3389/fneur.2020.579047

Migraine Symptoms Improvement During the COVID-19 Lockdown in a Cohort of Children and Adolescents

Gianfranco Dallavalle[1†], Elena Pezzotti[1†], Livio Provenzi[2], Federico Toni[1], Adriana Carpani[2] and Renato Borgatti[1,2]*

[1] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [2] Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy

OPEN ACCESS

Edited by:
Jesús Porta-Etessam,
Hospital Clínico San Carlos, Spain

Reviewed by:
Marianna Delussi,
University of Bari Aldo Moro, Italy
Adrian Garcia Ron,
Health Research Institute of the Hospital Clínico San Carlos (IdISSC), Spain

***Correspondence:**
Renato Borgatti
renato.borgatti@unipv.it

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: 01 July 2020
Accepted: 04 September 2020
Published: 08 October 2020

Citation:
Dallavalle G, Pezzotti E, Provenzi L, Toni F, Carpani A and Borgatti R (2020) Migraine Symptoms Improvement During the COVID-19 Lockdown in a Cohort of Children and Adolescents. Front. Neurol. 11:579047. doi: 10.3389/fneur.2020.579047

Background: Pediatric migraine is among the most common primary or comorbid neurologic disorders in children. Psychological stressors are widely acknowledged as potential triggers involved in recurring episodes of pediatric migraine. As the COVID-19 emergency may have affected the levels of stress perceived by children and adolescents with migraine, the present study was aimed to understand the effect of COVID-19 emergency on symptoms intensity and frequency in pediatric patients.

Methods: A cohort of 142 child and adolescent patients with a diagnosis of migraine was enrolled at the Child Neurology and Psychiatry Unit of the IRCCS Mondino Foundation in Pavia (Italy). Socio-demographic and clinical characteristics were obtained from medical records. An on-line survey was used to collect information on COVID-19 exposure, stress response to the lockdown period, anxious symptoms during COVID-19 emergency, as well as migraine symptoms intensity and frequency before and during the lockdown.

Results: The great majority were outpatients ($n = 125$, 88.0%), 52 (36.6%) had migraine with aura, whereas, 90 (63.4%) had migraine without aura. All the patients reporting worsening symptoms progression before COVID-19, had reduced intensity during the lockdown ($\chi^2 = 31.05$, $p < 0.0001$). Symptoms frequency reduction was observed in 50% of patients presenting worsening symptoms before the lockdown, 45% of those who were stable, and 12% of those who were already improving. All patients who had resolved symptoms before COVID-19 were stable during the lockdown ($\chi^2 = 38.66$, $p < 0.0001$). Anxious symptomatology was significantly associated with greater migraine symptoms frequency ($\chi^2 = 19.69$, $p < 0.001$). Repeating the analysis separately for individuals with and without aura did not affect the findings and significant associations were confirmed for both the patients' subgroups.

Discussion: A significant reduction of migraine symptoms intensity and frequency was observed in pediatric patients during the COVID-19 lockdown phase in northern Italy. The improvement in both intensity and frequency of the migraine symptoms was especially

significant in patients who were stable or worsening before the lockdown. The reduction of symptoms severity during a period of reduced environmental challenges and pressures further highlights the need of providing effective training in stress regulation and coping for these patients.

Keywords: COVID-19, children, adolescents, migraine, headache, stress, anxiety

≪Some patients I could help with drugs, and some with the magic of attention and interest…it now became apparent to me that many migraine attacks were drenched in emotional significance≫.

[Oliver Sacks – Migraine, 1970]

INTRODUCTION

During the 1st months of 2020, Northern Italy has been the hotspot of the coronavirus disease of 2019 (COVID-19) outbreak in Europe (1). The adopted mitigation and containment actions included physical distancing strategies that indirectly resulted in the lockdown of schools and changes in daily habits. In this scenario, citizens may have been exposed to high levels of stress and anxiety (2). The mental health impact of this unprecedented healthcare emergency might be especially significant for children who already were suffering from physical and/or psychosomatic conditions, as it is the case of pediatric population with migraine (3, 4). Pediatric patients with migraine have been previously reported to be especially vulnerable to stressful and anxious encounters (3, 4). Thus, these patients represent a specific at-risk population that should be monitored for COVID-19-related effects on their health and symptoms progression.

Pediatric migraine is among the most common primary or comorbid neurologic disorders in children, with prevalence ranging from 3% in preschool children to 23% in adolescents (5, 6). Migraine may be generally considered as a disorder of psychobiology adaptation where genetic predisposition plays a critical role together with internal and external sources of environmental influence, including psycho-social and psycho-emotional challenges, hormonal dysregulation, dietary and other factors (3). A complex mix of factors is plausibly involved in setting the risk for pediatric migraine, including neurogenic inflammation, excitatory/inhibitory balance, genetic background and disturbed energy metabolism (7–9). Psychosomatic contributions have recently supported by neuroimaging studies as the default mode network appears to play a critical role in mediating the effects of environmental stressors and coping strategies on the origin and emergence of migraine symptoms (7).

Psychological stressors are widely acknowledged as potential triggers involved in recurring episodes of pediatric migraine (10, 11). Stressful, challenging and emotionally overwhelming experiences in school or educational environments may contribute to the overreaction of the central nervous system to environmental requests that are perceived as too intense by the individual, increasing the risk of headache and migraine (12). In large cohort studies, children with frequent and more intense migraine symptoms also report higher levels of school, family and/or peer-relational stress compared to headache free counterparts (13–15).

There is evidence of COVID-19 pandemic effects' on the psychological and physical well-being of children and adults in the general population (16–19). Recent research conducted in Italy reported that, during the COVID-19 quarantine, subjects with migraine had fewer migraine attacks and lesser pain as well as moderate levels of depression (20). Nonetheless, no information is available for what pertains the health of at-risk children and adolescents with pediatric migraine. In the present study we report the results of a survey conducted at a tertiary level neurological hospital in northern Italy. The survey was aimed to collect evidence on the impact of COVID-19 lockdown phase on the frequency and intensity of migraine symptoms among children and adolescents.

METHODS

From March to April 2020, a cohort of 142 child and adolescent patients with a diagnosis of migraine was enrolled at the Child Neurology and Psychiatry Unit of the IRCCS Mondino Foundation in Pavia (Italy). This hospital receives families for inpatient and outpatient care from Lombardy and other Italian regions. Patients were consecutively enrolled provided that parents could speak and understand Italian language. Patients were included if they did not present any comorbidity (e.g., psychomotor delay, neuromuscular diseases, epileptic disorders, cerebral palsy). The parents were asked to respond to an *ad-hoc* on-line survey targeting the exposure to COVID-19, anxious symptoms during COVID-19 emergency, as well as migraine symptoms intensity and frequency before and during the lockdown (**Table 1**). Participation was anonymous and voluntary. Consent of parents was obtained according to local procedures.

Sociodemographic (sex, age, and ethnicity) and clinical variables (i.e., patient status, presence of aura) were obtained from medical charts. Separate χ^2 tests were used to test changes in migraine symptoms intensity and frequency from before COVID-19 to the lockdown period. A second set of χ^2 tests was used to test the association of anxious symptomatology with both intensity and frequency of migraine symptoms progression during the lockdown. Statistic tests were considered significant if $p < 0.05$. All p-values were 2-tailed.

RESULTS

The mean age of participants (78 females, 54.9%) was 15.04 years (range [5, 21], $SD = 3.23$). The great majority were

TABLE 1 | Survey structure and items description.

Item N	Item text	Response option
1	I live in a COVID-19 outbreak area	0, no; 1, yes
2	At least one family member was positive to COVID-19	0, no; 1, yes
3	At least one family member has to travel to COVID-19 areas for job duties	0, no; 1, yes
4	School activities were continuing in remote	0, no; 1, yes
5	Sport/leisure activities were suspended	0, no; 1, yes
6	My child anxious symptoms changed during the lockdown	0, worsening; 1, stable; 2, improving
7	The intensity of migraine symptoms was changing before the lockdown	0, worsening; 1, stable; 2, improving; 3, resolution
8	The intensity of migraine symptoms changed during the lockdown	0, worsening; 1, stable; 2, improving; 3, resolution
9	The frequency of migraine symptoms was changing before the lockdown	0, worsening; 1, stable; 2, improving; 3, resolution
10	The frequency of migraine symptoms changed during the lockdown	0, worsening; 1, stable; 2, improving; 3, resolution

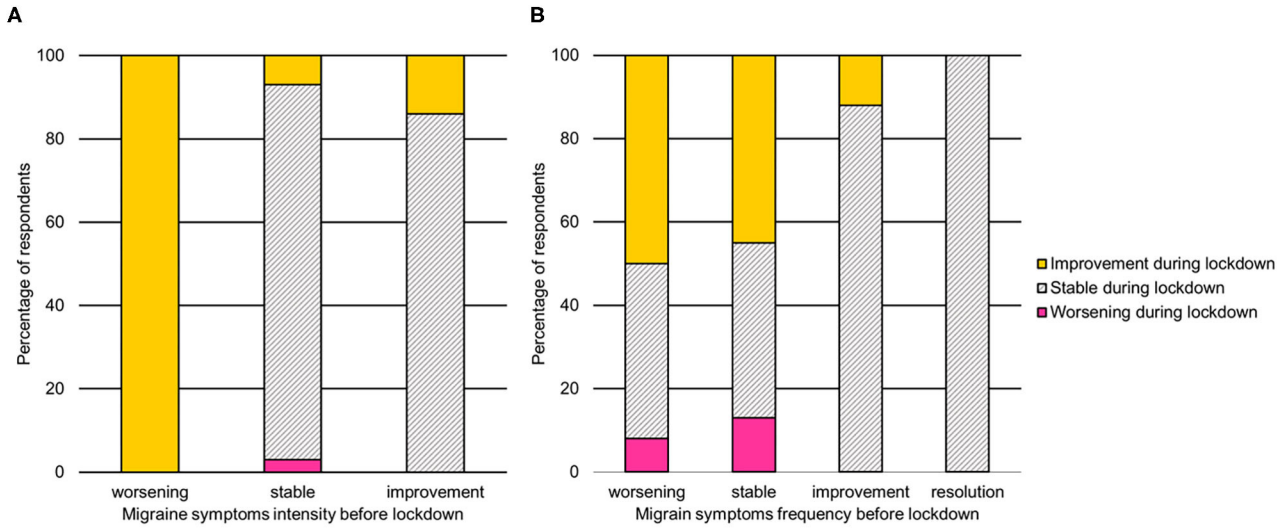


FIGURE 1 | Association between migraine symptoms intensity **(A)** and frequency **(B)** before and during the lockdown. Note. The symptoms severity before lockdown is reported on the x-axis, whereas the symptoms severity during the lockdown is reported using color gradients.

outpatients (n = 125, 88.0%), 52 (36.6%) had migraine with aura, whereas 90 (63.4%) had migraine without aura. Among patients with aura, 34 had visual aura (65.4%), three patients had brainstem aura (5.8%), one patient had sensory aura (1.9%) and one patient had aura with motor disturbances (1.9%). Moreover, 13 patients (25.0%) reported mixed aura including different patterns of visual, sensory, motor, language, and brainstem disturbances. Fifty-two patients (36.6%) were living in the first Italian geographical hotspot of COVID-19 spread. Twelve patients (8.5%) had at least one relative who was positive to the virus. Sixty patients (42.3%) had at least one parent who needed to travel to a COVID-19 area for job duties. School activities were continuing in remote for 130 patients (91.6%) and sport/leisure activities were suspended for 125 patients (88.0%) at the time of the survey.

The association between symptoms intensity and frequency before and during the lockdown is reported in **Figures 1A,B**. Migraine symptoms intensity worsened in four patients (2.8%) and improved in 13 cases (9.2%) during the lockdown. All the patients reporting worsening symptoms progression before COVID-19, had reduced intensity during the lockdown (χ^2 = 31.05, $p < 0.0001$). Frequency of migraine symptoms worsened in nine patients (6.3%) and improved in 40 cases (28.2%). Symptoms frequency reduction was observed in 50% of patients presenting worsening symptoms before the lockdown, 45% of those who were stable, and 12% of those who were already improving. All patients who had resolved symptoms before COVID-19 were stable during the lockdown (χ^2 = 38.66, $p < 0.0001$).

During the lockdown, anxiety symptoms worsened in 37 patients (26.1%), were stable in 104 patients (73.2%), and improved only in one patient. Anxious symptomatology was significantly associated with greater migraine symptoms frequency (χ^2 = 19.69, $p < 0.001$), but not intensity (χ^2 = 1.24, p = 0.54). Repeating the analysis separately for individuals with and without aura did not affect the findings and significant associations were confirmed for both the patients' subgroups.

DISCUSSION

This study highlighted a significant reduction of the intensity and frequency of migraine symptoms in the present cohort of children and adolescents during the COVID-19 lockdown phase in northern Italy. The improvement in both intensity and frequency of the migraine symptoms was especially significant in patients who were stable or worsening before the lockdown. Additionally, patients who were already improving before the healthcare emergency, reported a stable clinical picture of migraine symptoms severity in terms of intensity and frequency during the lockdown.

This finding is only apparently counterintuitive. For children and adolescents with recurring and worsening presentations of migraine, without any other comorbidity, the lockdown coincided with a dramatic reduction of potential stress-factors that may act as triggers for symptoms intensity and frequency. We hypothesized that the suspension of school and sport activities, the limitation of physical contacts with peers and the overall reduction of environmental requests may had potentially resulted in a fail-safe effect on the daily psychological stress usually lived by these patients before the lockdown. Psychological stressors are widely acknowledged as potential triggers involved in recurring episodes of pediatric migraine (10, 11). As such, the COVID-19 lockdown may have produced unexpected, yet relevant relief from migraine symptoms for these patients. Previous research suggested that stressful psychological experiences in school and/or family may widely affect pediatric migraine symptoms (12). From this point of view, this finding further suggests that pediatric migraine may have a relevant – yet partial – psychosomatic nature (10), and dramatic situations such as a sudden change in daily habits can lead to unexpected improvements in the clinical picture.

Additionally, clinical worsening of migraine frequency was only observed in those patients reporting higher anxiety during the lockdown phase. The comorbidity of anxious symptomatology with migraine is well-documented in children and adolescents (21, 22). Additionally, previous research reported on the significant association between migraine frequency and mood disorders (23). Moreover, anxious symptomatology is one of the psychosocial and affective factors involved in pediatric migraine onset and chronicity (21, 24) and similar mechanisms have been theorized to be in place for both anxiety and chronic pain (25, 26). This finding is of critical importance for at least two major reasons. First, the worsening of symptoms in patients who also reacted to the lockdown phase with increasing anxiety is reminiscent of the central involvement of psychological distress in the recurrence of headache symptoms in these children and adolescents. As anxiety symptoms were rated by parents, a careful exploration of anxious symptoms progression in daily life should be always considered by healthcare providers and may be conducted in partnership with the patient and the family. Second, a relatively small – yet clinically compelling – percentage of patients (i.e., 37 out of 142; 26%) reported anxiety symptoms worsening during the lockdown phase. This means that approximately one out of four patients with pediatric migraine may have experienced a relevant reduction of their mental health and psychological well-being during the COVID-19 emergency. As such, young patients with migraine should be considered as a specific vulnerable population that needs specialized and multi-professional attention during and after the epidemic, or major stressing events.

LIMITATIONS

Although this study only included the enrollment of patients from a single hospital, it should be highlighted that the IRCCS Mondino Foundation receives patients and families from different regions of the Italian territory. Moreover, this survey only included parent-reported data and the indirect nature of this survey did not allow the collection of observational data on the quality of life experienced by patients and their parents during the lockdown. The lack of standardized and quantitative measures of pain intensity and/or frequency is another limitation to this study. Similarly, internalizing behaviors may affect pain perception in children (27) and were not assessed in this study. Finally, socio-demographic and socio-economic confounders have been previously associated with the incidence and severity of migraine (28, 29) and their role in affecting patients' symptoms cannot be completely ruled out in the present survey.

CONCLUSIONS

Taken together, these findings suggest that the COVID-19 lockdown phase may had resulted in an unexpected relieving improvement of migraine symptoms' frequency and intensity in pediatric patients. It is well-known that daily sources of psychological stress may act as triggers of migraine symptoms in children and adolescents (30). One can speculate that this unexpected improvements in migraine symptoms could be – at least partially – related to a reduction in external or internal demands for high performance in daily social settings, such as school and sport or leisure activities (10). On a theoretical level, these findings further confirms the role played by psychosocial factors in the onset, progression and stabilization of migraine symptoms in children and adolescents (10). Moreover, as psychological stress inherent to academic and social life can be a prominent factor linked with migraine symptoms severity, this study also underlines the need of promoting interventions aimed at improving stress resilience and coping in pediatric patients' with migraine (31). For example, focusing on psychological and environmental aspects of child and adolescents' migraine in a multidisciplinary, continuous and integrated healthcare approach is warranted to improve patients' outcomes and quality of life (32, 33).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

ETHICS STATEMENT

The study was reviewed and approved by Ethics Committee Pavia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

RB: has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EP and GD: concept and design. AC, GD, EP, and FT: acquisition of data. LP: data analysis and drafting of the manuscript. RB: supervision. All authors interpretation of data and critical revision of the manuscript for important intellectual content.

FUNDING

This study was supported by funds to RB from Italian Ministry of Health (Ricerca Corrente 2020).

ACKNOWLEDGMENTS

The authors are thankful to patients and their caregivers who took part in this study.

REFERENCES

1. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet.* (2020) 395:1225–8. doi: 10.1016/S0140-6736(20)30627-9
2. Tull MT, Edmonds KA, Scamaldo KM, Richmond JR, Rose JP, Gratz KL. Psychological outcomes associated with stay-at-home orders and the perceived impact of COVID-19 on daily life. *Psychiatr Res.* (2020) 289:113098. doi: 10.1016/j.psychres.2020.113098
3. Guidetti V, Faedda N, Siniatchkin M. Migraine in childhood: biobehavioural or psychosomatic disorder? *J Headache Pain.* (2016) 17:82. doi: 10.1186/s10194-016-0675-0
4. Moon HJ, Seo JG, Park SP. Perceived stress in patients with migraine: a case-control study. *J Headache Pain.* (2017) 18:73. doi: 10.1186/s10194-017-0780-8
5. Genizi J, Khourieh Matar A, Zelnik N, Schertz M, Srugo I. Frequency of pediatric migraine with aura in a clinic-based sample. *Headache.* (2016) 56:113–7. doi: 10.1111/head.12741
6. Al-Twaijri WA, Shevell MI. Pediatric migraine equivalents: Occurrence and clinical features in practice. *Pediatr Neurol.* (2002) 26:365–8. doi: 10.1016/S0887-8994(01)00416-7
7. Tessitore A, Russo A, Giordano A, Conte F, Corbo D, De Stefano M, et al. Disrupted default mode network connectivity in migraine without aura. *J Headache Pain.* (2013) 14:89. doi: 10.1186/1129-2377-14-89
8. Chakravarty A, Mukherjee A, Roy D. Trigger factors in childhood migraine: a clinic-based study from Eastern India. *J Headache Pain.* (2009) 10:375–80. doi: 10.1007/s10194-009-0147-x
9. Millichap JG, Yee MM. The diet factor in pediatric and adolescent migraine. *Pediatr Neurol.* (2003) 28:9–15. doi: 10.1016/S0887-8994(02)00466-6
10. Balottin U, Chiappedi M, Rossi M, Termine C, Nappi G. Childhood and adolescent migraine: a neuropsychiatric disorder? *Med Hypotheses.* (2011) 76:778–81. doi: 10.1016/j.mehy.2011.02.016
11. Connelly M, Bickel J. An electronic daily diary process study of stress and health behavior triggers of primary headaches in children. *J Pediatr Psychol.* (2011) 36:852–62. doi: 10.1093/jpepsy/jsr017
12. Ashina S, Bendtsen L, Ashina M. Pathophysiology of tension-type headache. *Curr Pain Headache Rep.* (2005) 9:415–22. doi: 10.1007/s11916-005-0021-8
13. Hjern A, Alfven G, Östberg V. School stressors, psychological complaints and psychosomatic pain. *Acta Paediatr Int J Paediatr.* (2008) 97:112–7. doi: 10.1111/j.1651-2227.2007.00585.x
14. Hesketh T, Zhen Y, Lu L, Dong ZX, Jun YX, Xing ZW. Stress and psychosomatic symptoms in Chinese school children: cross-sectional survey. *Arch Dis Child.* (2010) 95:136–40. doi: 10.1136/adc.2009.171660
15. Martin PR. Behavioral management of migraine headache triggers: Learning to cope with triggers. *Curr Pain Headache Rep.* (2010) 14:221–7. doi: 10.1007/s11916-010-0112-z
16. Barello S, Palamenghi L, Graffigna G. Burnout and somatic symptoms among frontline healthcare professionals at the peak of the Italian COVID-19 pandemic. *Psychiatr Res.* (2020) 290:113129. doi: 10.1016/j.psychres.2020.113129
17. Zhong BL, Luo W, Li HM, Zhang QQ, Liu XG, Li WT, et al. Knowledge, attitudes, and practices towards COVID-19 among chinese residents during the rapid rise period of the COVID-19 outbreak: a quick online cross-sectional survey. *Int J Biol Sci.* (2020) 16:1745–52. doi: 10.7150/ijbs.45221
18. Moccia L, Janiri D, Pepe M, Dattoli L, Molinaro M, De Martin V, et al. Affective temperament, attachment style, and the psychological impact of the COVID-19 outbreak: an early report on the Italian general population. *Brain Behav Immun.* (2020) 87:75–9. doi: 10.1016/j.bbi.2020.04.048
19. Barari S, Caria S, Davola A, Ivchenko A, Jachimowicz J, King G, et al. Evaluating COVID-19 public health messaging in italy : self-reported compliance and growing mental health concerns. *medRxiv. [Preprint].* (2020) 1–19. doi: 10.1101/2020.03.27.20042820
20. Parodi IC, Poeta MG, Assini A, Schirinzi E, Del Sette P. Impact of quarantine due to COVID infection on migraine: a survey in Genova, Italy. *Neurol Sci.* (2020) 1:1–13. doi: 10.1007/s10072-020-04543-x
21. Smith MS, Martin-Herz SP, Womack WM, Marsigan JL. Comparative study of anxiety, depression, somatization, functional disability, and illness attribution in adolescents with chronic fatigue or migraine. *Pediatrics.* (2003) 111:e376–81. doi: 10.1542/peds.111.4.e376
22. Pesa J, Lage MJ. The medical costs of migraine and comorbid anxiety and depression. *Headache.* (2004) 44:562–70. doi: 10.1111/j.1526-4610.2004.446004.x
23. Baldacci F, Lucchesi C, Cafalli M, Poletti M, Ulivi M, Vedovello M, et al. Migraine features in migraineurs with and without anxiety-depression symptoms: A hospital-based study. *Clin Neurol Neurosurg.* (2015) 132:74–8. doi: 10.1016/j.clineuro.2015.02.017
24. Martin SE, Smith MS. Psychosocial factors in recurrent pediatric headache. *Pediatr Ann.* (1995) 24:464–74. doi: 10.3928/0090-4481-19950901-07
25. Katz J, Pagé MG, Fashler S, Rosenbloom BN, Asmundson GJG. Chronic pain and the anxiety disorders: Epidemiology, mechanisms and models of comorbidity, and treatment. In: Marchand S, Saravane D, Gaumond I, editors. *Mental Health and Pain: Somatic and Psychiatric Components of Pain in Mental Health* (Paris: Springer-Verlag). p. 119–155. doi: 10.1007/978-2-8178-0414-9_8
26. Fielding J, Young S, Martin PR, Waters AM. Headache symptoms consistent with migraine and tension-type headaches in children with anxiety disorders. *J Anxiety Disord.* (2016) 40:67–74. doi: 10.1016/j.janxdis.2016.04.006
27. Vinall J, Miller SP, Synnes AR, Grunau RE. Parent behaviors moderate the relationship between neonatal pain and internalizing behaviors at 18 months corrected age in children born very prematurely. *Pain.* (2013) 154:1831–9. doi: 10.1016/j.pain.2013.05.050
28. Hagen K, Vatten L, Stovner LJ, Zwart J-A, Krokstad S, Bovim G. Low socio-economic status is associated with increased risk of frequent headache: a prospective study of 22718 adults in Norway. *Cephalalgia.* (2002) 22:672–9. doi: 10.1046/j.1468-2982.2002.00413.x
29. Molarius A, Tegelberg Å, Öhrvik J. Socio-economic factors, lifestyle, and headache disorders - a population-based study in Sweden. *Headache J Head Face Pain.* (2008) 48:1426–37. doi: 10.1111/j.1526-4610.2008.01178.x

30. Neut D, Fily A, Cuvellier JC, Vallée L. The prevalence of triggers in paediatric migraine: A questionnaire study in 102 children and adolescents. *J Headache Pain.* (2012) 13:61–5. doi: 10.1007/s10194-011-0397-2
31. Faedda N, Natalucci G, Baglioni V, Giannotti F, Cerutti R, Guidetti V. Behavioral therapies in headache: focus on mindfulness and cognitive behavioral therapy in children and adolescents. *Expert Rev Neurother.* (2019) 19:1219–28. doi: 10.1080/14737175.2019.1654859
32. Ng QX, Venkatanarayanan N, Kumar L. A systematic review and meta-analysis of the efficacy of cognitive behavioral therapy for the management of pediatric migraine. *Headache.* (2017) 57:349–62. doi: 10.1111/head.13016
33. Sieberg CB, Huguet A, von Baeyer CL, Seshia S. Psychological interventions for headache in children and adolescents. *Can J Neurol Sci.* (2012) 39:26–34. doi: 10.1017/S0317167100012646

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 09 October 2020
doi: 10.3389/fneur.2020.581394

Stroke Care Within the COVID-19 Pandemic—Increasing Awareness of Transient and Mild Stroke Symptoms Needed

*Timo Uphaus, Sonja Gröschel, Eyad Hayani, Marianne Hahn, Falk Steffen and Klaus Gröschel**

Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

OPEN ACCESS

Edited by:
Tomohisa Nezu, Hiroshima University, Japan

Reviewed by:
Jaime Masjuan, Ramón y Cajal University Hospital, Spain
Carmen Serna-Candel, Klinikum Stuttgart, Germany

***Correspondence:**
Klaus Gröschel
klaus.groeschel@unimedizin-mainz.de

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *08 July 2020*
Accepted: *08 September 2020*
Published: *09 October 2020*

Citation:
Uphaus T, Gröschel S, Hayani E, Hahn M, Steffen F and Gröschel K (2020) Stroke Care Within the COVID-19 Pandemic—Increasing Awareness of Transient and Mild Stroke Symptoms Needed. Front. Neurol. 11:581394. doi: 10.3389/fneur.2020.581394

Background: The COVID-19 pandemic might affect health care resources and alter patient admission to hospital in case of stroke or transient ischemic attack (TIA). We aim to determine whether the COVID-19 pandemic is affecting utilization of recanalization procedures and numbers of patients with stroke and TIA admitted to a primary care stroke center.

Methods: In this retrospective observational study, we compared patients admitted from January 2019 until February 2020 with patients admitted during the COVID-19 pandemic (March/April 2020) in Germany. We included patients with stroke (hemorrhagic or ischemic) or TIA as classified by International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10).

Results: The number of patients per month with ischemic stroke or TIA was found to have significantly decreased from January 2019 until February 2020 compared to the COVID-19 pandemic (March/April 2020) (ischemic stroke 69.1 ± 4.5 vs. 55 ± 5.7, $p < 0.001$, TIA 22.1 ± 4.1 vs. 14.5 ± 6.4, $p < 0.034$). Contrarily, percentages and numbers of recanalization procedures per month were not influenced by the COVID-19 pandemic (intravenous thrombolysis [iv-tPA] 9.4 ± 3.7 vs. 10.5 ± 0.5, $p = 0.697$, mechanical thrombectomy [MT] 13.1 ± 3.1 vs. 14.5 ± 3.5, $p = 0.580$, iv-TPA or MT 19.4 ± 4.1 vs. 19.0 ± 0.0, $p = 0.889$).

Conclusions: During the COVID-19 pandemic, resources of the healthcare system in a primary care university hospital in Germany still allowed for unchanged numbers of recanalization procedures due to ischemic stroke. However, the numbers of patients admitted to the hospital specifically due to ischemic stroke or TIA decreased, suggesting that the awareness for non-disabling stroke symptoms has to be increased.

Keywords: cerebral ischemia, cerebral infarct, transient ischemic attack, COVID-19, mechanical thrombectomy

INTRODUCTION

On March 11, 2020, the Corona Virus Disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (1). Due to the predominantly pulmonary manifestation of COVID-19, it requires long and resource-consuming intensive care treatment (2) and resulted in a shortage of healthcare system capacities in southwest Europe (3). Therefore, by mid-March 2020, when COVID-19 cases exponentially increased in Germany, people were told to stay at home and avoid close contact with individuals outside their inner family in order to flatten the infection curve and thereby avoid similar shortages of intensive care capacities as in neighboring countries. Moreover, the organizational structure of hospitals changed in order to be prepared for an increased admission of COVID-19 patients by reducing non-emergency ambulatory patients and elective hospital admissions. These circumstances led to the question of what happens with other severe disease such as stroke, especially considering reports from Italian colleagues depicting almost a disappearance of patients with ischemic strokes within their hospitals (3) and similar reports from North America (4, 5) and Brazil (6). We aim to elucidate whether the COVID-19 pandemic affected either the admission of patients to our primary care stroke center or the rates of stroke recanalization therapies.

MATERIALS AND METHODS

Study Design and Participants

For the current analysis, we used data from patients admitted between January 2019 and April 2020 to our primary care university hospital in Mainz, Germany. Patients were selected by principal diagnosis of ischemic/hemorrhagic stroke or transient ischemic attack (TIA), as classified by the International Statistical Classification of Disease and related health problems−10th revision (ICD-10) used for financial reimbursement from the healthcare providers. Additionally, the acute stroke treatment was classified into no recanalization therapy vs. recanalization therapy (intravenous thrombolysis [iv-tPA] or mechanical thrombectomy [MT]) using procedural codes. We then divided the patient cohort into patients admitted from January 2019 until February 2020 and those admitted in March/April 2020. We performed an additional hand-search of all patients admitted to the stroke unit within March/April 2020 to identify patients who were not yet ICD-diagnosis/procedural coded. In line with regional legislation of the Ethics Committee of the Landesärztekammer Rheinland-Pfalz (Landeskrankenhausgesetz § 36 und § 37) due to the retrospective nature of the current analysis no ethical approval or informed consent to participate was deemed necessary.

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TIA, Transient ischemic attack; ICD-10, International Statistical Classification of Diseases and Related Health Problems tenths version; iv-tPA, intravenous thrombolysis; MT, mechanical thrombectomy; IQR, interquartile range; SD, standard deviation.

Statistical Analysis

Data is presented as median (Interquartile Range [IQR]), mean (±standard deviation [SD]), or numbers with percentages, if not indicated otherwise. For univariate analysis Student's *t*-test, Mann-Whitney *U*-test, and Chi-square tests were used. Number of strokes, TIA, and recanalization procedures per months between January 2019 and February 2020 were compared to number of strokes in March/April 2020 by unpaired *t*-test. A significant difference was considered for $p < 0.05$. Statistical analysis was performed using SPSS (version 23, IBM, Armonk, NY, USA).

RESULTS

In total, 1,490 stroke/TIA patients (mean age 72.6 ± 13.3 years, 46.4% female) were admitted to our primary care hospital during the study period, yielding 93.1 ± 10.0 patients per month (see **Figure 1**). In March/April 2020, there was a decrease in patients admitted due to ischemic/hemorrhagic stroke or TIA (74 ± 12.7) as compared to the preceding 14 months with an average of 95.9 ± 6.3 patients per month ($p < 0.001$) (see **Figure 1**). Patient characteristics such as age (72.9 ± 12.5 vs. 72.6 ± 13.4; $p = 0.777$), female sex (53.4 vs. 45.7%; $p = 0.075$), and days of hospitalization (7.8 ± 6.8 vs. 8.2 ± 7.1; $p = 0.583$) were equally distributed between the two observation periods. In order to get an impression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) situation in the location of the center examined within this report, we compared the incidence of confirmed SARS-CoV-2 cases in Mainz with other urban areas and Germany as a whole. To calculate the incidence we accessed the number of inhabitants in a central registry (7) and the confirmed SARS-CoV-2 cases at the Robert-Koch-Institut (8) on August 18. With regard to the incidence of SARS-CoV-2 cases, Mainz (325 cases/100,000 inhabitants) is in the range of other urban areas, e.g., Wiesbaden (249 cases/100,000 inhabitants) and Hamburg (322 cases/100,000 inhabitants) and Germany-wide (272 cases/100,000 inhabitants). However, there are parts of Germany that are more severely affected by SARS-CoV-2, e.g., Munich with 530 cases/100,000 inhabitants (see **Figure 2**).

The percentage of patients with ischemic strokes numerically increased ($n = 148$, 74.3% in March/April 2020 vs. $n = 960$, 71.5% between January 2019–February 2020, $p = 0.474$) whereas the distribution of patients with transient symptoms (TIA) decreased ($n = 29$, 19.6% March/April 2020 vs. $n = 306$, 22.8% from January 2019–February 2020, $p = 0.375$). No relevant percentage alteration of patients with hemorrhagic stroke was observed ($n = 9$, 6.1% March/April 2020 vs. $n = 76$, 5.7% January 2019–February 2020, $p = 0.726$). The numbers of patients per month with ischemic stroke (55 ± 5.7 in March/April 2020 vs. 69.1 ± 4.5 for January 2019–February 2020, $p < 0.001$), and TIA (14.5 ± 6.4 in March/April 2020 vs. 22.1 ± 4.1 for January 2019–February 2020, $p = 0.034$) significantly decreased (see **Table 1**, **Figure 3**), whereas the number of hemorrhagic stroke patients per month remained unchanged (4.5 ± 0.7 in March/April 2020 vs. 5.5 ± 2.1 for January 2019–February 2020, $p = 0.556$). With regard to hemorrhagic stroke subtypes, we were not able to find a difference

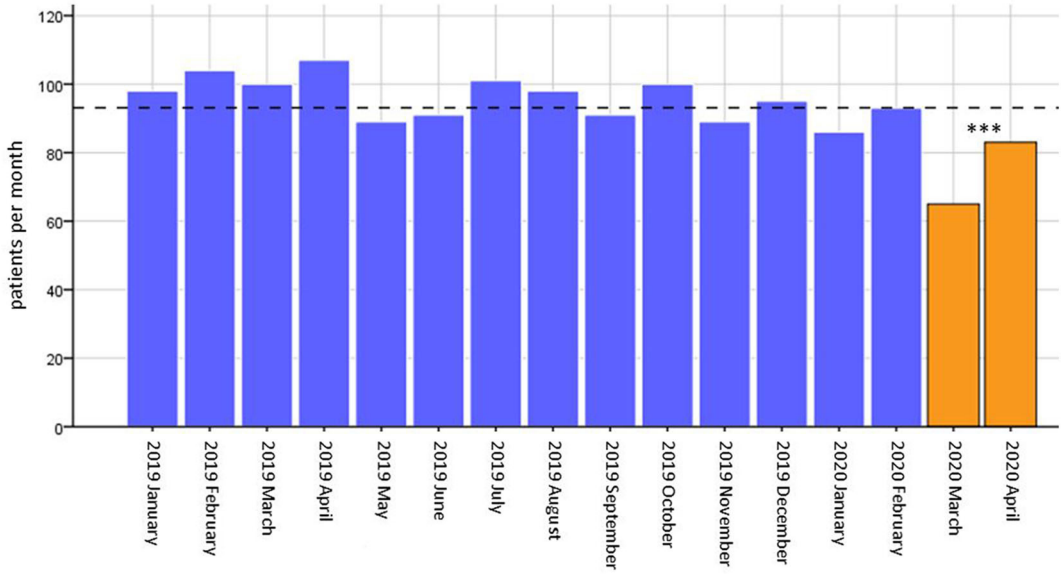


FIGURE 1 | Number of patients admitted per month. Absolute numbers of patients admitted per month plotted as bars. The mean of patients admitted per month is displayed as a dashed line (93.1 ± 10.0 patients per months). *** = $p < 0.001$ for difference between patients per month from January 2019 until February 2020 compared to March/April 2020.

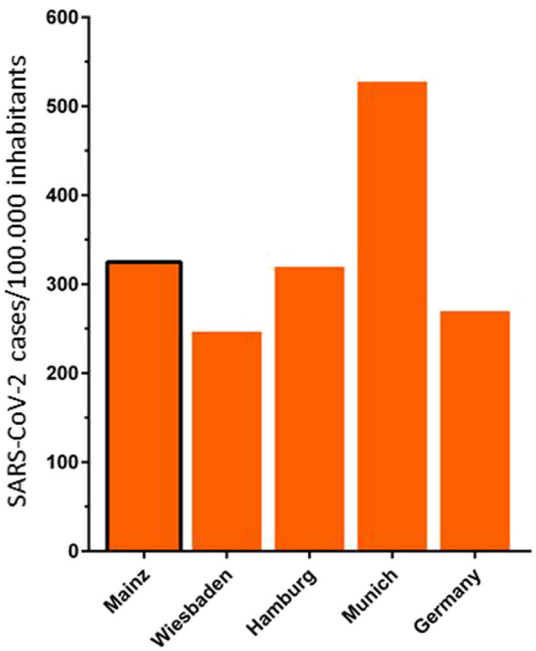


FIGURE 2 | Incidence of confirmed SARS-CoV-2 cases in Mainz, compared to other urban areas and Germany. Mainz 272 SARS-CoV-2 cases/100.000 inhabitants, Wiesbaden 249 SARS-CoV-2 cases/100,000 inhabitants, Hamburg 322 SARS-CoV-2 cases/100,000 inhabitants, Munich 530 SARS-CoV-2 cases/100,000 inhabitants, Germany 272 SARS-CoV-2 cases/100,000 inhabitants (7, 8).

TABLE 1 | Patient characteristics from January 2019 until February 2020 and in March/April 2020 during the COVID-19 pandemic.

	01.2019–02.2020	03.2020–04.2020	*p*-value
N	1,342	148	
N, per month [Mean ± SD]	95.9 ± 6.3	74 ± 12.7	<0.001
Age [Mean ± SD]	72.6 ± 13.4	72.9 ± 12.5	0.777
Female [*n*, %]	613, 45,7%	79, 53,4%	0.075
Hospitalization [*d*]	8.2 ± 7.1	7.8 ± 6.8	0.583
Diagnosis			
Stroke, ischemic [*n*, %]	960,71.5%	110,74.3%	0.474
N, per month [Mean ± SD]	69.1 ± 4.5	55 ± 5.7	0.001
Stroke, hemorrhagic [*n*, %]	76,5.7%	9,6.1%	0.726
N, per month [Mean ± SD]	5.5 ± 2.1	4.5 ± 0.7	0.556
ICH [*n*, %]	65, 4.8%	7,4.7%	0.951
SAH [*n*, %]	19, 1.4%	4, 2.7%	0.277
TIA [*n*, %]	306,22.8%	29,19.6%	0.375
N, per month [Mean ± SD]	22.1 ± 4.1	14.5 ± 6.4	0.034
Treatment with t-PA [*n*, %]	132;9,5%	21,14.2%	0.098
N, per month [Mean ± SD]	9.4 ± 3.7	10.5 ± 0.5	0.697
Thrombectomy [*n*, %]	184,13.7%	29;19.6%	0.052
N, per month [Mean ± SD]	13.1 ± 3.1	14.5 ± 3.5	0.580
t-PA or thrombectomy [*n*, %]	272,20.3%	38,25.7%	0.124
N, per month [Mean ± SD]	19.4 ± 4.1	19.0 ± 0.0	0.889

SD, Standard deviation; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage, TIA, transient ischemic attack; t-PA, tissue plasminogen activator.

in percentages of intracerebral hemorrhage (ICH, $n = 65$, 4.8% vs. $n = 7$, 4.7%, $p = 0.951$) and subarachnoid hemorrhage (SAH, $n = 19$, 1.4% vs. 4, 2.7%, $p = 0.277$) in the non-pandemic compared to the pandemic period. Due to possible seasonal variations in the incidence of cerebral hemorrhages, we also compared percentages and number of patients per month with

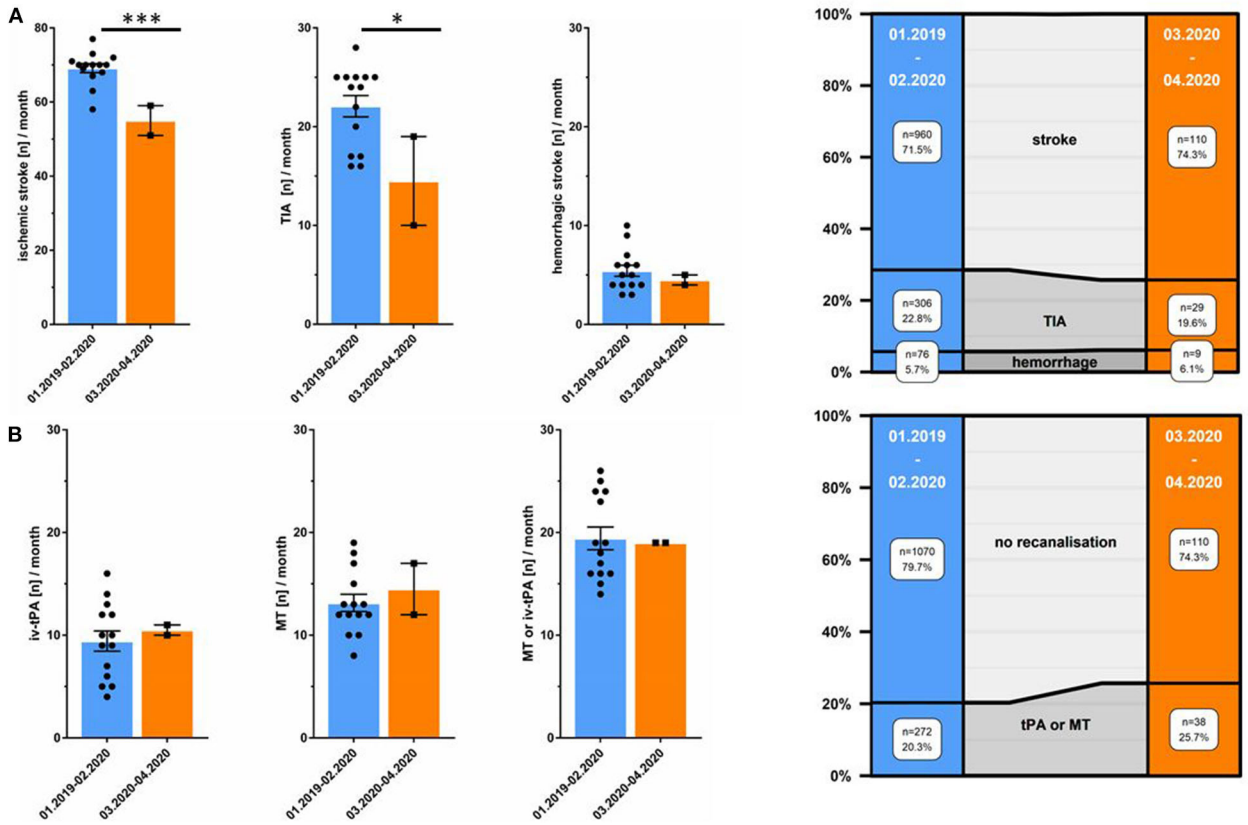


FIGURE 3 | Decreased total number of ischemic stroke, hemorrhagic stroke, and TIA whereas recanalization therapies are unchanged. **(A)** Total number of patients/month in March/April 2020 (orange) and from January 2019 until February 2020 (blue). On the right: distribution of ischemic stroke, TIA, and hemorrhagic stroke between January 2019 until February 2020 as opposed to March/April 2020 during the COVID-19 pandemic. **(B)** Total number of patients/month undergoing recanalization procedure in March/April 2020 (orange) and between January 2019 until February 2020 (blue). On the right: distribution of recanalization therapies (intravenous thrombolysis [tPA] and mechanical thrombectomy [MT]) as opposed to no recanalization therapy from January 2019 until February 2020 and in March/April 2020. *** $= p < 0.001$,* $= p < 0.05$.

hemorrhagic strokes and its subtypes between March/April 2019 and March/April 2020 and observed no differences. Neither the number of patients with hemorrhagic strokes per month ($n = 13$, 6.2% vs. $n = 9$, 6.1%, $p = 0.939$), nor incidence of ICH ($n = 12$, 5.7%, vs. $n = 7$, 4.7%, $p = 0.660$) and SAH ($n = 4$, 1.9% vs. $n = 4$, 2.7%, $p = 0.724$) were different between March/April 2019 and March/April 2020 (see **Table 2**).

With regard to recanalization therapy, we observed a trend toward a relative increase in rates of administration of iv-tPA ($n = 21$, 14.2% in March/April 2020 vs. $n = 132$, 9.5% from January 2019–February 2020, $p = 0.098$), and application of MT ($n = 29$, 19.6% March/April 2020 vs. $n = 184$, 13.7% January 2019–February 2020, $p = 0.052$). Similarly, a composite variable showed an increase in rates of iv-tPA and/or MT utilization ($n = 38$, 25.7% March/April 2020 vs. $n = 272$, 20.3% January 2019–February 2020, $p = 0.124$). Concerning the number of procedures per month, we observed no change in March/April 2020 as compared to the previous months (see **Table 1**, **Figure 3**). SARS-CoV-2 test was not mandatory; however, none of the patients included within this analysis was reported SARS-CoV-2 positive.

DISCUSSION

The initial weeks of the COVID-19 pandemic did not affect absolute numbers of acute stroke recanalization procedures (tPA or MT), but were found to have resulted in a decrease of the overall number of patients presenting with non-severe ischemic stroke or TIA in a primary care university hospital in Germany.

We observed a decrease by nearly one quarter in the number of patients admitted to our primary stroke center with stroke or TIA from a mean-rate of 95.9 (±6.3) per month between January 2019 and February 2020 to 74 (±12.7) in March/April 2020. Our observation is in line with numerous reports of decreased stroke rates during the pandemic from North America (4, 9, 10), Canada (5), and Brazil (6). In addition, a decrease in the usage of the RAPID-software, a tool used to assess infarct volume in case of acute stroke symptoms, was observed by mid-March 2020 (11) and telestroke services were less frequently used (9). Similar observations of reduced hospital admissions and patient presentations at emergency departments are reported in other diseases such as myocardial infarction (12, 13).

TABLE 2 | Patient characteristics in non-pandemic March/April 2019 compared to March/April 2020 during the COVID-19 pandemic.

	03/04.2019	03/04.2020	*p*-value
N, stroke total	207	148	
Stroke, hemorrhagic [*n*, %]	13, 6.2%	9, 6.1%	0.939
N, per month [Mean ± SD]	6.5 ± 3.5	4.5 ± 0.7	0.515
ICH [*n*, %]	12, 5.7%	7,4.7%	0.660
SAH [*n*, %]	4, 1.9%	4, 2.7%	0.724

ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

One reason for this observation might be that in March 2020 rising measures of personal and community restrictions were advised by the German government, encompassing closures of schools and numerous public places as well as prohibiting the gathering of people. Even more so, the population was advised to stay at home and avoid close contact with other individuals outside the primary family to limit the exponential spreading of COVID-19 infections. Thus, the reduced number of patients presenting with ischemic stroke and TIA observed within this analysis might be attributable to fewer people visiting the emergency department due to a fear of COVID-19 infection. This is underlined by the fact that a decrease in the percentages and absolute numbers of patients was especially detected in those presenting with transient symptoms, whereas the absolute number of recanalization therapies remained unchanged. Another explanation for decreased stroke rates might be an underestimation of stroke-related symptoms in patients with fever and respiratory symptoms. By an attempt of prioritization, neurological deficits, especially minor stroke or TIA-related symptoms, are prone to be overlooked. However, this is unlikely for disabling stroke symptoms such as aphasia and severe hemiparesis. This is in line with our observations showing that overall rates and numbers per month of recanalization procedures (iv-tPA and MT), representing patients with acute severe stroke symptoms, were unchanged in March/April 2020 compared to the previous months, and we even observed a trend toward a relative increase in percentages of recanalization procedures. Thus, we hypothesize that the absolute number of strokes is not falling during the COVID-pandemic, but patients are rather afraid of seeking hospitals and instead stay home in case of mild or transient stroke symptoms. Our hypothesis is strengthened by the fact that we observed unchanged rates of hemorrhagic stroke during the pandemic, which are usually accompanied by a more severe disability compared to ischemic strokes. This is further underlined by a retrospective analysis from Brazil also demonstrating unchanged rates of hemorrhagic stroke during the pandemic compared to pre-pandemic numbers and reporting an unchanged rate of severe strokes (6). In line with this, a multicenter analysis from Northern California reports decreased stroke rates in the early pandemic and even more severe strokes and large vessel occlusions (4).

These results underline the necessity of increasing the awareness of cerebrovascular events, in particular those with mild or transient symptoms, in order to allow for sufficient stroke unit work-up, thereby decreasing the already high rates of cerebral re-ischemia by detection of stroke etiology and consecutive prescription of secondary preventive medication (14).

The current study harbors the limitations of a retrospective, single-center experience. Moreover, a potential selection bias could exist, due to the fact that we solely included patients admitted to the neurology department stroke unit and thereby might potentially have overlooked cases, e.g., subarachnoid hemorrhages treated within the neurosurgery intensive care unit.

The overall unchanged rate of recanalization procedures in patients presenting with ischemic stroke reflects sufficient healthcare resources in a German primary stroke center during the COVID-19 pandemic. Due to a reduction in patients with minor and transient stroke symptoms, patients should be widely informed about typical stroke symptoms and encouraged not to stay at home even in exceptional situations such as a "lockdown" or a fear of in-hospital COVID-19 infection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TU contributed to conception and design of the study, interpretation of data, and drafted the manuscript. SG contributed to interpretation of data and substantively revised the manuscript. EH substantively revised the manuscript. FS contributed to interpretation of data, drafted the manuscript, and substantively revised it. KG contributed to conception and design of the study, interpretation of data, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Else Kröner-Fresenius Stiftung (2018_EKMS.21) to TU.

ACKNOWLEDGMENTS

We thanked Dr. Cheryl Ernest for proofread and edited the manuscript.

REFERENCES

1. Morfeld P, Erren CT. Deaths in nine regions of Italy in February/March 2020: "Mortality Excess Loupe" for SARS-CoV-2/COVID-19-Epidemiology in Germany. *Gesundheitswesen*. (2020) 82:400–6. doi: 10.1055/a-1160-5859
2. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet*. (2020) 395:1225–8. doi: 10.1016/S0140-6736(20)30627-9
3. Morelli N, Rota E, Terracciano C, Immovilli P, Spallazzi M, Colombi D, et al. The baffling case of ischemic stroke disappearance from the casualty department in the COVID-19 era. *Eur Neurol*. (2020) 83:213–5. doi: 10.1159/000507666
4. Nguyen-Huynh MN, Tang NX, Vinson RD, Flint CA, Alexander GJ, Meighan M, et al. Acute stroke presentation, care, and outcomes in community hospitals in Northern California during the COVID-19 pandemic. *Stroke*. (2020). doi: 10.1161/STROKEAHA.120.031099. [Epub ahead of print]
5. Bres Bullrich M, Fridman S, Mandzia LJ, Mai ML, Khaw A, Vargas Gonzalez JC, et al. COVID-19: stroke admissions, emergency department visits, and prevention clinic referrals. *Can J Neurol Sci*. (2020) 47:693–6. doi: 10.1017/cjn.2020.101
6. Diegoli H, Magalhaes CSP, Martins OCS, Moro CHC, Franca CHP, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke*. (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
7. Gemeindeverzeichnis. Available online at: https://www.statistikportal.de/de/produkte/gemeindeverzeichnis (accessed August 18, 2020).
8. RKI. *Neuartiges Coronavirus - Fallzahlen*. Available online at: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Fallzahlen.html (accessed August 18, 2020).
9. Huang FJ, Greenway FRM, Nasr MD, Chukwudelunzu EF, Sr., Demaerschalk MB, O'Carroll CB, et al. Telestroke in the time of COVID-19: the Mayo Clinic experience. *Mayo Clin Proc*. (2020) 95:1704–8. doi: 10.1016/j.mayocp.2020.06.007
10. Rosenbaum L. The untold toll - the pandemic's effects on patients without Covid-19. *New Engl J Med*. (2020) 382:2368–71. doi: 10.1056/NEJMms2009984
11. Kansagra PA, Goyal SM, Hamilton S, Albers WG. Collateral effect of Covid-19 on stroke evaluation in the United States. *New Engl J Med*. (2020) 383:400–1. doi: 10.1056/NEJMc2014816
12. De Filippo, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. *New Engl J Med*. (2020) 383:88–9. doi: 10.1056/NEJMc2009166
13. Solomon DM, McNulty JE, Rana SJ, Leong KT, Lee C, Sung HS, et al. The Covid-19 pandemic and the incidence of acute myocardial infarction. *New Engl J Med*. (2020) 383:691–3. doi: 10.1056/NEJMc2015630
14. Rothwell MP, Giles FM, Chandratheva A, Marquardt L, Geraghty O, Redgrave NJ, et al. Early use of Existing Preventive Strategies for Stroke, Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. (2007) 370:1432–42. doi: 10.1016/S0140-6736(07)61448-2

Conflict of Interest: TU reports personal fees from Merck Serono and Pfizer, outside the submitted work. KG reports personal fees and non-financial support from Bayer AG, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Bristol-Myers Squibb, personal fees and non-financial support from Daiichi Sankyo, personal fees and non-financial support from Pfizer, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 15 October 2020
doi: 10.3389/fneur.2020.566680

Revisiting the Immune Balance Theory: A Neurological Insight Into the Epidemic of COVID-19 and Its Alike

Junjiao Wu[1,2,3] *and Yu Tang*[1*]

[1] National Clinical Research Center for Geriatric Disorders, Department of Geriatrics, Xiangya Hospital, Central South University, Changsha, China, [2] Department of Rheumatology and Immunology, Xiangya Hospital, Central South University, Changsha, China, [3] Provincial Clinical Research Center for Rheumatic and Immunologic Diseases, Xiangya Hospital, Central South University, Changsha, China

As the pandemic of COVID-19 is raging around the world, the mysteriousness of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) coronavirus is being revealed by the concerted endeavors of scientists. Although fever and pneumonia are typical symptoms, COVID-19 patients exhibit multiple neurological complications. In this interim review, we will summarize the neurological manifestations and their potential causes in COVID-19. Similar to the other two fatal respiratory coronaviruses, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 also shows to be neuroinvasive that may spread from the periphery to brain, probably by the retrograde axonal transport. The invaded viruses may directly disrupt the complex neural circuits, and raise a chronic activation of immune responses. In another hand, multiple organ failure in severe COVID-19 is caused by the systemic acute immune responses, and unsurprisingly caused the brain inflammation and led to encephalitis. However, in the central nervous system (CNS), the activation of resident immune cells including microglia and astrocytes may lead to chronic immune imbalance, which underlies the potential long-term effects in synaptic changes and neuropsychiatric impairments. The neuroinvasive biology also provides a possible link with the Braak staging of neurodegenerative diseases such as Parkinson's disease (PD). Although with considerable advances, the neurotropic potential and chronic neurological effects caused by SARS-CoV-2 infections merit further investigations.

Keywords: COVID-19, SARS-CoV-2, neurological complications, neuroinvasion, cytokine storm, immune imbalance

OPEN ACCESS

Edited by:
Jesús Porta-Etessam, Hospital Clínico San Carlos, Spain

Reviewed by:
Pedro Jesus Serrano-Castro, Regional University Hospital of Malaga, Spain
Jeronimo Balsalobre Aznar, Hospiten Rambla, Spain

****Correspondence:***
Yu Tang
tangyu-sky@163.com;
tangyusky@csu.edu.cn

Specialty section:
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

Received: *28 May 2020*
Accepted: *09 September 2020*
Published: *15 October 2020*

Citation:
Wu J and Tang Y (2020) Revisiting the Immune Balance Theory: A Neurological Insight Into the Epidemic of COVID-19 and Its Alike. Front. Neurol. 11:566680. doi: 10.3389/fneur.2020.566680

INTRODUCTION

The ongoing spread of COVID-19 disease, is the first pandemic ever caused by coronaviruses in the human history, as announced by the World Health Organization (WHO) in March 2020. The ferocious virus, isolated as a new strain of zoonotic coronavirus named as severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has rapidly spread with over 23.2 million confirmed cases and 0.8 million deaths globally as of Aug 23 2020 (Johns Hopkins University). The pandemic has exhausted the entire worlds' personal protective equipment and medical ventilators, and is also strenuously hurting the global economy and raising considerable social issues. As we are in

the midst of this ongoing pandemic, it has gathered the concerted efforts of clinicians, public health experts, virologists, immunologists, and other scientists to understand the virus's biology and blocking agents. So far, a myriad of urgent endeavors has been maneuvered, aiming to reveal the multiple aspects of this wily virus, ranging from the genomic structures, sensing receptors to the development of specific medicines and vaccines.

Structurally, SARS-CoV-2 is a single-stranded RNA virus, whose genome contains 29,891 nucleotides in size and 12 putative functional open reading frames (ORFs) (1). Of those translated proteins, the spike proteins located on the virus surface mediate the virus entry into host cells (2, 3). Mechanistically, the spike of SARS-CoV-2 senses the angiotensin converting enzyme 2 (ACE2) receptor (2–5), the same as SARS-CoV, which normally helps regulate blood pressure and anti-atherosclerosis (6). This binding, in concert with host proteases, principally TMPRSS2, facilitates the virus getting through the cell membrane by endocytosis (4), followed by hijacking the host cell's translation machinery and producing massive virus copies and further invading new cells. As ACE2 is typically enriched in type II alveoli cells, the lung tissue becomes the major organ affected by the virus (7). The typical symptoms of COVID-19, unsurprisingly, are fever, cough, and pneumonia, which probably lead to acute respiratory distress syndrome (ARDS) and acute lung injury, as described in around 20% of COVID-19 patients (8).

Along with SARS-CoV broke out in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) since 2012, SARS-CoV-2 is the third coronavirus that can cause severe respiratory diseases. Genomic analysis shows that SARS-CoV-2 is in the same β-coronavirus clade as SARS-CoV and MERS-CoV, and shares a highly homologous sequence with SARS-CoV (9). Scientists thus have put great efforts in clarifying how it resembles and differs from SARS-CoV and MERS-CoV at multiple levels that may shed light on the COVID-19 therapeutics and drug repurposing. Specifically, the similarity goes to the systemic organ injury and cytokine storm in severe situations.

SYSTEMIC ORGAN INJURY

Although the symptoms in lungs are manifested at an early stage, they can be extended to multiple organs including the blood vessels, heart, gut, kidneys, testicles, and brain, which are well-known to express ACE2 and are potential targets of COVID-19 (10). Unlike the outbreak of SARS and MERS, the emerging single-cell RNA-sequencing (scRNA-seq) during recent years is rapidly advancing our ability to comprehensively map the cell types with ACE2/TMPRSS2 expression (11–15). It is shown that, besides pneumocytes, ACE2 receptors are present in various cell types including the nasal epithelial cells, oral mucosa epithelial cells, cholangiocytes, intestine enterocytes and, importantly, immune cells such as B cells, Natural killer T cells, monocytes, and macrophages (11, 13, 16–19). Notably, ACE2 is also expressing in the brain, in which eight cell types were identified including excitatory neurons, inhibitory neurons, oligodendrocyte progenitors, oligodendrocytes, microglia, astrocytes, pericytes, and endothelial cells (13). However, other studies showed contradictory results that glial cells may not express ACE2, but instead might express non-canonical docking receptors such as Basigin (BSG) or Neuropilin-1 (NRP1) to facilitate viral cell entry and replication (20, 21). Nevertheless, the present of ACE2 receptors in multiple organs underlies the systemic impairment by SARS-CoV-2 infection.

NEUROLOGICAL MANIFESTATIONS

Coronavirus infection has been associated with neurological manifestations such as stroke, seizure, convulsions, mental confusion, and encephalitis (22, 23). During the outbreak in 2003, SARS-CoV could induce neurological diseases such as polyneuropathy, encephalitis, and aortic ischemic stroke (24). The virus itself has been detected in the cerebrospinal fluid (CSF) samples, and even the brain of deceased patients (25, 26). In 2012, nearly 20% of patients with MERS-CoV infection developed neurological symptoms, including ischemic stroke, paralysis, unconsciousness, Guillain-Barre syndrome, and other infectious neuropathy (27). It is thus not surprising to see neurological manifestations in COVID-19 patients as well (28–30). In general, COVID-19 neurological manifestations could be classified into two categories: central nervous system (CNS) symptoms and peripheral nervous system (PNS) symptoms. CNS symptoms included headache, dizziness, acute cerebrovascular disease, ataxia, disturbance of consciousness, and epilepsy. However, PNS symptoms are less severe and manifested as neuralgia, hypoplasia, hyposmia, and hypogeusia. Notably, respiratory illness in COVID-19 patients may also result from the direct role of SARS-CoV-2 in respiratory control nuclei in the brain (31). Interestingly, still many patients who present with severe neurological complications have hardly any respiratory symptoms, suggesting a rather heterogenous neurological responds among individuals, and that neurological manifestations did not appear concomitantly with respiratory symptoms.

In a retrospective series of 214 COVID-19 patients at a hospital located in the epicenter of Wuhan, China, neurologic symptoms were recorded in 78 patients (36.4%) included headache and disturbed consciousness, and 6 patients had strokes (32). Half of the patients in Strasbourg, France by severe SARS-CoV-2 infection was associated with encephalopathy, prominent agitation and confusion, and some of them had single acute ischemic strokes after brain imaging (33). In Japan, a COVID-19 patient was brought in by the ambulance due to a convulsion accompanied by unconsciousness, which was diagnosed with aseptic meningitis/encephalitis (34). Notably for this case, the specific SARS-CoV-2 RNA was detected from the CSF sample. Similarly, a medical team at a hospital in Beijing, China confirmed the presence of SARS-CoV-2 in the CSF of a 56-year-old patient with COVID-19 by genome sequencing, thereby clinically verifying viral encephalitis (35). Notably, unlike encephalopathy, the acute stroke is most likely caused by endothelial injury due to a pro-inflammatory hypercoagulable state post SARS-CoV-2 infection (36, 37). Hence in China, the neurological symptoms have been added into the *Diagnosis and*

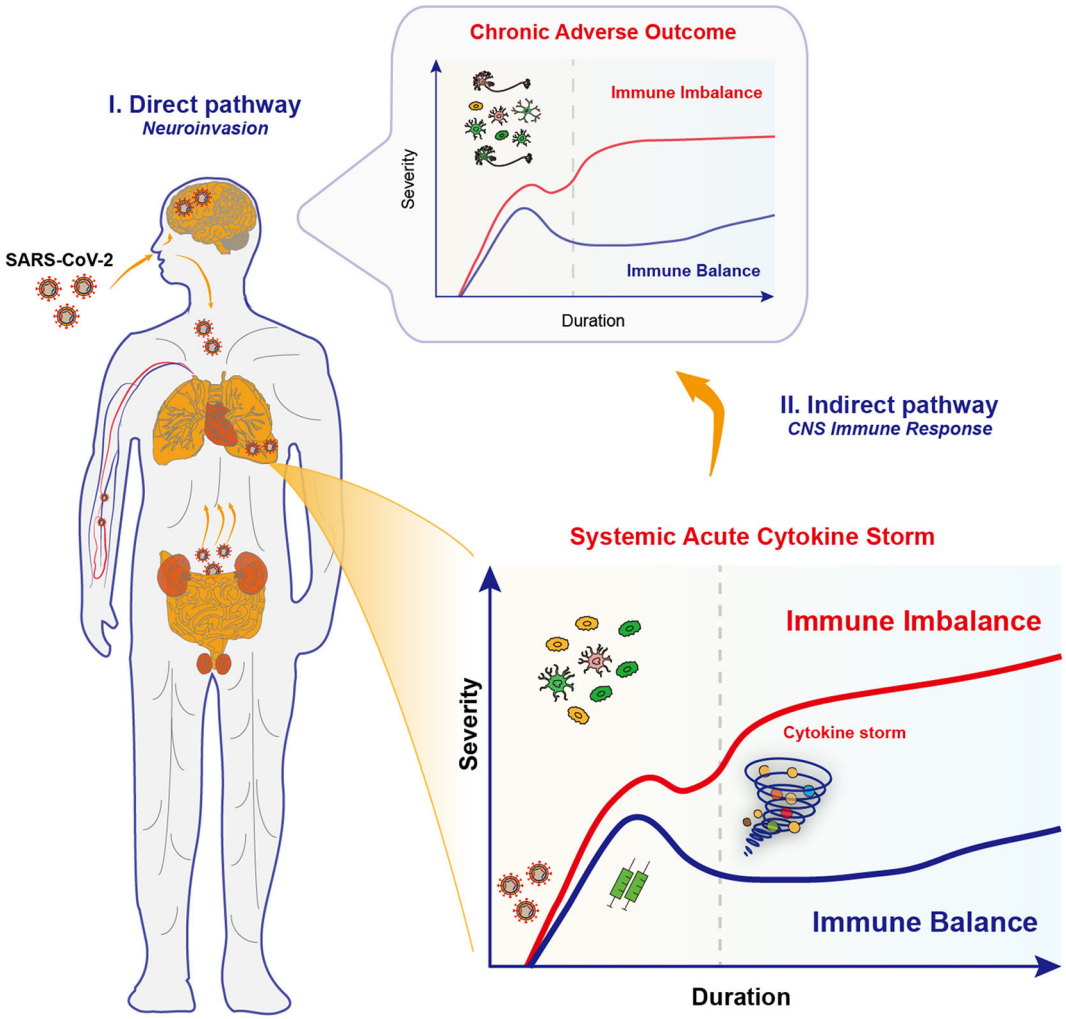


FIGURE 1 | Proposed neuroinvasion routes and immune responses in COVID-19. Upon infections by SARS-CoV-2 coronaviruses, COVID-19 patients exhibit multiple neurological complications, which might be due to the effects through the direct pathway and the indirect pathway. **(I)** The neuroinvasive properties of SARS-CoV-2 underlies the retrograde axonal transport in the direct pathway. Specifically, SARS-CoV-2 viruses may go upward through the olfactory nerve across the cribiform plate and to the brain, or alternatively, start from the gastrointestinal system to invade the enteric nervous system and finally the brain. Several other invasion routes for SARS-CoV-2 may include blood-borne diffusion through the blood-brain barrier, blood-cerebrospinal fluid barrier and meningeal cerebrospinal fluid barrier. Those invaded viruses may directly disrupt the complex neural circuits, and raise a chronic activation of immune responses. **(II)** Multiple organ failure in severe COVID-19 is caused by the systemic acute immune responses, the cytokine storm, and unsurprisingly caused the brain inflammation and led to encephalitis. However, the potential long-term effects in synaptic changes and neuropsychiatric impairments in key brain regions should not be neglected. This is probably caused by the activation of CNS immune cells that renders chronic immune imbalance.

Treatment Protocol for 2019 Novel Coronavirus Pneumonia (The 7th Trial Edition), released by National Health Commission & State Administration on March 3, 2020, which reminds us of taking nucleic or genomic tests with CSF samples and carefully handling with neurological complications to reduce the fatality of critical care patients.

Those neurological manifestations observed in COVID-19 patients are reminiscent of neuroinvasive potential of SARS-CoV-2 virus, like the other zoonotic coronaviruses SARS-CoV and MERS-CoV (31). An increasing number of patients with COVID-19 reported a sudden loss of smell (anosmia) or taste (dysgeusia) (38, 39) that may serve as initial manifestations and warning signs for possible subsequent CNS involvement. Given that ACE2 is highly expressed in nasal epithelial cells (11), people speculate that nose might be the first stop during the invasion of viruses, which then go upward through the olfactory nerve across the cribiform plate, and to the brain (29) (**Figure 1**). One recent study showed that, based on bulk and single-cell RNA sequencing, ACE2 expressed in supporting and stem cells in the human/mouse olfactory epithelium, as well as vascular pericytes in the mouse olfactory bulb, however, was not detected in olfactory sensory or bulb neurons (40). Furthermore, autopsy studies of COVID-19 patients found that olfactory epithelium showed prominent leukocytic infiltrates in the lamina propria

and focal atrophy of the mucosa, and olfactory nerve fibers in the lamina propria were lack of myelin, suggestive of axonal damage (41). However, the clear evidence is still lacking to confirm whether the olfactory neuropathy is due to direct viral infection or mediated by perturbing supporting non-neural cells.

The occurrence of diarrhea, as another COVID-19 symptom, suggests that the gastrointestinal system is a possible alternative pathway to invade the enteric nervous system and finally the brain (42) (**Figure 1**). Several invasion routes for coronaviruses have been postulated (28, 43), including retrograde axonal transport, blood-borne diffusion through the blood-brain barrier (BBB), blood-cerebrospinal fluid barrier, and meningeal cerebrospinal fluid barrier (44). Once in the brain, those viruses may directly destroy the complex organization of neural circuits through neuronal damage, and raise a chronic activation of the inflammatory responses.

CYTOKINE STORM

Apart from the direct infection of the brain, SARS-CoV-2 may cause neurological disorders indirectly by triggering an over-activated immune responses, characterized as cytokine storm. Cytokines are chemical signaling molecules that summon immune cells and mediate a balanced immune response, however, in the cytokine storm, levels of certain cytokines soared far beyond the required levels so that the recruited immune cells began to attack healthy tissues and caused catastrophic organ failures. Vital research suggests that for many patients who died from COVID-19, the fatal blow may be their own immune system rather than the virus itself.

The initiation of cytokine storm is a common complication caused by fatal respiratory coronaviruses, like SARS-CoV and MERS-CoV, and is the major cause of morbidity (45). Studies have shown that increased numbers of pro-inflammatory cytokines (such as IL-1β, IL-6, IL-12, IFN-γ, IP10, and MCP1) in the serum of severe SARS patients are associated with lung inflammation and extensive lung injury (46). Similarly in 2012, it was reported that MERS-CoV infection can induce substantially elevated concentrations of pro-inflammatory cytokines such as IL-6, IFN-γ, TNF-α, IL-15, and IL-17 (47, 48). Ongoing studies have also been revealing the features of cytokine storms in COVID-19 patients. For most severe patients with COVID-19, the levels of pro-inflammatory cytokines soared in the serum, similar to that in SARS and MERS, including IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1α, and TNF-α (8, 49–53). In addition, patients admitted to the intensive care unit (ICU) had higher G-CSF, IP10, MCP1, MIP1A, and TNF-α concentrations than patients not admitted to the ICU, suggesting that cytokine storm is associated with disease severity (8).

High levels of pro-inflammatory cytokines could cause shock and tissue damage, leading to respiratory failure, or multiple organ failure. They mediate extensive lung pathology, resulting in massive infiltration of neutrophils and macrophages, diffuse alveolar injury and the formation of clear membranes and diffuse thickening of the alveolar wall (54). Thus, it is urgently needed therapeutics based on suppressing cytokine storms. In the clinical practice, anti-inflammatory agents have been frequently used for the treatment of patients with severe illness by virus infections. For instance, corticosteroids were ever used in treating patients with SARS, which have actually saved many lives and families. However, long-term use of this powerful broad immunosuppressant can cause various complications such as increased cholesterol, brittle bones, cataracts, as well as depression that may greatly reduce the quality of life. More unfortunately, the latest evidence from SARS and MERS patients shows that receiving corticosteroids has no effect on mortality, but delays viral clearance (8, 55, 56). Therefore, according to the WHO's interim guidelines, corticosteroids should not be routinely given systemically.

It is noteworthy that, IL-6, one of the cytokines elevated in response to SARS-CoV-2 was the most reported in multiple clinical groups. For instance, in a series of 99 COVID-19 cases from hospitals in Wuhan and Shanghai, China, half of the patients show elevated IL-6 levels (57). Another group investigated the immune responses and cytokine release from patients in Chongqing, China. They found that IL-6 was higher in 76.19% of severe patients, whereas that was seen in only 30.39% of mild patients (58). It echoes that the elevated serum IL-6 correlates with pneumonia, ARDS, and adverse clinical outcomes (59–61). Elevated serum C-reactive protein, which is regulated by IL-6, also serves as a biomarker of severe coronavirus infection (62). Based on this fact, drugs such as Tocilizumab, Satralizumab, and Sarilumab, as IL-6 receptor (IL-6R)-targeted monoclonal antibodies (mAbs), might prove beneficial for the treatment of COVID-19 (63). Indeed, controlled clinical trials are underway around the world to test the treatment of IL-6 and IL-6R antagonists for COVID-19 patients with severe respiratory complications. Preliminary results from the study of 21 severe COVID-19 patients receiving Tocilizumab in Anhui province, China are encouraging (64). All patients have recovered from fever within the first day of Tocilizumab treatment (64). Other clinical trials are also underway in different countries. Although the efficacy of Tocilizumab in COVID-19 patients with ARDS requires further evaluation in a larger randomized controlled trial, this encouraging clinical trial suggests that neutralizing mAbs against other pro-inflammatory cytokines such as IL-1 and IL-17 might also be useful (54). For urgently treating the soaring number of severe patients, the *Chinese Diagnosis and Treatment Protocol for 2019 Novel Coronavirus Pneumonia* (The 7th Trial Edition) has updated a guideline for taking immunotherapy: for patients with extensive lung lesions and severe cases who also show an increased level of IL-6 in laboratory testing, Tocilizumab can be used for treatment. Although with exciting benefits, the inhibition of IL-6 pathway works mostly for severe cases, the long-term treatment strategy against the SARS-CoV-2 infection requires the rapid development of effective anti-viral drugs and, more importantly, vaccines.

CNS IMMUNE RESPONSES

The systemic cytokine storm caused the multiple organ failure, and unsurprisingly triggered the hyperinflammatory responses

inside the CNS that further exacerbated the neurological pathology. The spreading of infected leukocytes might across the compromised BBB, caused by increased pro-inflammatory cytokines, from the periphery to the brain. Previously, for most cases of SARS, autopsy detections of affected brain tissue samples have shown signs of extensive edema, microglial hyperplasia, neuron necrosis, nerve demyelination, as well as massive infiltration of monocytes and lymphocytes (65). Based on recent autopsy results, brain hyperemia and edema, partial neuron degeneration, as well as inflammatory cell infiltration in perivascular regions were also detected in COVID-19 patients from China (66). The persistence of coronavirus infection and its ability to infect macrophages, microglia, and astrocytes in the CNS are particularly critical in the pathogenesis of encephalitis (30). Notably, a neurotropic virus could directly activate glial cells and induce a pro-inflammatory phenotype (67). Studies have confirmed that primary glial cells cultured *in vitro* released a large number of pro-inflammatory factors, such as IL-6, IL-12, IL-15, and TNF-α, upon coronavirus infection (22).

Glial cells, as resident immune cells of the CNS, normally take a role in maintaining the homeostasis, responding promptly to CNS injuries such as trauma, ischemia, and infection, and also providing support and protection for neurons. Particularly, microglia are initially activated to clear the invaded pathogens by secreting pro-inflammatory mediators, followed by promoting tissue reconstitution and inflammation resolution. Microglia have been demonstrated to protect against lethal coronavirus encephalitis in mice (68). During the early days after infection, microglia were required to limit mouse hepatitis virus (MHV) replication and subsequent morbidity and lethality. The chemical depletion of microglia led to increased viral replication in the brain and caused ineffective T cell responses, reminiscent of the critical role of microglia in the early innate responses to virus infections (68). However, in addition to protective effects, microglia may also mediate hippocampal presynaptic membrane damage through complement system, resulting in long-term memory impairment and cognitive decline in patients with encephalitis, caused by coronavirus or human immunodeficiency virus (HIV) infection (69).

Thus, beyond the acute cytokine storm, the activation of immune cells in the brain might cause chronic inflammation and brain damages in COVID-19 patients. Taken together, in the short-term, SARS-CoV-2 infections may cause the CNS inflammation and lead to encephalitis. Potential long-term effects, such as changes in mood and cognitive behavior, and continuous changes in the expression of genes that regulate synaptic activity in key brain regions should not be neglected. Moreover, this speculation has drawing increasing attentions of clinicians and neuroscientists (21, 70–73). Hence, prognostic research on potential and longitudinal potential COVID-19-related neuropsychiatric diseases is crucial in disease surveillance and evidence-based treatment strategies (74).

LINKING WITH NEURODEGENERATIVE DISEASES

The multiple organ failure in COVID-19 is associated with the acute immune imbalance, whereas the chronic immune imbalance in the CNS, either by invaded virus or by infiltrated immune mediators, might be happening (**Figure 1**). An emerging hypothesis states that the inflammation caused by viral infection may trigger and propagate chronic neuronal dysfunction, which is an event before the clinical onset of multiple neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) (75). Notably, the chronic immune imbalance is the shared hallmark for neuropsychiatric and neurodegenerative diseases, due to the uncontrolled skewing of glial phenotypes into detrimental states (76). Experimental vaccination of mice with H5N1 influenza virus can mimic many aspects of PD-like initiation and pathogenesis (77, 78). The continued inflammation that follows in the viral trajectory leads to dysfunction or degeneration of dopaminergic neurons in the midbrain, just as seen in PD patients (77, 78). Therefore, it would be interesting to probe the relationship between the immune responses upon coronavirus infections and neurodegeneration/neuropsychiatric impairments.

The similar set of sustained elevated pro-inflammatory cytokines or chemokines, typically ILs, CXCLs, and TNF, that trigger the cytokine storm of COVID-19 are also frequently detected in the CSF and autopsy brain samples (79–81), which is critical in the development and progression of numerous neurodegenerative disorders. Since the role of neuroinflammation and specific inflammatory mediators have been recently extensively reviewed in respective diseases including PD, AD, amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS) (82–86), we will not discuss in much details but give some examples. For AD, pro-inflammatory factors are responsible for the increased amyloid precursor protein (APP) production and amyloid-β (Aβ) load, as well as tau hyperphosphorylation, the hallmarks of AD. Specifically, TNF-α can increase Aβ burden by promoting β-secretase production and increased γ-secretase activity (87). Elevated IL-6 levels have been shown to activate CDK5, a kinase that phosphorylate tau proteins (88). Such extensive neuroinflammation thus would cause neuronal death that leads to cognitive impairment and dementia.

Alpha-synuclein (α-synuclein), a major component of Lewy bodies in the pathogenesis of PD, plays an important role in mediating innate and adaptive immunity (89). Particularly, the mutant forms of α-synuclein in PD could induce microglial activation, releasing various pro-inflammatory cytokines (IL-6, IL-1β, and TNF-α etc.) and CXCL12, by recognizing toll-like receptors (TLRs) (90, 91). Similarly, for ALS, the aggregated proteins as mutated superoxide dismutase (mSOD1), caused motoneuron injury and triggered microgliosis in spinal cord cultures by releasing pro-inflammatory cytokines and free radicals (92). Overall, the aggregated proteins among multiple neurodegenerative diseases including α-synuclein, Aβ, and

mSOD1, can initiate a pro-inflammatory responses that lead to a sustained imbalance of neuroinflammation and neuronal loss due to the persistent protein aggregations (76).

In addition, the nerve demyelination was also observed in both SARS-CoV and SARS-CoV-2 infected patients, resembling the pathology of MS, which is also tightly associated with neuroinflammation (85). A similar pattern of elevated pro-inflammatory factors (IL-6, IL-8, TNF etc.) was recorded in the CSF samples of MS patients with severe gray matter damage (93). Interestingly, other neuropsychiatric diseases such as schizophrenia, bipolar disorders, depression, and among others, are also tightly linked with the neuroinflammatory responses (94). For instance, the levels of pro-inflammatory mediators including IL-6, IL-8, IL-1β, and TNF-α in the CSF or peripheral blood are obviously higher in schizophrenia patients (95, 96). Microglia that release pro-inflammatory factors such as TNF-α can promote the release of glutamate to induce oligodendrocyte dysfunction, resulting in abnormal neural networks in the brain of schizophrenic patients (97). Notably, the altered mental status and neuropsychiatric presentations were recorded in COVID-19 patients and other coronavirus infected diseases (98, 99).

Above all, the neuroinflammation imbalance toward pro-inflammatory states shows to be a shared hallmark of various neurological diseases, hence, the CNS infiltrated immune mediators in COVID-19 patients would probably take part in the chronic pathogenesis process and bring about certain irreversible neuronal impairments.

In another hand, given that SARS-CoV-2 viruses have invaded the CNS and can be detected in the CSF, their direct effects in the chronic modifications of neural circuits worth further investigations. Also, it is intriguing to address whether the infection increases the risk of developing chronic neurodegenerative diseases. The Braak hypothesis regarding the etiology of sporadic PD proposes that neurotropic viruses entering the nasal cavity and gastrointestinal tract may trigger Lewy pathology, which then spreads to the CNS through transneuronal transport, resulting in neurodegeneration in critical brain nuclei (100). Recent studies have confirmed the nasal-brain and gut-brain deliveries in the pathogenesis of PD (101, 102). Interestingly, the symptoms of anosmia and diarrhea of COVID-19 patients indicate the nasal and digestive system as the routes of viral infection, which may echo the Braak staging evidence that the prodromal or preclinical stage of PD is characterized by olfactory and gastrointestinal symptoms (103).

PERSPECTIVE

Even though COVID-19 respiratory tract infections and cardiovascular events are the main causes of death, the clinical awareness of neurological impairments can reduce the mortality of infected patients. To reduce the risk of those neurological complications, further investigations are needed to determine specific risk factors or protective determinants of neurological events. Although recovery from the acute phase of infection can of course be relieved from a public health perspective and help stop the spread of infection, the long-term neurological effects of the disease must also be considered. So far, mounting studies have reported various neurological manifestations, however, the neurotropic potential and chronic neurological effects of the SARS-CoV-2 virus remains to be fully addressed.

Currently, the urgent need for treating COVID-19 severe patients is still suppressing cytokine storms and balancing the immune system, particularly also in the CNS. Unfortunately, no specific medicine against COVID-19 has been developed till now. Apart from using mAbs such as Tocilizumab, Satralizumab, and Sarilumab, a recent study reported that dexamethasone, a corticosteroid used widely for its anti-inflammatory and immunosuppressant effects, showed to reduce the mortality by 1/3 among patients receiving invasive mechanical ventilation and by 1/5 among patients receiving oxygen by other means, but had no effects for patients without receiving respiratory support (104). However, this drug, as mentioned earlier as other corticosteroid drugs, was also under critical concerns of side effects. Different drugs work depending on the severity of disease and the timepoint for delivery. Adding the need of treating neurological complications, the therapeutic strategy becomes more complicated. It is possible that the anti-neuroinflammatory drugs that used for treating neurodegenerative diseases might be repurposed, due to their capability of crossing the BBB. However, the candidate drugs and doses would be really dependent on each individual, since neurological complications were heterogenous among populations, and importantly, their safety for normal people infected with SARS-CoV-2 will also await clinical trials to be proven.

Additionally, another method to alleviate the fierce immune responses is employing the anti-inflammatory and anti-apoptotic effects of mesenchymal stem cells (MSCs), which can repair lung epithelial cell damage and facilitate alveolar fluid clearance (54). So far, they are still in clinical trials and are waiting for evaluation. In the other way, fortunately, the development of vaccines for the public has been right on the track (105–108), some of which have been under Phase III Clinical Trials.

Lastly, while we are talking about the acute or chronic immune imbalance, it is better to appreciate that keeping the immune system in balance is pivotal for maintaining health from infections and other pathogenic agents. To achieve this goal, people should lead a healthy lifestyle, with diets rich in whole grains, vegetables, and fruits, but low in red meat and high-fat foods. Regular exercise and stress relief are also incorporated, so as to strengthen our immunity against viral infections.

AUTHOR CONTRIBUTIONS

YT conceived the manuscript. JW and YT wrote and revised the draft. All authors approved the submission.

FUNDING

This study was supported by grants from the National Natural Sciences Foundation of China [No. 81801200],

Hunan Provincial Natural Science Foundation of China [No. 2019JJ40476], and Talents Startup Funds [No. 2209090550] of Xiangya Hospital, Central South University, Changsha, China.

ACKNOWLEDGMENTS

We apologize to the authors whose work might have been unintentionally omitted due to space limitations.

REFERENCES

1. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. (2020) 9:221–36. doi: 10.1080/22221751.2020.1719902
2. Li F. Structure, function, and evolution of coronavirus spike proteins. *Annu Rev Virol*. (2016) 3:237–61. doi: 10.1146/annurev-virology-110615-042301
3. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. (2020) 367:1260–3. doi: 10.1126/science.abb2507
4. Ou X, Liu Y, Lei X, Li P, Mi D, Ren L, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun*. (2020) 11:1620. doi: 10.1038/s41467-020-15562-9
5. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*. (2020) 367:1444–8. doi: 10.1126/science.abb2762
6. Miller AJ, Arnold AC. The renin-angiotensin system in cardiovascular autonomic control: recent developments and clinical implications. *Clin Auton Res*. (2019) 29:231–43. doi: 10.1007/s10286-018-0572-5
7. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. (2003) 426:450–4. doi: 10.1038/nature02145
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
9. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. (2020) 395:565–74. doi: 10.1016/S0140-6736(20)30251-8
10. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. (2004) 203:631–7. doi: 10.1002/path.1570
11. Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. (2020) 26:681–7. doi: 10.1038/s41591-020-0868-6
12. Zhao Y, Zhao ZX, Wang YJ, Zhou YQ, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *Am J Respir Crit Care Med.* (2020) 202:756–9. doi: 10.1164/rccm.202001-0179LE
13. Zhu YY, Jiang MM, Gao L, Huang XY. Single cell analysis of ACE2 expression reveals the potential targets for 2019-nCoV. *Preprints*. (2020). doi: 10.20944/preprints202002.0221.v1. [Epub ahead of print].
14. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*. (2020) 181:1016–35.e19. doi: 10.1016/j.cell.2020.04.035
15. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med*. (2020) 14:185–92. doi: 10.1007/s11684-020-0754-0
16. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. *bioRxiv*. (2020) 368:931766. doi: 10.1101/2020.02.03.931766
17. Chen YW, Feng ZQ, Diao B, Wang RS, Wang G, Wang CH, et al. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. *medRxiv [Preprint]*. (2020). doi: 10.1101/2020.03.27.20045427
18. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. (2020) 12:8. doi: 10.1038/s41368-020-0074-x
19. Zhou J, Li C, Liu X, Chiu MC, Zhao X, Wang D, et al. Infection of bat and human intestinal organoids by SARS-CoV-2. *Nat Med*. (2020) 26:1077–83. doi: 10.1038/s41591-020-0912-6
20. Chen R, Wang K, Yu J, Chen Z, Wen C, Xu Z. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain *bioRxiv [Preprint]*. (2020). doi: 10.1101/2020.04.07.030650
21. Ladecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell Pre-proof*. (2020). doi: 10.1016/j.cell.2020.08.028
22. Bohmwald K, Galvez NMS, Rios M, Kalergis AM. Neurologic Alterations Due to Respiratory Virus Infections. *Front Cell Neurosci*. (2018) 12:386. doi: 10.3389/fncel.2018.00386
23. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dube M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses*. (2019) 12:14. doi: 10.3390/v12010014
24. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan*. (2005) 14:113–9. doi: 10.29819/ANT.200509.0002
25. Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome. (SARS): a report from China. *J Pathol*. (2003) 200:282–9. doi: 10.1002/path.1440
26. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis*. (2004) 10:342–4. doi: 10.3201/eid1002.030638
27. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological complications during treatment of middle east respiratory syndrome. *J Clin Neurol*. (2017) 13:227–33. doi: 10.3988/jcn.2017.13.3.227
28. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS Neurosci Ther*. (2020) 26:499–501. doi: 10.1111/cns.13372
29. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. (2020) 11:995–8. doi: 10.1021/acschemneuro.0c00122
30. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun*. (2020). doi: 10.1016/j.bbi.2020.03.031
31. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. (2020) 92:552–55. doi: 10.1002/jmv.25728
32. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
33. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
34. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
35. Xiang P, Xu XM, Gao LL, Wang HZ, Xiong HF, Li RH. First case of 2019 novel coronavirus disease with Encephalitis. *ChinaXiv*. (2020) T202003:200015.
36. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. (2020) 46:1089–98. doi: 10.1007/s00134-020-06062-x
37. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5

38. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. (2020) 71, 889–90. doi: 10.1093/cid/ciaa330
39. Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study. *J Otolaryngol Head Neck Surg*. (2020) 49:26. doi: 10.1186/s40463-020-00423-8
40. Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Science Adv*. (2020) 6:eabc5801. doi: 10.1126/sciadv.abc5801
41. Kirschenbaum D, Imbach LL, Ulrich S, Rushing EJ, Keller E, Reimann RR, et al. Inflammatory olfactory neuropathy in two patients with COVID-19. *Lancet*. (2020) 396:166. doi: 10.1016/S0140-6736(20)31525-7
42. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. *Gastroenterology*. (2020) 158:1518–9. doi: 10.1053/j.gastro.2020.02.054
43. Li Z, Liu T, Yang N, Han D, Mi X, Li Y, et al. Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain. *Front Med*. (2020). doi: 10.1007/s11684-020-0786-5. [Epub ahead of print].
44. Ludlow M, Kortekaas J, Herden C, Hoffmann B, Tappe D, Trebst C, et al. Neurotropic virus infections as the cause of immediate and delayed neuropathology. *Acta Neuropathol*. (2016) 131:159–84. doi: 10.1007/s00401-015-1511-3
45. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol*. (2017) 39:529–39. doi: 10.1007/s00281-017-0629-x
46. Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol*. (2004) 136:95–103. doi: 10.1111/j.1365-2249.2004.02415.x
47. Fehr AR, Channappanavar R, Perlman S. Middle east respiratory syndrome: emergence of a pathogenic human coronavirus. *Annu Rev Med*. (2017) 68:387–99. doi: 10.1146/annurev-med-051215-031152
48. Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. *Cytokine*. (2018) 104:8–13. doi: 10.1016/j.cyto.2018.01.025
49. Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Moller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell*. (2020) 181:1036–45.e9. doi: 10.1016/j.cell.2020.04.026
50. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. (2020) 71:762–768 doi: 10.1093/cid/ciaa248
51. Tan M, Liu Y, Zhou R, Deng X, Li F, Liang K, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. *Immunology*. (2020) 160:261–8. doi: 10.1111/imm.13223
52. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. (2020) 8:420–2. doi: 10.1016/S2213-2600(20)30076-X
53. Zhou YG, Fu BQ, Zheng XH, Wang DS, Zhao CC, Qi YJ, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. *bioRxiv [Preprint]*. (2020). doi: 10.1101/2020.02.12.945576
54. Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*. (2020) 20:269–70. doi: 10.1038/s41577-020-0308-3
55. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. (2006) 3:e343. doi: 10.1371/journal.pmed.0030343
56. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med*. (2018) 197:757–67. doi: 10.1164/rccm.201706-1172OC
57. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
58. Wan SX, Yi QJ, Fan SB, Lv JL, Zhang XX, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia. (NCP). *medRxiv [Preprint]*. (2020). doi: 10.1101/2020.02.10.20021832
59. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. (2020) 130:2620–9. doi: 10.1172/JCI137244
60. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, Bergwelt-Baildon MV, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol*. (2020) 146:128–36.e4. doi: 10.1016/j.jaci.2020.05.008
61. Ruan QR, Yang K, Wang WX, Jiang LY, Song JX. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. (2020) 46:1294–7. doi: 10.1007/s00134-020-06028-z
62. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science*. (2020) 368:473–4. doi: 10.1126/science.abb8925
63. Harrison C. Focus shifts to antibody cocktails for COVID-19 cytokine storm. *Nat Biotechnol*. (2020) 38:905–8. doi: 10.1038/s41587-020-0634-9
64. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. (2020) 117:10970–5. doi: 10.1073/pnas.2005615117
65. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. (2005) 202:415–24. doi: 10.1084/jem.20050828
66. Bian XW. Autopsy of COVID-19 victims in China. *Natl Sci Rev*. (2020) 7:1414–8. doi: 10.1093/nsr/nwaa123
67. Li Y, Fu L, Gonzales DM, Lavi E. Coronavirus neurovirulence correlates with the ability of the virus to induce pro-inflammatory cytokine signals from astrocytes and microglia. *J Virol*. (2004) 78:3398–406. doi: 10.1128/JVI.78.7.3398-3406.2004
68. Wheeler DL, Sariol A, Meyerholz DK, Perlman S. Microglia are required for protection against lethal coronavirus encephalitis in mice. *J Clin Invest*. (2018) 128:931–43. doi: 10.1172/JCI97229
69. Chen Z, Zhong D, Li G. The role of microglia in viral encephalitis: a review. *J Neuroinflamm*. (2019) 16:76. doi: 10.1186/s12974-019-1443-2
70. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol*. (2020) 19:767–83. doi: 10.1016/S1474-4422(20)30221-0
71. Hascup ER, Hascup KN. Does SARS-CoV-2 infection cause chronic neurological complications? *Geroscience*. (2020) 42:1083–7. doi: 10.1007/s11357-020-00207-y
72. Lippi A, Domingues R, Setz C, Outeiro TF, Krisko A. SARS-CoV-2: at the crossroad between aging and neurodegeneration. *Mov Disord*. (2020) 35:716–20. doi: 10.1002/mds.28084
73. Serrano-Castro PJ, Estivill-Torrus G, Cabezudo-Garcia P, Reyes-Bueno JA, Ciano Petersen N, Aguilar-Castillo MJ, et al. Impact of SARS-CoV-2 infection on neurodegenerative and neuropsychiatric diseases: a delayed pandemic? *Neurologia*. (2020) 35:245–51. doi: 10.1016/j.nrleng.2020.04.002
74. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun*. (2020) doi: 10.1016/j.bbi.2020.04.027
75. Deleidi M, Isacson O. Viral and inflammatory triggers of neurodegenerative diseases. *Sci Transl Med*. (2012) 4:121ps123. doi: 10.1126/scitranslmed.3003492
76. Tang Y, Le W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Mol Neurobiol*. (2016) 53:1181–94. doi: 10.1007/s12035-014-9070-5
77. Jang H, Boltz D, Sturm-Ramirez K, Shepherd KR, Jiao Y, Webster R, et al. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. *Proc Natl Acad Sci USA*. (2009) 106:14063–8. doi: 10.1073/pnas.0900096106
78. Jang H, Boltz D, McClaren J, Pani AK, Smeyne M, Korff A, et al. Inflammatory effects of highly pathogenic H5N1 influenza virus infection in the CNS of mice. *J Neurosci*. (2012) 32:1545–59. doi: 10.1523/JNEUROSCI.5123-11.2012

79. Gomez-Nicola D, Boche D. Post-mortem analysis of neuroinflammatory changes in human Alzheimer's disease. *Alzheimers Res Ther*. (2015) 7:42. doi: 10.1186/s13195-015-0126-1
80. Chen X, Hu Y, Cao Z, Liu Q, Cheng Y. Cerebrospinal fluid inflammatory cytokine aberrations in alzheimer's disease, parkinson's disease and amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Front Immunol*. (2018) 9:2122. doi: 10.3389/fimmu.2018.02122
81. Taipa R, das Neves SP, Sousa AL, Fernandes J, Pinto C, Correia AP, et al. Proinflammatory and anti-inflammatory cytokines in the CSF of patients with Alzheimer's disease and their correlation with cognitive decline. *Neurobiol Aging*. (2019) 76:125–32. doi: 10.1016/j.neurobiolaging.2018.12.019
82. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Transl Neurodegener*. (2015) 4:19. doi: 10.1186/s40035-015-0042-0
83. Liu J, Wang F. Role of neuroinflammation in amyotrophic lateral sclerosis: cellular mechanisms and therapeutic implications. *Front Immunol*. (2017) 8:1005. doi: 10.3389/fimmu.2017.01005
84. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement*. (2018) 4:575–90. doi: 10.1016/j.trci.2018.06.014
85. Matthews PM. Chronic inflammation in multiple sclerosis - seeing what was always there. *Nat Rev Neurol*. (2019) 15:582–93. doi: 10.1038/s41582-019-0240-y
86. Palpagama TH, Waldvogel HJ, Faull RLM, Kwakowsky A. The role of microglia and astrocytes in huntington's disease. *Front Mol Neurosci*. (2019) 12:258. doi: 10.3389/fnmol.2019.00258
87. Yamamoto M, Kiyota T, Horiba M, Buescher JL, Walsh SM, Gendelman HE, et al. Interferon-gamma and tumor necrosis factor-alpha regulate amyloid-beta plaque deposition and beta-secretase expression in Swedish mutant APP transgenic mice. *Am J Pathol*. (2007) 170:680–92. doi: 10.2353/ajpath.2007.060378
88. Quintanilla RA, Orellana DI, Gonzalez-Billault C, Maccioni RB. Interleukin-6 induces Alzheimer-type phosphorylation of tau protein by deregulating the cdk5/p35 pathway. *Exp Cell Res*. (2004) 295:245–57. doi: 10.1016/j.yexcr.2004.01.002
89. Zhang G, Xia Y, Wan F, Ma K, Guo X, Kou L, et al. New perspectives on roles of alpha-synuclein in parkinson's disease. *Front Aging Neurosci*. (2018) 10:370. doi: 10.3389/fnagi.2018.00370
90. Jiang T, Hoekstra J, Heng X, Kang W, Ding J, Liu J, et al. P2X7 receptor is critical in alpha-synuclein–mediated microglial NADPH oxidase activation. *Neurobiol Aging*. (2015) 36:2304–18. doi: 10.1016/j.neurobiolaging.2015.03.015
91. Li Y, Niu M, Zhao A, Kang W, Chen Z, Luo N, et al. CXCL12 is involved in alpha-synuclein-triggered neuroinflammation of Parkinson's disease. *J Neuroinflammation*. (2019) 16:263. doi: 10.1186/s12974-019-1646-6
92. Zhao W, Beers DR, Henkel JS, Zhang W, Urushitani M, Julien JP, et al. Extracellular mutant SOD1 induces microglial-mediated motoneuron injury. *Glia*. (2010) 58:231–43. doi: 10.1002/glia.20919
93. Magliozzi R, Howell OW, Nicholas R, Cruciani C, Castellaro M, Romualdi C, et al. Inflammatory intrathecal profiles and cortical damage in multiple sclerosis. *Ann Neurol*. (2018) 83:739–55. doi: 10.1002/ana.25197
94. Nakagawa Y, Chiba K. Role of microglial m1/m2 polarization in relapse and remission of psychiatric disorders and diseases. *Pharmaceuticals*. (2014) 7:1028–48. doi: 10.3390/ph7121028
95. Zhang XY, Zhou DF, Zhang PY, Wu GY, Cao LY, Shen YC. Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. *Schizophr Res*. (2002) 57:247–58. doi: 10.1016/S0920-9964(01)00296-1
96. Garver DL, Tamas RL, Holcomb JA. Elevated interleukin-6 in the cerebrospinal fluid of a previously delineated schizophrenia subtype. *Neuropsychopharmacology*. (2003) 28:1515–20. doi: 10.1038/sj.npp.1300217
97. Bezzi P, Domercq M, Brambilla L, Galli R, Schols D, De Clercq E, et al. CXCR4-activated astrocyte glutamate release via TNFalpha: amplification by microglia triggers neurotoxicity. *Nat Neurosci*. (2001) 4:702–10. doi: 10.1038/89490
98. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*. (2020) 7:611–27. doi: 10.1016/S2215-0366(20)30203-0
99. Ward CF, Figiel GS, McDonald WM. Altered mental status as a novel initial clinical presentation for COVID-19 infection in the elderly. *Am J Geriatr Psychiatry*. (2020) 28:808–11. doi: 10.1016/j.jagp.2020.05.013
100. Braak H, Rub U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm*. (2003) 110:517–36. doi: 10.1007/s00702-002-0808-2
101. Liu SY, Chan P, Stoessl AJ. The underlying mechanism of prodromal PD: insights from the parasympathetic nervous system and the olfactory system. *Transl Neurodegener*. (2017) 6:4. doi: 10.1186/s40035-017-0074-8
102. Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, et al. Transneuronal propagation of pathologic alpha-synuclein from the gut to the brain models parkinson's disease. *Neuron*. (2019) 103:627–41.e627. doi: 10.1016/j.neuron.2019.05.035
103. Mahlknecht P, Seppi K, Poewe W. The concept of prodromal parkinson's disease. *J Parkinsons Dis*. (2015) 5:681–97. doi: 10.3233/JPD-150685
104. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with covid-19 - preliminary report. *N Engl J Med*. (2020). doi: 10.1056/NEJMoa2021436. [Epub ahead of print].
105. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Rapid development of an inactivated vaccine candidate for SARS-CoV-2. *Science*. (2020) 369:77–81. doi: 10.1126/science.abc1932
106. Shin MD, Shukla S, Chung YH, Beiss V, Chan SK, Ortega-Rivera OA, et al. COVID-19 vaccine development and a potential nanomaterial path forward. *Nat Nanotechnol*. (2020) 15:646–55. doi: 10.1038/s41565-020-0737-y
107. Thanh Le T, Andreadakis Z, Kumar A, Gomez Roman R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. *Nat Rev Drug Discov*. (2020) 19:305–6. doi: 10.1038/d41573-020-00073-5
108. Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet*. (2020) 395:1845–54. doi: 10.1016/S0140-6736(20)31208-3

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 15 October 2020
doi: 10.3389/fneur.2020.01029

An Example of a Stroke Unit Reshaping in the Context of a Regional Hub and Spoke System in the COVID-19 Era

*Elisa Candeloro[1], Federico Carimati[1], Payam Tabaee Damavandi[1,2], Lucia Princiotta Cariddi[1,3], Paola Banfi[1], Alessandro Clemenzi[1], Marco Gallazzi[1], Marco Mauri[1,3], Valentina Rebecchi[1], Fabio Baruzzi[4], Andrea Giorgianni[4], Matteo Tozzi[3,5], Massimo Bianchi[6], Walter Ageno[3,6] and Maurizio Versino[1,3]**

[1] Neurology and Stroke Units, ASST-Settelaghi, Ospedale di Circolo Varese, Varese, Italy, [2] Department of Medicine and Surgery, Bicocca University, Milan, Italy, [3] Department of Medicine and Surgery, Insubria University, Varese, Italy, [4] Neuroradiology Unit, ASST-Settelaghi, Ospedale di Circolo Varese, Varese, Italy, [5] Vascular Surgery Unit, ASST-Settelaghi, Ospedale di Circolo Varese, Varese, Italy, [6] Emergency Department, ASST-Settelaghi, Ospedale di Circolo Varese, Varese, Italy

OPEN ACCESS

Edited by:
Tomohisa Nezu,
Hiroshima University, Japan

Reviewed by:
Peter Ringleb,
Heidelberg University, Germany
Koji Tanaka,
Kyushu University, Japan

***Correspondence:**
Maurizio Versino
maurizio.versino@asst-settelaghi.it
orcid.org/0000-0003-1813-9492

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *04 June 2020*
Accepted: *06 August 2020*
Published: *15 October 2020*

Citation:
Candeloro E, Carimati F, Tabaee Damavandi P, Princiotta Cariddi L, Banfi P, Clemenzi A, Gallazzi M, Mauri M, Rebecchi V, Baruzzi F, Giorgianni A, Tozzi M, Bianchi M, Ageno W and Versino M (2020) An Example of a Stroke Unit Reshaping in the Context of a Regional Hub and Spoke System in the COVID-19 Era. Front. Neurol. 11:1029. doi: 10.3389/fneur.2020.01029

During the COVID-19 outbreak, the Neurology and Stroke Unit (SU) of the hospital of Varese had to serve as a cerebrovascular hub, meaning that the referral area for the unit doubled. The number of beds in the SU was increased from 4 to 8. We took advantage of the temporary suspension of the out-patient clinic and reshaped our activity to guarantee the 24/7 availability of recombinant tissue Plasminogen Activator (rtPA) intravenous therapy (IVT) in the SU, and to ensure we were able to admit patients to the SU as soon as they completed endovascular treatment (EVT). In 42 days, 46 stroke patients were admitted to our hospital, and 34.7% of them underwent IVT and/or EVT, which means that we treated 0.38 patients per day; in the baseline period from 2016 to 2018, these same figures had been 23.5% and 0.23, respectively. The mean values of the door-to-first CT/MRI and the door-to-groin puncture, but not of the onset-to-door and the door-to-needle periods were slightly but significantly longer than those observed in the baseline period in 276 patients. On an individual basis, only one patient exceeded the door-to-groin puncture time limit computed from the baseline period by about 10 min. None of the patients had a major complication following the procedures. None of the patients was or became SARS-CoV2 positive. In conclusion, we were able to manage the new hub-and-spoke system safely and without significant delays. The reshaping of the SU was made possible by the significant reduction of out-patient activity. The consequences of this reduction are still unknown but eventually, this emergency will suggest ways to reconsider the management and the allocation of health system resources.

Keywords: stroke unit, reshaping, hub and spoke system, COVID-19 pandemic, timing

INTRODUCTION

Since the outbreak of COVID-19 in Lombardy, an Italian region with a population of 10 million people. During the pandemic, the ability to guarantee treatment for patients presenting with stroke within the time windows dictated by guidelines has become an issue. This is because most of the resources normally available in hospitals had to be devoted to the treatment of COVID-19 patients.

To face the problem of cerebrovascular and other time sensitive diseases, the Governor of Lombardy set up a hub-and-spoke organization with 10 hub hospitals. It is noteworthy that this decision was taken in a few days, with little time for the hub hospitals to reorganize their activity. The hospital of Varese had to serve as a cerebrovascular hub for the north-western areas of Lombardy, meaning that its referral area was doubled and that the stroke patients could have been taken to Varese either directly by the regional emergency transportation system (Agenzia Regionale dell'Emergenza Urgenza: AREU) or from a spoke hospital located somewhere in Lombardy.

Here we report how we have managed this situation and how our Stroke Unit (SU) was able to maintain consistent performance levels whilst also becoming a hub.

MATERIALS AND METHODS

Reshaping

Before the onset of the COVID-19 pandemic, the Neurology and Stroke Unit of the Circolo Hospital in Varese consisted of 14 beds. Four beds were dedicated to the Stroke Unit since there were four mobile monitoring systems available. The monitors were placed next to the patient's bed and could not be remotely controlled. The medical staff consisted of 8 full-time neurologists who belonged to the hospital and one half-time neurologist who belonged to the University of Insubria. With different levels of involvement, all neurologists worked in the Stroke Unit but none of them was exclusively assigned to it. During the week, from 8 a.m. to 8 p.m. (daytime) at least one neurologist had to be present in the hospital, whereas from 8 p.m. to 8 a.m. (night-time) one neurologist was available on call. On the weekends there was a neurologist in the hospital during daytime and one on-call during night-time. The nurse staff was shared with another 3 units located on the same floor. In total, 11 nurses dealt mainly with the Neurology and Stroke Unit, 8 of which were specifically trained for the Stroke Unit. Intravenous Therapy (IVT) with recombinant tissue Plasminogen Activator (rTPA) procedures were performed in the Emergency Department (ED) whilst Endovascular Therapy (EVT) procedures were conducted in the angiographic room. After the procedures the patients were moved to the Stroke Unit, kept under observation in the ED, and if a major complication occurred or the patient was clinically unstable, they were moved to the Intensive Care Unit (ICU).

Immediately after the promulgation of the decree, the Neurology and SU were relocated in the nearby cardiac surgery ward, since most of the cardiac surgeons had to move to another hospital that served as a hub for cardiac surgery. Thanks to this relocation, the SU gained 4 additional beds that were provided with a centrally and remotely controlled monitoring system. The number of neurologists was not increased but, given the substantial reduction of the outpatient clinic activity that was imposed by the lockdown, it was possible to reorganize the neurology department as follows: during the week, three neurologists were present in the SU during day-time, two of which were present in the ward, and one in the ED. In addition, one neurology resident was available 3 out of 5 weekdays. During night-time, one neurologist was on call and another one was available as a possible back-up. On the weekends, during the daytime, there was one neurologist and one resident available both for the Neurology and Stroke Unit and for the ED. During night-time, one neurologist was available on-call with an additional neurologist as a possible backup. As for the nurses, eight nurses were available during day-time and two at night-time.

The regional indications dictated the rules for swab testing and for the personnel protection equipment that are described in a report on our hospital's neurosurgery hub (1). The swab test became mandatory for all the patients admitted to the hospital only after April 14. Before that date, a swab test was performed on patients that were possibly considered to be SARS-CoV2 positive based on their clinical history, their body temperature, their respiratory symptoms and signs, and a chest x-ray (or CT).

The IVT procedures were performed inside the Stroke Unit and not in the ED. All patients admitted to the ED were transferred to the SU immediately after they underwent IVT or EVT or when neither of these procedures was deemed possible or appropriate unless they had to be transferred to the ICU. This was done to alleviate the burden on the ED.

Data Collection and Analysis

We collected the data on the patients that were referred to our hospital from March 9 to April 19 2020 either for ischemic or hemorrhagic stroke or for intracerebral cerebral hemorrhage (ICH), i.e., a timeframe of 42 days following the promulgation of the decree of the Lombardy Governor for the institution of the hub-and-spoke system.

Since the data were collected from patients' clinical records, and since they were all treated according to guidelines on best clinical practice, our institution did not require ethical approval for this study.

We performed a full diagnostic work-up on all patients and when indicated by Italian guidelines [Spread GL 2017 (2)], updated with the most recent AHA/ASA guidelines (3), an IVT and/or an EVT or a carotid endarterectomy (CEA).

For each patient we acknowledged how he/she had reached the hospital (without or with the regional emergency transportation system AREU), the individual risk factors, the kind of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (4), the location of the stroke according to Oxfordshire Classification (OCSP) (5), the therapeutic procedures (IVT, EVT, CEA), and a justification in case no procedure was undertaken, the NIH Stroke Scale (NIHSS) score before and after the procedure. We also acknowledged several time periods: onset-to-door (the time from the onset of the symptoms to the arrival at the ED), door-to-first CT/MRI

(the timeframe from the arrival of the patient at the hospital and the first neuroradiological procedure), door-to-needle (the timeframe from the arrival of the patient at the hospital and the beginning of IVT), and door-to-groin puncture (the timeframe from the arrival of the patient at the hospital and the beginning of EVT).

We defined as a baseline the data that has been collected from 276 patients over a 3 year period, from 2016 to 2018, and for the different time periods we defined the 95th percentile value as the upper normal (i.e., not COVID-19) limit.

For the evaluation of the mean values computed for the COVID-19 period, we calculated a z-value by considering the mean and the standard deviation values computed for the baseline period as the population values, and the number of observation in the COVID-19 period as the numerosity value.

For the comparison of observed frequencies computed for the COVID-19 period, we computed chi-square values using the corresponding frequencies during the baseline to compute the expected frequencies.

For the comparison of the variabilities, we computed an F value as the ratio between the baseline and the COVID-19 variances.

All the analyses were performed using Microsoft Excel ver. 16.39, and for all of them the significance value was set at $p = 0.050$.

RESULTS

We did not turn down any case requests for the admission of a patient referred to our hospital.

In the 42 days following the promulgation of the decree, we observed 52 patients: 6 TIAs and 46 strokes. In the same timeframe, 35 ICH patients were admitted to the hospital, mostly in the intensive care and in the neurosurgery units, while only 2 in the Neurology and Stroke Units.

Sixteen of these 46 patients (34.7%) underwent a revascularization procedure: 3 patients (18.8%) had IVT, 8 (50%) had EVT, and 5 patients (31.2%) had IVT followed by EVT (Bridging treatment). Of the patients treated during the COVID-19 period, 34.7% were found to be significantly higher when compared to the baseline period, where only 23.5% of patients were treated (chi-square = 4.4; $p = 0.037$).

We thus treated 0.38 stroke patients per day, whereas the corresponding figure for the baseline period was 0.23; again, these two figures proved to be significantly different (chi-square = 5.40; $p = 0.002$).

None of these patients had a major complication following the revascularization procedure, but 2 patients had to be admitted to the ICU for a few days before being transferred to the SU. No patients were or became SARS-CoV2 positive. All of these patients reached the hospital by ambulance after the activation of the AREU system.

The main clinical features of the patients who underwent to recanalization procedures are reported in **Table 1**.

The following stroke risk factors were found in the patients treated: atrial fibrillation in 8 (50%), ischemic heart disease in 5 (31.3%), diabetes in 3 (18.8%), a smoking habit in 6 (37.5%), hypertension in 12 (75%), previous stroke in 3 (18.8%), time-based clinical history of a previous TIA in 2 (12.5%).

TABLE 1 | Main clinical features of patients who underwent IVT and EVT recanalization procedures.

Gender (*n*; %)	Male	8	50%
	Female	8	50%
Age (median; range)		77	42–92
OCSP (*n*; %)	Partial Anterior Circulation Infarct	5	31.2%
	Total Anterior Circulation Infarct	6	37.5%
	POsterior Circulation Infarct	4	25%
	LACunar Infarct	1	6.3%
TOAST (*n*; %)	Large vessel	2	12.5%
	Cardioembolism	9	56.2%
	Small vessel	1	6.2%
	Other or undetermined	4	25%
mRS (median; range)	Pre-stroke	0	0–1
	At discharge	2	0–5
NIHSS (median; range)	Onset	10.5	2–25
	After 24h	4.5	1–25
	At discharge	2	0–5

mRS, modified Rankin Score.

Table 2 shows the interventional time periods. The mean values of door-to-CT/MRI and door-to—groin puncture were slightly, but significantly, longer than those measured in the large case series of 276 patients collected from 2016 to 2018, whereas the mean values of onset-to-door and door-to-needle were not. However, it is worth mentioning that if we considered the normal upper time limit computed from the data of the baseline period, only one patient exceeded the door-to-groin puncture time limit by about 10 min.

Another interesting point is that some of the data presented a larger variability in the baseline period compared to the COVID-19 period, as showed by the variances of the mean. This was true for the onset-to-door ($F = 4.7$; $p < 0.001$), the door-to-first CT/MRI ($F = 2.92$; $p < 0.001$), the door-to-groin puncture ($F = 2.33$; $p = 0.005$) but not for the door-to-needle ($F = 0.9$; $p = 0.600$) timeframes.

Four additional patients underwent CEA. They were 3 males and 1 female and their median age was 71 years with a range of 55–88 years. They all had a partial anterior circulation infarct and their median NIHSS score was 1 at onset (range 0–2) and 0 at discharge (0–1). Their mean (and standard deviation) values for the onset-to-door and the door-to-first CT/MRI were, respectively 109 (80) and 78 (53) min. We exceeded the normal time limit in one patient for the onset-to-door and in another patient for the door-to-CT/MRI time period. The time between the admission and the surgical procedure ranged from 2 to 10 days.

Among the patients who did not undergo any revascularization procedure, eight (27%) could not be treated due to inappropriate timing [i.e., onset-to-door larger than 6 h without DAWN/DEFUSE-3 trials criteria (6–8)]; in the baseline

TABLE 2 | The table reports the mean and the standard deviation (STD) of the different interventional time periods measured in the COVID-19 and the Baseline (from 2016 to 2018) periods.

	COVID-19		Baseline (2016–2018)					
Time periods (min)	**Mean**	**STD**	**Mean**	**STD**	***z***	***p***	**Baseline upper limit**	***N* (%) of patients exceeding upper reference limit**
Onset–to-door	84.1	21.4	86.2	46.44	0.18	0.850	178	0 (0%)
Door-to-first CT/MRI	54.9	18.5	30.62	31.62	3.07	0.002	108	0 (0%)
Door-to-needle	100.7	40.4	77.39	36.12	1.81	0.070	167.7	0(0%)
Door-to-groin puncture	189.1	49.2	137.12	75.13	2.49	0.010	308.8	1 (6.2%)

The z and p-values refer to the comparisons of the means.

period, the corresponding figure was the same (26%). Four of these patients did not activate the emergency system to get to the hospital.

DISCUSSION

The outbreak of COVID-19 has had a significant impact on health systems worldwide. The involvement of the nervous system in the SARS-CoV2 virus is now recognized (9, 10), and endothelial involvement is likely to play a key role (11–15). Thus, the management of stroke in the COVID-19 era has two aspects: one concerning COVID-19-related stroke (16, 17), and another about the need to meet the standards for the treatment of a time-dependent disease, despite having to allocate health system resources to the management of COVID-19. The latter had to be faced locally, and the reports about this topic were not available at the time of the pandemic onset (17–19).

Our data showed that despite the fact that the COVID-19 pandemic imposed a reallocation of health system resources, largely toward the management of COVID-19 patients, we were still able to guarantee a timely and safe approach for stroke patients. Eventually, we had no COVID-19 patients, but we still adopted an approach to safeguard them from potentially SARS-CoV2 positive patients.

Due to the hub-and-spoke system, the number of patients that underwent a recanalization procedure, and the percentage of patients eligible for treatment increased significantly. The onset-to-door and the door-to-needle mean time periods did not change as compared to the baseline period, whereas the door-to first CT/MRI and the door-to-groin puncture were slightly but significantly increased. On an individual basis, only one patient exceeded the door-to-groin puncture limit by about 10 min. The increase of the mean values was expected due to the additional safeguard measures that had to be adopted for potentially SARS-CoV2 positive patients. However, the variability of the duration of the different time periods was usually shorter in the COVID-19 than in the baseline period, suggesting that the control of the sequence of the procedures was improved.

This was made possible by the reshaping of the SU in terms of both equipment and human resources. The hospital increased the number of monitored beds available in the SU. The neurologists could focus on inpatient activity since the activity of the outpatient clinic was reduced and limited to those presenting for an acute or subacute problem. Moreover, during the pandemic, patients were reluctant to be referred to the hospital because they were afraid of being infected, as suggested by the unexpected reduction of consultations for cardiovascular disorders.

It is possible that when we go back to regular activity, we will find that many patients have underestimated their neurological symptoms. This could be the case of TIA, which can last a short time and be overlooked. The number of patients admitted for a TIA was quite low, in agreement with the report by Diegoli et al. (20). However, in the 3 months after the time period considered in this report, none of the patients that we admitted for a stroke had a clinical history positive for TIA. If in the future we confirm this scenario, we should reconsider how medical resources are distributed. In Italy we there is an issue of overuse of medical resources, and it is not unusual for a patient to have several medical consultations, laboratory, and instrumental examinations before concluding that "there is nothing wrong." Often, this conclusion could have been reached with a thorough initial examination and less referrals.

In conclusion, it is possible that this emergency period, which forced us to activate different procedures, will provide suggestions that will enable us to reconsider organization and lead to the implementation of more hub-and-spoke systems, to the reweighting of the out- and in-patient activities, and, therefore, to more careful examinations of the patient before asking for further clinical and instrumental examinations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed to the management of the patients, conceived the study, contributed to the draft manuscript, and read and approved the final version. Moreover, PT and FC collected the data in a suitable database for the following analyses. MV analyzed the data and wrote the manuscript.

REFERENCES

1. Agosti E, Giorgianni A, Pradella R, Locatelli D. Coronavirus Disease 2019 (COVID-19) outbreak: single-center experience in neurosurgical and neuroradiologic emergency network tailoring. *World Neurosurg.* (2020) 138:548–50. doi: 10.1016/j.wneu.2020.04.141
2. Lg S. *SPREAD – Stroke Prevention and Educational Awareness Diffusion Ictus Cerebrale: Linee guida italiane di prevenzione e trattamento*. (2017). Retrieved from: http://www.sinu.it/html/wlnews/14-11-2016/spread__stroke_prevention_and_educational_awareness_diffusion_ictus_cerebrale_linee_guida_italiane_di_prevenzione_e_trattamento.asp
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2018) 49:e46–110. doi: 10.1161/STR.0000000000000158
4. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke.* (1993) 24:35–41. doi: 10.1161/01.str.24.1.35
5. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet.* (2004) 363:1925–33. doi: 10.1016/S0140-6736(04)16405-2
6. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
7. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2019) 50:e344–418. doi: 10.1161/STR.0000000000000211
9. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol.* (2020) 70:311–22. doi: 10.33588/rn.7009.2020179
10. Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. *Eur J Neurol.* (2020) 27:1764–73. doi: 10.1111/ene.14277
11. Nalleballe K, Reddy Onteddu S, Sharma R, Dandu V, Brown A, Jasti M, et al. Spectrum of neuropsychiatric manifestations in COVID-19. *Brain Behav Immun.* (2020) 88:71–4. doi: 10.1016/j.bbi.2020.06.020
12. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the Young. *N Engl J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787
13. Princiotta Cariddi L, Tabaee Damavandi P, Carimati F, Banfi P, Clemenzi A, Marelli M, et al. Reversible Encephalopathy Syndrome (PRES) in a COVID-19 patient. *J Neurol.* (2020) 1–4. doi: 10.1007/s00415-020-10001-7. [Epub ahead of print].
14. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. *J Clin Med.* (2020) 9:1417. doi: 10.3390/jcm9051417
15. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5
16. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain Behav Immun.* (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077
17. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. *Transl Stroke Res.* (2020) 11:322–5. doi: 10.1007/s12975-020-00818-9
18. Baracchini C, Pieroni A, Viaro F, Cianci V, Cattelan AM, Tiberio I, et al. Acute stroke management pathway during Coronavirus-19 pandemic. *Neurol Sci.* (2020) 41:1003–5. doi: 10.1007/s10072-020-04375-9
19. Bersano A, Kraemer M, Touze E, Weber R, Alamowitch S, Sibon I, et al. Stroke care during the COVID-19 pandemic: experience from three large European countries. *Eur J Neurol.* (2020) 27:1794–800. doi: 10.1111/ene.14375
20. Diegoli H, Magalhaes PSC, Martins SCO, Moro CHC, Franca PHC, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke.* (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 16 October 2020
doi: 10.3389/fneur.2020.590406

Impact of Covid-19 on the Behavior of Community Residents With Suspected Transient Ischemic Attack

Sichen Yao[1†], Beiru Lin[2†], Yang Liu[3], Yunhe Luo[3], Qianqian Xu[1], Jiating Huang[3], Zhimin Yan[3] and Xiaochuan Liu[3,4*‡]*

[1] Wujing Community Health Service Center, Shanghai, China, [2] Maqiao Community Health Service Center, Shanghai, China, [3] Department of Neurology, Minhang Hospital, Fudan University, Shanghai, China, [4] WanNan Medical College, Anhui, China

OPEN ACCESS

Edited by:
Sheng-Feng Sung,
Ditmanson Medical Foundation
Chia-Yi Christian Hospital, Taiwan

Reviewed by:
Dimitri Hemelsoet,
Ghent University Hospital, Belgium
Po-lin Chen,
Taichung Veterans General
Hospital, Taiwan

***Correspondence:**
Xiaochuan Liu
xiaochuanliu05@163.com
Zhimin Yan
zhumin0706@163.com

[†] These authors have contributed equally to this work

‡ORCID:
Xiaochuan Liu
orcid.org/0000-0002-6605-9262

Specialty section:
This article was submitted to Stroke,
a section of the journal
Frontiers in Neurology

Received: 01 August 2020
Accepted: 03 September 2020
Published: 16 October 2020

Citation:
Yao S, Lin B, Liu Y, Luo Y, Xu Q, Huang J, Yan Z and Liu X (2020) Impact of Covid-19 on the Behavior of Community Residents With Suspected Transient Ischemic Attack. Front. Neurol. 11:590406. doi: 10.3389/fneur.2020.590406

Background and Purpose: To investigate the impact of the novel coronavirus disease 2019 (Covid-19) on the behavior of those seeking medical attention for community residents suspected of having had a transient ischemic attack (TIA) during the pandemic.

Methods: This was a community-based cross-sectional study with residents living in two communities located in the suburb of Shanghai. A face-to-face interview was prospectively conducted from 20 May 2020 to 30 June 2020 between community physicians and the community residents. Suspected TIA that occurred during the pandemic was identified by symptoms recalled from the community residents. The behavior of seeking medical attention after the suspected TIA was investigated.

Results: A total of 873 community residents (517 from the Wujing community and 356 from the Maqiao community) took part in face-to-face interviews. Among them, 143 (16.38%) suspected TIA cases were identified. Less than 20% of the community residents suspected of having a TIA went to the hospital during the Covid-19 pandemic. The most common reason for not seeking medical care during the pandemic was still that symptoms disappeared quickly (94.9%); however, the pandemic did have an impact on behavior. Fear of in-hospital infection (55.1%) and of complicated procedures involved in seeking medical attention during the pandemic (55.9%) made community residents hesitate to seek medical attention after the suspected TIA. Residents with a dual attack within 1 week or with aphasia or dysarthria were more likely to seek medical attention during the pandemic.

Conclusion: Our study indicated that the Covid-19 pandemic negatively affected the behavior of those seeking medical attention among community residents with suspected TIA and this might explain part of the reduction in patients presenting with stroke or TIA observed from other reports.

Keywords: COVID-19, community, TIA = transient ischemic attack, stroke, public awareness

INTRODUCTION

The novel coronavirus (COVID-19) has posed a great challenge to the global health care system, especially for those less developed countries (1, 2). With the reallocation of health resources to support the treatment of patients with Covid-19, negative outcomes were observed among other departments of the health care system. Stroke specialists worldwide have reported seeing a significant drop in the number of patients presenting at the stroke center with stroke or transient ischemic attack (TIA) (3–7). Speculation about the cause of this decline include fear of in-hospital infection, the negative impact of the stay-at-home order, and the potential decline in stroke incidence during the pandemic. It's worth noting that several studies from different countries have reported a significant reduction in presentation with TIA or minor stroke, while the risk of recurrent stroke of these patients was not less than that of major stroke (4–6). To our knowledge, only limited data have been available to explore the impact of the Covid-19 pandemic on the behavior of those community residents with suspected TIA seeking medical care. In other words, the pandemic had played a role in the community residents' reluctance to seek medical care after the TIA. In this study, we conducted face-to-face interviews with community residents to identify those who had suspected TIA during the pandemic and investigate the actions they took after the symptom onset. Factors associated with those seeking medical attention immediately after the suspected TIA were also explored.

METHODS AND MATERIALS

Study Design

This study was a community-based cross-sectional survey through face-to-face interviews between community physicians and community residents who seek medical help at community health service centers. Community health service centers in our country have played a role in the management of primary health care and secondary prevention of diseases. Community residents usually go to the community health service centers for the management of chronic diseases such as hypertension or diabetes. Community physicians, also known as general practitioners with 3 years of general practitioner training, treat acute and chronic illnesses and also promote health education to the community residents. The face-to-face interviews were conducted at two community health service centers located in the suburbs of the Minhang district, Shanghai. Wujing community health service center serves about 90,000 residents living in the Wujing community. Maqiao community health service center manages the primary health care for about 100,000 residents living in the Maqiao community. The direct distance between these two health service centers was about 12 km. This study protocol was approved by the Review Board of each health service center. Written informed consent was obtained from all participants. The original data that support this finding can be obtained from the corresponding author upon reasonable request.

Data Collection and Risk Factor Definition

Data were prospectively collected from May 20, 2020 to June 30, 2020. Qualified community physicians with 5 years' working experience conducted the face-to-face interviews to collect the residents' information, including demographic data, living habits, medical history, suspected TIA symptoms they experienced during the pandemic (from 1 February 2020 to 30 April 2020), and the action they took after the symptom onset. The details of the survey were shown in the **Supplementary Material**. We excluded residents who refused to participate at the time they were told the purpose of the survey. Residents with difficulties in communicating with the interviewers (such as dementia or impaired hearing) were also excluded. As for residents who seek medical help at the community health service center accompanied by their family members, we would also have a talk with them during face-face interviews to confirm the symptoms. All the community physicians (Sichen Yao, Beiru Lin) accepted nearly 1 h of online stroke education before the program started from an experienced stroke specialist (Zhimin Yan) to help them identify the transient ischemic attack symptoms and interpret the symptoms in a way that are understandable for community residents. Physical examinations had also been conducted during face-to-face interviews to rule out other common etiologies that may mislead the diagnosis of TIA.

The smoking and drinking habits of community residents were self-reported. Past medical history (hypertension, diabetes, hyperlipidemia, cancer, previous stroke) was defined according to standard definitions and with a medical record from local tertiary hospitals. As for residents with hypertension, an additional question regarding the control of the blood pressure during the pandemic would be asked. Blood pressure higher than 140/90 mmHg was marked in the survey even for only one instance.

Suspected TIA Cases and Public Knowledge of TIA

During the pandemic, suspected TIA cases were identified by symptoms recalled from community residents through face-to-face interviews conducted by trained community physicians. Residents with the following symptoms were considered as suspected TIA cases: sudden motor weakness or sensory deficit in two limbs or one limb and the face; sudden dysphasia; and sudden monocular or binocular blackening, blurred vision, and sudden blackening or absence of visual field (8). As for the suspected TIA cases, the duration of the symptoms and whether there is a "dual" suspected TIA within seven days were also recorded. Of those suspected TIA cases who didn't seek medical help, we listed three predefined potential reasons for them to choose, which included (1) the symptoms disappeared quickly, (2) fear of in-hospital infection with Covid-19, and (3) the complicated nature of procedures for seeking medical help during the pandemic hindered them from going to the hospital. In the last case, we investigated community residents' knowledge of the meaning of the term "transient ischemic attack." They were considered to know about TIA if they could name at least one of the typical symptoms and knew that it is related to ischemic stroke.

TABLE 1 | Baseline characteristics of community residents.

		Whole group	Wujing community	Maqiao community	
		n = 873	*n* = 517	*n* = 356	*P*
Age		65.69 (10.2)	65.79 (10.15)	65.53 (10.27)	0.623
Gender	Male	448 (51.32%)	265 (51.26%)	183 (51.40%)	0.966
	Female	425 (48.68%)	252 (48.74%)	173 (48.60%)	
Drinking habit		202 (23.14%)	123 (23.79%)	79 (22.19%)	0.582
Smoking habit		292 (33.49%)	191 (36.94%)	101 (28.45%)	**0.009**
Past medical history					
Hypertension		600 (68.73%)	312 (60.35%)	288 (80.90%)	**<0.001**
Diabetes		253 (29.01%)	146 (28.24%)	107(30.14%)	0.543
Previous stroke		106 (12.17%)	21 (4.06%)	85 (24.01%)	**<0.001**
Cancer of any type		29 (3.32%)	25 (4.84%)	4 (1.12%)	**0.003**

Data were shown as mean (standard deviation) or number (percentage). P value stands for the differences between the two communities. Bold values are statistically significantly.

Statistical Analysis

Baseline characteristics were compared by chi-square tests or Fisher exact tests for categorical variables and two-sample *t*-tests for continuous variables. The stroke risk prediction scores ABCD2 and ABCD3 for TIA were calculated by adding the score corresponding to the predictors (age, blood pressure, clinical signs, duration of the symptoms, diabetes, and dual attack within 7 days) (9). Factors independently associated with seeking medical help after the suspected TIA were identified through multivariate logistic regression analysis after adjusting for eight confounders (age, gender, drinking habits, smoking habits, hypertension, diabetes, previous stroke, and cancer of any type). Statistical analysis was performed on SPSS version 25.0 (IBM Corp., New York). A two-tailed *P*-value <0.05 was considered statistically significant.

RESULTS

The Baseline Characteristics of Community Residents

Eight hundred and seventy-three community residents (517 from the Wujing community and 356 from the Maqiao community) agreed to take part in a face-to-face interview. The response rate is 97.76%, with 20 residents excluded (four residents refused to participate, eight residents had difficulty communicating with community physicians, and eight residents with other diagnoses). No missing information was found among all the participants. The mean age of all community residents was 65.69 years (standard deviation 10.2, **Table 1**). The prevalence of hypertension, diabetes, previous stroke, and cancer of any type was 68.73, 29.01, 12.17, and 3.32%, respectively. The percentage of smokers in residents living in the Wujing community was higher than for those living in the Maqiao community (36.94 vs. 28.45%, $P = 0.009$). The number of residents with hypertension was larger in the Maqiao community in comparison to the Wujing community (80.9 vs. 60.35%, $P < 0.001$). It is worth noting the prevalence of prior stroke was almost six times higher for residents living in the Maqiao community than for residents living in the Wujing community (24.01 vs. 4.06%, $P < 0.001$). More residents had a past medical history of cancer in the Wujing community than in the Maqiao community (4.84% vs. 1.12%, $P = 0.003$).

The Prevalence of Suspected TIA During the Covid-19 Pandemic

A total of 143 (16.38%) suspected TIA cases were identified from the 873 community residents living in the suburb of Shanghai (89 of them from the Wujing community and 54 from the Maqiao community respectively). As for each subtype of the suspected TIA, 8.39% displayed only motor weakness, 1.4% of them had only aphasia, 25.17% of them suffered only from a visual-field defect, and 31.47% of them had only with the sensory deficit. There were 33.57% of all the suspected TIA cases with more than one typical symptom. Factors associated with the suspected TIA of the 873 community residents in the univariate analysis were older age (mean age 67.95 vs. 65.25, $P = 0.007$), higher prevalence of previous stroke (27.97 vs. 9.07%, $P < 0.001$), and cancer (6.99 vs. 2.6%, $P = 0.007$) (**Supplementary Table 1**).

The Behavior of Community Residents With Suspected TIA

Figure 1 indicates that <20% of the community residents with suspected TIA went to the hospital during the Covid-19 pandemic. The number of residents with suspected TIA who sought medical attention in the Maqiao community was 12 (22.2%) and 13 (14.6%) in the Wujing community respectively (**Figure 1**). Of all 25 residents who sought medical attention, four were diagnosed with high-risk TIA and prescribed dual antiplatelet therapy. Ten were diagnosed with TIA and prescribed antiplatelet therapy (aspirin or clopidogrel). All of them received a clinical assessment from physicians of the emergency department or neurology department. The most common reason for not seeking medical attention during the pandemic was still that the symptom relieved quickly (94.9%) (**Figure 2**). A total of 63.16% of the residents with suspected TIA living in the Wujing community avoided going to the hospital out

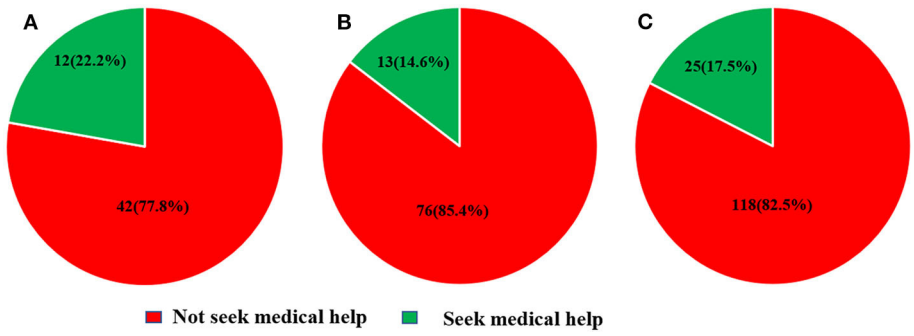


FIGURE 1 | The behavior of community residents with suspected transient ischemic attack. **(A)** Residents from Maqiao community. **(B)** Residents from Wujing community. **(C)** All residents.

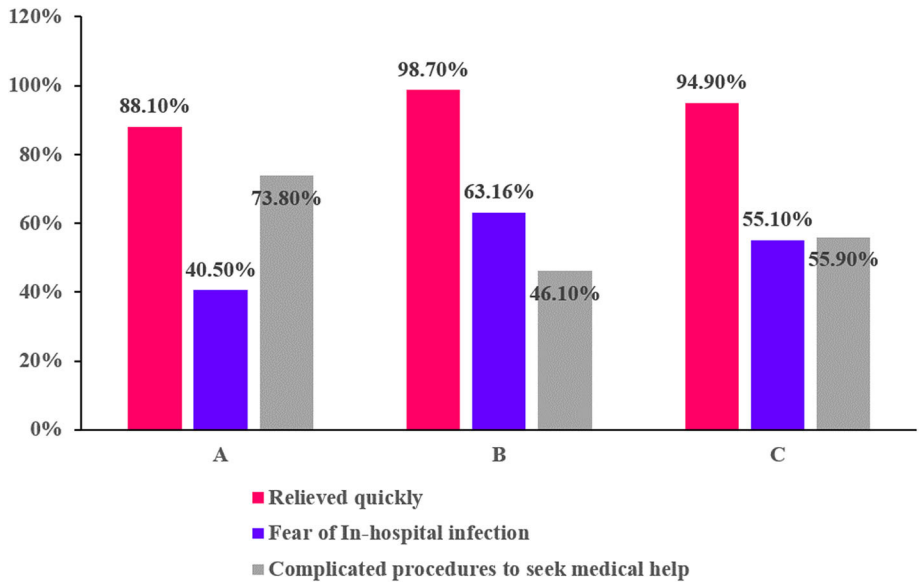


FIGURE 2 | Reasons for not seeking medical care. **(A)** Residents from the Maqiao community. **(B)** Residents from the Wujing community. **(C)** All residents.

of the consideration of in-hospital infection, while for residents living in the Maqiao community, 73.8% of them pointed out that the complicated procedures of seeking medical care during the pandemic made them hesitate to go to the hospital. Of all the residents, only 9 (1.03%) knew TIA. **Table 2** shows a multivariate analysis of factors associated with seeking medical attention during the pandemic. Female residents with suspected TIA were less likely to seek medical attention in comparison with male residents (odds ratio 0.25, 95% Confidence Interval 0.07–0.88, $P = 0.03$). Residents with the previous history of stroke tended to go to the hospital when they had suspected TIA (odds ratio 2.89, 95% Confidence interval 1.07–7.84, $P = 0.037$). As for the manifestation of the suspected TIA, residents with aphasia or dysarthria were more likely to seek medical help (odds ratio 4.25, 95% Confidence interval 1.12–16.08, $P = 0.033$). "Dual" suspected TIA within 1 week were also found to be strongly associated with seeking medical attention among the community residents (odds ratio 6.42, 95% Confidence interval 2.23–18.52, $P = 0.001$). As for the stroke risk prediction score, ABCD3, but not ABCD2, was significantly associated with seeking medical attention.

DISCUSSION

To our knowledge, this is the first study to explore the impact of the Covid-19 pandemic on the behavior of residents living in the community seeking medical attention after TIA. Our study indicates that more than half of community residents with suspected TIA did not go to the hospital during the pandemic. The major reason for this was still that symptoms disappeared quickly, though the pandemic did have an impact on the behavior of those seeking medical attention. When we combined the Covid-19-related causes, 5.08% of all the suspected TIA cases chose Covid-19-related arguments as their sole reasons for not

TABLE 2 | Factors associated with seeking medical attention during the Covid-19 pandemic.

	Univariate analysis	*P*	Multivariate analysis	*P*
	OR (95% CI)		OR (95% CI)	
Age	0.98 (0.93, 1.03)	0.407	0.95 (0.9, 1.01)	0.076
Gender (Female vs. Male)	0.56 (0.22, 1.39)	0.211	0.25 (0.07, 0.88)	**0.03**
Drinking habit	0.75 (0.28, 2.03)	0.571	0.35 (0.1, 1.25)	0.105
Smoking habit	0.65 (0.25, 1.69)	0.38	0.34 (0.1, 1.11)	0.074
Past medical history				
Hypertension	1.13 (0.41, 3.08)	0.814	1.57 (0.49, 5.05)	0.449
Diabetes	0.56 (0.21, 1.52)	0.258	0.41 (0.14, 1.25)	0.119
Previous stroke	2.97 (1.22, 7.24)	**0.017**	2.89 (1.07, 7.84)	**0.037**
Cancer of any type	1.2 (0.24, 0.6)	0.828	1.57 (0.27, 9.11)	0.62
Manifestation of the suspected TIA				
BP higher than 140/90 mmHg	1.39 (0.46, 4.18)	0.56	1.3 (0.38, 4.44)	0.68
Motor weakness in two limbs or in one limb and the face	1.53 (0.64, 3.68)	0.34	0.94 (0.33, 2.68)	0.91
Aphasia or dysarthria	6.17 (1.93, 19.67)	**0.002**	4.25 (1.12, 16.08)	**0.033**
Visual-field defect or monocular blindness	1.82 (0.76, 4.34)	0.18	2.71 (0.97, 7.61)	0.058
Sensory deficit in two limbs or in one limb and the face	1.14 (0.46, 2.78)	0.781	0.87 (0.31, 2.45)	0.79
Two or more of the above symptoms	2.57 (1.07, 6.18)	**0.035**	1.7 (0.61, 4.75)	0.312
Dual attack within 1 week	6.61 (2.61, 16.73)	**<0.001**	6.42 (2.23, 18.52)	**0.001**
Duration of the symptom (more than 1 h)	7.91 (1.25, 50.12)	**0.028**	7.24 (0.99, 53.08)	0.052
The stroke risk of the suspected TIA				
ABCD2	1.19 (0.91, 1.56)	0.213	1.08 (0.78, 1.51)	0.642
ABCD3	1.36 (1.01, 1.68)	**0.005**	1.35 (1.03, 1.78)	**0.03**

BP, blood pressure; TIA, transient ischemic attack; OR, odds ratio; CI, confidence interval; Age, ABCD2, and ABCD3 as continuous variable; Multivariate analysis adjusted for age, gender, drinking habits, smoking habits, hypertension, diabetes, previous stroke, and cancer of any type. Bold values are statistically significantly.

seeking medical care, while 74.58% of them chose Covid-19-related arguments and the quick disappearance of symptoms together as the reasons for not seeking medical care. The decision not to seek medical attention after a suspected TIA is likely to be made for multiple reasons, especially under the circumstances of the pandemic. Of all the suspected TIA cases, only those with dual attack within 1 week or aphasia (or dysarthria) were strongly associated with seeking medical attention during the pandemic. Since the stroke risk after TIA without timely medical care was huge, the outcome for those community residents with suspected TIA who chose to stay at home was potentially devastating (10).

Several hospital-based stroke registry data indicated that the number of admissions for stroke, TIA, or minor stroke decreased significantly during the Covid-19 pandemic. A study in Hong Kong compared the stroke registry data of a comprehensive stroke center 60 days after the first diagnosis of Covid-19 case with the same period in 2019 and noticed a nearly 80% reduction in the presentation with TIA (4). The drop in the presentation with TIA was also observed in Brazil, Germany, and Norway, ranging from 30 to 80% (3, 5, 6).

Following the outbreak of Covid-19 in the Chinese mainland, strict official policies from the centers for disease control and prevention have been released to prevent hospital-related infection of Covid-19. Community residents who want to seek medical attention during the pandemic, first of all, need to make an online appointment with the doctor on the hospital's website or application (11). All patients are required to take their body temperature and finish an online survey regarding travel history and any potential exposure to Covid-19 when they arrive at the hospital. A chest CT scan, blood tests, and nucleic acid testing for Covid-19 were also mandatory examinations for patients admitted to the hospital. As we have shown in the results, we observed that in addition to the impact on the behavior of those seeking medical care of the fear of in-hospital infection with Covid-19, the complicated nature of procedures for seeking medical care during the pandemic also hindered community residents from going to the hospital.

Public stroke education was recommended to be continued during the pandemic to improve the behavior of residents with stroke or TIA, while a study from the United Kingdom indicated that extensive FAST-based public education failed to improve the residents' response to TIA and minor stroke even without the impact of the pandemic (12). Public stroke education program tailored to minor stroke and TIA is urgently needed in the future. In the context of the Covid-19 pandemic, telemedicine seems to be a promising way to support the treatment of TIA (13). It allows communication between community residents and stroke physicians and at the same time avoids interaction with other people. Telemedicine has also shown its potential in delivering guided behavioral therapy for post-stroke anxiety (14).

Limitations

We have to admit that there are several limitations of this study. First, this is not a population-based study, and the residents were all living in the suburbs of Shanghai, resulting in differences in the prevalence of TIA in comparison with a population-based study published in 2015, which revealed that the prevalence of suspected TIA was 8.68% (15). The education level of community residents was lower in comparison with residents living in the city, which may lead to the discrepancy of seeking medical attention after TIA. Second, in addition to the three predefined potential reasons for not seeking medical care, there might be other reasons, such as living alone or the negative impact of the stay-at-home order. However, they were not the focus of this study. Third, in consideration of errors in recollection of the community residents, we conducted only one-month-and-a-half face-to-face interview, which may lead to less representative samples of the residents living in the two communities. Since the participants in our study are seeking management of chronic diseases when they arrive at the community health service center, older age and higher prevalence of vascular risk factors may also limit the generalizability of the conclusion. Last, the diagnosis of TIA can sometimes be challenging even for experienced stroke physicians. Although we conducted an online stroke education for the two community physicians, those identified suspected TIA cases were not adjudicated or verified by a stroke physician, leading to potential misdiagnosis of the patient. As indicated in a population-based study including 98,658 participants from 31 provinces across mainland China, the prevalence of suspected TIA identified by trained staff was 8560/98658 (8.68%), while it decreased to 2780/98658 (2.82%) after being verified by neurologists (15). The over-diagnosis of suspected TIA may lead to a lower rate of patients with suspected TIA during the pandemic seeking medical attention.

CONCLUSION

Our study indicates that <20% of the community residents with suspected TIA went to the hospital during the Covid-19 pandemic. The most common reason for not going to the hospital was still that the symptoms disappeared quickly; however, the pandemic did have an impact on the behavior of seeking medical attention. Fear of in-hospital infection and complicated procedures involved in seeking medical attention during the pandemic contributed to the failure to seek medical attention after the suspected TIA. Residents with a dual attack within 1 week or with aphasia or dysarthria were more likely to seek medical attention during the pandemic.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

These studies involving human participants were reviewed and approved by Institutional Review Board of Wujing community health service center and Maqiao community health service center. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SY and BL: study concept, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. YLi and YLu: analysis and interpretation of data, drafting of the manuscript. QX: acquisition of data, analysis and interpretation of data. JH: analysis and interpretation of data. ZY: study design, study supervision or coordination, and revising the manuscript. XL: study concept and design, study supervision or coordination, and revising the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

I want to thank SY and BL personally for their selfless help and passion that are so critical to this work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.590406/full#supplementary-material

REFERENCES

1. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke*. (2020) 15:361–4. doi: 10.1177/1747493020923472
2. Mahase E. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. *BMJ*. (2020) 368:m1036. doi: 10.1136/bmj.m1036
3. Kristoffersen ES, Jahr SH, Thommessen B, Ronning OM. Effect of Covid-19 pandemic on stroke admission rates in a Norwegian population. *Acta Neurol Scand*. (2020). doi: 10.1111/ane.13307. [Epub ahead of print].
4. Teo KC, Leung WCY, Wong YK, Liu RKC, Chan AHY, Choi OMY, et al. Delays in stroke onset to hospital arrival time during COVID-19. *Stroke*. (2020) 51:2228–31. doi: 10.1161/STROKEAHA.120.030105
5. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmunzer B, Barlinn K, et al. Acute stroke in times of the COVID-19 pandemic: a multicenter study. *Stroke*. (2020) 51:2224–7. doi: 10.1161/STROKEAHA.120.030395
6. Diegoli H, Magalhaes PSC, Martins SCO, Moro CHC, Franca PHC, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke*. (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
7. Montaner J, Barragan-Prieto A, Perez-Sanchez S, Escudero-Martinez I, Moniche F, Sanchez-Miura JA, et al. Break in

the stroke chain of survival due to COVID-19. *Stroke*. (2020) 51:2307–14. doi: 10.1161/STROKEAHA.120.030106
8. Amarenco P. Transient ischemic attack. *N Engl J Med*. (2020) 382:1933–41. doi: 10.1056/NEJMcp1908837
9. Kiyohara T, Kamouchi M, Kumai Y, Ninomiya T, Hata J, Yoshimura S, et al. ABCD3D and ABCD3D-I scores are superior to ABCD2 score in the prediction of short- and long-term risks of stroke after transient ischemic attack. *Stroke*. (2014) 45:418–25. doi: 10.1161/STROKEAHA.113.003077
10. Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular S. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ*. (2004) 328:326. doi: 10.1136/bmj.37991.635266.44
11. Wang X, Chen Y, Li Z, Wang D, Wang Y. Providing uninterrupted care during COVID-19 pandemic: experience from Beijing Tiantan Hospital. *Stroke Vasc Neurol*. (2020) 5:180–4. doi: 10.1136/svn-20200-000400
12. Wolters FJ, Li L, Gutnikov SA, Mehta Z, Rothwell PM. Medical attention seeking after transient ischemic attack and minor stroke before and after the UK Face, Arm, Speech, Time (FAST) public education campaign: results from the Oxford vascular study. *JAMA Neurol*. (2018) 75:1225–33. doi: 10.1001/jamaneurol.2018.1603
13. Klein BC, Busis NA. COVID-19 is catalyzing the adoption of teleneurology. *Neurology*. (2020) 94:903–4. doi: 10.1212/WNL.0000000000009494
14. Chun HY, Carson AJ, Tsanas A, Dennis MS, Mead GE, Calabria C, et al. Telemedicine cognitive behavioral therapy for anxiety after stroke: proof-of-concept randomized controlled trial. *Stroke*. (2020) 51:2297–306. doi: 10.1161/STROKEAHA.120.029042
15. Wang Y, Zhao X, Jiang Y, Li H, Wang L, Johnston SC, et al. Prevalence, knowledge, and treatment of transient ischemic attacks in China. *Neurology*. (2015) 84:2354–61. doi: 10.1212/WNL.0000000000001665

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 19 October 2020
doi: 10.3389/fneur.2020.587226

Encephalopathy in COVID-19 Presenting With Acute Aphasia Mimicking Stroke

*Umberto Pensato[1†], Lorenzo Muccioli[1†], Elena Pasini[2], Maria Tappatà[2], Lorenzo Ferri[1], Lilia Volpi[2], Laura Licchetta[2], Stella Battaglia[2], Giada Rossini[3], Isabella Bon[3], Maria Carla Re[3], Luigi Cirillo[2], Luigi Simonetti[2], Laura Ludovica Gramegna[2], Roberto Michelucci[2], Pietro Cortelli[1,2], Andrea Zini[2] and Francesca Bisulli[1,2]**

[1] Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy, [2] IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy[‡], [3] Microbiology Unit, DIMES, University of Bologna, Bologna, Italy

Introduction: Neurological manifestations are emerging as relatively frequent complications of corona virus disease 2019 (COVID-19), including stroke and encephalopathy. Clinical characteristics of the latter are heterogeneous and not yet fully elucidated, while the pathogenesis appears related to neuroinflammation in a subset of patients.

Case: A middle-aged man presented with acute language disturbance at the emergency department. Examination revealed expressive aphasia, mild ideomotor slowing, and severe hypocapnic hypoxemia. Multimodal CT assessment and electroencephalogram (EEG) did not reveal any abnormalities. COVID-19 was diagnosed based on chest CT findings and positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription PCR (RT-PCR) on nasopharyngeal swab. The following day, neurological symptoms progressed to agitated delirium and respiratory status worsened, requiring admission to the ICU and mechanical ventilation. Brain MRI and cerebrospinal fluid (CSF) studies were unremarkable. RT-PCR for SARS-CoV-2 on CSF was negative. He received supportive treatment and intravenous low-dose steroids. His neurological and respiratory status resolved completely within 2 weeks.

Conclusions: We report a patient with reversible COVID-19-related encephalopathy presenting as acute aphasia, mimicking stroke or status epilepticus, eventually evolving into delirium. Although large-vessel stroke is frequently encountered in COVID-19, our case suggests that focal neurological deficits may occur as the earliest feature of encephalopathy. Neurological status reversibility and the absence of abnormalities on brain MRI are consistent with a functional rather than a structural neuronal network impairment.

Keywords: cytokine release syndrome, car-t, ICANS, neurology, delirium, SARS-CoV-2, encephalitis

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh, Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Paolo Calabresi, Catholic University of the Sacred Heart, Italy
Krishna Nalleballe, University of Arkansas for Medical Sciences, United States

***Correspondence:**
Francesca Bisulli
francesca.bisulli@unibo.it

[†] *These authors have contributed equally to this work*

[‡] *Full Member of the ERN EpiCARE*

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *25 July 2020*
Accepted: *24 August 2020*
Published: *19 October 2020*

Citation:
Pensato U, Muccioli L, Pasini E, Tappatà M, Ferri L, Volpi L, Licchetta L, Battaglia S, Rossini G, Bon I, Re MC, Cirillo L, Simonetti L, Gramegna LL, Michelucci R, Cortelli P, Zini A and Bisulli F (2020) Encephalopathy in COVID-19 Presenting With Acute Aphasia Mimicking Stroke. Front. Neurol. 11:587226. doi: 10.3389/fneur.2020.587226

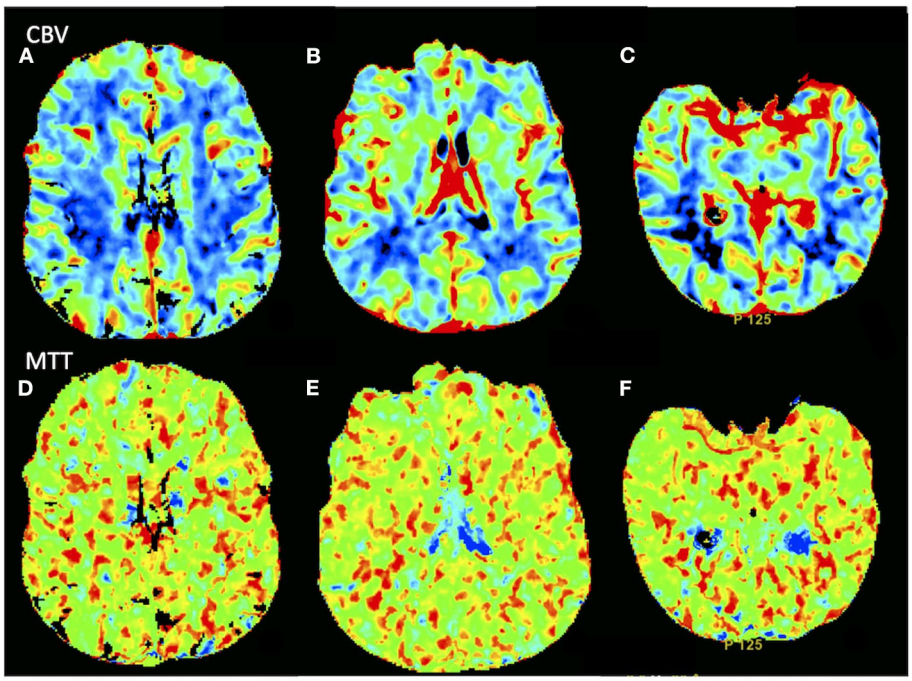


FIGURE 1 | Computed tomography perfusion showed no asymmetry in **(A–C)** CBV and **(D–F)** MTT parametric maps. CBV, cerebral blood volume; MTT, mean transit time.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is characterized predominantly by respiratory symptoms, although neurological manifestations are increasingly described, including encephalopathy and stroke (1, 2). A higher incidence of large artery ischemic stroke has been reported, also in young patients without cardiovascular risk factors (3). Coagulopathy and endothelial dysfunction secondary to an infection-induced systemic inflammatory response likely play a major role (4). The pathogenesis of encephalopathy remains more debated. A role of neuroinvasion by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not supported in most cases (1, 5, 6), whereas indirect effects related to hypoxemia, multiple organ dysfunction syndrome, and cytokine storm are suggested as potentially underlying causes (7). Hereby, we report the case of a middle-aged man who was thoroughly investigated for acute expressive aphasia mimicking stroke or status epilepticus, eventually evolving to encephalopathy with a self-limited course.

CASE

A hypertensive, dyslipidemic, right-handed 54-years-old man with a 1-week history of sore throat, dysgeusia, and hyposmia presented with acute language disturbance developed within 1 h at the emergency department.

Body temperature was 37.5°C. Neurological examination revealed expressive aphasia and mild ideomotor slowing without further cognitive alterations. His speech was slow, effortful, and contained phonological and neological paraphasias, whereas comprehension was preserved. Suspecting a stroke, the patient underwent multimodal CT assessment, which was unrevealing (**Figure 1**). Electroencephalogram (EEG) and brain MRI were also unremarkable. Arterial blood gas analysis and blood tests showed hypocapnic hypoxemia (PaO_2/FiO_2 = 252), elevated D-dimer level (3.32 mg/L), lymphopenia, and elevated inflammatory markers (**Supplementary Table 1**). COVID-19 was diagnosed on the basis of bilateral interstitial pneumonia on chest CT and positive RT-PCR for SARS-CoV-2 on nasopharyngeal swab. Cerebrospinal fluid (CSF) examination showed proteins 41 mg/dl, glucose 62 mg/dl, and nucleated cells 2/mmc. Microbiology analysis of CSF was unremarkable, including negative RT-PCR for SARS-CoV-2, herpesvirus DNA [herpes simplex virus types 1 and 2 (HSV1, HSV2), cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus 6 (HHV6), and varicella zoster virus (VZV)], enterovirus DNA, Gram stain, and bacterial culture. The patient was hospitalized and started on oxygen therapy, hydroxychloroquine, low-molecular-weight heparin, intravenous low-dose steroids, and antibiotics. The following day, neurological symptoms progressed to agitated delirium, and his respiratory status worsened, requiring admission to the ICU. The patient was sedated and placed on mechanical ventilation for 5 days. Subsequently, he appeared oppositional and disinhibited, while his language disturbance resolved, with the exception of

Abbreviations: CRS, cytokine releasing syndrome; CAR, chimeric antigen receptor; ICANS, immune-effector-associated neurotoxicity syndrome.

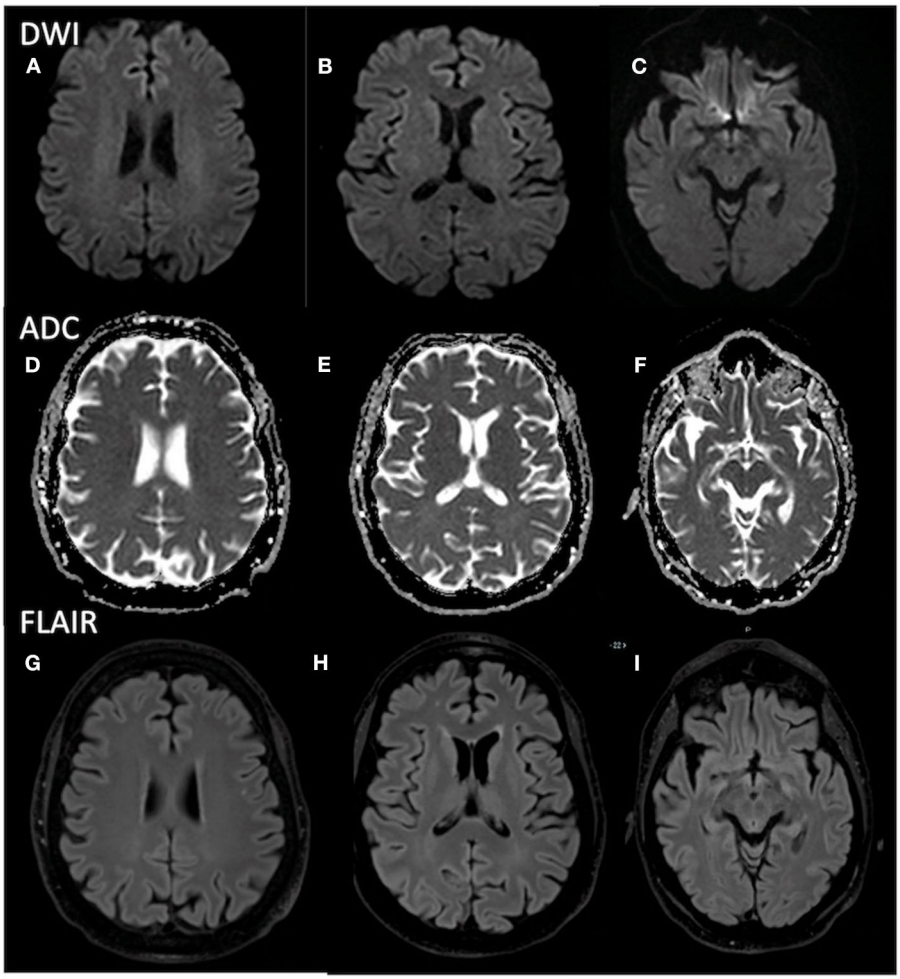


FIGURE 2 | Brain MRI shows no abnormalities in **(A–C)** DWI, **(D–F)** ADC maps, and **(G–I)** FLAIR images. MRI, magnetic resonance imaging; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; FLAIR, fluid-attenuated inversion recovery.

rare anomia. In the following days, both his respiratory and neurological status progressively improved, normalizing in 7 days. A follow-up EEG and brain MRI performed 10 days after aphasia onset (**Figure 2**) did not show any abnormalities. After 60 days, the patient referred only mild dysgeusia and was otherwise asymptomatic.

DISCUSSION

Our patient presented with acute expressive aphasia mimicking an acute stroke, lasting >24 h, in the context of symptoms related to SARS-CoV-2 infection. He had cardiovascular risk factors and elevated D-dimer levels at presentation. COVID-19 has been associated with an increased incidence of stroke (2, 8, 9), which may also represent the presenting manifestation (3, 10). Large-vessel ischemic strokes in COVID-19 patients have been reported to occur in multiple vascular territories, in young patients without cardiovascular risk factors, and in patients with prophylactic anticoagulation. Likely, the virus-related systemic inflammation leads to vascular endothelial dysfunction and coagulopathy. Accordingly, COVID-19 patients who develop ischemic stroke usually showed markedly elevated D-dimer levels and more severe systemic involvement compared with COVID-19 patients without cerebrovascular events (11). Surprisingly, multimodal CT assessment studies did not reveal any focal hypoperfusion area or artery vessel abnormalities in our patient, and two brain MRI definitively excluded stroke or structural lesions. A focal status epilepticus ("aphasic status") was also excluded, based on the absence of EEG abnormalities (12).

Neurological status rapidly progressed to encephalopathy; thus, we interpreted his language disturbance as an early focal feature of a generalized central nervous system (CNS) involvement. Encephalopathy in COVID-19 has been shown to have various manifestations with ranging severities, characterized by subacute onset and fluctuations or progressive course, eventually reversible (5). Although language disturbances have already been described in this syndrome as early features (13),

an acute presentation mimicking stroke has never been reported so far. Encephalopathy in the contest of potentially neurotropic virus infection, such as SARS-CoV-2, may raise suspicion of a viral encephalitis; however, CSF and MRI findings in our patient were inconsistent with this hypothesis, in line with the vast majority of COVID-19 patients presenting with central neurological manifestations (1, 5, 6). Accordingly, clinical responses observed to various immunomodulatory treatments, such as corticosteroids (13, 14) and plasmapheresis (15), suggest an immune-mediated pathogenesis, at least for a subgroup of patients. Recently, cytokine-mediated neuroinflammation has been proposed as the underlying pathogenesis of COVID-19-related encephalopathy/encephalitis (7, 13, 16), a peculiar pathogenic mechanism also responsible for immune effector cell-associated neurotoxicity syndrome (ICANS) (17–20). This is a neuropsychiatric complication of chimeric antigen receptor T-cell therapy, which also shares clinical features with encephalopathy related to COVID-19 (20) and is typically associated with cytokine release syndrome (18). Interestingly, expressive aphasia often represents the first manifestation of neurotoxicity (18, 19), and a case series reported language impairment as the earliest feature in 19/22 patients who later developed severe ICANS (17). In this disease, aphasia usually develops over hours/days, although, as in our patient, language symptoms may present also acutely mimicking stroke (19). In our patient, focal neurological symptoms presented without a concomitant brain lesion, suggesting a functional rather than structural neuronal network impairment, as in ICANS. Some limitations to this report should be noted. Indeed, we did not test repetition, reading and writing at first evaluation, and did not perform frontal assessment batteries; thus, we could not rule out with certainty that the language disturbance was secondary to bradypsychia related to an incoming global encephalopathy. However, at presentation, there were no signs of frontal lobe syndrome or encephalopathy such as fluctuating/decreased attention or level of consciousness. Thus, his neurological presentation was clinically indistinguishable from acute onset expressive aphasia caused by cerebrovascular diseases, requiring a comprehensive diagnostic evaluation for stroke.

CONCLUSIONS

We report a patient with COVID-19-related encephalopathy presenting with acute aphasia, mimicking stroke. Although large-vessel stroke is frequently encountered in COVID-19, our case suggests that COVID-19-related encephalopathy may present with acute language disturbances as the earliest feature. Neurologists should be aware of this clinical presentation, as it may have an impact on the differential diagnosis and management of these patients.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

UP and LM drafted the manuscript. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.587226/full#supplementary-material

REFERENCES

1. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
3. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. *N Engl J Med*. (2020) 382:e60. doi: 10.1056/NEJMc2009787
4. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. *Transl Stroke Res*. (2020) 11:322–5. doi: 10.1007/s12975-020-00818-9
5. Koralnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. *Ann Neurol*. (2020) 88:1–11. doi: 10.1002/ana.25807
6. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of covid-19. *N Engl J Med*. (2020) 383:989–92. doi: 10.1056/NEJMc2019373
7. Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N, et al. Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. *Gen Hosp Psychiatry*. (2020) 65:47–53. doi: 10.1016/j.genhosppsych.2020.05.008
8. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke*. (2020) 15:361–4. doi: 10.1177/1747493020923472
9. Frisullo G, De Belvis AG, Marca GD, Angioletti C, Calabresi P. Stroke integrated care pathway during COVID-19 pandemic. *Neurol Sci*. (2020) 41:1673–5. doi: 10.1007/s10072-020-04480-9
10. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain Behav Immun*. (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077
11. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586
12. Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, et al. Focal status epilepticus as unique clinical feature of COVID-19: a case report. *Seizure*. (2020) 78:109–12. doi: 10.1016/j.seizure.2020.04.009
13. Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonghi I, Gazzina S, et al. Steroid-responsive encephalitis in coronavirus disease 2019. *Ann Neurol*. (2020) 88:423–7. doi: 10.1002/ana.25783

14. Pugin D, Vargas MI, Thieffry C, Schibler M, Grosgurin O, Pugin J, et al. et al. COVID-19-related encephalopathy responsive to high doses glucocorticoids. *Neurology*. (2020) 95:543–6. doi: 10.1212/WNL.0000000000010354
15. Dogan L, Kaya D, Sarikaya T, Zengin R, Dincer A, Akinci IO, et al. Plasmapheresis treatment in COVID-19-related autoimmune meningoencephalitis: case series. *Brain Behav Immun*. (2020) 87:155–8. doi: 10.1016/j.bbi.2020.05.022
16. Cani I, Barone V, D'Angelo R, Pisani L, Allegri V, Spinardi L, et al. Frontal encephalopathy related to hyperinflammation in COVID-19. *J Neurol*. (2020). doi: 10.1007/s00415-020-10057-5. [Epub ahead of print].
17. Santomasso BD, Park JH, Salloum D, Riviere I, Flynn J, Mead E, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov*. (2018) 8:958–71. doi: 10.1158/2159-8290.CD-17-1319
18. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. (2019) 25:625–38. doi: 10.1016/j.bbmt.2018.12.758
19. Rubin DB, Danish HH, Ali AB, Li K, LaRose S, Monk AD, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. *Brain*. (2019) 142:1334–48. doi: 10.1093/brain/awz053
20. Muccioli L, Pensato U, Cani I, Guarino M, Cortelli P, Bisulli F. COVID-19-associated encephalopathy and cytokine-mediated neuroinflammation. *Ann Neurol*. (2020) 88:860–1. doi: 10.1002/ana.25855

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 20 October 2020
doi: 10.3389/fneur.2020.555202

Differential Diagnosis and Hospital Emergency Management for Fastlane Treatment of Central Nervous System Infection Under the COVID-19 Epidemic in Changsha, China

*Haojun Yang[1], Yunfang Chi[2], Zhuohui Chen[1], Yishu Fan[1], Haiyue Wu[1], Xinhang Hu[1], Tong Wu[1], Bo Xiao[1] and Mengqi Zhang[1]**

[1] Department of Neurology, Xiangya Hospital of Central South University, Changsha, China, [2] Laizhou People's Hospital, Yantai, China

Importance: Corona virus disease 2019 (COVID-19) has long latent period, strong infectivity, and non-specific symptoms and signs in the upper respiratory tract. Some initial neurological symptoms appear, including dizziness, headache, seizures, slurred speech, disturbance of consciousness, and limb paralysis among a few COVID-19 patients, which share similar manifestations with central nervous system (CNS) infection. Improving the diagnostic efficiency of suspected CNS infection patients on the basis of preventing and controlling COVID-19 plays a key role in preventing nosocomial and cross infections. This study intends to formulate a hospital emergency management system of fastlane treatment of CNS infection for epidemic prevention and control, aiming at providing references and guidelines for the government and medical institutions to improve the efficiency of treating CNS infection patients in the clinical practice during COVID-19.

Observations: This study formulated a framework of a fastlane treatment of CNS infection based on the cooperation of resources and experience, aiming at the key and difficult problems faced by the hospital emergency management system during the COVID-19 outbreak in Changsha, China. The main problem of formulating the hospital emergency management system is efficiently identifying whether CNS infection was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The framework improves the efficiency of diagnosing and treating CNS infections by standardizing the diagnosis and treatment process of patients in emergency observation and strengthening the management of inpatient wards, aiming at assisting medical staff during clinical practice.

Conclusions and Relevance: The hospital emergency management system of a fastlane treatment of CNS infection for epidemic prevention and control of the COVID-19 outbreak is a professional and multisystem project, which needs the cooperation of various resources and the experience of clinical leadership.

Keywords: corona virus disease 2019, management, epidemic prevention and control, differential diagnosis, CNS infection

OPEN ACCESS

Edited by:
Jesús Porta-Etessam, Hospital Clínico San Carlos, Spain

Reviewed by:
Sar Garcia-Ptacek, Karolinska Institutet (KI), Sweden
David García-Azorín, Hospital Clínico Universitario de Valladolid, Spain

***Correspondence:**
Mengqi Zhang
zhangmengqi8912@163.com

Specialty section:
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

Received: *03 June 2020*
Accepted: *09 September 2020*
Published: *20 October 2020*

Citation:
Yang H, Chi Y, Chen Z, Fan Y, Wu H, Hu X, Wu T, Xiao B and Zhang M (2020) Differential Diagnosis and Hospital Emergency Management for Fastlane Treatment of Central Nervous System Infection Under the COVID-19 Epidemic in Changsha, China. Front. Neurol. 11:555202. doi: 10.3389/fneur.2020.555202

INTRODUCTION

In December 2019, an outbreak of novel coronavirus pneumonia (NCP) occurred in Wuhan, Hubei province, and rapidly spread to the whole of China, Southeast Asia, Europe, and the Americas. The State Health Committee of the People's Republic of China (PRC) included novel coronavirus pneumonia as a category B infectious disease, but management measures for category A infectious diseases were adopted in China due to its strong infectivity, meaning that new discovered cases are required to be reported within 2 and 6 h in the city and countryside, respectively (1). The World Health Organization (WHO) named the disease as coronavirus disease 2019 (COVID-19), and the International Committee on the Taxonomy of Viruses named the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Major clinical presentations of COVID-19 are initially characterized by fever, fatigue, and cough, which are almost indistinguishable from influenza (3, 4). However, some patients present with non-respiratory symptoms at onset, such as in the nervous, digestive, and cardiovascular systems (5–7). Central nervous system (CNS) infections mostly refers to inflammation caused by pathogens (i.e., bacteria, viruses, and parasites) invading into the CNS, which are mostly manifested as headache, vomiting, convulsions, dysphagia, paresis, anosmia, etc. (8, 9). Patients infected by SARS-CoV-2 can complicate with some neurological symptoms, such as headache, confusion, dizziness, impaired consciousness, altered mental status, ataxia, epilepsy, and skeletal muscle symptoms (10–14), combined with some respiratory symptoms, which could be misdiagnosed as CNS infections caused by other pathogens. These misdiagnoses not only delay the treatment but also increase the exposure risk of other patients and healthcare workers, or even nosocomial exposure risk (9, 15). Therefore, additional attention should be paid to the screening and identification of patients with CNS infection in clinical practice. In this paper, we discuss and summarize the difficulties and countermeasures faced in the fastlane treatment for diagnosis of CNS infections during the COVID-19 outbreak, hoping to provide reference and assistance to other physicians.

RESEARCH OVERVIEW ON CORONAVIRUS DISEASE 2019

Coronaviruses (CoVs) are a family of enveloped, unsegmented, positive-sense single-strand RNA viruses that are divided into four genera (α, β, γ, δ), with a diameter of 80–120 nm, and a whole-genome length of 27–32 kb. Currently, CoVs have the largest genome size among RNA viruses (16). CoVs mainly infect the respiratory, digestive, and CNS of humans and livestock (17, 18). CoVs were first isolated from chickens in 1937 and humans in 1965. Electron microscope observations showed that the outer membrane of the virus particles contain obvious and regularly arranged protrusions that resemble the crowns of European monarchs in the Middle Ages. Therefore, they were named as "coronaviruses." The RNA of CoVs is extremely similar to the mRNA of eukaryotic cells as its 5′ end contains a methylation cap structure, and its 3′ end contains a polyA tail (19). This causes its genomic RNA to skip the RNA–DNA–RNA transcription process, as the RNA can be used as a template for translation. Therefore, there is an extremely high recombination rate between RNAs in CoVs, causing the virus to be prone to mutations (20). The severe acute respiratory syndrome (SARS) outbreak in 2003 and the Middle East respiratory syndrome (MERS) outbreak in 2012 showed that novel CoVs have the potential for animal-to-human and human-to-human transmissions. On December 2019, an outbreak of COVID-19 occurred in Wuhan in the Hubei province and rapidly spread to the whole of China, Southeast Asia, Europe, and the Americas due to its high infectivity, which has attracted global attention. Globally, as of 3:49 pm CEST, July 21, 2020, there have been 14,562,550 confirmed cases of COVID-19, including 607,781 deaths, reported to WHO (21). SARS-CoV-2 is an enveloped positive-sense single-strand RNA virus that contains 29,000 nucleotides and is highly homologous to SARS-like coronaviruses in bats (96.2%) (12). SARS-CoV-2 is the seventh coronavirus to infect humans that has been discovered (the others are HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS-CoV). Its main transmission routes include respiratory droplets and direct contact (12, 22). Other routes such as aerosol, fecal–oral, and mother-to-child transmission still require further studies for confirmation (23, 24). In addition, the human population is generally susceptible, the prognosis is poorer, and the mortality rate is higher in patients with underlying diseases. Compared with SARS, COVID-19 has a longer incubation period, higher infectivity, and patients may not show specific upper respiratory tract signs and symptoms (25). COVID-19 also tends to spread widely, which poses a great challenge in epidemic control. As there is no effective treatment or vaccine at present, the best measures currently are to control sources of infection, early diagnosis, reporting, quarantine, supportive treatment, and timely release of information on the epidemic to prevent unnecessary panic. For individuals, reasonable preventive measures such as good personal hygiene, effective masks, timely indoor ventilation, and avoiding crowded places, can aid in controlling COVID-19.

EFFECTS AND EFFECTOR MECHANISMS OF SARS-CoV-2 ON CNS

Coronavirus particles contain an envelope that is composed of a lipid bilayer and mostly glycosylated surface proteins. The envelope surface contains three types of glycoproteins: (1) spike proteins that are key structures for CoV infection and pathogenicity that can recognize and bind to surface receptors on host cells; (2) membrane proteins that are responsible for transmembrane transportation, budding, and release of viruses; and (3) envelope proteins that are responsible for envelope binding. CoVs cannot only invade the respiratory system and immune system but also the nervous, digestive, and cardiovascular systems to cause multisystem damage (26). A study showed that neurotrophic mouse hepatitis virus (MHV) can invade the brain 7 days after intranasal infection to cause encephalitis, meningitis, and demyelination (27). In recent

years, SARS-CoV, MERS-CoV, MHV, HCoV-OC43, and other β-coronaviruses have been shown to invade the nervous system. These viruses can infect monocytes and macrophages or vascular endothelial cells to cross the blood–brain barrier and enter the brain. Angiotensin-converting enzyme 2 (ACE2) is widely expressed in monocytes and macrophages as well as alveolar, tracheal, bronchial, and neuronal cells, and is an important target for SARS-CoV invasion (28, 29). SARS-CoV uses the spike protein on its envelope surface to recognize and bind to ACE2 to cause fusion between the virus and host cell, and the genomic RNA of the virus is released into the cytoplasm for replication. SARS-CoV-infected cells can promote T-lymphocyte infiltration, the release of inflammatory factors, and demyelination, resulting in encephalitis and meningitis. SARS-CoV-2 may also have nerve invasion ability since it has the same receptor as SARS-CoV, but further studies are still needed (30, 31).

CLINICAL PRESENTATION OF NERVOUS SYSTEM INFECTION IN COVID-19

Major clinical presentations of COVID-19 include fever, fatigue, and dry cough. However, some patients present with non-respiratory symptoms at onset, such as in the nervous, digestive, and cardiovascular systems. A retrospective study of 214 confirmed COVID-19 patients in Wuhan found that 36.4% showed characteristic nervous system presentation (5). Neurological manifestations can further be subdivided into the CNS symptoms (dizziness, headache, seizures, ataxia, and altered mental status) (32, 33) and peripheral nervous system (anosmia, chemosensory dysfunction, myalgia, weakness, and neuropathy) (33–35) symptomatology. However, it is difficult to distinguish causal relationship from incidental comorbidity. Some other groups reported that nervous system symptoms such as acute cerebrovascular disorder, loss of consciousness, and muscle damage were more frequent and severe in patients with more severe disease course (36). Furthermore, altered mental status, mainly caused by several metabolic and systemic disturbances, has been associated with a worse prognosis (37, 38), and headache and anosmia, which could be an isolated symptom of COVID-19, has been related with a lower probability of death (39, 40). The presence of chronic neurological disorders (CNDs) is also an independent predictor of mortality in hospitalized COVID-19 patients (41). Because the abovementioned CNS symptoms can also appear in patients with hypoxemia, it is impossible to diagnose SARS-CoV-2 infection from clinical manifestations alone. Previous studies indicate the possibility of the neuroinvasive potential of SARS-CoV-2 being the cause of acute respiratory failure, which manifests as respiratory distress and inability to breathe spontaneously (42). Disturbance in smell and taste have become the predominant neurological symptom of COVID-19, which is seen in nearly 80% of patients infected with SARS-CoV-2 (43–47). The loss of smell and taste is found to be more predictive than all other symptoms, such as fatigue, fever, or cough in one recent observation study, which included more than 2 million participants (48). Postviral anosmia has been hypothesized to be the consequence of direct damage to the olfactory sensory neurons (OSNs) responsible for odor detection in the olfactory epithelium (49, 50). However, more evidence in hamster and COVID-19 patients has shown that sustentacular cells are primary targets for SARS-CoV-2 infection rather than OSN (51–53). It still needs further evidence to reveal the mechanisms through which SARS-CoV-2 influences chemical sensing.

AUXILIARY TESTS FOR NERVOUS SYSTEM INFECTIONS IN COVID-19

Blood routine tests show normal or slightly reduced total white blood cell and lymphocyte counts at the early stage of disease. Additionally, studies found lower blood lymphocyte counts among patients with CNS symptoms, which were more frequent and severe in patients with more severe disease course, than those without (5, 12, 34). However, severely ill patients with lower blood lymphocyte counts were more prone to develop neurological complications (54), so we still cannot tell the causal relationship. The D-dimer levels of severe patients were higher than non-severe patients, which may explain why cerebrovascular disease was more frequent and severe in patients with more severe course of COVID-19. Patients with muscular symptoms had higher creatine kinase and lactate dehydrogenase levels than those without muscular symptoms (55). Not every neurologic problem stems from a primary brain injury (56). It is important to rule out systemic causes of neurological symptoms in COVID-19 patients, such as hepatic, renal failure, hypercapnia/hypoxic encephalopathies, coinfections, and treatment-related adverse effects, by blood gas analysis (ABG), liver and renal function tests, blood ammonia, evoked potential (EP), quantitative spectral electroencephalography (EEG) analysis, cerebrospinal fluid (CSF) test, magnetic resonance imaging (MRI), medication and treatment history, etc. (57–60). Previous studies have found some red flags to suspect COVID-19 presence in patients with headache, such as fever, cough, systemic symptoms, prior medical history, some neurologic symptoms, and increased C-reactive protein (61). There were no universal red flags, being the necessary comprehensive evaluation of all of them.

EEG

A retrospective study showed that the most common indications for EEG among acutely ill COVID-19 patients were new onset encephalopathy (68.2%) and seizure-like events (63.6%), even among patients without prior history of seizures (62). Additionally, sporadic epileptiform discharges (EDs) were present in 40.9% COVID-19 patients, among whom frontal sharp waves (88.9%) were found (62). Triphasic sporadic waves, generalized periodic discharges (GPDs), multifocal periodic discharges (MPDs), and rhythmic delta activity (RDA) were also found among COVID-19 patients with neurological symptoms (63–65). EEG alterations were not specific, which may be related to an underlying morbid status or metabolic and coagulation derangements (65). The EEG of hypercapnia is not specific, with background slowing progressing to discontinuous patterns

and burst suppression (56). Although much information may be gleaned from EEG, non-specific EEG findings or abnormalities should not be considered as being specific for COVID-19-related encephalopathy.

Cranial Imaging

CT or MRI examinations of encephalitis patients may/may not show abnormalities. Preliminary screening with CT can aid in excluding space-occupying lesions. The most frequent MRI findings were signal abnormalities in the medial temporal lobe (43%), non-confluent multifocal white matter hyperintense lesions on FLAIR and diffusion sequences with variable enhancement and associated with hemorrhagic lesions (30%), and extensive and isolated white matter microhemorrhages (24%) (66–68). A consistent MRI finding, multifocal laminar cortical brain lesions were reported in neuro-COVID-19 patients, which were speculated to be related to a possible transient dysregulation of vasomotor reactivity (69, 70). In particular, the cortical involvement may indicate a possible vascular mechanism more shifted toward transient vasoconstriction (69). Additionally, the presence of microbleeds in unusual distribution were found in nine critically ill COVID-19 patients, with a specific predilection for the corpus callosum with or without "blooming artifact" (71, 72). The anterior or posterior limbs of the internal capsule (5/9 patients) and middle cerebellar peduncles (5/9 patients) were other uncommon locations of microbleeds, which could only be depicted in SWI sequence as hypoattenuating foci (71). The study of structural brain abnormalities in 19 non-survivors of COVID-19 performed early ($\leq$24 h) after death found parenchymal brain abnormalities, such as subcortical micro- and macrobleeds (two decedents), non-specific deep white matter changes (one decedent) and cortico-subcortical edematous changes evocative of posterior reversible encephalopathy syndrome (one decedent), and asymmetric olfactory bulbs without downstream olfactory tract abnormalities (four other decedents) (73). Autopsy of COVID-19 patients found that cerebral congestion and edema, and partial neuronal degeneration were present (74, 75), indicating that brain tissue edema may appear in brain MRI among COVID-19 patients.

CSF

Lumbar puncture and cerebrospinal fluid (CSF) test: in viral encephalitis patients, lumbar puncture pressure is mostly normal or slightly elevated, cerebrospinal fluid white blood cell count is increased but usually $<250 \times 10^6$/L, and leukocyte subset counts show that lymphocyte percentage is increased. However, neutrophil percentage may increase during early infection. Protein concentration is increased but usually <150 mg/dl, and glucose and chloride are usually normal (75–80). According to a research aiming to evaluate the accuracy and sensitivity of a laboratory-modified CDC-based SARS-CoV-2 N1 and N2 assays across a range of sample types, the N2 target appeared to be most sensitive in SARS-CoV-2 detection in CSF with an LoD of one copy/reaction (81). Previous reports have detected coronavirus nucleic acids such as SARS-CoV, HCoV-OC43, etc., in the CSF of patients with viral encephalitis or multiple sclerosis. More case reports of COVID-19 patients, with positive testing for SARS-CoV-2 by RT-PCR in the CSF, who were also diagnosed with ventriculitis and/or encephalitis, have also followed (82–84). In addition, the presence of SARS-CoV-2 RNA has been detected in the CSF of a patient with clinically proven meningoencephalitis by genome sequencing in Japan (83). Notably, anti-SARS-COV-2 antibodies were detected in the patients' CSF samples (85). Although the specificity remains to be established, it still may constitute a critical diagnostic marker. A definitive diagnosis of central nervous system infection is obtained when the cerebrospinal fluid is positive for SARS-CoV-2 nucleic acid or IgM antibodies. However, most recent studies demonstrate that SARS-CoV-2 is usually not present in the CSF of patients with neurological symptoms, indicating that most neurological symptoms seem to be caused by indirect mechanisms such as systemic critical illness and secondary immune phenomena (86). Like in other virus infections of the brain, a negative PCR test does not exclude the presence of the virus in the brain tissue. Therefore, we should take nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, CSF, and feces as samples and treat real-time fluorescent RT-PCR, genome sequencing, and serological specific antibody detection as the gold standard for diagnosis, when facing COVID-19-suspected patients.

DIFFERENTIAL DIAGNOSIS OF CNS INFECTION IN THE COVID-19 EPIDEMIC

CNS infections are one of the most common infections of the nervous system and mostly refers to pathogens (i.e., bacteria, viruses, parasites) invading into the CNS, thereby resulting in inflammation. Viral, purulent, tuberculous, and cryptococcal meningitis are also among these CNS infections. These infections mostly present as chills, fever, and other upper respiratory tract infection symptoms and nervous system symptoms such as headache, vomiting, and convulsions. Severe neurological sequelae will often result if timely treatment is not administered. The different types of encephalitis (meningitis) can be differentiated by season; clinical presentation; physical examination; complete blood count; routine, biochemical, and microbiological tests on the cerebrospinal fluid tests; and imaging tests.

Viral meningitis has become the most common form of meningitis in countries with high rates of immunization coverage as the prevalence of bacterial meningitis is decreasing (87). Enteroviruses (Coxsackie or Echovirus groups) are the most common causes of viral meningitis in all age groups, while parechoviruses are also common in children (88). Viral meningitis most commonly occurs in children with the incidence decreasing with age. Summer and autumn are the high seasons for viral meningitis in temperate climates, which can be present all year round in tropical and subtropical areas (89). Viral meningitis in adults is more prone to present with meningeal symptoms and an elevated CSF protein, while children with viral meningitis are more likely to have fever, respiratory symptoms, and leukocytosis (90). Viral meningitis is characterized by a CSF mononuclear pleocytosis, which may initially be a neutrophilic

predominance in the first 24 h of illness and is not a reliable indicator to distinguish viral and bacterial meningitis (91). Meningoencephalitis, myocarditis, and pericarditis are the most common severe complications of enteroviral meningitis, while in children, neurological complications can include acute flaccid paralysis and rhombencephalitis (92, 93).

Due to the lack of clinical findings to help distinguish viral and bacterial meningitis, identifying some predictors of bacterial meningitis has always been research hotspots. The bacterial meningitis score (BMS) was originally developed for children with meningitis, which was comprised of four laboratory predictors including positive Gram stain, CSF protein >80 ml/dl, peripheral absolute neutrophil count >10,000 cells/mm^3, and CSF absolute neutrophil count >1,000 cells/mm^3, and one clinical predictor (seizures at or before the presentation) (94). Individual predictors of bacterial rather than viral meningitis have also been found, which include CSF glucose <34 mg/dl, CSF WBC >2,000 cells/mm^3, CSF neutrophils >1,180, CSF protein >220 mg/dl, and a ratio of CSF to blood glucose <0.23 (95). Additionally, CSF lactate has been indicated to be a great indicator to differentiate bacterial from aseptic meningitis (96, 97). The combination of CSF test and the BMS can increase specificity and sensitivity of distinction (98, 99). Meningococcus, characterized by profound endotoxinemia leading to vasomotor collapse, multiple organ failure, and disseminated intravascular coagulation, is an important and serious bacterial infection. Rapidly enlarging skin and mucosal hemorrhagic lesions (purpura fulminans), and gangrene of digits and limbs caused by arterial thrombi are the clinical hallmarks (100, 101). The predominant feature in children, who do not have adequate immunity against Neisseria meningitides, is septic shock caused by cardiovascular collapse (102).

Viral encephalitis is responsible for high rates of morbidity, permanent neurologic sequelae, and high mortality rates, which usually occur after hematogenic viral dissemination into the CNS (103). Herpesviruses 1 and 2 (HSV-1 and HSV-2), non-polio enterovirus and arboviruses are the most common etiologies. The frequency of specific viruses varies according to season, geographic location, and patient immunological status (104). Host factors and clinical characteristics of infection are important to consider in identifying the cause for viral encephalitis. CSF tests, serology/polymerase chain reaction studies, and neuroimaging are cornerstones of diagnostic evaluation in viral encephalitis (105).

Autoimmune encephalitis is a consequence of inflammation or dysfunction of parts of the brain caused by antibodies against specific brain antigens, usually located in the limbic system, leading to clinical presentations of limbic encephalitis (106). The prevalence of autoimmune encephalitis is increasing, which has surpassed infectious causes of encephalitis in developed countries (107). About 50% of patients with autoimmune encephalitis present or develop fever during the disease course, and most autoimmune encephalitis is associated with CSF lymphocytic pleocytosis (106, 108). Prodromal symptoms including headache and flu-like symptoms occur frequently in autoimmune encephalitis, which may also result in the suspicion of an infectious etiology (109). Fever and inflammation of the CSF are less common than in the infectious causes, but psychiatric symptoms are more frequent (110). Brain MRI can be useful in the differential diagnosis of encephalitis, especially the limbic encephalitis (109).

As the clinical presentation of COVID-19 patients with initial neurological symptoms is highly similar to patients with CNS infection, this not only leads to COVID-19 misdiagnosis and cause them to be invisible spreaders but also tends to lead to nosocomial infection and cross-infection. Therefore, rapidly and correctly identifying patients for admission to the hospital is an important problem currently facing neurologists. Suspected CNS infections caused by SARS-CoV-2 should be differentiated from other viruses, bacteria, and fungi. Extra attention should be paid when collecting the epidemiological history of the patient. Routine, etiological, and serological tests, chest imaging, and plain and enhanced brain MRI tests should be completed. qRT-PCR testing of the cerebrospinal fluid should be carried out as soon as possible in suspected patients to confirm if they have COVID-19. Next-generation sequencing (NGS) and cerebrospinal fluid cultures can be used for etiological tests.

TREATMENT OF PATIENTS WITH SARS-CoV-2 CNS INFECTION IN CHINA

Treatment should be carried out in suspected and confirmed cases in designated hospitals with effective isolation and protection conditions. Suspected patients should be quarantined in a single room alone for treatment, while multiple confirmed cases can be treated in the same room. The admission is usually recommended for patients with pneumonia, special risk factors, and/or poor prognostic factors. Critical patients should be admitted to the ICU for treatment as soon as possible.

For patients with symptoms of CNS infections, symptomatic treatments such as dehydration, neuroprotectant, antiepilepsy, and antipsychotic symptoms, should be performed on the basis of general treatment (bed rest, more nutrition, maintaining internal environment stability, monitoring vital signs closely, dynamic monitoring of blood routine, urine routine, C-reactive protein, biochemical indicators, coagulation function, arterial blood gas analysis, chest CT, pressure, and indicators such as cytology, biochemistry, etiology, and autoimmunity-related antibodies of cerebrospinal fluid) and antiviral therapy (remdesivir/α-interferon/lobinavir/ritonavir/ribavirin/chloroquine phosphate/arbidol) (111). The use of antiviral therapy can be considered for COVID-19 patients with moderate to severe course including pneumonia, those with worsening clinical findings, and those who are likely to progress to severe COVID-19 disease (the elderly, those with chronic diseases, and immunocompromised patients) after the diagnosis or as early as possible (112). Chloroquine (CQ) and hydroxychloroquine (HCQ) have been demonstrated as mechanisms of preventing viral entry and fusion, but these agents should not be used to treat or prevent COVID-19 because of potential serious adverse effects on the cardiovascular, hematologic, hepatic, and renal systems (113–115). Among

several potential drugs for the treatment of SARS-CoV-2 infection, remdesivir has shown to be the most promising antiviral therapeutic (116, 117), but recent studies have shown its uncertainties about adverse effects such as nausea, vomiting, hepatic toxicity and rectal hemorrhage, and clinical efficacy (118). Corticosteroids are often used in viral pneumonia, particularly complicated with specific conditions or comorbidities (chronic obstructive pulmonary disease, asthma exacerbation, and septic shock). However, systemic corticosteroids are not currently recommended for the treatment of lung injury associated with SARS-CoV-2 infection (119). The specific mechanism by which steroids act on sustained lung inflammation, as well as the definition of the best drug to use, and even the appropriate treatment duration, are still objectives of ongoing clinical trials (120, 121). There is currently no specific drug targeting SARS-CoV-2 infection in the CNS. Drugs against SARS-CoV-2, which could cross the blood–brain barrier, may be effective theoretically (122). As a result, neurologists should pay attention to the neurological adverse effects of antiviral agents, and the drug interactions related to the use of antiviral agents and antineural symptoms agents, such as antiepileptic drugs and antipsychotic drugs.

For neuro-critical patients, there should be aggressive treatment of complications and underlying disease, prevention of secondary infection, and timely organ function, respiratory, and circulatory support on the basis of symptomatic treatment and microcirculation improvement on the basis of sufficient fluid supplementation. The blood–brain barrier (BBB) hinders most drugs from entering the CNS from the blood stream, leading to the difficulty of delivering drugs to the brain for treatment via the circulatory system (123). Therefore, neurologists prefer antiviral drugs crossing the BBB efficiently and a higher dose for the treatment of CNS infection (124, 125).

For patients with hypertension and suspected CNS infection by SARS-CoV-2, it is theoretically possible that drugs known to increase ACE2 expression, such as ACE inhibitor (ACEI) and angiotensin II receptor blockers (ARBs) could promote SARS-CoV-2 proliferation (126, 127). However, there is insufficient evidence to withdraw ACEIs and ARBs among individuals diagnosed with COVID-19. In fact, most major medical organizations, such as the American Heart Association and European Society of Cardiology supported to maintain ACEI or ARB therapy in all hypertensive patients with COVID-19 (128, 129). Emerging evidence from human studies overwhelmingly suggests that the administration of ACEIs or ARBs does not increase ACE2 expression (130, 131). Furthermore, animal data indicates a potential protective effect of ARBs against COVID-19 pneumonia for the prevention of aggravation of acute lung injury in mice infected with SARS-CoV, which is closely related to SARS-CoV-2 (132, 133). The potential of these agents to facilitate viral disease is still under investigation, irrespective of the purported benefits of ACEIs or ARBs. Management of hypertension with a drug that may reduce inflammation in viral myocarditis (134), which has been considered to be a serious and potentially fatal manifestation of COVID-19 (135, 136), and does not pose a theoretical risk of promoting COVID-19 proliferation, would appear to be a rational strategy to optimize patient outcomes, such as verapamil. Until further data are available, ACEI and ARB medications are still recommended to be continued for the treatment of patients with hypertension and suspected CNS infection by SARS-CoV-2, especially those at high risk.

CONSTRUCTION OF A HOSPITAL EMERGENCY MANAGEMENT SYSTEM FOR FASTLANE TREATMENT OF CNS INFECTION DURING EPIDEMIC CONTROL

In this paper, we propose a basic framework for the treatment of suspected CNS infection patients during an epidemic to increase COVID-19 differential diagnosis efficiency. The aim of this framework is to provide a reference and guide to medical staff, especially neurologists, to improve identification and treatment efficiency in hospitals and reduce the risk of infection exposure in medical staff, which is carried out in Changsha, China.

Strengthening Staff Control and Standardizing Emergency Department Screening

The hospital emergency management of Xiangya Hospital for fastlane treatment of CNS infection patients could alleviate the fever emergency department, protect health care personnel, and control the cross-infection during the COVID-19 epidemic. We recommend this hospital emergency management for fastlane treatment of CNS infection to hospitals with sustainable supply chains of qualified personal protection equipment and adequate rotating medical staff.

As the initial neurological symptoms of COVID-19 include fever, headache, and epilepsy, it is necessary to strengthen the differentiation of such patients in an emergency department admission. **Figure 1** shows the current emergency department admission procedures. Before a suspected CNS infection patient comes into the neurology emergency department, he/she should have a fever prescreening by medical triage staff, ascertainment of history around epidemiology and exposure, and respiratory symptoms. Then the patients with non-suspected COVID-19 infection come into the neurology emergency department; neurologists should follow the left framework for further examination, diagnosis, and treatment. Those suspected COVID-19 infection patients go to the fever isolation emergency for further examination and diagnosis by doctors of the department of infection (following the right framework).

To differentiate CNS infection caused by COVID-19 from potentially lethal central nervous system diseases, some auxiliary tests, such as blood routine test, RT-PCR tests for CSF, and nasopharyngeal swab may be helpful. Herpes simplex virus DNA can be found in CSF, so CSF test may be a helpful way to differentiate CNS infection caused by COVID-19 from herpes simplex encephalitis.

It should be noted that despite the involvement of the central nervous system in COVID-19 infection has been frequently mentioned, only a few cases of encephalitis caused by this infection have been reported. Therefore, in case of signs and

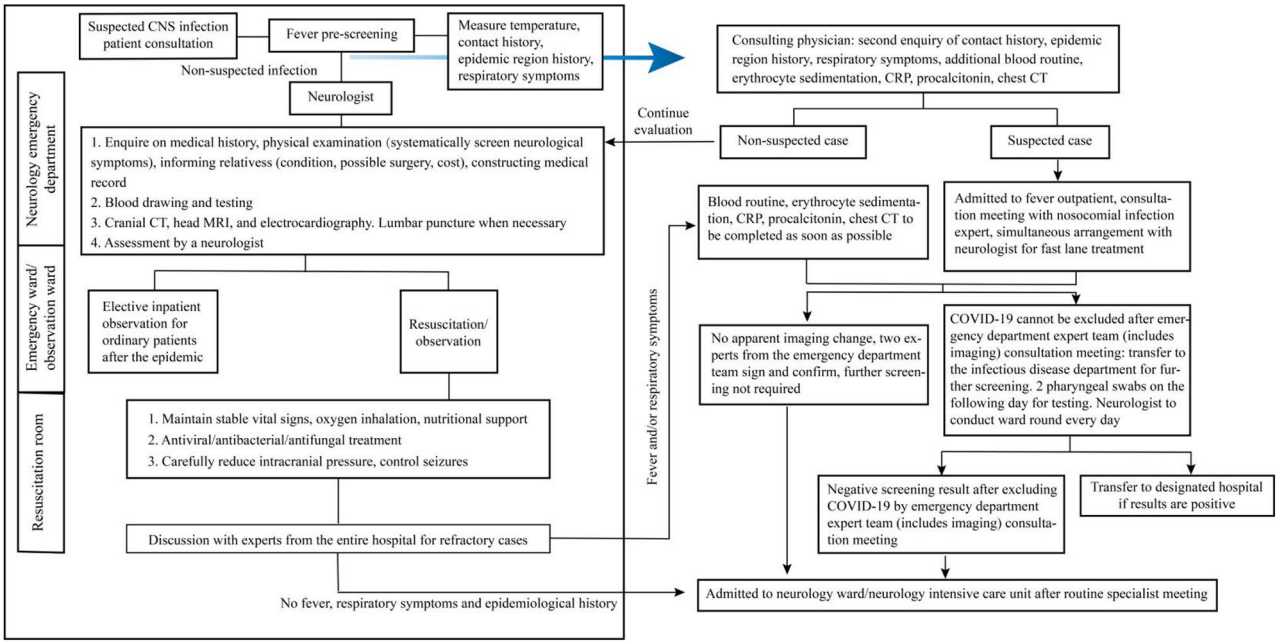


FIGURE 1 | Management flowchart for emergency department admission of suspected central nervous system (CNS) infection patients.

symptoms of encephalitis in COVID-19 patients, other causes of damage to the nervous systems should also be carefully considered (137).

Strengthening Prevention and Control in Medical Staff

Conducting Training for the Entire Department

Training on COVID-19 case identification and reporting, epidemiological survey, sampling, laboratory tests, medical treatment and prevention of nosocomial infection, and personal protection should be carried out in the entire department, so that they are equipped with COVID-19 control knowledge, methods, and skills, and understand legal responsibilities and obligations related to epidemic control to achieve early identification, reporting, quarantine, diagnosis, and treatment.

Coordinated Deployment of Medical Resources

There should be coordinated deployment of medical resources in the department, rational establishment of a medical echelon, rational shift arrangements, and establishment of an echelon for external assistance. Graded protection is carried out according to the position and zone protection standards and material allocation requirements. Department staff are supervised to strictly comply with the "Medical staff protective gear gowning/degowning procedure," and suspected medical staff are quarantined and treated in a timely manner. The protective measures for different positions are as follows:

①Primary protection: a. diagnosis, treatment, and nursing of ordinary inpatients; b. triaging of outpatients, triaging and registration of outpatients in the fever outpatient clinic, and timely data reporting; c. cleaning and disinfection of ordinary zones; d. collection of medical waste from ordinary patients; e. ordinary cleaning work; f. testing of ordinary patients by medical technicians; and g. during processing of samples from suspected patients in the laboratory, it is recommended that staff wear masks (N95) and protective goggles (anti-fog) or face shield on the basis of primary protection.

②Secondary protection: (a) staff who diagnose and treat, care, or dispose of medical waste from infected and suspected patients; (b) staff who collect medical waste from infected and suspected patients; and c. staff who carry out cleaning work for suspected or confirmed COVID-19 patients. Work clothes, isolation gown, medical cap, surgical mask with goggles, and surgical gloves are required for secondary protection.

③Tertiary protection: diagnosis and treatment, care, and operation (such as tracheotomy, intubation) in infected or suspected severe patients. On the basis of secondary protection, protective faceshield, waterproof boots, waterproof boot covers, shoe covers, protective clothing plus isolation gown, and double-layer medical surgical gloves are still needed. Surgical mask with goggles and faceshield can be replaced by electric air supply filter respirator.

Concern for the Physical and Mental Health of Staff

During a COVID-19 epidemic, clinical staff will face physical, intellectual, and psychological tests, and protecting medical staff is key to overcoming the epidemic. Therefore, rational arrangements of manpower and shifts should be carried out to avoid exhaustion in medical staff. Proactive health monitoring should be carried out based on the characteristics and risk assessment of different positions. Many measures should be adopted to protect the physical and mental

health of medical staff and help the families of frontline medical staff. A detailed psychological intervention plan was developed by The Second Xiangya Hospital, which mainly covered the following three areas: building a psychological intervention medical team, which provided online courses to guide medical staff to deal with common psychological problems; a psychological assistance hotline team, which provided guidance and supervision to solve psychological problems; and psychological interventions, which provided various group activities to release stress (138).

SUMMARY

Patients with SARS-CoV-2 infection have different neurological presentations, such as dizziness, headache, seizures, ataxia, altered mental status, anosmia, chemosensory dysfunction, myalgia, weakness, and neuropathy. Improving the identification efficiency for COVID-19 during the admission of CNS infection patients during the COVID-19 epidemic is an important area and challenge in prevention work in the neurology department. This review summarized the mechanism of SARS-CoV-2 on the CNS, clinical presentations, auxiliary tests, differential diagnosis, and treatment of patients with neurological symptoms of SARS-CoV-2 infection, as well as a hospital emergency management system of fastlane treatment of CNS infection for epidemic prevention and control, aiming at providing references and guidelines for the government and medical institutions to improve the efficiency of treating CNS infection patients in the clinical practice during COVID-19. CoV is a serious global health threat. Due to climate and ecological changes, human–animal interactions continue to increase. The emergence and outbreak of SARS-CoV-2 suggest that CoV outbreaks will be unavoidable in the future. Therefore, development of effective treatments and vaccines for CoVs is urgently required. At present, there are no specific prophylactic drugs for SARS-CoV-2. Therefore, strengthening identification during clinical treatment is important in preventing nosocomial and cross-infections.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by National Natural Science Foundation of China (81501025) and Hunan Natural Science Foundation (2020JJ4134).

REFERENCES

1. Society of Pathological Doctors Chinese Medical Doctors Association, Chinese Society of Pathology, Chinese Medical Association. Provisional guidelines on autopsy practice for deaths associated with COVID-19. *Zhonghua Bing Li Xue Za Zhi.* (2020). 49:406–10. doi: 10.3760/cma.j.cn112151-20200309-00184
2. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* (2020). 5:536–44. doi: 10.1038/s41564-020-0695-z
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
4. Wang DW, Hu B, Hu C, Zhu FF, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019. Novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
5. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ.* (2020). 368:m606. doi: 10.1136/bmj.m606
6. Wang M, Guo L, Chen Q, Xia G, Wang B. Typical radiological progression and clinical features of patients with coronavirus disease 2019. *Aging.* (2020) 12:7652–9. doi: 10.18632/aging.103170
7. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med.* (2020) 382:1199–207. doi: 10.1056/NEJMoa2001316
8. Kural C, Kirmizigoz S, Ezgu MC,Bedir O, Kutlay M, Izci Y. Intracranial infections: lessons learned from 52 surgically treated cases. *Neurosurg Focus.* (2019) 47:E10. doi: 10.3171/2019.5.FOCUS19238
9. Kobets AJ, Goodrich JT. The history of intracranial infections. *Childs Nerv Syst.* (2018) 34:1849–57. doi: 10.1007/s00381-018-3888-5
10. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:552–5. doi: 10.1002/jmv.25728
11. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
12. Chen NS, Zhou M, Dong X, Qu JM, Gong FY, Han Y, et al. epidemiological and clinical characteristics of 99 cases of 2019. Novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
13. Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, et al. Neurological manifestations of COVID-19 (SARS-CoV-2): a review. *Front Neurol.* (2020) 11:518. doi: 10.3389/fneur.2020.00518
14. Yang WJ, Cao QQ, Qin L, Wang XY, Cheng ZH, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019. Novel coronavirus disease (COVID-19): a multi-center study in Wenzhou City, Zhejiang, China. *J Infect.* (2020) 80:388–93. doi: 10.1016/j.jinf.2020.02.016
15. Ye J, Tan LH, Shen ZP, Yu YS, Lai DM, Fan J, et al. Polymyxin for the treatment of intracranial infections of extensively drug-resistant bacteria in children after neurosurgical operation. *World J Pediatr.* (2020) 16:528–32. doi: 10.1007/s12519-020-00350-8
16. Lam TT, Jia N, Zhang YW, Shum MH, Jiang JF, Zhu HC, et al. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. *Nature.* (2020) 583:282–5. doi: 10.1038/s41586-020-2169-0
17. Jamieson AM. Host resilience to emerging coronaviruses. *Fut. Virol.* (2016). 11:529–34. doi: 10.2217/fvl-2016-0060
18. D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transpl.* (2020) 26:832–4. doi: 10.1002/lt.25756
19. Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. *Eur Heart J.* (2020) 41:1798–800. doi: 10.1093/eurheartj/ehaa231
20. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol.* (2016) 24:490–502. doi: 10.1016/j.tim.2016.03.003

21. *WHO Coronavirus Disease (COVID-19) Dashboard*. [EB/OL]. WHO (2020). Available online at: https://covid19.who.int.
22. Su YJ, Lai YC. Comparison of clinical characteristics of coronavirus disease (COVID-19) and severe acute respiratory syndrome (SARS) as experienced in Taiwan. *Travel Med Infect Dis.* (2020). 14:101625. doi: 10.1016/j.tmaid.2020.101625
23. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. *JAMA*. (2020) 323:1848–9. doi: 10.1001/jama.2020.4861
24. Dong L, Tian JH, He SM, Zhu CC, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA*. (2020) 323:1846–8. doi: 10.1001/jama.2020.4621
25. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
26. Glass WG, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *J Immunol.* (2004) 173:4030–9. doi: 10.4049/jimmunol.173.6.4030
27. Hulswit RJ, de Haan CA, Bosch BJ. Coronavirus spike protein and tropism changes. *Adv Virus Res.* (2016). 96:29–57. doi: 10.1016/bs.aivir.2016.08.004
28. Dijkman R, Jebbink MF, Deijs M, Milewska A, Pyrc K, Buelow E, et al. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. *J Gen Virol.* (2012) 93:1924–929. doi: 10.1099/vir.0.043919-0
29. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* (2020) 395:565–74. doi: 10.1016/S0140-6736(20)30251-8
30. Xu H, Zhong L, Deng J, Peng JK, Dan HX, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci.* (2020) 12:8. doi: 10.1038/s41368-020-0074-x
31. Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, leydig and sertoli cells. *Cells.* (2020) 9:E920. doi: 10.3390/cells9040920
32. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol.* (2020) 92:577–83. doi: 10.1002/jmv.25757
33. Lahiri D, Ardila A. COVID-19 pandemic: a neurological perspective. *Cureus.* (2020) 12:e7889. doi: 10.7759/cureus.7889
34. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. *J Clin Neurosci.* (2020) 77:8–12. doi: 10.1016/j.jocn.2020.05.017
35. Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: a review and a call for action. *J Neurol.* (2020) 267:1573–76. doi: 10.1007/s00415-020-09896-z
36. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol.* (2020) 5:279–84. doi: 10.1136/svn-2020-000431
37. Ward CF, Figiel GS, McDonald WM. Altered mental status as a novel initial clinical presentation for COVID-19 infection in the elderly. *Am J Geriatr Psychiatry.* (2020) 28:808–11. doi: 10.1016/j.jagp.2020.05.013
38. Díaz-Pérez C, Ramos C, López-Cruz A, Muñoz Olmedo J, Lázaro González J, De Vega-Ríos E, et al. Acutely altered mental status as the main clinical presentation of multiple strokes in critically ill patients with COVID-19. *Neurol Sci.* (2020) 17:1–4. doi: 10.21203/rs.3.rs-31769/v1
39. Trigo J, García-Azorín D, Planchuelo-Gómez Á, Martínez-Pías E, Talavera B, Hernández-Pérez I, et al. Factors associated with the presence of headache in hospitalized COVID-19 patients and impact on prognosis: a retrospective cohort study. *J Headache Pain.* (2020) 21:94. doi: 10.1186/s10194-020-01165-8
40. Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: a review based on up-to-date knowledge. *Am J Otolaryngol.* (2020) 41:102581. doi: 10.1016/j.amjoto.2020.102581
41. García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, Talavera B, et al. Neurological comorbidity is a predictor of death in covid-19 disease: a cohort study on 576 patients. *Front Neurol.* (2020) 11:781. doi: 10.3389/fneur.2020.00781
42. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* (2020) 11:995–98. doi: 10.1021/acschemneuro.0c00122
43. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M., Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clin Infect Dis.* (2020) 71:889–90. doi: 10.1093/cid/ciaa330
44. Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny JC III. COVID-19 anosmia reporting tool: initial findings. *Otolaryngol Head Neck Surg.* (2020) 163:132–4. doi: 10.1177/0194599820922992
45. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* (2020) 277:2251–61. doi: 10.1007/s00405-020-05965-1
46. Parma V, Ohla K, Veldhuizen MG, Niv MY, Kelly CE, Bakke AJ, et al. More than smell - COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. *Chem Senses.* (2020) 45:609–22. doi: 10.1093/chemse/bjaa041
47. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA*. (2020) 323:2089–90. doi: 10.1001/jama.2020.6771
48. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med.* (2020) 26:1037–40. doi: 10.1038/s41591-020-0916-2
49. van Riel D, Verdijk R, Kuiken T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol.* (2015) 235:277–87. doi: 10.1002/path.4461
50. Cavazzana A, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. *Laryngoscope.* (2018) 128:10–5. doi: 10.1002/lary.26606
51. Cooper KW, Brann DH, Farruggia MC, Bhutani S, Pellegrino R, Tsukahara T, et al. COVID-19 and the chemical senses: supporting players take center stage. *Neuron.* (2020) 107:219–33. doi: 10.1016/j.neuron.2020.06.032
52. Bryche B, St Albin A, Murri S, Lacôte S, Pulido C, Gouilh MA, et al. Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. *Brain Behav Immun.* (2020) 89:579–86. doi: 10.1016/j.bbi.2020.06.032
53. Sia SF, Yan LM, Chin AWH, Fung K, Choy KT, Wong AYL, et al. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. *Nature.* (2020) 583:834–8. doi: 10.1038/s41586-020-2342-5
54. Kotfis K, Biernawska J, Zegan-Barańska M, Zukowski M. Peripheral blood lymphocyte subsets ($CD4^+$, $CD8^+$ T Cells, NK Cells) in patients with cardiovascular and neurological complications after carotid endarterectomy. *Int J Mol Sci.* (2015) 16:10077–94. doi: 10.3390/ijms160510077
55. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. *Respir Res.* (2020) 21:74. doi: 10.1186/s12931-020-01338-8
56. Gélisse P, Rossetti AO, Genton P, Crespel A, Kaplan PW. How to carry out and interpret EEG recordings in COVID-19 patients in ICU? *Clin Neurophysiol.* (2020) 131:2023–31. doi: 10.1016/j.clinph.2020.05.006
57. Patidar KR, Bajaj JS. Covert and overt hepatic encephalopathy: diagnosis and management. *Clin Gastroenterol Hepatol.* (2015) 13:2048–61. doi: 10.1016/j.cgh.2015.06.039
58. Resende LA, Kirchner DR, Ruiz e Resende LS. Solving the conundrum of job: a probable biblical description of chronic renal failure with neurological symptoms. *Arq Neuropsiquiatr.* (2009) 67:544–7. doi: 10.1590/S0004-282X2009000300037
59. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res Ther.* (2020) 12:69. doi: 10.1186/s13195-020-00640-3
60. García CAC, Sánchez EBA, Huerta DH, Gómez-Arnau J. Covid-19 treatment-induced neuropsychiatric adverse effects. *Gen Hosp Psychiatry.* (2020). doi: 10.1016/j.genhosppsych.2020.06.001. [Epub ahead of print].

61. García-Azorín D, Trigo J, Talavera B, Martínez-Pías E, Sierra Á, Porta-Etessam J, et al. Frequency and type of red flags in patients with covid-19 and headache: a series of 104 hospitalized patients. *Headache.* (2020) 60:1664–72. doi: 10.1111/head.13927
62. Galanopoulou AS, Ferastraoaru V, Correa DJ, Cherian K, Duberstein S, Gursky J, et al. EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: A small case series preliminary report. *Epilepsia Open.* (2020) 5:314–24. doi: 10.1002/epi4.12399
63. Petrescu AM, Taussig D, Bouilleret V. Electroencephalogram (EEG) in COVID-19: a systematic retrospective study. *Neurophysiol Clin.* (2020) 50:155–65. doi: 10.1016/j.neucli.2020.06.001
64. Pasini E, Bisulli F, Volpi L, Minardi I, Tappatà M, Muccioli L, et al. EEG findings in COVID-19 related encephalopathy. *Clin Neurophysiol.* (2020) 131:2265–7. doi: 10.1016/j.clinph.2020.07.003
65. Cecchetti G, Vabanesi M, Chieffo R, Fanelli G, Minicucci F, Agosta F, et al. Cerebral involvement in COVID-19 is associated with metabolic and coagulation derangements: an EEG study. *J Neurol.* (2020) 15:1–5. doi: 10.1007/s00415-020-09958-2
66. Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Brain MRI findings in severe COVID-19: a retrospective observational study. *Radiology.* (2020) 16:202222. doi: 10.1148/radiol.2020202222
67. Tsivgoulis G, Palaiodimou L, Katsanos AH, Caso V, Köhrmann M, Molina C, et al. Neurological manifestations and implications of COVID-19 pandemic. *Ther Adv Neurol Disord.* (2020) 13:1756286420932036. doi: 10.1177/1756286420932036
68. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. neurologic features in severe SARS-CoV-2 infection. *N Engl J Med.* (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
69. Anzalone N, Castellano A, Scotti R, Scandroglio AM, Filippi M, Ciceri F, et al. Multifocal laminar cortical brain lesions: a consistent MRI finding in neuro-COVID-19 patients. *J Neurol.* (2020) 6:1–4. doi: 10.1101/2020.05.19.20103168
70. Espinosa PS, Rizvi Z, Sharma P, Hindi F, Filatov A. neurological complications of coronavirus disease (COVID-19): encephalopathy, MRI brain and cerebrospinal fluid findings: case 2. *Cureus.* (2020) 12:e7930. doi: 10.7759/cureus.7930
71. Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI. Unusual microbleeds in brain MRI of covid-19 patients. *J Neuroimaging.* (2020) 8:10.1111/jon.12755.
72. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI Findings in patients in the intensive care unit with COVID-19 infection. *Radiology.* (2020) 297:201697. doi: 10.1148/radiol.2020201697
73. Coolen T, Lolli V, Sadeghi N, Rovaï A, Trotta N, Taccone FS, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. *Neurology.* (2020) 95:e2016–27. doi: 10.1212/WNL.0000000000010116
74. Huang J, Zheng M, Tang X, Chen Y, Tong A, Zhou L. Potential of SARS-CoV-2 to cause CNS infection: biologic fundamental and clinical experience. *Front Neurol.* (2020) 11:659. doi: 10.3389/fneur.2020.00659
75. Lin L, Li TS. Interpretation of "guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the national health commission (Trial Version 5)". *Zhonghua Xue Zhi.* (2020) 100:805–7. doi: 10.3760/cma.j.issn.0376-2491.2020.0001
76. Zhao Y, Zhao Z, Wang Y, Zhou YQ, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *Am J Respir Crit Care Med.* (2020) 202:756–9. doi: 10.1101/2020.01.26.919985
77. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci.* (2018) 12:386. doi: 10.3389/fncel.2018.00386
78. Tsai LK, Hsieh ST, Chao CC, Chen YC, Lin YH, Chang SC, et al. Neuromuscular disorders in severe acute respiratory syndrome. *Arch Neurol.* (2004) 61:1669–73. doi: 10.1001/archneur.61.11.1669
79. Anada R, Nukui T, Hayashi T, Konishi H, Dougu N, Nakatsuji Y. A case of clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) associated with infectious endocarditis caused by *Staphylococcus aureus*. *Rinsho Shinkeigaku.* (2019) 59:666–8. doi: 10.5692/clinicalneurol.cn-001335
80. Lyons S, O'Kelly B, Woods S, Rowan C, Brady D, Sheehan G, et al. Seizure with CSF lymphocytosis as a presenting feature of COVID-19 in an otherwise healthy young man. *Seizure.* (2020) 80:113–4. doi: 10.1016/j.seizure.2020.06.010
81. Perchetti GA, Nalla AK, Huang ML, Zhu H, Wei Y, Stensland L, et al. Validation of SARS-CoV-2 detection across multiple specimen types. *J Clin Virol.* (2020) 128:104438. doi: 10.1016/j.jcv.2020.104438
82. Domingues RB, Mendes-Correa MC, de Moura Leite FBV, Sabino EC, Salarini DZ, Claro I, et al. First case of SARS-COV-2 sequencing in cerebrospinal fluid of a patient with suspected demyelinating disease. *J Neurol.* (2020). doi: 10.1007/s00415-020-09996-w. [Epub ahead of print].
83. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/ encephalitis associated with SARS-coronavirus-2. *Int J Infect Dis.* (2020) 94:55–58. doi: 10.1016/j.ijid.2020.03.062
84. Zhou L, Zhang M, Wang J, Gao J. Sars-Cov-2: underestimated damage to nervous system. *Travel Med Infect Dis.* (2020) 2020:101642. doi: 10.1016/j.tmaid.2020.101642
85. Andriuta D, Roger PA, Thibault W, Toublanc B, Sauzay C, Castelain S, et al. COVID-19 encephalopathy: detection of antibodies against SARS-CoV-2 in CSF. *J Neurol.* (2020) 11:1–2. doi: 10.1007/s00415-020-09975-1
86. Neumann B, Schmidbauer ML, Dimitriadis K, Otto S, Knier B, Niesen WD, et al. Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. *J Neurol Sci.* (2020) 418:117090. doi: 10.1016/j.jns.2020.117090
87. McGill F, Griffiths MJ, Solomon T. Viral meningitis: current issues in diagnosis and treatment. *Curr. Opin Infect Dis.* (2017) 30:248–56. doi: 10.1097/QCO.0000000000000355
88. Sadarangani M, Willis L, Kadambari S, Gormley S, Young Z, Beckley R, et al. Childhood meningitis in the conjugate vaccine era: a prospective cohort study. *Arch Dis Child.* (2015) 100:292–4. doi: 10.1136/archdischild-2014-306813
89. Wright WF, Pinto CN, Palisoc K, Baghli S. Viral (aseptic) meningitis: a review. *J Neurol Sci.* (2019) 398:176–83. doi: 10.1016/j.jns.2019.01.050
90. Shukla B, Aguilera EA, Salazar L, Wootton SH, Kaewpoowat Q, Hasbun R. Aseptic meningitis in adults and children: diagnostic and management challenges. *J Clin Virol.* (2017) 94:110–4. doi: 10.1016/j.jcv.2017.07.016
91. Negrini B, Kelleher KJ, Wald ER. Cerebrospinal fluid findings in aseptic versus bacterial meningitis. *Pediatrics.* (2000) 105:316–9. doi: 10.1542/peds.105.2.316
92. Drysdale SB, Kelly DF. Fifteen-minute consultation: enterovirus meningitis and encephalitis-when can we stop the antibiotics? *Arch Dis Child Educ Pract Ed.* (2017) 102:66–71. doi: 10.1136/archdischild-2016-310632
93. Rudolph H, Schroten H, Tenenbaum T. enterovirus infections of the central nervous system in children: an update. *Pediatr Infect Dis J.* (2016) 35:567–9. doi: 10.1097/INF.0000000000001090
94. McArthur R, Edlow JA, Nigrovic LE. Validation of the bacterial meningitis score in adults presenting to the ED with meningitis. *Am J Emerg Med.* (2016) 34:1265–7. doi: 10.1016/j.ajem.2016.04.003
95. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* (2004) 39:1267–84. doi: 10.1086/425368
96. Huy NT, Thao NT, Diep DT, Kikuchi M, Zamora J, Hirayama K. Cerebrospinal fluid lactate concentration to distinguish bacterial from aseptic meningitis: a systemic review and meta-analysis. *Crit Care.* (2010). 14:R240. doi: 10.1186/cc9395
97. Sakushima K, Hayashino Y, Kawaguchi T, Jackson JL, Fukuhara S. Diagnostic accuracy of cerebrospinal fluid lactate for differentiating bacterial meningitis from aseptic meningitis: a meta-analysis. *J Infect.* (2011) 62:255–62. doi: 10.1016/j.jinf.2011.02.010
98. Cantu RM, M Das J. *Viral Meningitis*. Treasure Island, FL: StatPearls Publishing (2020).
99. Pires FR, Franco ACBF, Gilio AE, Troster EJ. Comparison of enterovirus detection in cerebrospinal fluid with bacterial meningitis score in children. *Einstein.* (2017) 15:167–72. doi: 10.1590/s1679-45082017ao3880
100. Alberio L, Lämmle B, Esmon CT. Protein C replacement in severe meningococcemia: rationale and clinical experience. *Clin Infect Dis.* (2001) 32:1338–46. doi: 10.1086/319995
101. Yung AP, McDonald MI. Early clinical clues to meningococcaemia. *Med J Aust.* (2003) 178:134–7. doi: 10.5694/j.1326-5377.2003.tb05106.x

102. Siddiqui JA, Gulick PG. *Meningococcemia*. Treasure Island, FL: StatPearls Publishing (2020).
103. Costa BKD, Sato DK. Viral encephalitis: a practical review on diagnostic approach and treatment. *J Pediatr.* (2020) 96:12–9. doi: 10.1016/j.jpedp.2019.07.005
104. Tunkel AR, Glaser CA, Bloch KC, Sejvar JJ, Marra CM, Roos KL, et al. The management of encephalitis: clinical practice guidelines by the infectious diseases society of America. *Clin Infect Dis.* (2008) 47:303–27. doi: 10.1086/589747
105. Venkatesan A, Murphy OC. Viral encephalitis. *Neurol Clin.* (2018) 36:705–24. doi: 10.1016/j.ncl.2018.07.001
106. Granerod J, Ambrose HE, Davies NWS, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis.* (2010) 10:835–44. doi: 10.1016/S1473-3099(10)70222-X
107. Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol.* (2018) 83:166–77. doi: 10.1002/ana.25131
108. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. *Eur J Clin Microbiol Infect Dis.* (2009) 28:1421–9. doi: 10.1007/s10096-009-0799-0
109. Armangue T, Leypoldt F, Dalmau J. Autoimmune encephalitis as differential diagnosis of infectious encephalitis. *Curr Opin Neurol.* (2014) 27:361–8. doi: 10.1097/WCO.0000000000000087
110. Lancaster E. the diagnosis and treatment of autoimmune encephalitis. *J Clin Neurol.* (2016) 12:1–3. doi: 10.3988/jcn.2016.12.1.1
111. Simşek Yavuz S, Ünal S. Antiviral treatment of COVID-19. *Turk J Med Sci.* (2020) 50:611–9. doi: 10.3906/sag-2004-145
112. Kim SB, Huh K, Heo JY, Joo EJ, Kim YJ, Choi WS, et al. Interim guidelines on antiviral therapy for COVID-19. *Infect Chemother.* (2020) 52:281–304. doi: 10.3947/ic.2020.52.2.281
113. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care.* (2020). 57:279–83. doi: 10.1016/j.jcrc.2020.03.005
114. Barlow A, Landolf KM, Barlow B, Yeung SYA, Heavner JJ, Claassen CW, et al. Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019. *Pharmacotherapy.* (2020) 40:416–37. doi: 10.1002/phar.2398
115. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience Trends.* (2020) 14:72. doi: 10.5582/bst.2020.01047
116. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov.* (2020) 19:149e50. doi: 10.1038/d41573-020-00016-0
117. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med.* (2020) 382:929e36. doi: 10.1056/NEJMoa2001191
118. Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: the reality and challenges. *J Microbiol Immunol Infect.* (2020) 53:436–43. doi: 10.1016/j.jmii.2020.03.034
119. Berton AM, Prencipe N, Giordano R, Ghigo E, Grottoli S. Systemic steroids in patients with COVID-19: pros and contras, An endocrinological point of view. *J Endocrinol Invest.* (2020) 8:1–3. doi: 10.1007/s40618-020-01325-2
120. Kolilekas L, Loverdos K, Giannakaki S, Vlassi L, Levounets A, Zervas E, et al. Can steroids reverse the severe COVID-19 induced "cytokine storm?". *J Med Virol.* (2020) 92:2866–9. doi: 10.1002/jmv.26165
121. Gazzaruso C, Carlo Stella N, Mariani G, Tamburlini A, Garini P, Freddi E, et al. Impact of anti-rheumatic drugs and steroids on clinical course and prognosis of COVID-19. *Clin Rheumatol.* (2020) 39:2475–7. doi: 10.1007/s10067-020-05239-5
122. Bostanciklioglu M. Temporal correlation between neurological and gastrointestinal symptoms of SARS-CoV-2. *Inflamm Bowel Dis.* (2020) 26:e89–91. doi: 10.1093/ibd/izaa131
123. Li X, Tsibouklis J, Weng T, Zhang B, Yin G, Feng G, et al. Nano carriers for drug transport across the blood-brain barrier. *J Drug Target.* (2017) 25:17–28. doi: 10.1080/1061186X.2016.1184272
124. Liu KW, Zhang LQ. The advances in the treatment of drug-resistant tuberculous meningitis. *Zhonghua Jie He Hu Xi Za Zhi.* (2019) 42:382–5. doi: 10.3760/cma.j.issn.1001-0939.2019.05.013
125. Zhang J, Hu X, Hu X, Ye Y, Shang M, An Y, et al. Clinical features, outcomes and molecular profiles of drug resistance in tuberculous meningitis in non-HIV patients. *Sci Rep.* (2016) 6:19072. doi: 10.1038/srep19072
126. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA.* (2020) 323:1769–70. doi: 10.1001/jama.2020.4812
127. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med.* (2020) 382:1653–9. doi: 10.1056/NEJMsr2005760
128. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19?. *Eur Heart J.* (2020) 41:1801–3. doi: 10.1093/eurheartj/ehaa235
129. Antwi-Amoabeng D, Beutler BD, Moody AE, Kanji Z, Gullapalli N, Rowan CJ. Management of hypertension in COVID-19. *World J Cardiol.* (2020) 12:228–30. doi: 10.4330/wjc.v12.i5.228
130. Sriram K, Insel PA. Risks of ace inhibitor and ARB usage in COVID-19: evaluating the evidence. *Clin Pharmacol Ther.* (2020) 108:236–41. doi: 10.1002/cpt.1863
131. Bosso M, Thanaraj TA, Abu-Farha M, Alanbaei M, Abubaker J, Al-Mulla F. The two faces of ACE2: the role of ACE2 receptor and its polymorphisms in hypertension and COVID-19. *Mol Ther Methods Clin Dev.* (2020) 18:321–7. doi: 10.1016/j.omtm.2020.06.017
132. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. *Hypertens Res.* (2020) 43:648–54. doi: 10.1038/s41440-020-0455-8
133. Groß S, Jahn C, Cushman S, Bär C, Thum T. SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: from basic science to clinical implications. *J Mol Cell Cardiol.* (2020) 144:47–53. doi: 10.1016/j.yjmcc.2020.04.031
134. Dong R, Liu P, Wee L, Butany J, Sole MJ. Verapamil ameliorates the clinical and pathological course of murine myocarditis. *J Clin Invest.* (1992) 90:2022–30. doi: 10.1172/JCI116082
135. Wilson MP, Coulden RA, Low G. COVID-19-related cardiac involvement and potential implications for cardiothoracic imaging. *Clin Radiol.* (2020) 75:476–7. doi: 10.1016/j.crad.2020.04.004
136. Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac involvement in a patient with coronavirus disease 2019. (COVID-19). *JAMA Cardiol.* (2020) 5:1–6. doi: 10.1001/jamacardio.2020.1096
137. Lovati C, Osio M, Pantoni L. Diagnosing herpes simplex-1 encephalitis at the time of COVID-19 pandemic. *Neurol Sci.* (2020) 41:1361–4. doi: 10.1007/s10072-020-04461-y
138. Chen Q, Liang M, Li Y, Guo J, Fei D, Wang L, et al. Mental health care for medical staff in China during the COVID-19 outbreak. *Lancet Psychiatry.* (2020) 7:e15–16. doi: 10.1016/S2215-0366(20)30078-X

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 27 October 2020
doi: 10.3389/fneur.2020.582613

Adopting Virtual Visits for Parkinson's Disease Patients During the COVID-19 Pandemic in a Developing Country

Ali Shalash, Mai Fathy, Noha L. Dawood and Eman Hamid*

Department of Neurology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Objective: Telemedicine has been increasingly used, especially during the COVID-19 pandemic; however, limited data are available from developing countries. The present study aimed to evaluate the feasibility, satisfaction of patients and physicians, and quality of service provided during virtual visits for Parkinson's disease (PD) patients during the COVID-19 pandemic and the associated limitations.

Methods: Thirty-nine PD patients were contacted to schedule virtual visits using the Zoom application. Thereafter, we rated the feasibility, satisfaction, and quality of service provided by virtual visits using patients' and physicians' questionnaires.

Results: Twenty-one out of 39 PD patients were scheduled for virtual visits. Nineteen virtual visits out of 21 (90.5%) were conducted successfully; 16 of these were accomplished in the first attempt (76.2%). The scores of satisfaction, quality of service, and set-up/preparation were 9.5 (8.5–10), 9.5 (9–10), and 8 (5–10) for the patients and 9 (7–10), 8 (6–10), and 10 (10–10) for the physicians, respectively. The average time that was saved was 270.79 ± 142.17 min, while an average of 76.38 ± 95.15 km of travel was avoided for the patients per visit. The most common limitations for conducting virtual visits were a lack of Internet connection and the inability to use technology (75%).

Conclusions: The present study showed the feasibility and the high satisfaction level of patients and physicians as well as the favorable service quality of virtual visits for PD in a developing country during the COVID-19 pandemic. However, the lack of Internet connectivity and the inability to use technology were the main limitations.

Keywords: Parkinson's disease, telemedicine, COVID-19, virtual visits, feasability

OPEN ACCESS

Edited by:
Shen-Yang Lim,
University of Malaya, Malaysia

Reviewed by:
Ruth Schneider,
University of Rochester, United States
Marta Ruiz-Lopez,
University Hospital Fundación Jiménez Díaz, Spain

****Correspondence:***
Ali Shalash
ali_neuro@yahoo.com;
drali_shalash@med.asu.edu.eg

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *12 July 2020*
Accepted: *29 September 2020*
Published: *27 October 2020*

Citation:
Shalash A, Fathy M, Dawood NL and Hamid E (2020) Adopting Virtual Visits for Parkinson's Disease Patients During the COVID-19 Pandemic in a Developing Country. Front. Neurol. 11:582613. doi: 10.3389/fneur.2020.582613

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, and the healthcare burden of this disease is increasing across the world. Recently, telemedicine has been increasingly adopted for managing PD patients, owing to the rising burden, limited availability of specialists, recent evidence of its applicability, and advances in technology (1, 2).

Furthermore, healthcare services for chronically ill patients, including PD patients, were compromised during the COVID-19 pandemic, owing to the lockdown and the direction of healthcare resources toward its containment. Moreover, impaired mental health, compromised physical activity, and poorer quality of life of PD patients have been reported during the COVID-19 pandemic, implying the importance of continuing their care, especially *via* telemedicine (3). The current situation has led to the use of telemedicine by physicians as an alternative to in-person visits.

Several studies have demonstrated the feasibility, time-saving ability, cost-efficiency, high satisfaction level, and comparable outcomes of virtual visits and in-person visits (4–7). However, these studies have reported major limitations, including incomplete neurological examination, reimbursement of physicians, the inability of older and less educated patients to use it, and technological obstacles, especially those with limited access to optimum Internet services (2). However, all these reports were from studies performed in developed countries. In developing countries, cultural acceptance and awareness might be greater barriers than technical issues for the adoption of telemedicine (8, 9). Therefore, further research is needed on different populations to identify the barriers for the adoption of telemedicine.

The present study was designed with the aim of evaluating the feasibility and the satisfaction level of patients and physicians as well as the quality of service and the limitations involved in virtual visits for PD patients during the COVID-19 pandemic.

METHODS

Fifty-one PD patients who were regularly followed up in the movement disorders clinic, Ain Shams hospitals, Cairo, with available data and recent comprehensive assessment in a previous in-person visit from August 2019 to February 2020 (within 6 months before the COVID-19 pandemic-related lockdown in Egypt) were identified from our data registry. Available data and assessments included the contact information, demographic data, socioeconomic status, education years, motor assessment using Movement Disorders Society—Unified Parkinson's Disease Rating Scale and Hoehn and Yahr Scale, and cognitive evaluation using the Mini-Mental State Examination (MMSE). The patients were previously diagnosed with PD as per the MDS diagnostic criteria (10). Patients with atypical or secondary Parkinsonism and those who were unable to complete the questionnaire, such as those with severe cognitive impairment, were excluded. Thirty-nine out of the 51 patients could be reached *via* telephone and were asked whether they were interested in and capable of participating in virtual follow-up visits; they were then invited for a free one-time virtual visit.

Telemedicine sessions were performed by the movement disorders experts during May and June 2020, using the Zoom application. Before the visits, test sessions were offered and performed when required by the patients or their caregivers; furthermore, instructions for a proper virtual visit were discussed, such as the use of a device with a high-resolution camera, good lighting, the help of another person, and avoiding overexposure. The meeting link and prescribed medications were sent to the patients *via* WhatsApp messages.

During the virtual visits, the patients were assessed for motor and non-motor symptoms, medications, physical activity, and the impact of the COVID-19 pandemic. The motor examination was conducted during the virtual visit, including finger tapping, hand movements, and leg agility for bradykinesia, tremor assessment (during rest, posture, and action), and arising from chairs and gait, while rigidity and postural instability could not be examined virtually. The feasibility of virtual visits was calculated as the ratio of successful visits to that of the scheduled visits (5, 6).

Following the virtual visits, the patients were asked *via* phone calls about the quality of service, visit set-up/preparation, and their satisfaction using a patient questionnaire (16 questions) developed by Hanson and colleagues, (6) in addition to two questions about the use of telemedicine during the COVID-19 pandemic. The calls were made by physicians other than the interviewing physicians within 2 days from the virtual visit. The patient questionnaire was translated into Arabic and validated as per standard methods. In a similar manner, the interviewing physician rated similar visit outcomes using the physician questionnaire (11 questions) developed by Hanson and colleagues (6). Both questionnaires include questions with a 10-point Likert scale, with 1 = highly disagree or least satisfied and 10 = highly agree or most satisfied for a comparison of the virtual and previous in-person visits regarding the following three domains: service quality, visit set-up/preparation, and patients'/physicians' satisfaction (6). Furthermore, the patients were asked about the cost and the distance involved in actual hospital visits.

All the patients provided their consent for study participation; the study was approved by the ethical committee of the Faculty of Medicine, Ain Shams University, and conformed to the ethical standards of the Declaration of Helsinki.

Statistical Analyses

Data were analyzed using SSPS®, version 20.0 (IBM, San Francisco, CA, USA). The data were described as frequency and percentage values for qualitative data and mean and standard deviation or median and range values for quantitative data. Chi-square test was used to compare the non-parametric variables, while *t*-test was used to compare the parametric variables between patients who declined virtual visits and those for whom virtual visits were performed successfully.

RESULTS

Twenty-seven of the 39 patients (69.2%) expressed their interest and capability to participate in virtual visits, while 12 refused owing to the lack of Internet connection (seven patients) or inability to use technology (five patients). The aforementioned 27 patients were invited to schedule an online virtual visit. Twenty-one of the 27 patients were scheduled for virtual visits, while six patients apologized for the following reasons: bad Internet connection (one patient), inability to use the application (three

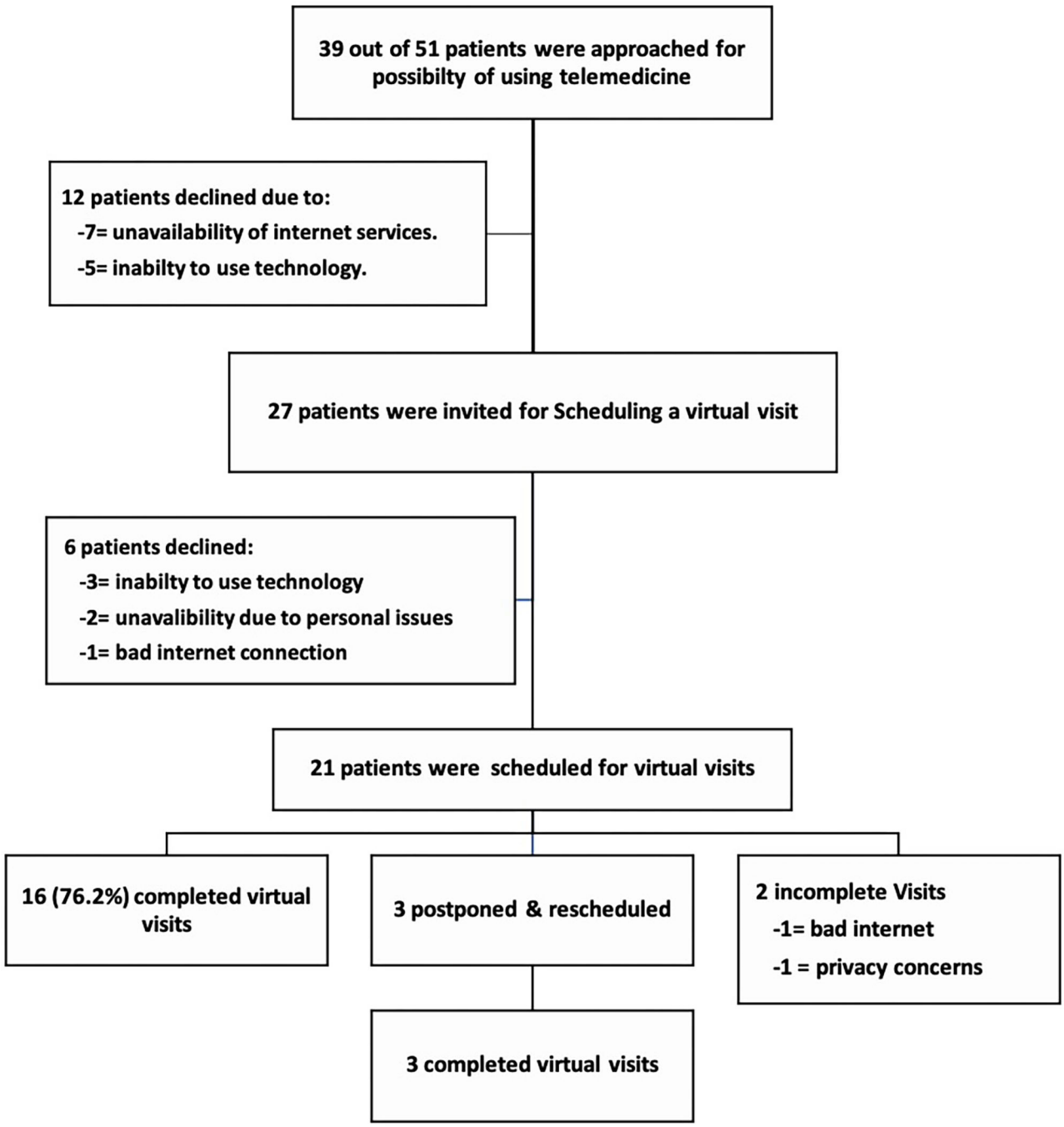


FIGURE 1 | Flow chart of the invitation, enrollment, and performance of virtual visits for patients with Parkinson's disease during the COVID-19 pandemic.

patients), and unavailability due to personal issues (two patients) (**Figure 1**).

Sixteen of the 21 virtual visits were completed from the first appointment (76.2%); three virtual visits were postponed, then rescheduled, and completed. Thus, 19 visits (90.5%) were successfully performed at the patients' homes, while two visits could not be conducted; one was not feasible owing to Internet disconnection and another owing to privacy concerns (**Figure 1**). Thus, 48.7% of the approached patients (19 out of 39) could participate in the virtual visits, while the feasibility of the conducted virtual visits was 90.5% (including rescheduled visits) and 76.2% from the first attempt.

All the patients used smartphones and were assisted by a family member, while the doctors used their laptops. Test

sessions were carried out successfully for five patients (26.3%) and followed by virtual visits.

Barriers in Patient Enrollment and Virtual Visits

Virtual visits could not be performed for 20 of the 39 invited patients (51.3%). The main causes were absent or unstable Internet connection (nine patients, 35%) and the inability to use technology without caregiver support (eight patients, 40%). One patient declined owing to privacy concerns (5%), while two patients withdrew owing to personal issues. There were no significant differences in age ($p = 0.757$), sex ($p = 0.888$), education years ($p = 0.226$), residence ($p = 0.716$), functioning ($p = 0.462$), and MMSE ($p = 0.359$) of patients who declined visits owing to Internet and technology usage problems (17 patients) and those for whom virtual visits were performed successfully (19 patients).

Patients' and Physicians' Satisfaction

All patients for whom virtual visits were initiated were able to complete the visit and the questionnaire. The median scores for satisfaction, quality of service, and set-up/preparation of patients were 9.5 (8.5–10), 9.5 (9–10), and 8 (5–10), respectively (**Table 1**). Twelve patients established a personal connection with the physicians; however, this percentage was lower than that for in-person visits (63.1%); four patients reported a similar personal connection (21%), while three did not establish a personal connection (15.9%). Most patients were highly satisfied (15, 78.9%) or satisfied (three, 15.9%) with the recommendations.

Furthermore, the patients were very likely (17, 89.5%) or likely (two, 10.5%) to recommend telemedicine to other patients. Most patients (14, 73.7%) expressed a desire to use virtual visits beyond the pandemic, while five patients (26.3%) were interested in virtual visits only during the pandemic. All patients, except one, reported that virtual visits could be a satisfactory alternative to in-person visits during the pandemic (**Supplementary Table 1**).

Regarding physicians, the scores of satisfaction, quality of service, and set-up/preparation were 9 (7–10), 8 (6–10), and 10 (10–10), respectively. They highly preferred future telemedicine visits when possible (eight, 7–9) (**Supplementary Table 2**). The patients reported a comparable overall care of virtual visits compared to in-person visits (eight, 4–10) more than the physicians (seven, 4–9). Both the patients and the physicians were highly pleased with the outcomes of the virtual visits (10 and nine, respectively) (**Figure 2**).

Time- and Cost-Saving

The average time of the visit set-up was 12.9 ± 14.3 for patients and 6 ± 3.55 for physicians. On average, 270.79 ± 142.17 min was saved, while 76.38 ± 95.15 km of travel for patients per visit was prevented. Furthermore, the average reduction in transportation costs was 163.95 ± 204.98 Egyptian pounds for patients per visit.

Visit Assessments and Recommendations

The major motor complaints of the patients were bradykinesia/rigidity (63.2%), tremor (47.4%), and gait problems (57.9%), while the reported non-motor complaints included depression/anxiety (47.4%), constipation (36.8%), and sleep disturbance (31.6%). Bradykinesia and gait were assessed in all patients, while tremor and dyskinesia were observed in nine (47.4%) and five (26.3%) patients, respectively. The most common actions were the promotion of protective measures for COVID-19 (100%), adjustment of medication (94.7%), and promotion of physical activity during lockdown (84.2%).

DISCUSSION

The current study demonstrated the feasibility, high satisfaction level of patients and physicians, cost and time saving, and comparable quality of service of virtual visits for PD patients (as well as barriers of using telemedicine) at home in a developing country during a special situation. Moreover, the study identified the barriers of using telemedicine for PD in developing countries. To our knowledge, this is the first study on virtual visits for PD from developing countries during the COVID-19 pandemic.

The patients reported high satisfaction and comparable care of virtual visits, consistent with previous studies (4–7). However, lower feasibility and satisfaction scores were detected in the present study compared to the previous studies that could be attributed to bad Internet connectivity, poor quality of the patients' devices, and lower education and socioeconomic levels of the participants. Furthermore, lower physician satisfaction could be attributed to the interrupted Internet connection, poor resolution of some patients' devices, and less exposure from the patients' side.

It is noteworthy that most of our patients reported less personal connection with physicians than during in-person visits, in contrast to prior studies. Hanson and colleagues showed that 69.2% established similar personal connections with the interviewing physicians (6). A recent randomized controlled study reported no significant difference in the patients' satisfaction related to communication in the virtual and in-person visits (11). Low personal communication could be explained by technical problems, low quality of the image from the patients' side, and cultural perceptions. Cultural issues, including the patients' acceptance and resistance, are common barriers in telemedicine in developing countries, including Egypt (9, 12).

It is noteworthy that about half of our patients (52.6%) were illiterate or had a low education level in contrast to prior studies that mainly included highly educated and technologically competent patients. However, virtual visits had been conducted successfully through the support of an educated relative, denoting the possibility of reaching out to these patients *via* easily used and widely available online applications. The patients showed lower set-up and preparation scores than the physicians and that in previous studies; this could be due to the lower education level, unfamiliarity with technology, and lack of training in the application used.

Several studies used smartphones for remote assessment and monitoring of PD patients at home (1, 2). Moreover, virtual visits were conducted using smartphones in about 50% of the

TABLE 1 | Demographic and clinical characteristics of patients and outcomes of the virtual visits.

	Mean/No/Median	SD/frequency	Range
Age	56.0	10.51	31–72
Sex: male/female	13/6	68.4/31.6%	
Socioeconomic status	Low: 11 (57.89%), middle: 8 (42.10%), High: 0		
Highest level of education	Illiterate	5 (26.3%)	
	Read and write	2 (10.5)	
	Preparatory school	3 (15.8%)	
	High school	4 (21.1%)	
	University	5 (26.3%)	
Years of education	8.368	6.3614	0–18
Age of onset	50.158	11.3285	25–62
Duration of illness	5.605	3.5652	0.5–14
MDS UPDRS-III-OFF[a]	42.294	20.2632	10.0–71.0
Hoehn and Yahr Scale[a]	2.444	0.8726	1.0–4.0
MMSE-total[a]	27.588	2.3994	23.0–30.0
Duration of virtual visit (min)	27.778	7.01	20.0–44.0
Patients' outcome			
Patients' satisfaction (median Q7, 8, 9, 17, 18, 19)	9.5		8.5–10
Patients' set-up/preparation (median Q5)	8.0		5–10
Patients' quality of service (median Q10, 11, 12, 13)	9.5		9–10
Saved costs for patients (Egyptian pounds)	163.95	204.98	15–800
Saved time for patients (transportation–waiting) (min)	270.79	142.17	105–540
Saved kilometers for patients	76.38	95.15	5.2–318
COVID-related questions			
Favoring future telemedicine in general or during pandemic	Yes, all the time Only in COVID-19 No, I do not want		14 (73.7%) 5 (26.3%) 0
Do you think that telemedicine sessions can be an alternative for healthcare services during the COVID-19 pandemic?	10		5–10
Physicians' outcome			
Physicians' satisfaction (median Q14,15,16)	9		7- 10
Physicians' set-up/preparation (median Q5)	10		10–10
Physicians' quality of service (median Q7,8,9, 10, 11, 12, 13)	8		6–10
Saved time for physicians (transportation)	90	0.0	90–90
Saved kilometers for physicians	40.84	18.26	20–56

MDS-UPDRS, MDS-unified Parkinson's disease rating scale; MMSE, mini-mental state examination.
[a]*Conducted in the last in-person visit before the pandemic lockdown.*

patients in previous studies (7). The current study showed 100% use of smartphones, implying more availability of these devices among patients belonging to different socioeconomic levels. The application (Zoom) currently used was easily used by the patients with a short time of setting up; however, delayed audio connection at the time of logging in was a common technical challenge.

The current study showed time and cost saving similar to that in previous studies (2, 5). Despite less money being saved as compared to that in other studies, due to the depreciation of

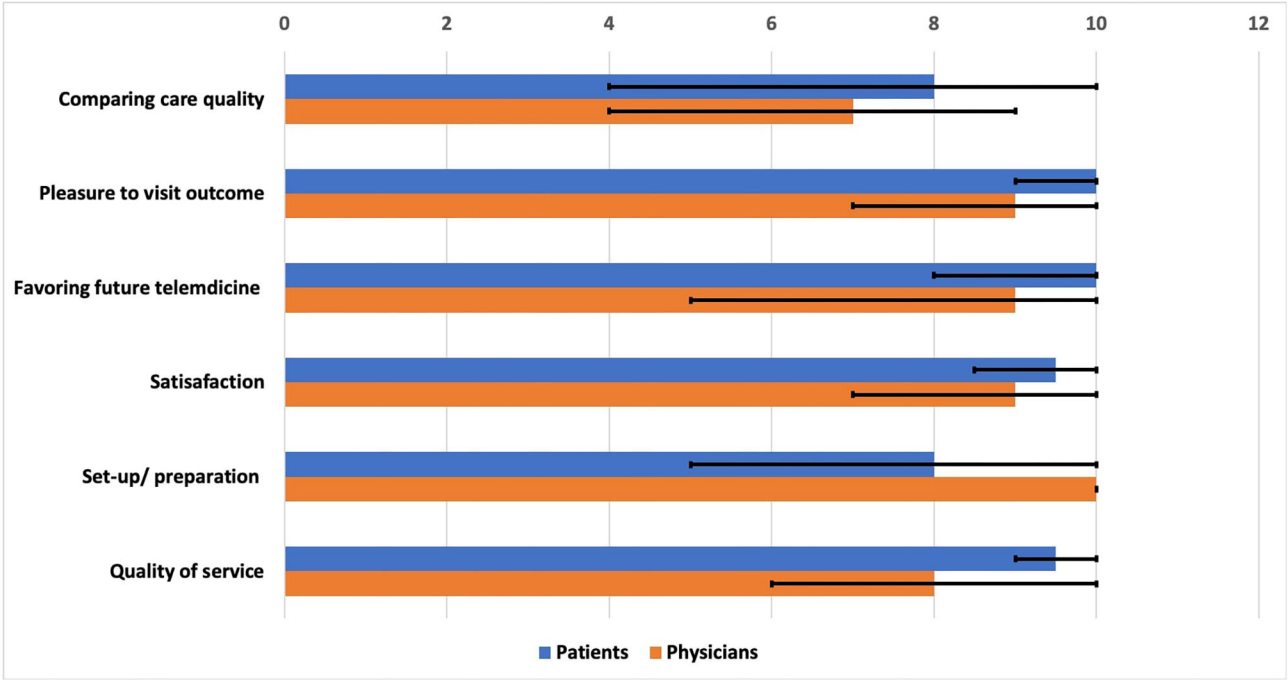


FIGURE 2 | Satisfaction, set-up, preparation, and service quality of virtual visits for Parkinson's disease patients as rated by the patients and the physicians. The chart describes the median and the ranges of different items.

the local currency and the fact that most patients lived in the same governorate (68.4%), the money saved was substantial for the patients, given their low socioeconomic level.

Virtual visits enabled the physicians to provide healthcare to PD patients, including comprehensive assessment, adjustment of medications, and delivery of recommendations. This study included ideal aspects of telemedicine, such as easy-to-use technology, combined use of synchronous and asynchronous programs, and previous in-person visits. However, other aspects, such as the use of high-resolution devices, support by technology experts, and high-speed Internet connectivity, were inadequate (2, 5).

Lack of awareness was described as a major barrier for adopting telemedicine in developing Middle Eastern countries, resulting in resistance from the doctors and the patients, in addition to poor infrastructure, lack of funding, and poor technological training (8, 9). In contrast, this study demonstrated the high feasibility of scheduled visits and acceptance of virtual visits among the participants. Moreover, most patients favored its use beyond the pandemic, while technical limitations were the main barrier. Moreover, it showed that social support could facilitate the use of telemedicine for patients with poor education level. However, further studies are required to confirm these findings in actual clinical practice.

Despite the high feasibility of scheduled virtual visits in the current study, about half (51.3%) of the approached patients declined the use of telemedicine virtual visits. The absence of or bad Internet connection and the inability to use technology were the main barriers, representing 85% of the declined invitations. These barriers, in addition to cultural resistance and lack of regulations, have been variably reported among Middle Eastern countries and other developing countries (9, 13). Consistently, most PD patients who participated in the virtual visit studies in developed countries were well-educated and more familiar with the technology (14). Furthermore, older patients with chronic illnesses have less access to the Internet (2). However, patients who did and did not participate in the visits showed similar cognition, education level, and age, emphasizing the impact of Internet availability and social support in technology use. Privacy concern was reported by a female patient; this is related to cultural and religious beliefs as a relevant obstacle for telemedicine in our region (9).

Overcoming the barriers of adopting telemedicine in developing countries is crucial for better healthcare of PD patients. Providing good Internet services and advanced infrastructure of communication technology to underserved as well as rural areas and support patients for good access to the Internet is necessary. The use of simple systems for telehealth services, patients' training, and the availability of well-educated family members might help overcome the technology-related obstacles (9). Furthermore, establishing satellite clinics in underserved and rural areas with a good Internet connection is another way to overcome the lack of Internet and technological problems at homes and increase access to telehealth services (15). These strategies could be implemented through a comprehensive telemedicine program for developing countries that use well-organized services, apply simple technology, adopt patient and healthcare provider training, and receive continuous funding

(13). Moreover, promoting public awareness about the benefits of telemedicine is important for reforming the social perception of telemedicine, especially in developing countries (9). The COVID-19 pandemic and the related challenges emphasize the importance of establishing well-organized telehealth services all over the world, especially for chronic neurological diseases.

The relatively small study population was a major study limitation that could be attributed to the inclusion of only patients with available data and recent comprehensive assessment in the past 6 months before the lockdown and the mitigation of the lockdown restrictions in Egypt by the end of June 2020. Another limitation was the application of less organized telemedicine services, owing to the unusual emerging situation. However, this represents a real-life situation and more practical use of telemedicine. The current findings should be interpreted in the context of the unusual situation of inaccessibility of in-person health services that might impact the patients' acceptance of virtual visits. Therefore, further studies are warranted to investigate the use of telemedicine for PD patients in developing countries with a larger number of patients and longer follow-up periods during usual clinical practice.

CONCLUSION

The current study describes the high feasibility, high satisfaction level, and favorable quality of service of virtual visits, implying the possibility of the rapid adoption of telemedicine in emerging situations and in developing countries. Furthermore, it identifies the barriers against telemedicine use in a developing country, especially poor Internet service and technical challenges. Stable Internet connectivity, use of simple technology, promotion of public awareness, availability of well-organized services, formulation of regulations, and reimbursement are required for the long-term establishment of effective telemedicine services.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethical committee of the faculty of medicine, Ain Shams University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS contributed to the idea and conception, study design, data collection, statistical design and execution, writing of the first draft, and review and critique of the manuscript. MF and ND contributed to the research project execution, data collection, statistical analysis design and execution, writing and review of the first draft of the manuscript, and review and critique of the manuscript. EH contributed to the study design, research project execution, data collection, statistical analysis design and execution, writing of the first draft of the manuscript, and review and critique of the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank the patients who participated in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.582613/full#supplementary-material

REFERENCES

1. Achey M, Aldred JL, Aljehani N, Bloem BR, Biglan KM, Chan P, et al. The past, present, and future of telemedicine for Parkinson's disease. *Mov. Disord.* (2014) 29:871–83. doi: 10.1002/mds.25903
2. Ben-Pazi H, Browne P, Chan P, Cubo E, Guttman M, Hassan A, et al. The promise of telemedicine for movement disorders: an interdisciplinary approach. *Curr. Neurol. Neurosci. Rep.* (2018) 18:26. doi: 10.1007/s11910-018-0834-6
3. Shalash A, Roushdy T, Essam M, Fathy M, Dawood NL, Abushady EM, et al. Mental health, physical activity, and quality of life in Parkinson's disease during COVID-19 pandemic. *Mov. Disord.* (2020) 35:1097–9. doi: 10.1002/mds.28134
4. Dorsey ER, Vlaanderen FP, Engelen LJ, Kieburtz K, Zhu W, Biglan KM, et al. Moving Parkinson care to the home. *Mov. Disord.* (2016) 31:1258–62. doi: 10.1002/mds.26744
5. Eisenberg J, Hou JG, Barbour P. Current perspectives on the role of telemedicine in the management of Parkinson's disease. *Smart Homecare Technol. TeleHealth*. (2018) 2018:1–12. doi: 10.2147/SHTT.S152018
6. Hanson RE, Truesdell M, Stebbins GT, Weathers AL, Goetz CG. Telemedicine vs office visits in a movement disorders clinic: comparative satisfaction of physicians and patients. *Mov. Disord. Clin. Pract.* (2019) 6:65–9. doi: 10.1002/mdc3.12703
7. Korn RE, Wagle Shukla AW, Katz M, Keenan HT, Goldenthal S, Auinger P, et al. Virtual visits for Parkinson disease: a multicenter noncontrolled cohort. Neurology. *Clin. Pract*. (2017) 7:283–95. doi: 10.1212/CPJ.0000000000000371
8. Alajlani M, Clarke M. Effect of culture on acceptance of telemedicine in middle eastern countries: case study of Jordan and Syria. *Telemed. J. E. Health.* (2013) 19:305–11. doi: 10.1089/tmj.2012.0106
9. Al-Samarraie H, Ghazal S, Alzahrani AI, Moody L. Telemedicine in middle eastern countries: progress, barriers, and policy recommendations. *Int. J. Med. Inform*. (2020) 141:104232. doi: 10.1016/j.ijmedinf.2020.104232
10. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord.* (2015) 30:1591–601. doi: 10.1002/mds.26424
11. Wilkinson JR, Spindler M, Wood SM, Marcus SC, Weintraub D, Morley JF, et al. High patient satisfaction with telehealth in Parkinson disease: a randomized controlled study. *Neurol. Clin. Pract.* (2016) 6:241–51. doi: 10.1212/CPJ.0000000000000252
12. Khalil H, Chahine L, Siddiqui J, Aldaajani Z, Bajwa JA. Parkinson's disease in the MENASA countries. *Lancet Neurol.* (2020) 19:293–4. doi: 10.1016/S1474-4422(20)30026-0

13. Khanal S, Burgon J, Leonard S, Griffiths M, Eddowes LA. Recommendations for the improved effectiveness and reporting of telemedicine programs in developing countries: results of a systematic literature review. *Telemed. J. E. Health*. (2015) 21:903–15. doi: 10.1089/tmj.2014.0194
14. Dorsey ER, Achey MA, Beck CA, Beran DB, Biglan KM, Boyd CM, et al. National randomized controlled trial of virtual house calls for people with Parkinson's disease: interest and barriers. *Telemed. J. E. Health*. (2016) 22:590–8. doi: 10.1089/tmj.2015.0191
15. Schneider RB, Biglan KM. The promise of telemedicine for chronic neurological disorders: the example of Parkinson's disease. *Lancet Neurol*. (2017) 16:541–51. doi: 10.1016/S1474-4422(17)30167-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 27 October 2020
doi: 10.3389/fneur.2020.571996

COVID-19 Associated Ischemic Stroke and Hemorrhagic Stroke: Incidence, Potential Pathological Mechanism, and Management

Zilan Wang[1†], Yanbo Yang[1†], Xiaolong Liang[2], Bixi Gao[1], Meirong Liu[3], Wen Li[4], Zhouqing Chen[1] and Zhong Wang[1*]*

[1] Department of Neurosurgery and Brain and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, China, [2] Department of Orthopedics, The First Affiliated Hospital of Soochow University, Suzhou, China, [3] Department of Neurology, The First Affiliated Hospital of Soochow University, Suzhou, China, [4] Department of Neurology, The Second Affiliated Hospital of Soochow University, Suzhou, China

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Narayanaswamy Venketasubramanian,
Raffles Medical Group, Singapore
Chun-Jen Lin,
Taipei Veterans General Hospital, Taiwan

***Correspondence:**
Zhouqing Chen
zqchen6@163.com
Zhong Wang
wangzhong761@163.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 12 June 2020
Accepted: 27 August 2020
Published: 27 October 2020

Citation:
Wang Z, Yang Y, Liang X, Gao B, Liu M, Li W, Chen Z and Wang Z (2020) COVID-19 Associated Ischemic Stroke and Hemorrhagic Stroke: Incidence, Potential Pathological Mechanism, and Management. Front. Neurol. 11:571996. doi: 10.3389/fneur.2020.571996

The outbreak of the novel coronavirus infectious disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has rapidly spread around the world. Increasing evidence has suggested that patients with COVID-19 may present neurological symptoms, and cerebrovascular diseases are one of the most frequent comorbidities. The markedly elevated D-dimer levels in patients with acute ischemic stroke suggests that SARS-CoV-2 infection may induce an inflammatory response and trigger a hypercoagulation state, thus leading to acute ischemic stroke. Cardioembolism and atherosclerosis in patients with COVID-19 infection may also increase the risk of ischemic stroke. The reduction of the angiotensin-converting enzyme II (ACE2) caused by SARS-CoV-2 binding to the ACE2 receptor can lead to abnormally elevated blood pressure and increase the risk of hemorrhagic stroke. Additionally, the cytokine storm induced by the immune response against the viral infection increases the risk of acute stroke. The management for COVID-19 patients with stroke is not only based on the traditional guidelines, but also based on the experience and new instructions from healthcare workers worldwide who are combatting COVID-19.

Keywords: COVID-19, SARS-CoV-2, ischemic stroke, hemorrhagic stroke, nervous system

INTRODUCTION

As COVID-19 has rapidly spread worldwide, increasing evidence suggests that SARS-CoV-2 may also invade the central nervous system and induce neurological symptoms (1–3). Research from Wuhan reported neurologic manifestations in 36.4% of 214 COVID-19 patients (4). An increasing number of studies have revealed that in addition to the typical respiratory symptoms such as fever and dry cough, patients with COVID-19 may develop neurological manifestations, ranging from mild to severe (4–9).

Stroke presents as one of the most frequent causes of death and disability all around the world. More than 9,000 new stroke cases occur each day in China (10). Previous studies have suggested that cerebrovascular disease is an independent risk factor for severe cases of COVID-19 infection (11). The risk of cross-infection and lack of experienced stroke care experts during the COVID-19

pandemic have impacted stroke centers and caused a worldwide drop of over 30% in the number of patients with stroke or transient ischemic attacks (TIA) seeking emergency care, which could affect the prognosis in these patients (10, 12–15). What is worse, being in quarantine alone during the epidemic may increase the risk of missing the therapeutic window if the patient does not seek care in a timely way. Thus, new guidelines for the management of patients with stroke in the context of the COVID-19 pandemic are urgently needed. This review aims to summarize current evidence of the epidemiology and potential mechanisms of various cerebrovascular diseases with COVID-19 to provide clinical insight for the management of such patients.

POSSIBLE MECHANISMS UNDERLYING THE CENTRAL NERVOUS SYSTEM INVASION

As with other neurotropic respiratory viruses, two major pathways, the hematogenous and neuronal retrograde, have been proposed as possible routes for SARS-CoV-2 to enter the central nervous system (CNS) (16–18) (**Figure 1**) After systemic circulatory dissemination following infection of the lung, the virus may enter the brain *via* cerebral circulation (17). According to a postmortem examination of a COVID-19 patient, viral-like particles in the brain capillary endothelium were observed actively budding across endothelial cells, suggesting the hematogenous route as the most likely pathway for SARS-CoV-2 entering the brain (19). Second, cases of olfactory dysfunction in COVID-19 patients suggests retrograde axonal transport *via* the olfactory bulb as another possible entry route (9, 20, 21).

Similar to SARS-CoV, SARS-CoV-2 exploits the angiotensin-converting enzyme II (ACE2) receptor for cell entry (22). Previous studies identified that ACE2 receptors were expressed in the brain, which suggests the potential for nervous system invasion of SARS-CoV and SARS-CoV-2 (17, 23, 24). Both SARS-CoV and SARS-CoV-2 have been detected in postmortem examinations from the brains of SARS or COVID-19 infected patients (19, 24). Given that the SARS-CoV-2 spike protein can interact with ACE2 expressed in the capillary endothelium, the virus may also damage the blood-brain barrier and enter the CNS by attacking the vascular system (17). Moreover, a case of COVID-19 with encephalitis has also been confirmed to contain SARS-CoV-2 in the cerebrospinal fluid (CSF) (6).

COVID-19 INFECTION MAY INDUCE VENOUS AND ARTERIAL THROMBOEMBOLISM

Severe COVID-19 infection can cause the release of pro-inflammatory cytokines, which induce the expression of tissue factor (TF) by endothelial and mononuclear cells and leads to coagulation activation and thrombin generation (25, 26). It has been reported that the procoagulant state caused by COVID-19 infection may induce venous and arterial thromboembolism. A retrospective analysis from Wuhan revealed that abnormal coagulation parameters, especially markedly elevated D-dimer and fibrin degradation product levels are associated with poor prognosis in patients with COVID-19 ($P < 0.05$) (27). D-dimer is a degradation product of cross-linked fibrin and is a frequently used marker of hypercoagulable and thrombotic events (28). Moderately elevated levels of D-dimer are associated with the risk of venous and arterial events in patients with vascular disease (28). A multi-center study evaluated the incidence of the composite outcome of the venous and arterial thrombotic complications (including symptomatic acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism) in all 184 COVID-19 patients admitted to the ICU (29). The cumulative incidence of the composite outcome was 31%, of which venous thromboembolism made up 27% and arterial thrombotic events (all ischemic strokes) made up 3.7% (29). Another similar study from Italy also analyzed the venous and arterial thromboembolic complications in 388 COVID-19 patients (30). The results showed that, despite the use of anticoagulant prophylaxis, the rate of venous and arterial thromboembolic complications in hospitalized COVID-19 patients accounts for ∼8% of the included patients (30). Additionally, more than half of these diagnoses of thromboembolic events were made within the first 24 h of hospital admission (30). Ischemic stroke was diagnosed in nine (2.5%) patients, and in six patients stroke was the primary reason for hospitalization. They also showed that the D-dimer levels rapidly increased in non-survivors during hospitalization (30). These clinical studies suggest the urgent need for developing pharmacological thrombosis prophylaxis strategies in severe COVID-19 patients.

COVID-19 INFECTION WITH THE NEW ONSET OF ISCHEMIC STROKE

The reported incidence of acute ischemic stroke in COVID-19 patients ranges from 2.5 to 5%. Stroke usually develops several days after COVID-19 infection. In rare cases, it can be the primary reason for the hospitalization of COVID-19 infection (25). According to research conducted during the epidemic, large vessel occlusion was more common in COVID-19 infected patients with stroke.

The first study focused on the neurological manifestations of patients with COVID-19 from the epicenter of the pandemic in Wuhan, China, and reported neurological complications in 78 (36.4%) of 214 patients (4). Acute cerebrovascular disease was more common among patients with severe COVID-19 than those with a non-severe disease (5 [5.7%]: four patients with ischemic stroke and one with cerebral hemorrhage who died later of respiratory failure; vs. 1 [0.8%]: one patient with ischemic stroke; $P = 0.03$) (4). Of the six patients with acute cerebrovascular disease, two arrived at the emergency department presenting with sudden onset of hemiplegia but without any typical symptoms of COVID-19 (4). To note, reported patients with severe infection were found to have higher D-dimer levels than that of patients with non-severe infection (4). A retrospective study by Li et al. (31) on acute cerebrovascular disease from

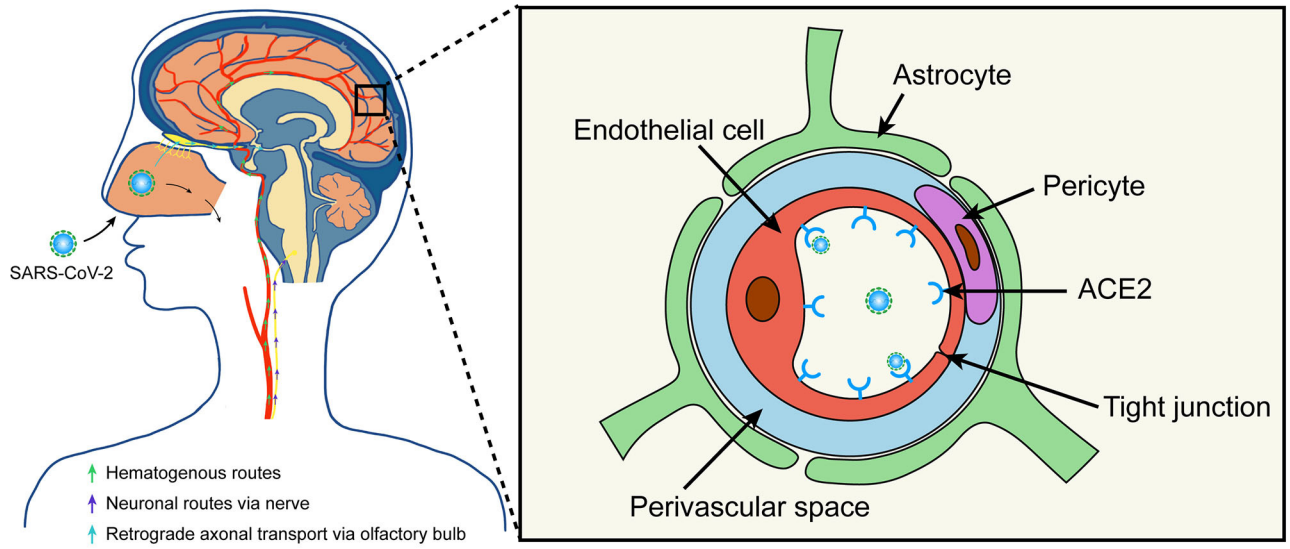


FIGURE 1 | Possible routes for SARS-CoV-2 to enter the brain. SARS-CoV-2 may enter the central nervous system through hematogenous or neuronal routes. The virus may enter the brain *via* cerebral circulation after systemic circulatory dissemination. Moreover, the virus may enter the brain *via* central or peripheral nerve, especially the retrograde axonal transport from the olfactory bulb. Additionally, SARS-CoV-2 can bind and engage with the ACE2 receptor in the capillary endothelium to damage the blood-brain barrier. ACE2, angiotensin-converting enzyme II.

Wuhan, China showed that of the 219 patients with COVID-19, 10 (4.6%) developed acute ischemic stroke and one (0.5%) had a cerebral hemorrhage. The median duration from the first symptoms of COVID-19 infection to stroke was 10 days. Of the 10 patients with ischemic stroke, five were large vessel occlusion, two were small vessel occlusion, and three were of cardioembolic type according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (31). Moreover, older patients (75.7 ± 10.8 vs. 52.1 ± 15.3 years) with risk factors such as hypertension, diabetes, and previous medical history of cerebrovascular disease are more likely to develop acute cerebrovascular disease (31). In addition, an increased inflammatory response and hypercoagulable state were observed in these patients as reflected in C-reaction protein [51.1 (1.3–127.9) vs. 12.1 (0.1–212.0) mg/L, $P < 0.05$] and D-dimer [6.9 (0.3–20.0) vs. 0.5 (0.1–20.0) mg/L, $P < 0.001$] (31). According to their findings, the significantly increased inflammatory response could be the cause of abnormal blood coagulation function in the early-stage and could be one of the main reasons for the new onset of cerebrovascular disease (31).

A case series (25) from the UK reported six patients with acute ischemic stroke and COVID-19. All six patients had large vessel occlusion with markedly elevated D-dimer levels (≥1,000 μg/L), and most of the strokes occurred 8–24 days after the onset of COVID-19 symptoms (25). However, a causal relationship between COVID-19 and ischemic stroke cannot be confirmed, as competing vascular risk factors such as atrial fibrillation were present. Another case series (32) from New York reported on four COVID-19 patients older than 70, all of whom had acute large vessel occlusion. A similar study conducted by Oxley et al. (7) from New York reported five cases of large vessel occlusion in COVID-19. To note, all of these patients are under 50 years of age and only presented with mild symptoms of COVID-19. These findings suggest that COVID-19 primarily causes large vessel occlusion.

THE POTENTIAL MECHANISM OF COVID-19 RELATED ISCHEMIC STROKE

Previous studies indicate that acute bacterial and viral infections, especially respiratory-related infections, are transiently independent risk factors for stroke (33, 34). The association between acute infection and stroke is believed to be caused by the systemic inflammatory response to infection, which can lead to endothelial dysfunction and induce a procoagulant state (34, 35). It has been proposed that the inflammatory response in COVID-19 patients is associated with multiple pathways. As shown in **Figure 2**, after the infection of SARS-CoV-2, the activated monocyte-derived macrophages can release massive amounts of pro-inflammatory cytokines such as interleukin (IL), tumor necrosis factor (TNF) (35–37). In response to pro-inflammatory cytokines (mainly IL-6), TF is released from monocyte-derived macrophages and endothelial cells (35, 38, 39). TF is known to activate the extrinsic coagulation pathway and leads to fibrin deposition and blood clotting. Moreover, when ACE2 is endocytosed together with SARS-CoV, ACE2 on cells is reduced, followed by an increase of serum angiotensin II (Ang2), which will also induce a pro-inflammatory effect (40–42). The markedly elevated D-dimer levels in patients with acute onset of ischemic stroke also supports that SARS-CoV-2 may cause an acute

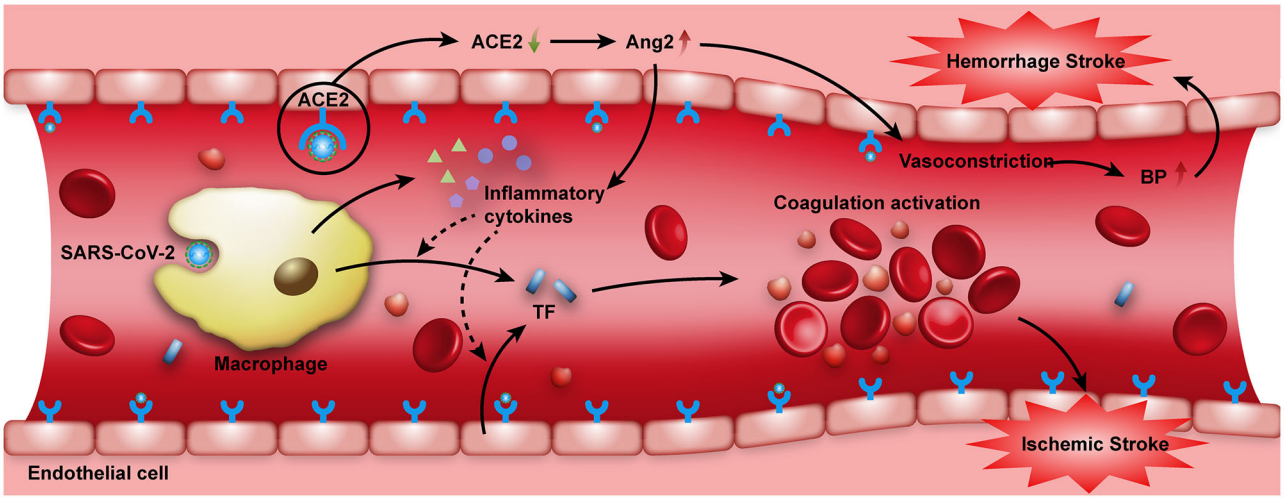


FIGURE 2 | SARS-CoV-2 attacking the vascular system. When the SARS-CoV-2 virus invades the human body, activated monocyte-derived macrophages can release massive amounts of pro-inflammatory cytokines such as IL and TNF to combat the infection. Moreover, when ACE2 receptors on the cell surface are occupied by SARS-CoV-2, the expression and function of ACE2 are reduced, Ang2 in the serum then increases, which also has a pro-inflammatory effect. These pro-inflammatory cytokines can induce the expression of TF. TF expressed by activated monocyte-derived macrophages and endothelial cells can activate the extrinsic coagulation pathway, leading to fibrin deposition and blood clotting. All these factors may increase the risk of acute ischemic stroke. On the other hand, the intracranial cytokine storms induced by SARS-CoV-2 infection may result in the breakdown of the blood-brain-barrier, thus causing hemorrhagic stroke. In addition, the binding of SARS-CoV-2 to ACE2 receptors may increase the synthesis of Ang2, and may thus elevate blood pressure and increase the risk of hemorrhagic stroke. ACE2, angiotensin-converting enzyme II; Ang2, angiotensin II; BP, blood pressure; IL, interleukin; TF, tissue factor; TNF, tumor necrosis factor.

inflammatory response in the blood vessel walls and trigger a hypercoagulation state.

The traditional causes of stroke in these patients with COVID-19 infection cannot be overlooked. Etiologically, ischemic stroke is caused by cardioembolism, artery-to-artery embolism, or *in-situ* small vessel disease (43). The TOAST classification system has classified ischemic stroke into five subtypes: large artery atherosclerosis, cardioembolism, small artery occlusion, stroke of other determined etiology, and stroke of undetermined etiology (44). Atherosclerosis in patients with a COVID-19 infection may increase the risk of ischemic stroke as a viral infection can potentially destabilize atherosclerotic plaques through systemic inflammatory responses, a cytokine storm, as well as specific changes of immune cell polarization toward more unstable phenotypes (45). In addition, COVID-19 infected patients with cardiovascular comorbidities may have the potential risk of dysrhythmia, which can cause cardioembolism and increase the risk of stroke. A study from Northern Italy showed that the rate of thromboembolic events was higher in COVID-19 patients with a history of cardiovascular disease (23 vs. 6%) (46). What's worse, as COVID-19 is known to have a great effect on the cardiovascular system, the subsequent cardiac dysfunction needs to be considered (13, 47). A recent study reported that 16.7% of 138 hospitalized COVID-19 patients developed dysrhythmia, which presented as a common complication (8). Moreover, viral infections could induce metabolic dysfunction, myocardial inflammation, and activation of the sympathetic nervous system, which would contribute to the development of dysrhythmia (45).

COVID-19 INFECTION WITH THE NEW ONSET OF HEMORRHAGIC STROKE

There are fewer cases of hemorrhagic stroke compared with ischemic stroke in patients with COVID-19, and it remains uncertain whether hemorrhagic stroke is directly related to COVID-19 infection.

Sharifi-Razavi et al. (48) reported a case of a 79-years-old man with a fever and cough who developed acute loss of consciousness 3 days later. The patient had a blood pressure of 140/65 mmHg at admission and no history of hypertension or anticoagulation therapy (48). A cerebral CT scan revealed a massive intracerebral hemorrhage (ICH) in the right hemisphere, accompanied by an intraventricular and subarachnoid hemorrhage (48). An oropharyngeal swab confirmed COVID-19 infection, however, a CSF analysis was not performed in this case.

The retrospective study (31) of 11 COVID-19 patients with acute cerebrovascular disease from Wuhan, previously mentioned, also reported on a 60-years-old male who developed cerebral hemorrhage 10 days after severe COVID-19 infection. The patient had increased blood pressure (150/80 mmHg) and died 13 days after the stroke (31).

Poyiadji et al. (49) reported on a female in her late 50's who was diagnosed with COVID-19-associated acute necrotizing hemorrhagic encephalopathy (ANE). Her brain MRI images showed hemorrhagic rim enhancing lesions in the bilateral thalami, medial temporal lobes, and subinsular regions (49). However, testing for the presence of SARS-CoV-2 in the CSF was not performed (49). ANE is a rare CNS complication

secondary to viral infections. It has been related to intracranial cytokine storms, which result in blood-brain-barrier breakdown but without direct viral invasion or parainfectious demyelination (49). As evidence shows that severe COVID-19 infection may be associated with cytokine storms (36), we need to be alert to these patients with regard to the occurrence of ANE and other nervous system diseases induced by intracranial cytokine storms.

THE POTENTIAL MECHANISM OF COVID-19 RELATED HEMORRHAGIC STROKE

ACE2 is known as a critical enzyme in the renin-angiotensin system (RAS) that regulates blood pressure, fluid, and electrolyte balance, and vascular resistance. It is also the inactivator of Ang2 (50, 51). As shown in **Figure 2**, the downregulation of ACE2 expression during SARS-CoV-2 infection may increase Ang2 in the serum, which can impair endothelial function and contribute to dysregulation of blood pressure, thus increasing the risk of hemorrhagic stroke (52). As for patients with hypertension, the expression of ACE2 is already low; when SARS-CoV-2 binds to ACE2 receptors, the ability of ACE2 to lower blood pressure is concomitantly reduced, so COVID-19 infection is more likely to induce a cerebral hemorrhage in such patients (53, 54). Thus, it is reasonable to hypothesize that in patients with COVID-19, the cytokine storm and elevated blood pressure can increase the risk of hemorrhagic stroke. However, whether or not hemorrhagic stroke is directly related to COVID-19 infection is difficult to ascertain.

MANAGEMENT OF COVID-19 INFECTION WITH STROKE

Neurologists and neurosurgeons worldwide are sharing their experience with the management of COVID-19 patients with neurological manifestation (55–60). What we need to note is that due to the delay in hospital admission caused by the screening of potentially infected patients during the epidemic, stroke patients may miss the optimal therapeutic window.

As ischemic stroke can occur in a systemic prothrombotic state under COVID-19 infection, anticoagulant treatment seems to be reasonable. In the retrospective study from Li et al. (31) previously mentioned, of the 10 patients with ischemic stroke, four received anticoagulant treatment with low-molecular-weight heparin (LMWH) and only one of them died, while six received antiplatelet treatment with Aspirin or Clopidogrel and three of them died. A retrospective analysis of 449 patients with severe COVID-19 performed by Tang et al. (61) revealed that anticoagulant therapy mainly with LMWH appears to be associated with a better prognosis in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer. The case series (25) from the UK also supports early therapeutic anticoagulation with LMWH. A systematic review of COVID-19 literature reporting on measures of clotting activation also suggests that for COVID-19 patients with elevated D-dimer, antithrombotic treatment may be used (62). However, the efficacy and safety of these anticoagulants in patients with COVID-19 require further investigation, with particular consideration for the risk of bleeding. A detailed assessment of the coagulation profile is necessary. It also needs to be determined by the comprehensive judgment of TOAST classification, clinical syndrome, National Institutes of Health Stroke Scale (NIHSS) score, and laboratory findings.

Thrombectomy also plays a crucial role in treating acute stroke patients. However, endovascular treatments have been reduced in stroke units during the epidemic era. A significant decrease of 61% in the number of patients for thrombectomy was observed in a multicenter study (15). Yaeger et al. reported 10 patients with large vessel occlusion undergoing thrombectomy with a successful reperfusion rate of 90% and concluded that thrombectomy continues to be an effective therapy (63). A study on acute ischemic stroke patients with large artery occlusion who underwent endovascular thrombectomy (EVT) showed that the rate of successful reperfusion was not significantly different in the pre-pandemic group vs. the pandemic group [88.2% ($n = 30$) vs. 85.7% ($n = 18$) (64)]. However, the successful reperfusion rate between COVID-19 infected patients and non-infected patients was unknown. Wang et al. reported on five patients with COVID-19 with large vessel occlusions who underwent EVT and concluded that those patients were more likely to have worse radiographic and clinical outcomes after EVT (64, 65). It cannot be denied that reperfusion therapy during the COVID-19 pandemic could be challenging and that personal protective equipment is necessary to minimize the infection of healthcare workers.

Blood pressure destabilization increases the incidence of heart failure, stroke, and other cardiovascular diseases (66, 67). Accordingly, the management of blood pressure might require specific attention during the hyper-acute and acute stroke phases (68). Angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are both antihypertensive drugs for blocking the RAS and lowering blood pressure. Recently, there has been a debate on whether the use of ACEIs/ARBs increases the expression of ACE2, thereby increasing the susceptibility to SARS-CoV-2 (69–71). A single-center retrospective study (72) on the effects of ARBs and ACEIs on COVID-19 patients with pre-existing hypertension showed that ARBs/ACEIs treatment significantly reduced the concentrations of CRP [11.5 (4.0–58.2) vs. 33.9 (5.1–119.2); $P = 0.049$] and procalcitonin [0.061 (0.044–0.131) vs. 0.121 (0.052–0.295); $P = 0.008$], when compared with non-ARBs/ACEIs treatment. Furthermore, a lower proportion of critical patients (9.3 vs. 22.9%; $P = 0.061$), and a lower death rate (4.7 vs. 13.3%; $P = 0.216$) were observed in the ARBs/ACEIs group, although these differences failed to reach statistical significance (72). These findings thus support the use of ARBs/ACEIs in COVID-19 patients with pre-existing hypertension (72). Some literature reviews also support the use of ARBs/ACEIs in COVID-19 patients (73, 74). Other treatments that target the RAS system may also be promising therapies for COVID-19 (73, 75). For example, angiotensin (1–7) has already shown promise in preclinical stroke models and it is in a clinical trial for patients with COVID-19 (NCT04332666). Recombinant human

ACE2 (APN01), developed in 2010, has been demonstrated to be able to reduce levels of both Ang2 and IL-6 in a phase II study of acute respiratory distress syndrome. It is also under investigation in China in severe cases of COVID-19 infection (76). On the other hand, treatment of hypertension patients with ACEIs or ARBs can reduce the synthesis or function of Ang2, thus downregulating the production of inflammatory cytokines (77), which may benefit COVID-19 patients with stroke. As there are fewer reports of hemorrhagic stroke in COVID-19 infection, most of the suggestions are concluded from small and retrospective analyses, and more clinical trials are needed to determine the safety and efficacy of these medicines.

To conclude, stroke involves multiple pathophysiological mechanisms. Although COVID-19 may directedly lead to stroke, the common vascular risk factors cannot be overlooked. The management protocol for COVID-19 patients with stroke should also depend on the traditional guidelines. Furthermore, the importance of the use of personal protective equipment and other strategies to minimize exposure during the treatment of stroke patients with COVID-19 cannot be understated.

CONCLUSION

Based on current evidence, the causative relationship between cerebrovascular events and COVID-19 is not conclusive. However, previous studies show that acute inflammatory response to COVID-19 infection could induce a procoagulant state and increase the risk of ischemic stroke. Furthermore, the cytokine storm and abnormally elevated blood pressure resulting from the reduction of ACE2 caused by SARS-CoV-2, can increase the risk of hemorrhagic stroke. Given that SARS-CoV-2 could interact with ACE2 expressed in the capillary endothelium, the virus may also damage the blood-brain barrier and enter the CNS. The occurrence of cerebrovascular events is, potentially, related to a direct effect of the viral infection itself. Thus, it is prudent to account for cerebrovascular events and cerebrovascular risk factors as crucial components in the risk model for COVID-19 infection. More studies are needed to establish the mechanisms of cerebrovascular diseases associated with COVID-19. Strategies are urgently needed for specific stroke management during the COVID-19 outbreak and to ensure that stroke patients can get appropriate treatment in time.

AUTHOR CONTRIBUTIONS

ZiW and YY designed the study. ZiW, YY, XL, BG, and WL contributed to drafting the article. ML and WL revised the manuscript and polish the language. ZC and ZhW contributed to the critical revision of the article. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Suzhou Health Talents Training Project (GSWS2019002).

ACKNOWLEDGMENTS

We gratefully acknowledge the help of Catherine Paige Broyles in aiding in the clarification of our manuscript.

REFERENCES

1. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* (2020) 130:2620–9. doi: 10.1172/JCI137244
2. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. *J Neurol Sci.* (2020) 413:116832. doi: 10.1016/j.jns.2020.116832
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–720. doi: 10.1056/NEJMoa2002032
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
5. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clin Infect Dis.* (2020) 71:889–90. doi: 10.1093/cid/ciaa330
6. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/Encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis.* (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
7. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-Vessel stroke as a presenting feature of covid-19 in the young. *N Engl J Med.* (2020) 382:60. doi: 10.1056/NEJMc2009787
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
9. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* (2020) 277:2251–61. doi: 10.1007/s00405-020-05965-1
10. Zhao J, Rudd, Liu A. R. Challenges and potential solutions of stroke care during the coronavirus disease 2019 (COVID-19) outbreak. *Stroke.* (2020) 51:1356–7. doi: 10.1161/STROKEAHA.120.029701
11. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging.* (2020) 12:6049–57. doi: 10.18632/aging.103000
12. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral effect of covid-19 on stroke evaluation in the United States. *N Engl J Med.* (2020) 383:400–1. doi: 10.1056/NEJMc2014816
13. Kim JS. Coronavirus disease 2019 and stroke. *J Stroke.* (2020) 22:157–8. doi: 10.5853/jos.2020.01760
14. Diegoli H, Magalhães Pedro SC, Martins Sheila CO, Moro Carla HC, França Paulo HC, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke.* (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
15. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmünzer B, Barlinn K, et al. Acute stroke in times of the COVID-19 pandemic: a multicenter study. *Stroke.* (2020) 51:2224–7. doi: 10.1161/STROKEAHA.120.030395
16. Desforges M, Le Coupanec A, Dubeau P, Bourgouin A, Lajoie L, Dubé M, et al. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses.* (2019) 12:14. doi: 10.3390/v12010014
17. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* (2020) 11:995–8. doi: 10.1021/acschemneuro.0c00122

18. Das G, Mukherjee N, Ghosh S. Neurological insights of COVID-19 pandemic. *ACS Chem Neurosci.* (2020) 11:1206–9. doi: 10.1021/acschemneuro.0c00201
19. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol.* (2020) 92:699–702. doi: 10.1002/jmv.25915
20. Menni C, Valdes A, Freydin MB, Ganesh S, El-Sayed Moustafa J, Visconti A, et al. (2020) Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. *medRxiv*. doi: 10.1101/2020.04.05.20048421
21. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS Neurosci Ther.* (2020) 26:499–501. doi: 10.1111/cns.13372
22. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* (2020) 579:270–3. doi: 10.1038/s41586-020-2012-7
23. Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. *J Neurochem.* (2008) 107:1482–94. doi: 10.1111/j.1471-4159.2008.05723.x
24. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Infect Dis.* (2005) 41:1089–96. doi: 10.1086/444461
25. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry.* (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586
26. Montalvan V, Toledo JD, Nugent K. Mechanisms of stroke in coronavirus disease 2019. *J Stroke.* (2020) 22:282–3. doi: 10.5853/jos.2020.01802
27. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* (2020) 18:844–7. doi: 10.1111/jth.14768
28. Simes J, Robledo KP, White HD, Espinoza D, Stewart RA, Sullivan DR, et al. D-Dimer predicts long-term cause-specific mortality, cardiovascular events, and cancer in patients with stable coronary heart disease: LIPID study. *Circulation.* (2018) 138:712–23. doi: 10.1161/CIRCULATIONAHA.117.029901
29. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.013
30. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res.* (2020) 191:9–14. doi: 10.1016/j.thromres.2020.04.024
31. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol.* (2020) 5:279–84. doi: 10.1136/svn-2020-000431
32. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain Behav Immun.* (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077
33. Ameriso SF, Wong VL, Quismorio FP Jr. Fisher M. Immunohematologic characteristics of infection-associated cerebral infarction. *Stroke.* (1991) 22:1004. doi: 10.1161/01.STR.22.8.1004
34. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. *Nat Rev Neurol.* (2010) 6:681–94. doi: 10.1038/nrneurol.2010.163
35. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunolo.* (2020) 20:355–62. doi: 10.1038/s41577-020-0331-4
36. Yao Z, Zheng Z, Wu K, Junhua Z. Immune environment modulation in pneumonia patients caused by coronavirus: SARS-CoV, MERS-CoV and SARS-CoV-2. *Aging.* (2020) 12:7639–51. doi: 10.18632/aging.103101
37. Pedersen, Ho SF. Y. C. SARS-CoV-2: a storm is raging. *J Clin Invest.* (2020) 130:2202–5. doi: 10.1172/JCI137647
38. Szotowski B, Antoniak S, Poller W, Schultheiss HP, Rauch U. Procoagulant soluble tissue factor is released from endothelial cells in response to inflammatory cytokines. *Circ Res.* (2005) 96:1233–9. doi: 10.1161/01.RES.0000171805.24799.fa
39. Van Den Hengel LG, Versteeg HH. Tissue factor signaling: a multi-faceted function in biological processes. *Front Biosci.* (2011) 3:240. doi: 10.2741/240
40. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nat Med.* (2005) 11:875–9. doi: 10.1038/nm1267
41. Eguchi S, Kawai T, Scalia R, Rizzo V. Understanding angiotensin II type 1 receptor signaling in vascular pathophysiology. *Hypertension.* (2018) 71:804–10. doi: 10.1161/HYPERTENSIONAHA.118.10266
42. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res.* (2020) 126:1456–74. doi: 10.1161/CIRCRESAHA.120.317015
43. Hankey GJ. Stroke. *Lancet.* (2017) 389:641–54. doi: 10.1016/S0140-6736(16)30962-X
44. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke.* (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
45. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, treatment options. *Cardiovasc Res.* (2020) 116:1666–87. doi: 10.1093/cvr/cvaa106
46. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J.* (2020) 41:1821–9. doi: 10.1093/eurheartj/ehaa388
47. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol.* (2020) 5:831–40. doi: 10.1001/jamacardio.2020.1286
48. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? *New Microbes New Infect.* (2020) 35:100669. doi: 10.1016/j.nmni.2020.100669
49. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology.* (2020) 292:119–20. doi: 10.1148/radiol.2020201187
50. Hirano T, Murakami M. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. *Immunity.* (2020) 52:731–3. doi: 10.1016/j.immuni.2020.04.003
51. Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. *Am J Physiol Heart Circ Physiol.* (2019) 316:958–70. doi: 10.1152/ajpheart.00723.2018
52. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* (2020) 87:18–22. doi: 10.1016/j.bbi.2020.03.031
53. Wang HY, Li XL, Yan ZR, Sun XP, Han J, Zhang BW. Potential neurological symptoms of COVID-19. *Ther Adv Neurol Disord.* (2020) 13:1756286420917830. doi: 10.1177/1756286420917830
54. Liu K, Pan M, Xiao Z, Xu X. Neurological manifestations of the coronavirus (SARS-CoV-2). pandemic 2019-2020. *J Neurol Neurosurg Psychiatry.* (2020) 91:669–70. doi: 10.1136/jnnp-2020-323177
55. Zhou Y, Li W, Wang D, Mao L, Jin H, Li Y, et al. Clinical time course of COVID-19, its neurological manifestation and some thoughts on its management. *Stroke Vasc Neurol.* (2020) 5:177–9. doi: 10.1136/svn-2020-000398
56. Baracchini C, Pieroni A, Viaro F, Cianci V, Cattelan AM, Tiberio I, et al. Acute stroke management pathway during Coronavirus-19 pandemic. *Neurol Sci.* (2020) 41:1003–5. doi: 10.1007/s10072-020-04375-9
57. Leira EC, Russman AN, Biller J, Brown DL, Bushnell CD, Caso V, et al. Preserving stroke care during the COVID-19 pandemic: potential issues and solutions. *Neurology.* (2020) 95:124–33. doi: 10.1212/WNL.0000000000009713
58. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon B. K. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19). *Pandemic. Stroke.* (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.029838
59. Qureshi AI, Abd-Allah F, Alsenani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. *Int J Stroke.* (2020) 15:540–54. doi: 10.1177/1747493020923234

60. Lin P, Chang Y, Huang C, Lin C, Chuang M, Chen P, et al. Management of hyperacute stroke during the coronavirus disease of 2019 pandemic: the modified code stroke in a medical center in Taiwan. *J Stroke.* (2020) 22:278–81. doi: 10.5853/jos.2020.01599
61. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* (2020) 18:1094–9. doi: 10.1111/jth.14817
62. Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and antithrombotic treatment in coronavirus 2019: A New Challenge. *Thromb Haemost.* (2020) 120:949–56. doi: 10.1055/s-0040-1710317
63. Yaeger KA, Fifi JT, Lara-Reyna J, Rossitto C, Ladner T, Yim B, et al. Initial stroke thrombectomy experience in New York city during the COVID-19 pandemic. *AJNR Am J Neuroradiol.* (2020) 41:1357–60. doi: 10.3174/ajnr.A6652
64. Yang B, Wang T, Chen J, Chen Y, Wang Y, Gao P, et al. Impact of the COVID-19 pandemic on the process and outcome of thrombectomy for acute ischemic stroke. *J Neurointerv Surg.* (2020) 12:664–8. doi: 10.1136/neurintsurg-2020-016177
65. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg.* (2020) 12:648–53. doi: 10.1136/neurintsurg-2020-016220
66. Strauss MH, Hall AS. The divergent cardiovascular effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on myocardial infarction and death. *Prog Cardiovasc Dis.* (2016) 58:473–82. doi: 10.1016/j.pcad.2015.11.004
67. Kai, Kai H. M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. *Hypertension Res.* (2020) 43:648–54. doi: 10.1038/s41440-020-0455-8
68. Divani AA, Liu X, Di Napoli M, Lattanzi S, Ziai W, James ML, et al. Blood pressure variability predicts poor in-hospital outcome in spontaneous intracerebral hemorrhage. *Stroke.* (2019) 50:2023–9. doi: 10.1161/STROKEAHA.119.025514
69. Bian J, Zhao R, Zhai S, Li Z. Anti-RAS drugs and SARS-CoV-2 infection. *Acta pharmaceutica Sinica. B.* (2020) 10:1251–2. doi: 10.1016/j.apsb.2020.04.013
70. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.* (2020) 8:21. doi: 10.1016/S2213-2600(20)30116-8
71. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA*. (2020) 323:1769–70. doi: 10.1001/jama.2020.4812
72. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, et al. Effects Of ARBs and ACEIs On virus infection, inflammatory status and clinical outcomes In COVID-19 patients with hypertension: a single center retrospective study. *Hypertension.* (2020) 76:51–58. doi: 10.1161/HYPERTENSIONAHA.120.15143
73. Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-converting enzyme 2 and antihypertensives (angiotensin receptor blockers and angiotensin-converting enzyme inhibitors) in Coronavirus Disease 2019. *Mayo Clin Proc.* (2020) 95:1222–30. doi: 10.1016/j.mayocp.2020.03.026
74. Sriram, Insel K. P. A. Risks of ACE inhibitor and ARB usage in COVID-19: evaluating the evidence. *Clin Pharmacol Ther.* (2020) 108:236–41. doi: 10.1002/cpt.1863
75. Hess DC, Eldahshan W, Rutkowski E. COVID-19-Related stroke. *Transl Stroke Res.* (2020) 11:322–5. doi: 10.1007/s12975-020-00818-9
76. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. *Circulation.* (2020) 141:1648–55. doi: 10.1161/CIRCULATIONAHA.120.046941
77. Ferder L, Inserra F, Martínez-Maldonado M. Inflammation and the metabolic syndrome: role of angiotensin II and oxidative stress. *Curr Hypertens Rep.* (2006) 8:191–8. doi: 10.1007/s11906-006-0050-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 30 October 2020
doi: 10.3389/fneur.2020.585944

Neurological Predictors of Clinical Outcomes in Hospitalized Patients With COVID-19

*Hisham Salahuddin[1,2†], Ehad Afreen[2†], Irfan S. Sheikh[2], Sohaib Lateef[2], Giana Dawod[2], Judy Daboul[2,3], Nurose Karim[2], Khaled Gharaibeh[2], Mustafa Al-Chalabi[2], Sihyeong Park[2], Alicia C. Castonguay[2], Ragheb Assaly[4], Fadi Safi[4], Marla Matal[5], Ajaz Sheikh[2], Gretchen Tietjen[2], Deepa Malaiyandi[2], Elysia James[2], Imran Ali[2], Syed F. Zaidi[1,2], Ahmad Abdelwahed[6], Vieh Kung[2], Richard Burgess[2] and Mouhammad A. Jumaa[1,2]**

[1] ProMedica Neurosciences Center, Toledo, OH, United States, [2] Department of Neurology, College of Medicine and Life Sciences University of Toledo, Toledo, OH, United States, [3] St. Luke's Hospital, Maumee, OH, United States, [4] Department of Internal Medicine, College of Medicine and Life Sciences, University of Toledo, Toledo, OH, United States, [5] Anesthesiology and Critical Medicine, ProMedica Physicians, Toledo, OH, United States, [6] Pulmonary Medicine, Critical Care Medicine, Sleep Medicine, ProMedica Physicians, Toledo, OH, United States

Introduction: Multiple risk factors of mortality have been identified in patients with COVID-19. Here, we sought to determine the effect of a history of neurological disorder and development of neurological manifestations on mortality in hospitalized patients with COVID-19.

Methods: From March 20 to May 20, 2020, hospitalized patients with laboratory confirmed or highly suspected COVID-19 were identified at four hospitals in Ohio. Previous history of neurological disease was classified by severity (major or minor). Neurological manifestations during disease course were also grouped into major and minor manifestations. Encephalopathy, ischemic or hemorrhagic stroke, and seizures were defined as major manifestations, whereas minor neurological manifestations included headache, anosmia, dysgeusia, dizziness or vertigo, and myalgias. Multivariate logistic regression models were used to determine significant predictors of mortality in patients with COVID-19 infection.

Results: 574/626 hospitalized patients were eligible for inclusion. Mean age of the 574 patients included in the analysis was 62.8 (SD 17.6), with 298 (51.9%) women. Of the cohort, 240(41.8%) patients had a prior history of neurological disease (HND), of which 204 (35.5%) had a major history of neurological disease (HND). Mortality rates were higher in patients with a major HND (30.9 vs. 15.4%; $p = 0.00002$), although this was not a significant predictor of death. Major neurological manifestations were recorded in 203/574 (35.4%) patients during disease course. The mortality rate in patients who had major neurological manifestations was 37.4% compared to 11.9% ($p = 2 \times 10^{-12}$) in those who did not. In multivariate analysis, major neurological manifestation (OR 2.1, CI 1.3-3.4; $p = 0.002$) was a predictor of death.

OPEN ACCESS

Edited by:
Ricardo F. Allegri,
Fundación Para la Lucha Contra las Enfermedades Neurológicas de la Infancia (FLENI), Argentina

Reviewed by:
Brent Bluett,
Stanford University, United States
Christopher Lawrence Kramer,
University of Chicago Medicine, United States

***Correspondence:**
Mouhammad A. Jumaa
Mouhammad.Jumaa@utoledo.edu

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: 22 July 2020
Accepted: 05 October 2020
Published: 30 October 2020

Citation:
Salahuddin H, Afreen E, Sheikh IS, Lateef S, Dawod G, Daboul J, Karim N, Gharaibeh K, Al-Chalabi M, Park S, Castonguay AC, Assaly R, Safi F, Matal M, Sheikh A, Tietjen G, Malaiyandi D, James E, Ali I, Zaidi SF, Abdelwahed A, Kung V, Burgess R and Jumaa MA (2020) Neurological Predictors of Clinical Outcomes in Hospitalized Patients With COVID-19. Front. Neurol. 11:585944. doi: 10.3389/fneur.2020.585944

Conclusions: In this retrospective study, history of pre-existing neurological disease in hospitalized COVID-19 patients did not impact mortality; however, development of major neurological manifestations during disease course was found to be an independent predictor of death. Larger studies are needed to validate our findings.

Keywords: neurological, COVID-19, coronavirus, mortality, encephalopathy, stroke

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), causative agent of the coronavirus disease 2019 (COVID-19) pandemic, is one of seven coronaviruses known to infect humans. The COVID-19 pandemic has become the most challenging public health crisis in decades. High mortality rate has been noted in elderly patients, patients with underlying medical risk factors, and nursing home residents. Along with age, chronic cardiac disease, and chronic pulmonary disease, a prior history of cerebrovascular disease was among the predictors of death in patients with COVID-19 (1, 2). However, limited data exists on the outcome of COVID-19 patients with other underlying neurological diseases.

Fever and cough are the most common symptoms of COVID-19, but disease presentations and clinical course are widely variable (3). Similar to severe acute respiratory syndrome coronavirus(SARS-CoV) and Middle East respiratory syndrome coronavirus(MERS-CoV), SARS-CoV-2 is hypothesized to have neurotropic properties (4). Many neurological manifestations were previously reported during outbreaks of SARS-CoV in 2003 and the MERS-CoV in 2012 (5). Although SARS-CoV-2 is primarily a respiratory virus, a growing body of literature has highlighted a high incidence of neurological manifestations in hospitalized patients, which range from nonspecific symptoms, such as headache, dizziness, and myalgias to more severe complications including encephalopathy, cerebrovascular diseases, and myositis (6–8). An alarming incidence of neurological emergencies as early COVID-19 manifestations have also been reported (9, 10). The outcome of COVID-19 patients with neurological manifestations during the disease course remains unclear.

In this study, we evaluate the outcome of hospitalized COVID-19 patients with underlying neurological diseases and those who suffer from neurological manifestations during disease course.

METHODS

The study was approved by Institutional Review Boards at the four participating hospitals. Informed consent was waived due to the retrospective, expedited nature of the study. We retrospectively reviewed medical records of all hospitalized patients treated for COVID-19 at four regional hospitals, one of which was a designated COVID-19 hospital, between the 20th of March and May 20th, 2020. Patients were included in the analysis if they had a confirmed COVID-19 test by polymerase chain reaction (PCR) from nasopharyngeal swab or were determined to be highly suspected for COVID-19 infection with consistent CT chest imaging, and no alternative explanation for presenting symptoms as assessed by a fellowship trained infectious disease specialist.

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were collected from review of electronic medical records (HS, EA, ISS, SL, NK, MA, KG, PS, GD, JD) using a standardized data collection form. The data collection form focused on history of neurological disease, neurological manifestations at presentation and while in hospital. Data was compiled by one of the authors (HS) and data was checked for discrepancies by two of the authors (HS, MJ).

Neurological Disease and Manifestations

History of pre-existing neurological disease (HND) was grouped into major or minor disease. History of major neurological disease included dementia, ischemic or hemorrhagic stroke, epilepsy, traumatic brain injury, multiple sclerosis, Parkinson's disease, and developmental delay. Neurological manifestations were grouped according to whether patient presented to the hospital with early neurological manifestations (ENM) and/or developed neurological manifestations while in hospital (NMH). We also grouped neurological manifestations into major and minor categories. We defined Major ENM and NMH to include encephalopathy, ischemic or hemorrhagic stroke, and seizures. Minor ENM and NMH included but were not limited to dizziness or vertigo, anosmia, dysgeusia, headache, and myalgia. As myalgias may also be considered a non-neurological manifestation, we also recorded the number of patients who developed myalgia as the only neurological manifestation.

Statistical Analysis

The data set was compiled in Microsoft Excel and exported to a statistical analysis software R: A language and environment for statistical computing; EZR version 1.32 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Continuous and categorical variables were presented as mean (standard deviation) and median (interquartile range). Univariate analysis was performed to find significant factors associated with mortality. To limit overfitting the multivariate analysis, we used the strongest univariate predictors from past medical history and presenting symptoms.

RESULTS

Study Population

Over a two-month period between March 20–May 20, 2020, 626 patients were admitted and treated for COVID-19 in four

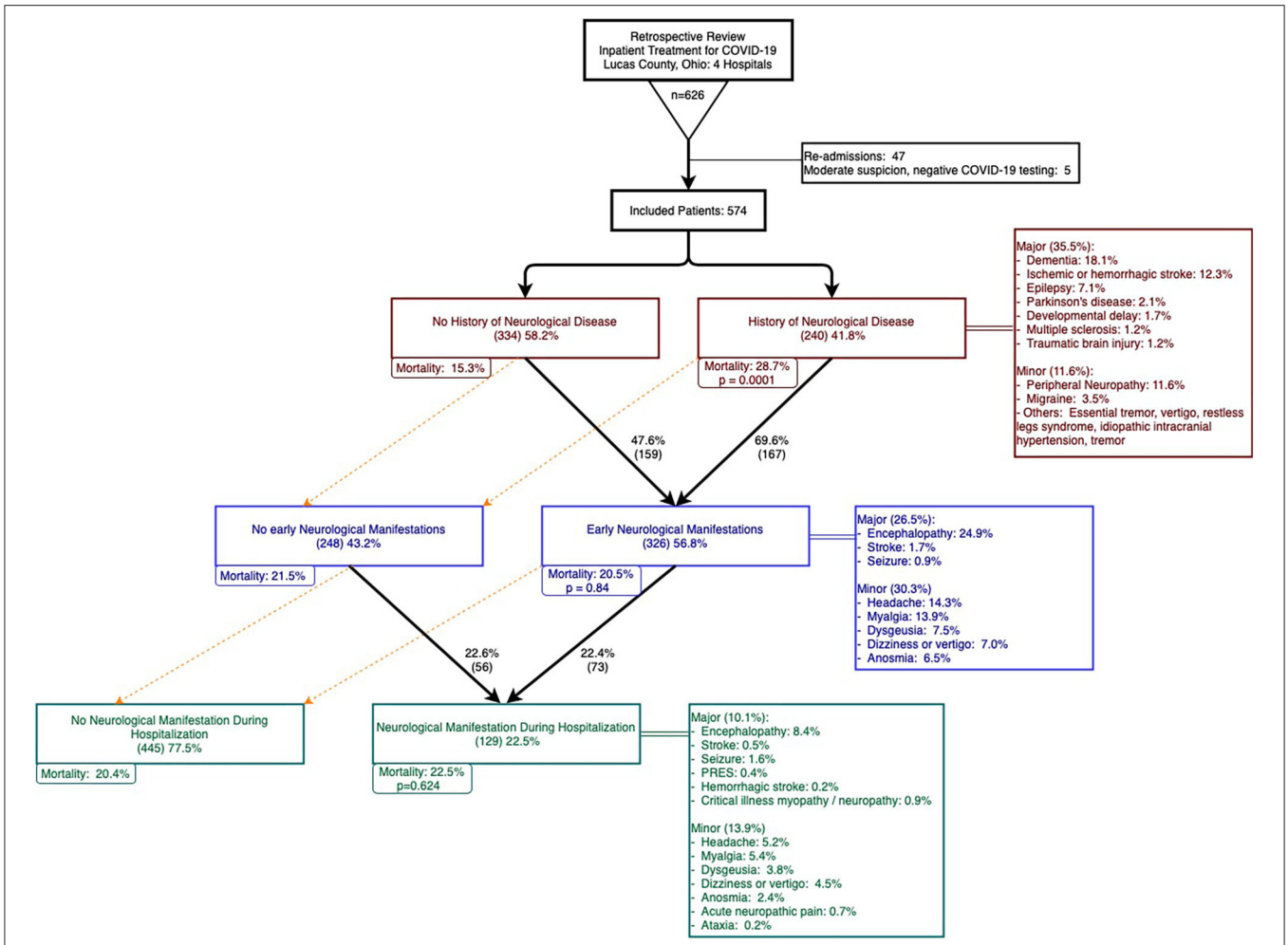


FIGURE 1 | Patient selection, history of neurological disease (HND), early neurological manifestations (ENM), and neurological manifestations in hospital (NMH).

hospitals in Lucas County, Ohio. After excluding re-admissions and patients with negative COVID tests with moderate suspicion of COVID-19, 574 patients were included in our analysis. Among these patients, 562 patients (97.9%) had a positive SARS-CoV-2 PCR test and two patients had positive SARS-CoV-2 antibodies. The remaining 10 patients had negative SARS-CoV-2 tests but were deemed to be highly suspicious as determined by infectious disease experts. **Figure 1** summarizes patient selection in the study.

Demographics and Clinical Characteristics

Baseline demographics and co-morbidities are summarized in **Table 1**. Mean age of the cohort was 62.8 ± 17.6 years, with the youngest and oldest patients being 3 months and 98 years old respectively, and patients over the age of 55 years constituted 71.3% of the cohort. Approximately one fifth of the population presented from an extended care facility (ECF) (19.9%), and 384 (66.9%) of patients presented from home. The remaining patients presented from assisted living facilities (12.7%) or a correctional facility (0.5%). Most patients were Caucasian (57.1%) or African American (38%). Mean body mass index was 32.9 (SD 13.3) and 9% of patients were healthcare workers.

The majority of patients (80.7%) had at least two or more comorbidities. The most common comorbidities were hypertension (71.1%), hyperlipidemia (51.1%), mental health disorders (39.9%), diabetes mellitus (39.6%), chronic kidney disease (22.1%), and coronary artery disease (20%). Common symptoms at presentation included shortness of breath or hypoxia (79.8%), fever (64.5%), cough (69.7%), and fatigue (45.5%). According to the WHO classification for COVID-19 (11), 60.8, 25.8, and 13.4% of the cohort had moderate, severe, or critical disease severity, respectively. In hospital medical complications included acute kidney injury (39.4%), sepsis or septic shock (27.9%), cardiac arrhythmias (19.9%), acute respiratory distress syndrome (17.4%), and cardiac injury (16.2%). Details of presenting illness and admission laboratory values are summarized in **Supplementary Tables 1, 2**.

Mean length of stay was 10.2 (SD 8.5) days with 30.5% of the cohort requiring intensive care unit (ICU) level of care and an average of 4.5 (SD 8.8) days in the ICU. Approximately one

TABLE 1 | Baseline demographics of COVID-19 cohort.

	Participants $n = 574$ (%)	Mean	SD
Age		62.83	17.55
Gender			
Male	276 (48.1)		
Female	298 (51.9)		
Ethnicity			
White	328 (57.1)		
African American	218 (38.0)		
Asian	5 (0.9)		
Hispanic	19 (3.3)		
Other	4 (0.7)		
BMI		32.9	13.3
Presentation from			
Home	384 (66.9)		
Assisted living	73 (12.7)		
ECF	114 (19.9)		
Correctional facility	3 (0.5)		
Healthcare workers	52 (9.1)		
Past medical history			
Hypertension	408 (71.1)		
DM	227 (39.6)		
Arrhythmia	97 (16.9)		
Asthma	77 (13.4)		
CAD	115 (20.0)		
CHF	91 (15.9)		
Cirrhosis	7 (1.2)		
CKD	127 (22.1)		
COPD	98 (17.0)		
Hyperlipidemia	293 (51.1)		
Malignancy	71 (12.4)		
Active	12 (2.1)		
History of malignancy	59 (10.3)		
OSA	91 (15.9)		
Peptic ulcer disease	18 (3.1)		
Mental health disorder	229 (39.9)		
Depression	155 (27)		
Anxiety	97 (16.9)		
Bipolar disorder	31 (5.4)		
Schizophrenia/Schizoaffective	32 (5.6)		
Other	19 (3.3)		

BMI, body mass index; ECF, extended care facility; DM, diabetes mellitus; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

TABLE 2 | History of pre-existing neurological problems.

	Participants $n = 574$ (%)
History of neurological problems	**240 (41.8)**
Major CNS problem	**204 (35.5)**
Dementia	104 (18.1)
Stroke (ischemic or hemorrhagic)	71 (12.4)
Transient ischemic attack	21 (3.7)
Epilepsy	41 (7.1)
Parkinson's disease	12 (2.1)
Developmental delay	11 (1.9)
Multiple sclerosis	7 (1.2)
Traumatic brain injury	7 (1.2)
Minor CNS problem	**36 (6.27)**

CNS, central nervous system. Bolding signifies that the number is part of the whole category.

fifth (22.1%) of the study group required mechanical ventilation and half of all patients were placed in prone position as part of their treatment. Re-admission during the two-month period for worsening COVID symptoms or disease complications occurred in 5.7% of patients. **Supplementary Tables 3, 4** summarizes hospital course, death rate, and reasons for re-admission.

Upon discharge, all patients who were admitted from an extended care facility (ECF) were discharged back to an ECF. An additional nine patients were discharged to an ECF, 5 patients to an inpatient rehabilitation facility, and the remaining 326 patients (56.8%) were discharged back home, to an assisted living facility, or correctional facility. One fifth of the population expired in the hospital or were discharged to hospice care (120; 20.9%). Death rates in patients between 45 and 54 and above 85 years of age were 1.2 and 44.6%, respectively. **Supplementary Figure 1** summarizes death rates by age group. In univariate and multivariate analyses, age was the strongest predictor of death in our cohort.

History of Neurological Disease

Our study focused on patients with a history of neurological disease (HND) and those who developed neurological manifestations with COVID-19. Patients with a history of any neurological disease comprised of 41.8% of the cohort and 35.5% had a history of a major neurological disease (**Figure 1**, HNDs are summarized in **Table 2**). Major HNDs included a history of dementia (18.1%), ischemic or hemorrhagic stroke (12.3%), epilepsy (7.1%), transient ischemic attack (TIA) (3.7%), Parkinson's disease (2.1%), developmental delay (1.9%), multiple sclerosis (1.2%), or traumatic brain injury (1.2%). Patients with any HND (28.7 vs. 15.3%; $p = 0.0001$) or a major HND (30.9 vs 15.4%; $p = 0.00002$) were more likely to expire.

Neurological Manifestations

Approximately two thirds of the cohort developed neurological manifestations during the course of COVID-19. Forty four percent of patients presented to the hospital with Early Neurological Manifestations (ENM), 9.8% developed Neurological Manifestations during Hospitalization (NMH), and 12.7% of the cohort had both ENM and NMH (see **Table 3**).

Patients with neurological manifestations (either at presentation or during their hospital stay) had significantly higher rates of ICU admission (33.5 vs. 22.4%; $p = 0.007$), longer mean ICU stays (8.3 ± 11.6 vs. 2.2 ± 5.3 days; $p = 0.00003$), longer overall hospital stays (14.1 ± 11.6 vs. 8.1 ± 5.2 days, $p = 0.06$), and required more days on mechanical ventilation (7 ± 10.9 vs. 1.6 ± 4.8 days; $p = 0.001$) (**Supplementary Table 5**).

TABLE 3 | Neurological symptoms at presentation and during hospital encounter.

	Participants *n* = 574 (%)
Early neurological manifestations (ENM)	**326 (56.8)**
Major neurological symptoms	**152 (26.5)**
Encephalopathy	143 (24.9)
Seizure	5 (0.9)
Stroke	7 (1.2)
Minor neurological symptoms	**174 (30.3)**
Headache	82 (14.3)
Myalgia	80 (13.9)
Anosmia	37 (6.5)
Dizziness or vertigo	40 (7.0)
Dysgeusia	43 (7.5)
Neurological manifestation while in hospital (NMD)	**129 (22.5)**
Major in-hospital neurological complications	**58 (10.1)**
Encephalopathy	48 (8.4)
Seizure	9 (1.6)
Ischemic stroke	3 (0.5)
Critical illness myopathy/neuropathy	5 (0.9)
Posterior reversible encephalopathy syndrome (PRES)	2 (0.4)
Cerebral venous sinus thrombosis	1 (0.2)
Minor in-hospital neurological complications	**80 (13.9)**
Myalgia	31 (5.4)
Headache	30 (5.2)
Dizziness	26 (4.5)
Dysgeusia	22 (3.8)
Anosmia	14 (2.4)
Acute neuropathic pain	4 (0.7)
Ataxia	1 (0.2)
Fatigue	64 (11.2)

Major neurological manifestations were present in 45.8, 30.5, and 23.6% of patients with moderate, severe, and critical COVID-19, respectively. (See **Figure 2** for mortality by neurological manifestations and COVID-19 severity.) Major neurological manifestations were recorded in 203 (35.4%) patients, with 145 (25.3%) patients with ENM, 51 (8.9%) patients with NMH, and 7 (1.2%) patients with both ENM and NMH. Mortality was higher in patients with a major ENM (36.2 vs. 15.4%; $p = 0.0000002$) or major NMH (41.4 vs. 18.6%; $p = 0.00024$). Similarly, patients who developed a major neurological manifestation at any time during infection with COVID-19 had higher rates of mortality than those without any major neurological manifestations (37.4 vs. 11.9%; $p = 2 \times 10^{-12}$).

Early Neurological Manifestations (ENM)

Of 326 patients with Early Neurological Manifestations (ENM), 152 (26.5%) patients had major and 174 had minor neurological symptoms. Encephalopathy was the most common major ENM (24.9%), followed by stroke (1.2%), and seizure (0.9%). Amongst minor neurological symptoms, headache (14.3%) was most common, followed by myalgia (13.9), dysgeusia (7.5%), dizziness or vertigo (7%), and anosmia (6.5%). Presentation with myalgia only as a minor neurological condition occurred in 47 patients (8%).

Neurological Manifestations During Hospitalization (NMH)

Neurological Manifestations during Hospitalization (NMH) occurred in 129 (22.5%) patients. Median duration to development of neurological symptoms in-hospital was 3 (IQR 1–7) days. Development of major NMH occurred in 58 (10.1%) of patients, of which 7 patients had major ENM as well. Encephalopathy was the most common major NMH (8.4%), followed by seizure (1.6%), critical illness myopathy or neuropathy (0.9%), and ischemic stroke (0.5%). Minor NMH occurred in 13.9% of patients, with myalgia (5.4%), headache (5.2%), dizziness (4.5%), dysgeusia (3.8%), and anosmia (2.4%) the most common.

Uncommon neurological disorders with concurrent COVID-19 in our population included two patients with posterior reversible encephalopathy syndrome, one patient with cerebral venous sinus thrombosis, and one patient with a posterior inferior cerebellar artery pseudoaneurysm resulting in subarachnoid hemorrhage.

Predictors of Mortality

After adjustment for gender, hypertension, disease severity on presentation, cardiac injury, ferritin, neutrophil, and lymphocyte counts, multivariate analysis revealed that age (OR 1.05; CI 1.03-1.07; $p = 2.3 \times 10^{-8}$), major neurological manifestation at any time (OR 2.1; CI 1.31-3.4; $p = 0.0022$), chronic kidney disease (OR 1.81; CI 1.1-2.95; $p = 0.018$), diarrhea on presentation (OR 0.53; CI 0.29-0.97; $p = 0.041$), heart failure (OR 9.5; CI 1.71-52.9; $p = 0.01$), and active or history of malignancy (OR 1.75; CI 1.09-2.81; $p = 0.021$) were predictors of death.

DISCUSSION

This retrospective cohort study of hospitalized patients with COVID-19 identified "major neurological manifestations" during disease course as an independent predictor of death. This finding can add a prognostic value to the care of this patient population. Encephalopathy was the most common ENM in our cohort (24.9%), with additional 8.4% developing encephalopathy during hospital stay. Impaired consciousness is a relatively common symptom of COVID-19 infection, and was reported in 37% of hospitalized patients in a cohort from Wuhan (6). Results from the ALBACOVID registry from Spain documented disorders of consciousness in 19.6% of infected patients, mostly in the severe infection group. Disorders of consciousness were associated strongly with older age, higher CK levels, lymphopenia, and advanced stages of COVID-19 (12). Encephalopathy presents with typical hallmark symptoms of fluctuating attention and arousal, with variable degrees of impairment in consciousness. Factors contributing to encephalopathy in COVID-19 patients include among many, hypoxia, metabolic abnormalities, cytokine storm, renal dysfunction, and sepsis (13).

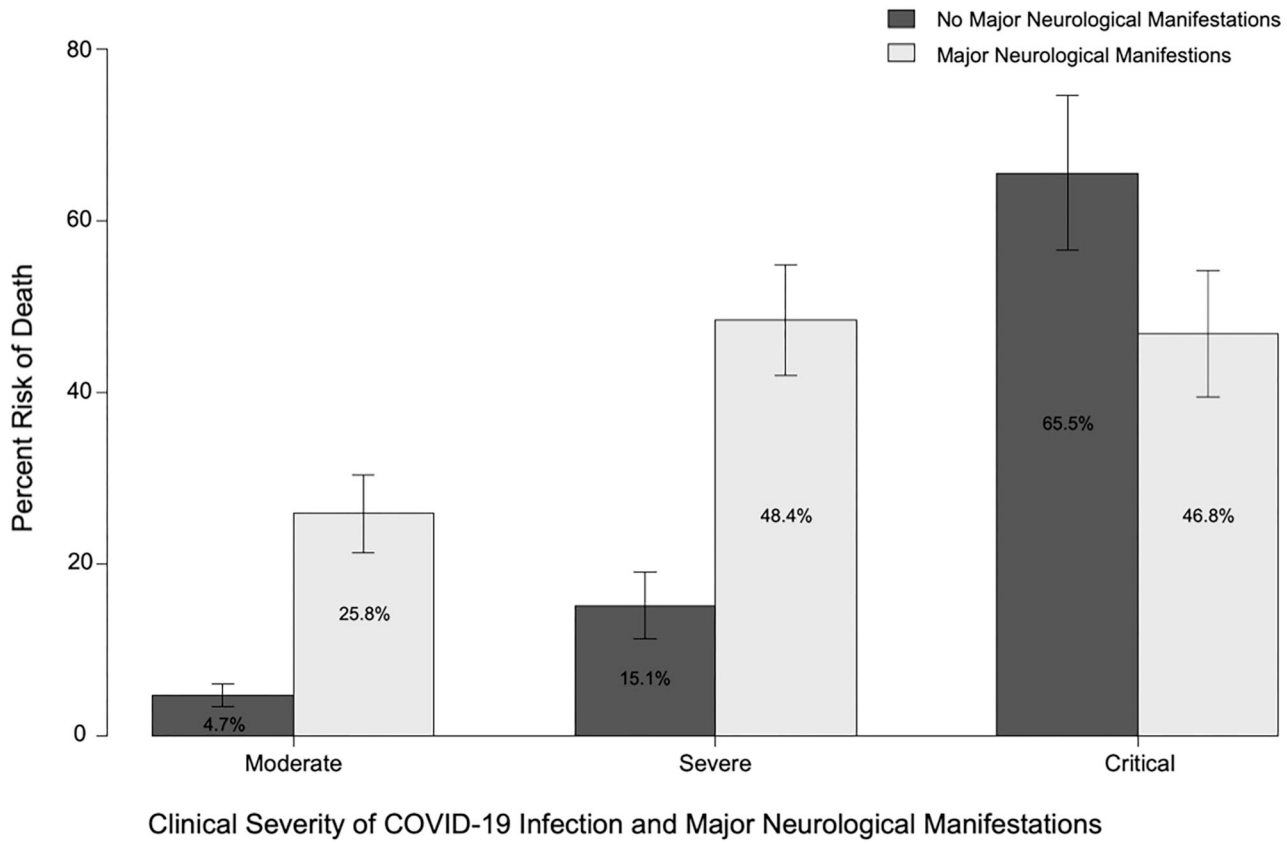


FIGURE 2 | Risk of death in patients with or without major neurological manifestations (at any time) and moderate, severe, or critical COVID-19 disease.

Although meningoencephalitis could theoretically represent another explanation for encephalopathy, and SARS-CoV-1 and MERS-CoV are known to invade the central nervous system, such evidence is not yet clear in SARS-CoV-2. Moriguchi et al. reported a 24 year old patient with COVID-19 presenting with symptoms of altered mental status, fever, headache and seizures, who was confirmed (with MRI and cerebrospinal fluid (CSF) PCR) to have right temporal lateral-ventriculitis (14). In another report, a patient with encephalopathy was confirmed radiologically to exhibit bilateral thalamic, medial temporal, and sub-insular ring enhancing lesions (diagnosed with acute hemorrhagic necrotizing encephalopathy) (14). Two patients in our cohort underwent PCR testing in (CSF), both were negative.

Ischemic stroke occurred in 1.7% of patients in our cohort and all but one presented outside the time window or did not meet criteria for thrombolysis and/ or mechanical thrombectomy. One patient underwent mechanical thrombectomy and subsequently died from disease complications. The stroke incidence in our cohort is consistent with other recent studies (6, 15), despite the older median age and higher percentage of nursing home patients noted in our cohort. Ischemic stroke may occur due to concurrent risk factors (such as atrial fibrillation in patients with mild or asymptomatic COVID-19), as a complication of severe COVID-19 pathology (such as hypercoagulability or a proinflammatory state), or due to critical illness in patients with previously asymptomatic cerebrovascular disorders (16). We did observe a high mortality rate (30%) in patients who experienced a stroke in our study.

Seizures occurred in 2.4% of our cohort, 85% of which were new onset seizures. No cases of status epilepticus were confirmed in our cohort. Although seizures have been reported with other coronavirus infections, the evidence for association with COVID-19 remains unclear and may be related to cerebral hypoxia in some patients. A recent study of 304 patients diagnosed with COVID-19 (108 with severe infection) only documented two "seizure like" episodes, attributed to acute stress reaction and hypocalcemia, with no confirmed cases of new-onset seizures (17). Seizures were reported in six patients (0.7%) in the ALBACOVID registry, mostly in severe stages of disease. Of these, only one had a previous diagnosis of epilepsy. None of the cases were complicated by status epilepticus (12). Overall, our cohort and other recent studies do not support an additional risk of symptomatic seizures or status epilepticus in patients with COVID-19, although sub-clinical seizures may be under-recorded, especially in patients with stupor and coma.

We observed an overall mortality rate of 20.9%. One hundred fourteen of our hospitalized patients came from extended care facilities (ECF), including skilled nursing facilities and nursing

homes. In this subset of ECF patients alone, the mortality rate was 32.5%, significantly higher than patients not presenting from an ECF (18%; $p = 0.002$). ECFs are believed to be high-risk settings, possessing a multitude of intrinsic risk factors allowing for ease of transmission of infectious diseases amongst residents. These risk factors include having an elderly population abiding within close quarters, with many, if not all of them, diagnosed with chronic diseases. Several studies in the United States, as well as in Europe and Asia, have further looked into the vulnerability of this patient population during this pandemic. This was first observed in the US in late March, when 101 ECF residents were confirmed to have COVID-19, all linked to one ECF in King County, Washington, with a respective mortality rate of 33.7% (18).

We were curious as to how the presence of underlying neurological disease, whether designated as a major disease vs. a minor disease, impacted COVID-19 disease progression and outcomes. In our study, we found that although patients with HND were more likely to die, HND was not an independent predictor of death. Du et al. identified history of cerebrovascular diseases as a predictor of mortality in COVID-19 patients (1). Twelve percent of patients in our cohort had history of cerebrovascular diseases, mortality rate in this group was 29.6% compared to patients without a history of cerebrovascular disease (19.7%; $p = 0.06$).

LIMITATIONS

Our study has many limitations, mainly derived from its retrospective design. Treatment protocols, utilization of neuroimaging and electroencephalogram, neurology team consultations, and thorough neurological assessments were variable among this cohort and during the study period. Diagnosis of encephalopathy was not confirmed by a neurologist in most cases, although neurology teams were involved in the care of all patients with ischemic strokes and seizures. Our outcomes were recorded at discharge as long-term outcomes were not available at this time. Lastly, clinical severity and mortality were high due to the large number of nursing home patients in this cohort.

CONCLUSIONS

In our cohort of hospitalized COVID-19 patients, a major neurological manifestation during disease course was an independent predictor of mortality. Additionally, having a pre-existing underlying neurological disease did not independently influence the outcome of COVID-19. Given the limitations of this retrospective study, we view these findings as a preliminary hypothesis generating framework for larger studies to investigate the impact of major neurological manifestations in hospitalized COVID-19 patients.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because all data generated for this study is contained within the manuscript. Requests to access the datasets should be directed to Mouhammad.Jumaa@utoledo.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Toledo and ProMedica Toledo Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HS, EA, and MJ designed and conceptualized the study. HS, EA, IS, SL, GD, JD, NK, KG, MA-C, SP, RA, and FS played a major role in data acquisition. HS and MJ analyzed and interpreted the data. All authors revised the manuscript for intellectual content.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.585944/full#supplementary-material

REFERENCES

1. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with covid-19 pneumonia caused by sars-cov-2: a prospective cohort study. *Eur Respir J.* (2020) 55:2000524. doi: 10.1183/13993003.00524-2020
2. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with covid-19 in new york city: A prospective cohort study. *Lancet.* (2020) 395:1763–70. doi: 10.1016/S0140-6736(20)31189-2
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in china. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
4. Cheng Q, Yang Y, Gao J. Infectivity of human coronavirus in the brain. *EBioMedicine.* (2020) 56:102799. doi: 10.1016/j.ebiom.2020.102799
5. Ng Kee Kwong KC, Mehta PR, Shukla G, Mehta AR. Covid-19, sars and mers: a neurological perspective. *J Clin Neurosci.* (2020) 77:13–6. doi: 10.1016/j.jocn.2020.04.124
6. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, china. *JAMA Neurol.* (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
7. Xiong W, Mu J, Guo J, Lu L, Liu D, Luo J, et al. New onset neurologic events in people with covid-19 infection in three regions in china. *Neurology*. (2020) 95:e1479–87. doi: 10.1212/WNL.0000000000010034
8. Zhou Y, Li W, Wang D, Mao L, Jin H, Li Y, et al. Clinical time course of covid-19, its neurological manifestation and some thoughts on its management. *Stroke Vasc Neurol.* (2020) 5:177–9. doi: 10.1136/svn-2020-000398
9. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of covid-19 in the young. *N Engl J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787

10. Somani S, Pati S, Gaston T, Chitlangia A, Agnihotri S. De novo status epilepticus in patients with covid-19. *Ann Clin Transl Neurol.* (2020) 7:1240–44. doi: 10.1002/acn3.51071
11. World Health Organization. *Clinical Management of Covid-19: Interim Guidance*. (2020). Retrieved from: https://www.who.int/publications/i/item/clinical-management-of-covid-19
12. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, Sanchez-Larsen A, Layos-Romero A, Garcia-Garcia J, et al. Neurologic manifestations in hospitalized patients with covid-19: the albacovid registry. *Neurology*. (2020) 95:e1060–70. doi: 10.1212/WNL.0000000000009937
13. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in covid-19. *J Infect.* (2020) 80:607–13. doi: 10.1016/j.jinf.2020.03.037
14. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with sars-coronavirus-2. *Int J Infect Dis.* (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
15. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with covid-19 versus patients with influenza. *medRxiv*. (2020) e202730. doi: 10.1101/2020.05.18.20105494
16. Salahuddin H, Castonguay AC, Zaidi SF, Burgess R, Jadhav AP, Jumaa MA. Interventional stroke care in the era of covid-19. *Front Neurol.* (2020) 11:468. doi: 10.3389/fneur.2020.00468
17. Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. *Epilepsia.* (2020) 61:e49–e53. doi: 10.1111/epi.16524
18. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, et al. Epidemiology of covid-19 in a long-term care facility in king county, washington. *N Engl J Med.* (2020) 382:2005–11. doi: 10.1056/NEJMoa2005412

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

OPINION
published: 05 November 2020
doi: 10.3389/fneur.2020.596218

The One-Two Punch of Delirium and Dementia During the COVID-19 Pandemic and Beyond

Sara C. LaHue[1,2]*, *Vanja C. Douglas*[1,2] *and Bruce L. Miller*[1,2]

[1] *Department of Neurology, School of Medicine, University of California, San Francisco, San Francisco, CA, United States,*
[2] *Department of Neurology, Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA, United States*

Keywords: delirium, dementia, Alzheimer's disease and related dementias (ADRD), COVID-19, hospitalization, accessibiity, technology

OPEN ACCESS

Edited by:
Ricardo F. Allegri,
Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Argentina

Reviewed by:
Laiss Bertola,
University of São Paulo, Brazil
Anthoula Charalampos Tsolaki,
Aristotle University of Thessaloniki, Greece

***Correspondence:**
Sara C. LaHue
sara.lahue@ucsf.edu

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *18 August 2020*
Accepted: *07 October 2020*
Published: *05 November 2020*

Citation:
LaHue SC, Douglas VC and Miller BL (2020) The One-Two Punch of Delirium and Dementia During the COVID-19 Pandemic and Beyond. Front. Neurol. 11:596218. doi: 10.3389/fneur.2020.596218

INTRODUCTION

While the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is an unprecedented threat to all of us, older adults are especially at risk for serious complications from coronavirus disease 2019 (COVID-19) that necessitate hospitalization (1, 2). Significant attention has rightfully been given to the respiratory and cardiovascular consequences of COVID-19. Less is understood about the neurologic complications associated with this virus, especially its potential impact on delirium and cognitive decline.

The prevalence of delirium is expected to increase during this pandemic due to several factors detailed below (3). Delirium is independently associated with accelerated cognitive decline for those with and without preexisting dementia (4). Adults with Alzheimer's disease and related dementias (ADRD) are particularly vulnerable during this pandemic due to dependence on others and increased likelihood of living in assisted living facilities (5). Further, 30% of all COVID-19 deaths in the United States occur in patients living in nursing homes; a high percentage of these individuals also suffer from mild cognitive impairment or dementia (6). If hospitalized, those with ADRD are more likely to become delirious (7). Our goals are to highlight the heightened risk of this neurologic "one-two punch" as well as provide pragmatic, evidence-based management recommendations for a several clinical environments during the COVID-19 pandemic and subsequent recovery period.

RECOGNIZING THE HIDDEN DELIRIUM EPIDEMIC WITHIN THE PANDEMIC

Delirium is a common acute disturbance in mental status characterized by fluctuations in attention and cognition, that is more common in older adults and those with dementia (4). Compared with non-delirious patients, hospitalized delirious patients are more likely to develop functional impairment, be discharged to a facility, and be readmitted to the hospital (4, 8). While there are established clinical pathway interventions that modify the risk of developing delirium, there is no drug currently recommended for the prevention or treatment of delirium other than medications needed to treat an identified provoker (e.g., antibiotics for infection) (3, 9). Rather, delirium management centers on non-pharmacologic measures, and the removal of psychoactive medications unless necessary for significant agitation (3). Identifying and managing patients with delirium is paramount as the ability to safely discharge patients home, which is necessary for sustaining strained healthcare systems with limited hospital resources during this pandemic.

While quantifying the impact of this pandemic on delirium is in its early stages, COVID-19 has been demonstrated in small studies to be associated with an increased risk of delirium (10, 11). This

association is likely due to an exacerbation of established risk factors, including the development of hypoxia, metabolic derangements, and infection leading to a heightened inflammatory state, as well as the need for intensive care (12, 13). In one point-prevalence cohort study of 71 hospitalized individuals with COVID-19, 31 patients were diagnosed with delirium by DSM-IV criteria (11). Importantly, only 12 of these patients were recognized as being delirious by the primary clinical team (11). Such a discrepancy is not surprising since, without the use of a targeted screening tool, misidentification of delirium for depression or other psychiatric diagnoses, especially in older patients is not uncommon (14, 15). This underdiagnosis of delirium highlights the need for structured clinical pathways with systematic screening to identify delirium so as to appropriately manage these patients (9). Accurate delirium identification is also instrumental for providing informed projections of the long-term resources needed to support those who survive.

One critical outcome of this pandemic is the anticipated exacerbation of delirium in all hospitalized patients, regardless of COVID-19 status (3, 16). This is in large part due to challenges with implementing proper delirium prevention guidelines (3). For example, prior to this pandemic, many hospitals across the United States housed Acute Care for Elders (ACE) Units that incorporated evidence-based practices for delirium prevention spearheaded by the Hospital Elder Life Program (4). Such programs significantly reduced hospital-associated complications for older adults, including delirium, which can be prevented in as many as 40% of cases with these modest interventions (4). However, the management of hospitalized adults has undergone significant systematic changes in response to COVID-19, regardless of COVID-19 status (3, 17). With many hospitals reaching or exceeding patient capacity during this pandemic, some ACE units have disbanded in order to reallocate resources for the care of patients with COVID-19, subsequently fracturing delirium prevention care pathways as well. Furthermore, hospitals have placed restrictions on visitors of hospitalized patients, some prohibiting all visitors regardless of COVID-19 status, with rare exceptions (3, 16, 18). Such restrictions also often apply to caregivers for patients who are delirious or have ADRD, despite playing an essential role in patient care by encouraging physical and cognitive stimulation to prevent delirium, protecting their loved one from falls, and advocating for their basic needs, such as oral hydration (3, 9, 16).

Delirium prevention is even more challenging for hospitalized adults with COVID-19. In addition to strict visitor restrictions, all patients hospitalized for COVID-19 experience heighted solitude and reduced physical activity from quarantine in order to reduce exposure to staff and preserve personal protective equipment (PPE) (16). Sleep may be disrupted if tests occur at night to ensure adequate time for equipment sterilization. While designed to minimize infection risk, these policies also foster a deliriogenic environment (3). Though these unfavorable environmental changes are new, this novel virus has largely incited a resurgence of traditional risk factors for hospital-acquired delirium, and in doing so has exposed fissures in the clinical care of these patients that require urgent, creative solutions.

NOVEL CHALLENGES FOR ADULTS WITH ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Adults with ADRD are especially vulnerable to COVID-19 infection due to their older age, frequency of comorbid conditions such as cardiovascular disease and diabetes, increased reliance on assistance from others for survival, and a higher likelihood of living in assisted living or nursing home, making self-quarantine difficult for many (5, 19). Depending on the severity of the dementia or presence of associated behavioral symptoms, those with ADRD may have difficulty understanding or remembering public health recommendations, such as maintaining good hand hygiene, social distancing, and wearing a face covering (20). Further, in the event that support systems fail—if a family member becomes ill, grocery delivery is not possible, or medication refills delayed—additional harm can result (21). Combined, these challenges may lead to significant psychosocial stressors for those with ADRD and their families during this pandemic, which are only exacerbated in the event of hospitalization (3, 21–23).

Adults with ADRD, especially those diagnosed with COVID-19, are at heightened risk for both hospitalization and delirium during this pandemic (7, 24). While changes to hospital policies, such as restricted visitation and need for isolation, are important for infection control, the consequences of these guidelines are anticipated to be especially detrimental to this population. Even once delirium resolves, its effects can persist, as delirium is associated with an accelerated rate of cognitive decline in those with ADRD (7). Delirium is also an independent risk factor for new cognitive decline in those without pre-existing cognitive impairment (25). In one prospective study, 9.5% of cognitively normal adults with post-operative delirium developed mild cognitive impairment or dementia within a year (25). In addition to the physical and psychological challenges that COVID-19 survivors face, a surge in delirium during this pandemic may lead to a delayed epidemic of cognitive impairment.

ADAPTING EVIDENCE-BASED PRACTICES FOR DELIRIUM AND ADRD MANAGEMENT

The tenets of delirium prevention are evidence-based and are not antithetical to the precautions needed to care for hospitalized patients, especially those with ADRD, during this pandemic (3). Rather, these recommendations can be adapted for patients with COVID-19, as well as those without COVID-19 but who are still significantly affected by changes in hospital and community policies (**Table 1**).

There are several novel strategies for coping with the isolation from social distancing, largely revolving around technological tools (3, 16). Ideally, the caregivers of hospitalized COVID-19 negative patients with delirium or ADRD would be viewed as essential to patient care and allowed visitation, while still adhering to hospital policies on symptom screening and PPE. If this is not possible, then adapting hospital teleconferencing tools, such as providing electronic tablets, can enhance communication

TABLE 1 | Adapting management practices for hospitalized patients with delirium or dementia during the COVID-19 pandemic.

Clinical practice adaptations
Hospital policies:
Allow visitation[a,b,c] for essential caregivers of COVID-19-negative patients with delirium and dementia
Limit non-urgent nighttime disturbances (e.g., testing, room changes)[a,b,c]
Screen for cognitive and functional impairments on admission, including visual and hearing impairment; provide assistive devices if needed[a,b,c]
Communication and accessibility:
Provide reorientation, including medical staff roles, with each patient encounter[a,b,c]
Provide a card with your name, role, and photograph[d]
Offer teleconferencing tools for providers to more readily communicate with patients[e]
Offer teleconferencing tools for patients to easily communicate with their families[f]
Modify communication tools (e.g., voice recognition, automatic call acceptance) as needed
Psychosocial stressors:
Offer teleconferencing access to spiritual/psychological support staff[b]
Limit use of deliriogenic medications for anxiety and mood, such as benzodiazepines[a,b,c]
Discharge anticipatory guidance:
May require additional support from family/caregivers[g] due to overburdened outpatient facilities
Coordination of follow-up with outpatient team,[a,g] including training caregiver on use of telehealth tools[e] prior to discharge
Document delirium diagnosis[g] and refer to outpatient for follow-up,[a,b] including cognitive assessment

[a] *Hshieh et al. (9).*
[b] *Inouye et al. (26).*
[c] *Wang et al. (27).*
[d] *Arora et al. (28).*
[e] *Hatcher-Martin et al. (29).*
[f] *Hart et al. (18).*
[g] *Khachaturian et al. (30).*

between patients and their families (18). These tools can also increase access to nursing and spiritual/psychological support staff while minimizing infection risk and PPE use.

An important caveat that receives insufficient consideration is that many of these modifications assume abilities on the part of the patient. For instance, those with hearing impairment are at increased risk for delirium and should be provided with assistive devices, such as pocket amplification devices, in order to use teleconferencing tools (9, 26, 27, 31). Recognizing a patient's premorbid cognitive and functional status is important for providing accessible means of communication. Voice recognition software on smartphones and computers allows for placing calls without physically interacting with the device; however, this may not be feasible for individuals with delirium, advanced ADRD or language impairment. One innovative alternative for these individuals is to enable the automatic call accept feature found on many devices, permitting the device to automatically answer telephone calls, or video calls such as FaceTime, from known contacts. This exciting accessibility feature may facilitate more frequent patient contact with family and staff for those who have difficulty interfacing with digital tools. Employing technology creatively to reduce social isolation, provide cognitive stimulation, and more readily assess basic needs in patients with delirium and advanced ADRD is an area that warrants increased attention.

In addition to hospital-specific considerations, the management of adults with ADRD during this pandemic must span the entire continuum of care. Disruption to clinic appointments, even with telemedicine capabilities, will likely result in increased demand for care. Community outpatient access is vital for keeping those with ADRD supported at home and out of the hospital. The rapid expansion of access to teleconferencing tools, including the waiving of Health Insurance Portability and Accountability Act compliance in order to permit more popular video chat applications, is a valuable step (32). Clinical assessments must also be adapted to suit the constraints of digital technologies. For many medical specialties, including several neurologic subspecialities, there is a trend toward non-inferiority of remote assessments compared to in-person visits (17, 29). While it is possible to offer cognitive testing by telemedicine, accuracy may be affected by hearing and vision impairment and so the results of these tests must be interpreted these limitations in mind (33–35). In addition to the special considerations for patients with ADRD, adults diagnosed with hospital-associated delirium should receive outpatient follow-up, including cognitive assessments to screen for cognitive decline. Just as battling this pandemic has been resource-intensive, so too will providing adequate resources to support survivors long-term.

CONCLUSIONS

Delirium is a common complication faced by hospitalized older adults that can often be prevented with modest interventions. Unfortunately, the rate of delirium will likely increase during the COVID-19 pandemic due to both infectious and environmental considerations. While ADRD is a risk factor for delirium, delirium is also an independent risk factor for cognitive decline. If delirium prevention is neglected, and we fail to adapt clinical care to meet these unique challenges, we risk an unprecedented accelerated growth in cognitive impairment in the months and years to come. We cannot afford to let our guard down at this critical juncture.

AUTHOR CONTRIBUTIONS

SL made substantial contributions to conception or design of the work, drafted the work, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. VD and BM made substantial contributions to conception or design of the work, revised the work critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Bianchetti A, Bellelli G, Guerini F, Marengoni A, Padovani A, Rozzini R, et al. Improving the care of older patients during the COVID-19 pandemic. *Aging Clin Exp Res*. (2020) 32:1883–8. doi: 10.1007/s40520-020-01641-w
2. Wu Z, Mcgoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
3. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Crit Care*. (2020) 24:176. doi: 10.1186/s13054-020-02882-x
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. (2014) 383:911–22. doi: 10.1016/S0140-6736(13)60688-1
5. Wang H, Li T, Barbarino P, Gauthier S, Brodaty H, Molinuevo JL, et al. Dementia care during COVID-19. *Lancet*. (2020) 395:1190–1. doi: 10.1016/S0140-6736(20)30755-8
6. Behrens LL, Naylor MD. "We are alone in this battle": a framework for a coordinated response to COVID-19 in nursing homes. *J Aging Soc Policy*. (2020) 32:316–22. doi: 10.1080/08959420.2020.1773190
7. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. *Lancet Neurol*. (2015) 14:823–32. doi: 10.1016/S1474-4422(15)00101-5
8. Lahue SC, Douglas VC, Kuo T, Conell CA, Liu VX, Josephson SA, et al. Association between inpatient delirium and hospital readmission in patients >/= 65 years of age: a retrospective cohort study. *J Hosp Med*. (2019) 14:201–6. doi: 10.12788/jhm.3130
9. Hshieh TT, Yang T, Gartaganis SL, Yue J, Inouye SK. Hospital elder life program: systematic review and meta-analysis of effectiveness. *Am J Geriatr Psychiatry*. (2018) 26:1015–33. doi: 10.1016/j.jagp.2018.06.007
10. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology*. (2020) 95:e910–20. doi: 10.1212/WNL.0000000000009848
11. Mcloughlin BC, Miles A, Webb TE, Knopp P, Eyres C, Fabbri A, et al. Functional and cognitive outcomes after COVID-19 delirium. *Eur Geriatr Med*. (2020) 11:857–62. doi: 10.1007/s41999-020-00353-8
12. Fotuhi M, Mian A, Meysami S, Raji CA. Neurobiology of COVID-19. *J Alzheimers Dis*. (2020) 76:3–19. doi: 10.3233/JAD-200581
13. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. (2020) 143:3104–20. doi: 10.1093/brain/awaa240
14. Farrell KR, Ganzini L. Misdiagnosing delirium as depression in medically ill elderly patients. *Arch Intern Med*. (1995) 155:2459–64.
15. Otani VHO, Otani T, Freirias A, Calfat ELB, Aoki PS, Cordeiro QJ, et al. Misidentification of mental health symptoms in presence of organic diseases and delirium during psychiatric liaison consulting. *Int J Psychiatry Clin Pract*. (2017) 21:215–20. doi: 10.1080/13651501.2017.1301483
16. Lahue SC, James TC, Newman JC, Esmaili AM, Ormseth CH, Ely EW. Collaborative delirium prevention in the age of COVID-19. *J Am Geriatr Soc*. (2020) 68:947–49. doi: 10.1111/jgs.16480
17. Chen PM, Hemmen TM. Evolving healthcare delivery in neurology during the coronavirus disease 2019 (COVID-19) pandemic. *Front Neurol*. (2020) 11:578. doi: 10.3389/fneur.2020.00578
18. Hart JL, Turnbull AE, Oppenheim IM, Courtright KR. Family-centered care during the COVID-19 era. *J Pain Symptom Manage*. (2020) 60:e93–7. doi: 10.1016/j.jpainsymman.2020.04.017
19. Iaboni A, Cockburn A, Marcil M, Rodrigues K, Marshall C, Garcia MA, et al. Achieving safe, effective, and compassionate quarantine or isolation of older adults with dementia in nursing homes. *Am J Geriatr Psychiatry*. (2020) 28:835–8. doi: 10.1016/j.jagp.2020.04.025
20. Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and mitigating the impact of the COVID-19 pandemic on Alzheimer's disease and related dementias. *Am J Geriatr Psychiatry*. (2020) 28:712–21. doi: 10.1016/j.jagp.2020.04.010
21. Greenberg NE, Wallick A, Brown LM. Impact of COVID-19 pandemic restrictions on community-dwelling caregivers and persons with dementia. *Psychol Trauma*. (2020) 12:S220–1. doi: 10.1037/tra0000793
22. Boutoleau-Bretonniere C, Pouclet-Courtemanche H, Gillet A, Bernard A, Deruet AL, Gouraud I, et al. The effects of confinement on neuropsychiatric symptoms in Alzheimer's disease during the COVID-19 crisis. *J Alzheimers Dis*. (2020) 76:41–7. doi: 10.3233/JAD-200604
23. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*. (2020) 395:912–20. doi: 10.1016/S0140-6736(20)30460-8
24. Miyashita S, Yamada T, Mikami T, Miyashita H, Chopra N, Rizk D. Impact of dementia on clinical outcomes in elderly patients with coronavirus 2019 (COVID-19): an experience in New York. *Geriatr Gerontol Int*. (2020) 20:732–4. doi: 10.1111/ggi.13942
25. Sprung J, Roberts RO, Weingarten TN, Nunes Cavalcante A, Knopman DS, Petersen RC, et al. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. *Br J Anaesth*. (2017) 119:316–23. doi: 10.1093/bja/aex130
26. Inouye SK, Bogardus ST Jr, Baker DI, Leo-Summers L, Cooney LM Jr. The hospital elder life program: a model of care to prevent cognitive and functional decline in older hospitalized patients. *Hosp Elder Life Program J Am Geriatr Soc*. (2000) 48:1697–706. doi: 10.1111/j.1532-5415.2000.tb03885.x
27. Wang YY, Yue JR, Xie DM, Carter P, Li QL, Gartaganis SL, et al. Effect of the tailored, family-involved hospital elder life program on postoperative delirium and function in older adults: a randomized clinical trial. *JAMA Intern Med*. (2019) 180:e194446. doi: 10.1001/jamainternmed.2019.4446
28. Arora V, Gangireddy S, Mehrotra A, Ginde R, Tormey M, Meltzer D. Ability of hospitalized patients to identify their in-hospital physicians. *Arch Intern Med*. (2009) 169:199–201. doi: 10.1001/archinternmed.2008.565
29. Hatcher-Martin JM, Adams JL, Anderson ER, Bove R, Burrus TM, Chehrenama M, et al. Telemedicine in neurology: telemedicine work group of the American Academy of Neurology update. *Neurology*. (2020) 94:30–8. doi: 10.1212/WNL.0000000000008708
30. Khachaturian AS, Hayden KM, Devlin JW, Fleisher LA, Lock SL, Cunningham C, et al. International drive to illuminate delirium: a developing public health blueprint for action. *Alzheimers Dement*. (2020) 16:711–25. doi: 10.1002/alz.12075
31. Lahue SC, Liu VX. Loud and clear: sensory impairment, delirium, and functional recovery in critical illness. *Am J Respir Crit Care Med*. (2016) 194:252–3. doi: 10.1164/rccm.201602-0372ED
32. Padala SP, Jendro AM, Orr LC. Facetime to reduce behavioral problems in a nursing home resident with Alzheimer's dementia during COVID-19. *Psychiatry Res*. (2020) 288:113028. doi: 10.1016/j.psychres.2020.113028
33. Brearly TW, Shura RD, Martindale SL, Lazowski RA, Luxton DD, Shenal BV, et al. Neuropsychological test administration by videoconference: a systematic review and meta-analysis. *Neuropsychol Rev*. (2017) 27:174–86. doi: 10.1007/s11065-017-9349-1
34. Hantke NC, Gould C. Examining older adult cognitive status in the time of COVID-19. *J Am Geriatr Soc*. (2020) 68:1387–9. doi: 10.1111/jgs.16514
35. Phillips NA, Chertkow H, Pichora-Fuller MK, Wittich W. Special issues on using the montreal cognitive assessment for telemedicine assessment during COVID-19. *J Am Geriatr Soc*. (2020) 68:942–4. doi: 10.1111/jgs.16469

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 05 November 2020
doi: 10.3389/fneur.2020.584734

Reductions in Hospital Admissions and Delays in Acute Stroke Care During the Pandemic of COVID-19

Yiqun Wu[1†], Fei Chen[2†], Zijing Wang[1], Wuwei Feng[3], Ying Liu[4], Yuping Wang[2,5] and Haiqing Song[2,5*]*

[1] Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China, [2] Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China, [3] Department of Neurology, Duke University School of Medicine, Durham, NC, United States, [4] Beijing Municipal Health Commission, Beijing, China, [5] Beijing Stroke Quality Control Center, Beijing, China

Background: Rapid and effective medical care for stroke is paramount to achieve maximal functional recovery. Because of the wide spreading of the coronavirus disease in 2019 (COVID-19), acute stroke care is negatively impacted. How much acute care for stroke has been affected during the pandemic remains to be assessed.

Methods: The first-level response to major public health was launched from January 24th to April 29th, 2020 in Beijing to contain the spread of COVID-19. Based on a database connecting all 77 stroke centers, the quantity and quality in emergency care for stroke during the 97 lockdown days were compared with the equivalent period in 2019. During the pandemic, 15 of the 77 stroke centers were designated to receive patients sick with COVID-19. Subgroup analyses were carried out by different types of hospitals (designated and undesignated).

Results: There were 1,281 and 2,354 stroke emergency hospital admissions in the lockdown period and the parallel period in 2019, respectively. A reduction of 45.6% in admission was shown in the lockdown period, with more reductions for hemorrhagic stroke (69.0%) compared with ischemic stroke (42.9%). More reductions happened in COVID-19 designated hospitals (52.6%) compared with undesignated hospitals (41.8%). The mean NIHSS score at hospital arrival was significantly higher in the lockdown period (9.4 ± 7.7 in 2020 vs. 8.4 ± 7.8 in 2019, $P < 0.001$). For the metrics measuring the quality of acute stroke care, the onset to door (OTD), onset to needle (ONT), and onset to recanalization (OTR) times didn't change significantly, while significant delays are shown for the door to CT scan (DTC, 1 min delay), door to needle (DTN, 4 min delays), and door to puncture (DTP, 29 min delays) times, which mainly happened in COVID-19 undesignated hospitals.

Conclusions: Profound reductions in stroke hospital admissions and significant delays in emergency care for acute ischemic stroke occurred during the pandemic of COVID-19. Engagement and effective communication with all stakeholders including patients, health care providers, governmental policymakers, and other implementation partners are required for future success in similar crises.

Keywords: stroke, acute care, COVID-19, hospital admission, quality of care

OPEN ACCESS

Edited by:
Beom Joon Kim, Seoul National University Bundang Hospital, South Korea

Reviewed by:
Mirjam R. Heldner, University Hospital Bern, Switzerland
Wen-Jun Tu, Chinese Academy of Medical Sciences and Peking Union Medical College, China

****Correspondence:***
Haiqing Song
songhq@xwhosp.org
Yuping Wang
wangyuping01@sina.cn

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *18 July 2020*
Accepted: *14 September 2020*
Published: *05 November 2020*

Citation:
Wu Y, Chen F, Wang Z, Feng W, Liu Y, Wang Y and Song H (2020) Reductions in Hospital Admissions and Delays in Acute Stroke Care During the Pandemic of COVID-19. Front. Neurol. 11:584734. doi: 10.3389/fneur.2020.584734

INTRODUCTION

The coronavirus disease in 2019 (COVID-19) was declared a pandemic by the World Health Organization on 11th March 2020 (1). More than 200 countries have reported over 5 million cases and the disease progression is still ongoing. Because of the rapid spreading and clustering onset of this disease (2–4), it causes a major crisis to the whole healthcare system. Despite the stay-at-home orders in many countries, the incidence of other conditions is not diminishing, and rapid and effective medical care for serious and life-threatening conditions, such as stroke, is still paramount to achieve maximal functional recovery. To deliver timely and effective care with a balance to the risk of COVID-19 infectious exposure, the American Heart Association and American Stroke Association have issued series guides for stroke hyperacute management (5, 6). Similar academic societies in various regions and neurological physicians from different hospitals continue to make recommendations/guidelines and share treatment experiences (1, 7–10). Despite these efforts, acute stroke care is still negatively impacted (11–15). Reductions of 10–70% in stroke hospital admission are reported in several countries (13, 16–19), though COVID-19 may probably increase the risk of ischemic stroke as a result of endothelial injury and hypercoagulable status and other impacts on the central nervous system (20–22).

The adverse effect of the pandemic on stroke care is not only in quantity but also in quality. How much the emergency care for stroke has been affected during the prehospital and in-hospital stages in the lockdown period was still uncertain. In this study, we aimed to investigate the impact of the COVID-19 outbreak on stroke emergency care in Beijing (capital of China) during the pandemic. The results may provide valuable information to reorganize or optimize the current system of emergency care and to better prepare for a future pandemic.

METHODS

Study Design

To contain the spread of COVID-19, the Chinese government launched the first-level response to major public health in 30 provinces from January to April. In Beijing, the lockdown period lasted for 97 days, with the same policies across all the administrative districts, from 01/24/2020 to 04/29/2020. We compare the stroke acute care using major stroke metrics in these 97 days with the same period in 2019.

Data Collection

Since January 2018, an integrated database (the Beijing Emergency Care Database) connecting the emergency medical services (EMS) system and all the stroke centers was constructed in the city of Beijing by using a smartphone application (named "Green"). All emergency admissions for stroke were recorded in the database with a group of key metrics measuring the quality of acute stroke care, including time records for last known well, hospital arrival, images, intravenous thrombolysis (IVT), endovascular treatment (EVT), revascularization, and so on. In this study, the number of hospital admissions, as well as several quality measures for acute care of acute ischemic stroke (AIS), such as onset to door (OTD) time, door to CT scan (DTC) time, door-to-needle (DTN) time, door to puncture (DTP) time, onset to needle (OTN) time, onset to recanalization (OTR) time, were obtained from the database. The eligibility for IVT and EVT was in line with the recent guidelines (23, 24). During the lockdown period and the comparison period in 2019, there were 1,455 and 2,925 admissions recorded in the database, respectively. After deleting 174 and 571 patients in each period with diagnosis as other diseases or unknown, the remaining 1,281 and 2,354 stroke emergency admissions were analyzed in the study. To explore the correlation between stroke emergency hospital admissions and the number of newly diagnosed COVID-19 cases, the daily number of COVID-19 cases in Beijing was obtained from Beijing Municipal Health Commission (http://wjw.beijing.gov.cn/wjwh/ztzl/xxgzbd/gzbdyqtb/index_5.html).

Statistical Analysis

The stroke hospital admissions in the lockdown period were compared with the numbers in the same period in 2019 and the percentage reduction was calculated. Descriptive statistics were used to compare the characteristics of stroke patients and the quality of care between two periods. Spearman correlation test was used to check the correlation between the number of weekly new diagnosed COVID-19 cases and the weekly stroke hospital admissions. The data on hospital admissions for stroke and COVID-19 cases were analyzed on a weekly basis. Quantitative variables were reported as mean (standard deviation, sd) or median (interquartile range, IQR). Categorical variables were represented as numbers and percentages. The differences between groups were tested using the Student *t*-test, Wilcox test, or Chi-square test. During the pandemic, 15 of 77 hospitals providing acute stroke care in Beijing were designated to receive patients sick with COVID-19. All the COVID-19 cases were sent to the 15 designated hospitals and received treatment there, while the remaining 62 undesignated hospitals did not treat any COVID-19 case. Therefore, all stroke admissions were divided into two groups according to whether the hospital was a designated COVID-19 hospital or not. Subgroup analyses were carried out by different types of hospitals (designated and undesignated). All analyses were conducted in R (V.3.6.3) (25).

RESULTS

Number of Stroke Hospital Admissions

From 24th January to 29th April 2020, there were 1,281 stroke hospital admissions in Beijing, this reflects a reduction of 45.6% compared with the same period in 2019 (2,354 admissions, **Table 1**). Compared with ischemic stroke (42.9%), there were more reductions for hemorrhagic stroke (69.0%). The reduction in emergency hospital admissions transferred by private car (48.1%) was slightly higher than transferred by ambulance (43.4%). More reductions happened in COVID-19 designated hospitals (52.6%) compared with undesignated hospitals (41.8%). The reduction in hospitals located in districts with fewer than 20 COVID-19 cases was similar to that in hospitals located in districts with 20 or more COVID-19 cases (**Table 1**). A negative

TABLE 1 | Effects of the pandemic on the Number of stroke admissions in Beijing.

	Number of stroke admissions		Reductions (%)
	Comparison period in 2019	Lockdown period in 2020	
All stroke admissions	2,354	1,281	45.6
Stroke types*			
Ischemic stroke	1,984	1,132	42.9
Hemorrhagic stroke	290	90	69.0
Other	80	59	26.3
Methods reaching to hospitals			
Ambulance	1,226	694	43.4
Private car	1,053	547	48.1
In-hospital stroke	75	40	46.7
COVID-19 designated hospitals*			
Yes	829	393	52.6
No	1,525	888	41.8
COVID-19 cases in the local district			
<20	771	417	45.9
≥20	1,583	864	45.4

*The difference in distributions between two periods was statistically significant ($P < 0.05$).

correlation was shown between newly diagnosed COVID-19 cases and stroke emergency hospital admissions with marginal statistical significance ($r = -0.176$, $P = 0.084$). During the lockdown period, the number of stroke hospital admissions increased significantly from the 4th week and became steady from the 11th week (**Figure 1A**), which were the two points that newly diagnosed COVID-19 cases sharply dropped (**Figure 1B**).

Characteristics of Stroke Patients

There were no significant differences in the mean age and sex distribution for stroke patients between two observational periods (**Table 2**). The NIHSS score of stroke patients at hospital arrival was significantly higher in the lockdown period (9.4 ± 7.7 in 2020 vs. 8.4 ± 7.8 in 2019, $P < 0.001$). The proportion of moderate stroke (NIHSS <6) was much lower, and the proportion of severe stroke (NIHSS >16) was much higher in the pandemic, especially in hospitals undesignated for COVID-19 (**Table 2**). For AIS, the proportions of patients receiving IVT or EVT therapy were significantly higher in the lockdown period when compared with the equivalent period in 2019 (**Table 2**).

Quality Metrics for AIS

The time in workflow for AIS was shown in **Figure 2** and **Table 3**. For the prehospital stage, there was no significant difference between the OTD times in two periods (**Figure 2A**). After hospital arrival, the DTC, DTN, and DTP times in the lockdown period were significantly longer than those in the equivalent period of 2019 (**Figures 2B,C,E**). The longer DTC, DTN, and DTP times in the lockdown period were shown in both COVID-19 designated and undesignated hospitals, but only the differences for DTN and DTP between two periods in undesignated hospitals were statistically significant (**Figures 2B,C,E**). During the whole emergency care workflow, there was no significant difference in the ONT and ORT times between two periods, except for the longer OTN time in undesignated hospitals during the pandemic (**Figures 2D,F**).

In line with the longer DTN time in the lockdown period, the proportions of DTN ≤45 min and DTN ≤60 min decreased significantly in both designated and undesignated hospitals, except for the proportion of DTN ≤45 min in designated hospitals (**Table 3**). It is noteworthy that despite the longer DTC and DTP time in the pandemic, the proportions of DTC ≤25 min and DTP ≤90 min didn't change significantly, except for the drop in the proportion of DTC ≤25 min in undesignated hospitals (**Table 3**). Besides, the proportions of OTN ≤3, 3.5, 4.5, and OTR ≤24 h didn't change significantly in both designated and undesignated hospitals (**Table 3**).

Clinical Outcomes

For AIS patients who received IVT, although the mean NIHSS score after therapy was significantly higher in the lockdown period, the difference in the proportion of patients with NIHSS ≤1 between two periods was not statistically significant (**Table 3**). For AIS patients who received EVT, the differences in the mean NIHSS scores after therapy and the proportion of patients with NIHSS ≤1 between two periods were both not statistically significant (**Table 3**). The recanalization rate in the lockdown period was significantly higher than that in the comparison period of 2019 (**Table 3**).

DISCUSSION

Based on records from all stroke centers in Beijing, we found that during the 97 days of the lockdown period, the number of stroke emergency hospital admissions reduced significantly by almost 50% compared with the equivalent period in 2019. There were delays in DTC, DTN, and DTP times for AIS, which mostly occurred after stroke patients arrived in the emergency room in COVID-19 undesignated hospitals.

During the pandemic, one major negative impact on acute care for stroke was the decline in emergency hospital admissions, consistent with reports in different regions in China or other countries. The degree of reduction varied from 10 to 70% (11, 13, 13, 16–19, 26–31). One recent report in China also reported a 40% reduction in stroke hospital admissions (16), similar to our results (45.6%). Similar hospitalization reduction was also observed in patients with acute coronary syndrome (32). Several reasons may contribute to the declines, the most possible one may be that stroke patients and their families didn't come to hospitals because of the social distance requirement and the concerns for in-hospital cross-infection (16). Patients with mild stroke symptoms may choose not to come to the hospital. In our data, patients with NIHSS <6 dropped by nearly 7% (47.0 vs. 40.3%). According to our data, we can see a negative correlation between the newly diagnosed COVID-19 cases and stroke admissions in the lockdown period, though the correlation was not statistically significant. Besides, a concordance of the decrease in newly diagnosed COVID-19 cases and the increase in stroke admissions was shown in the 4th week during the lockdown period. This

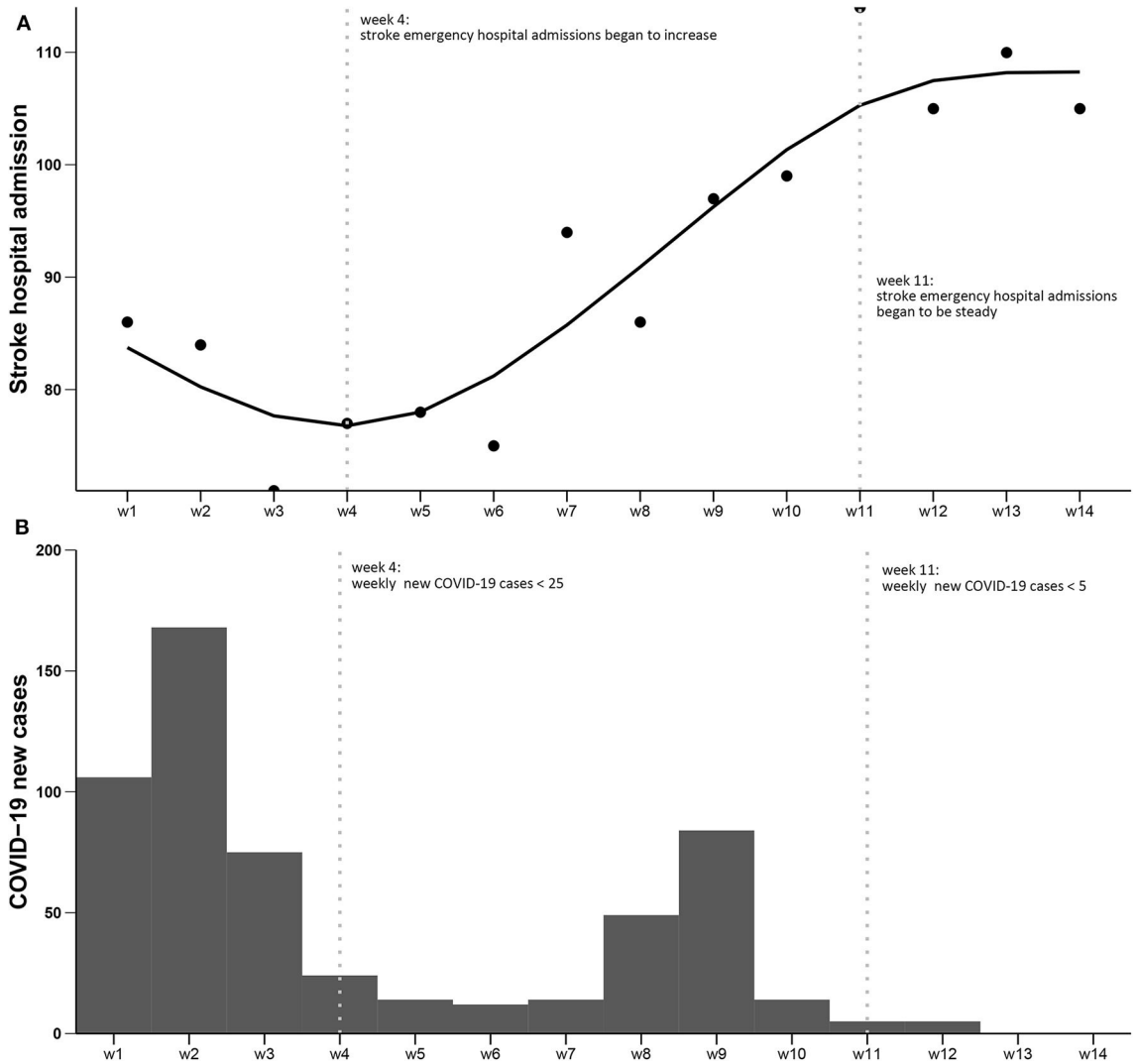


FIGURE 1 | Numbers of stroke hospital admissions and numbers of COVID-19 cases from January 24th to April 29th, 2020 in Beijing. **(A)** Numbers of stroke hospital admissions; **(B)** Numbers of newly diagnosed COVID-19 cases. The two dotted vertical lines: (left) week 4, from February 14th, there were <25 newly diagnosed COVID-19 cases per week in the following month, and the stroke emergency hospital admissions began to increase; (right) week 11, from April 3rd, there were <5 newly diagnosed COVID-19 cases per week in the following month, and the stroke emergency hospital admissions reached a plateau.

may indirectly reflect the severity of the pandemic related to stroke patients' behavior in seeking emergency care during this crisis. Thus, an early rapid response to COVID-19 and early control of disease could be critical to mitigating the negative impact on other diseases, such as stroke, requiring emergency care. On the other hand, during the pandemic, patients with life-threatening conditions should be encouraged to seek medical services and be assured that efforts were made by hospitals to prevent in-hospital cross-infection.

More declines were seen in hospitals designated for COVID-19 than in undesignated hospitals. Reasons from two aspects may contribute to this result. For reasons from patients and their families, they may reluctant to bother hospitals busy with taking care of COVID-19 cases and be fear of getting infected in designated hospitals (33). For reasons from the stroke emergency care system, more stroke patients who called the emergency centers may be recommended to undesignated hospitals purposely for appropriate allocation of health care resources. Our data showed that for stroke patients transferred by ambulance in the lockdown period, there were 22.3% (155/694) and 77.7% (539/694) of them sent to designated and undesignated hospitals, respectively, while the percentages were 41.9% (229/547) and 58.1% (318/547) for patients who reached hospitals by private cars. A recent survey in China also reported the capacity for stroke care reduced in most COVID-19 designated hospitals (16).

Our results showed more reductions for hemorrhagic stroke (69.0%) compared with ischemic stroke (42.9%). While we do not

TABLE 2 | Main characteristics of stroke patients*.

	All hospitals			Designated COVID-19 hospitals			Undesignated hospitals		
	Comparison period in 2019	Lockdown period in 2020	*P*-value	Comparison period in 2019	Lockdown period in 2020	*P*-value	Comparison period in 2019	Lockdown period in 2020	*P*-value
Age, y, mean ± sd	66.0 ± 13.3	65.7 ± 13.1	0.603	65.2 ± 12.6	64.2 ± 11.8	0.202	66.4 ± 13.6	66.4 ± 13.6	0.999
Sex, males, *N* (%)	1,583 (67.2)	854 (66.7)	0.750	546 (65.9)	270 (68.7)	0.358	1,037 (68.0)	584 (65.8)	0.279
Baseline NIHSS, mean ± sd	8.4 ± 7.8	9.4 ± 7.7	<0.001	7.5 ± 7.2	8.0 ± 6.5	0.225	8.9 ± 8.0	10.1 ± 8.2	0.002
Baseline NIHSS subgroups, *N* (%)†									
0–5	1,075 (47.0)	468 (40.3)	<0.001	441 (53.6)	175 (46.9)	0.066	634 (43.3)	293 (37.2)	0.001
6–16	886 (38.8)	501 (43.2)		286 (34.8)	155 (41.6)		600 (41.0)	346 (43.9)	
17–42	324 (14.2)	192 (16.5)		95 (11.6)	43 (11.5)		229 (15.7)	149 (18.9)	
Type of reperfusion therapy for AIS, *N* (%)			<0.001			<0.001			<0.001
IVT only	1,199 (60.4)	791 (69.9)		494 (66.5)	312 (80.6)		705 (56.8)	479 (64.3)	
EVT (with or without IVT)	250 (12.6)	185 (16.3)		80 (10.8)	55 (14.2)		170 (13.7)	130 (17.4)	
Not eligible for IVT or EVT	535 (27.0)	156 (13.8)		169 (22.7)	20 (5.2)		366 (29.5)	136 (18.3)	

**AIS, acute ischemic stroke; IVT, intravenous treatment; EVT, endovascular treatment; NIHSS, NIH Stroke Scale/Score.*
†With missing values.

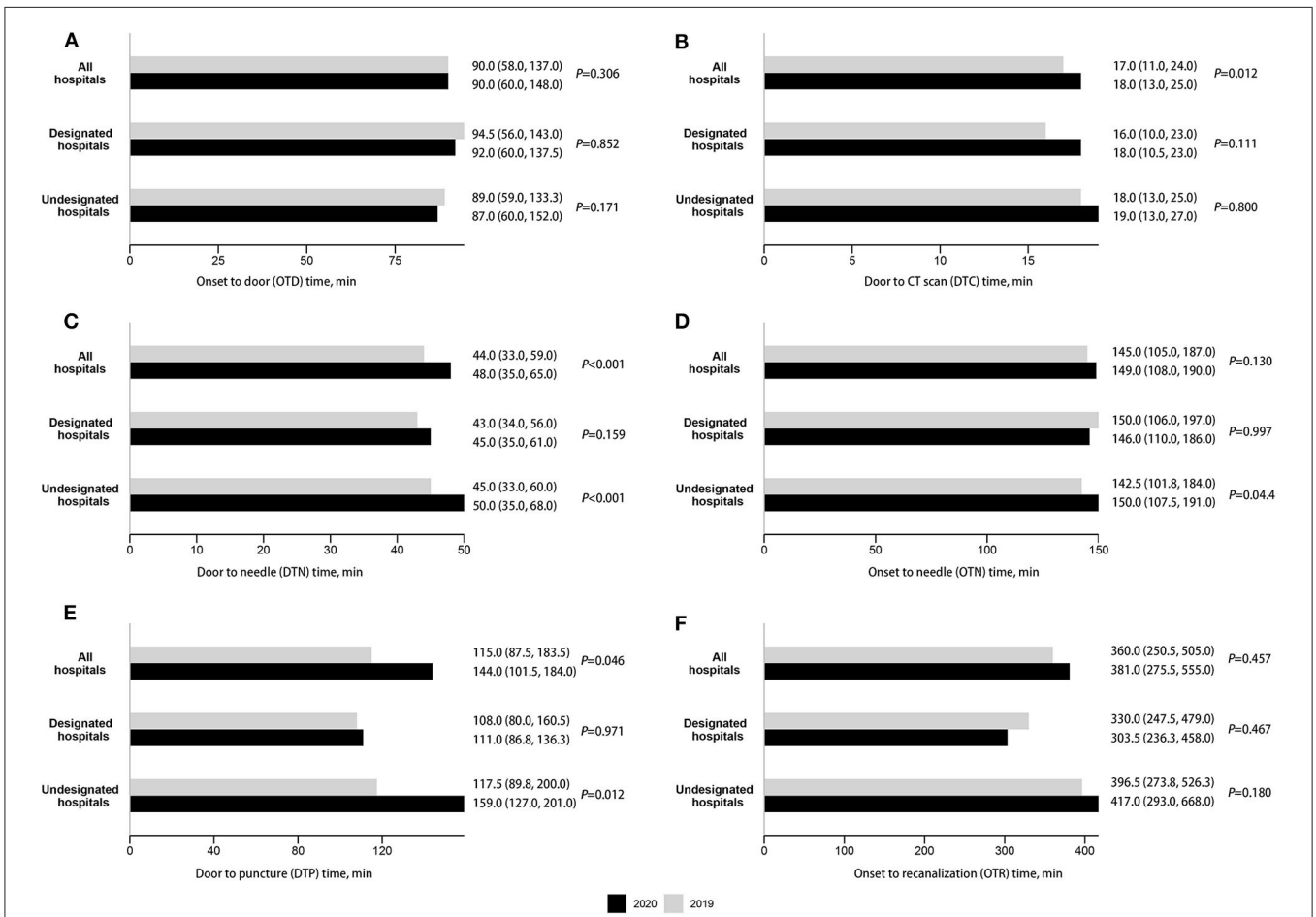


FIGURE 2 | Time in workflows for the acute care provided to acute ischemic stroke (AIS), median (IQR). **(A)** Onset to door (OTD) time. **(B)** Door to CT scan (DTC) time. **(C)** Door to needle (DTN) time. **(D)** Onset to needle (OTN) time. **(E)** Door to puncture (DTP) time. **(F)** Onset to recanalization (OTR) time.

TABLE 3 | Quality measures of the acute care provided for AIS*.

	All hospitals			Designated COVID-19 hospitals			Undesignated hospitals		
	Comparison period in 2019	Lockdown period in 2020	*P*-value	Comparison period in 2019	Lockdown period in 2020	*P*-value	Comparison period in 2019	Lockdown period in 2020	*P*-value
TIME IN THE WORKFLOW, *N* (%)									
DTC time									
DTC ≤25 min	923 (78.8)	596 (75.9)	0.150	389 (81.0)	241 (84.0)	0.331	534 (77.2)	355 (71.3)	0.022
IVT only									
DTN time									
DTN ≤45 min	552 (53.4)	307 (45.8)	<0.001	239 (55.7)	129 (52.2)	0.423	313 (51.8)	178 (42.1)	0.002
DTN ≤60 min	814 (78.8)	473 (70.6)	<0.001	345 (80.4)	180 (72.9)	0.027	469 (77.6)	293 (69.3)	0.003
OTN time									
OTN ≤3 h	751 (72.7)	482 (71.9)	0.739	303 (70.6)	181 (73.3)	0.480	448 (74.2)	301 (71.2)	0.286
OTN ≤3.5 h	854 (82.7)	544 (81.2)	0.438	340 (79.3)	200 (81.0)	0.620	514 (85.1)	344 (81.3)	0.124
OTN ≤4.5 h	986 (95.5)	640 (95.5)	1.000	407 (94.9)	232 (93.9)	0.602	579 (95.9)	408 (96.5)	0.744
EVT (with or without IVT)									
DTP time									
DTP ≤90 min	43 (30.9)	23 (20.0)	0.061	19 (37.3)	12 (30.0)	0.511	24 (27.3)	11 (14.7)	0.057
OTR time									
OTR ≤24 h	133 (95.7)	112 (97.4)	0.518	50 (98.0)	40 (100.0)	1.000	83 (94.3)	72 (96.0)	0.727
THERAPY OUTCOME									
IVT only									
NHISS after acute care, mean ± sd	5.2 ± 5.8	6.4 ± 6.5	<0.001	4.7 ± 5.6	6.1 ± 6.3	0.002	5.5 ± 6.0	6.5 ± 6.7	0.011
NHISS after acute care, ≤1, *N* (%)	149 (14.4)	75 (11.2)	0.057	77 (17.9)	31 (12.6)	0.081	72 (11.9)	44 (10.4)	0.484
EVT (with or without IVT)									
NHISS after acute care, mean ± sd	11.3 ± 8.9	11.9 ± 9.3	0.583	10.7 ± 7.1	11.5 ± 8.4	0.608	11.6 ± 9.8	12.1 ± 9.9	0.768
NHISS after acute care, ≤1, *N* (%)	20 (14.4)	14 (12.2)	0.712	4 (7.8)	6 (15.0)	0.325	16 (18.2)	8 (10.7)	0.192
Recanalization, *n* (%)	133 (95.7)	115 (100.0)	0.034	49 (96.1)	40 (100.0)	0.502	84 (95.5)	75 (100.0)	0.125

**AIS, acute ischemic stroke; IVT, intravenous treatment; EVT, endovascular treatment; NIHSS, NIH Stroke Scale/Score; DTC, door to CT scan; DTN, door to needle; OTN, onset to needle; DTP, door to puncture; OTR, onset to recanalization.*

have a clear answer to explain the discrepancy, we speculate that staying-at-home makes patients more likely to take medication which subsequently may better control the blood pressure and reduced the incidence of hemorrhagic stroke.

We didn't observe a constant rate of reduction in admission with moderate and severe strokes. According to the results, the baseline NIHSS score for patients in the lockdown period was significantly higher than the comparable period. This was similar to previous report (29). Patients with mild symptoms may reluctant to seek medical care with concerns of COVID-19. Patients were advised to cancel or postpone some non-essential medical procedures in the lockdown period. However, for patients with stroke, whether they need an emergency intervention or not requires the assessment by professional neurologists but not by themselves. Therefore, in this situation, improving the awareness of the importance of stroke emergency care in general, especially in the high-risk population was paramount.

Our study also examined the question whether there was a delay in emergency care for AIS. In the previous reports, significant delays happened in prehospital stage (14, 34), but whether there were delays in workflow metrics during the acute care was conflict (13, 14, 26, 28). According to our results, in the prehospital stage, the OTD time became shorter in the lockdown period, which may benefit from the better traffic situation. The delay happened after hospital arrival, that the DTC, DTN, and DTP time became longer in the lockdown period. This may because of the protected workflow in a pandemic crisis, including an additional screen for infection and the use of personal protection equipment (8). Despite the longer DTC and DTP time, the percentages of patients with DTC ≤25 min and with DTP ≤90 min didn't drop significantly. Besides, the OTN and OTR time, which reflect the whole emergency care workflow, were not increased significantly during the lockdown period. These results reflected a relatively efficacious stroke emergency care system in Beijing. Even though, the percentage of patients

with DTN ≤45 min and DTN ≤60 min were dropped in the pandemic. Further optimization in the stroke emergency care system is needed.

A discrepancy in two types of hospitals was shown that the delays mostly happened in undesignated hospitals. We think the possible reason is that in COVID-19 designated hospitals, the more reductions for all kinds of patients may reduce the transfer and intersect time between departments. Moreover, the health providers in these hospitals were well-trained to avoid in-hospital infections because of COVID-19 cases in their hospitals. They may be more familiar with the protected stroke care workflow than providers in undesignated hospitals. If this is true, strengthed training and practice programs for protected workflows in health providers in undesigned hospitals may reduce the delays in stroke emergency care or even other medical procedures. To find the reason clearly, further investigations are needed to compare the relevant details in two kinds of hospitals. Such researches are valuable to improve the whole stroke emergency care system in a region and make it less vulnerable to a similar crisis in the future.

There were several limitations in this study. Firstly, during the lockdown period, most of AIS patients had severe symptoms, and we may expect worse prognosis outcomes. Because of the limited variables we got, the outcomes for AIS emergency care should be evaluated in more detail by further studies. Detail information for etiology types and vessel occlusion sites were also not recorded, we cannot estimate the impact on acute care of stroke with different aetiological types or with different vessel occlusion sites. Secondly, our database did not record the status of COVID-19 and is unable to examine the potential association of COVID-19 and stroke. However, there were only about 600 reported COVID-19 cases in Beijing during the lockdown period, and the number is relatively small. Thirdly, as there was a suspicion on the association between COVID-19 infection and the risk of stroke, as well as the medical resource encroachment from COVID-19 cases, the influence on stroke emergency care in regions with higher infection rates may differ. Fourth, we chose the same period in 2019 as the comparison group mainly because of the seasonal fluctuation in stroke hospital admissions reported previously (35). However, there was also an increasing secular trend in stroke hospital admissions and a consistent improvement in the acute care process which result in decreases in therapy time. We could not exclude the possibility that the estimation of the impact was biased downward. Thus, the interpretation of these results should be careful. Even though, we can still see a significant negative effect on stroke emergency care in a region with a low infection rate.

In conclusion, our study demonstrated a major reduction of stroke hospitalization admissions in the lockdown period in Beijing. There were delays in acute care for AIS, and there are differences between COVID-19 designated hospitals and undesignated hospitals. These results have important implications to better prepare acute stroke care in future pandemics like this. Engagement and effective communication with all stakeholders including patients, health care providers, governmental policymakers, and other implementation partners are required for future success.

DATA AVAILABILITY STATEMENT

Summarized data can be shared by request from any qualified investigator to the correspondence author.

ETHICS STATEMENT

The study was reviewed and approved by Ethics Committee of Xuan Wu Hospital, Capital Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HS, YWu, YWa, and YL contributed to the study concept and had full access to all the data in the study. YWu and ZW responsibility for the integrity of the data and interpreted the findings. YWu and FC contributed to data analysis and drafted the article. WF and YWa interpreted the data. All authors contributed to the critical revision of the article for important intellectual content and agreed to the final version of the manuscript. YWa and HS attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

FUNDING

This study was supported by grants from the Capital's Funds for Health Improvement and Research (2020-2-2014) and Natural Science Foundation of China (81703291).

REFERENCES

1. Elisabeth M. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. *BMJ.* (2020) 368:m1036. doi: 10.1136/bmj.m1036
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
4. Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis.* (2020) 71:748–55. doi: 10.1093/cid/ciaa243
5. AHA/ASA Stroke Council Leadership. Temporary emergency guidance to US stroke centers during the coronavirus disease 2019 (COVID-19) pandemic: on behalf of the American heart association/American

stroke association stroke council leadership. *Stroke*. (2020) 51:1910–12. doi: 10.1161/STROKEAHA.120.030023
6. Goyal M, Ospel JM, Southerland AM, Wira C, Amin-Hanjani S, Fraser JF, et al. Prehospital triage of acute stroke patients during the COVID-19 pandemic. *Stroke.* (2020) 51:2263–7. doi: 10.1161/STROKEAHA.120.030340
7. Baracchini C, Pieroni A, Kneihsl M, Azevedo E, Diomedi M, Pascazio L, et al. Practice recommendations for the neurovascular ultrasound investigations of acute stroke patients in the setting of COVID-19 pandemic: an expert consensus from the European society of neurosonology and cerebral hemodynamics. *Eur J Neurol.* (2020). doi: 10.1111/ene.14334. [Epub ahead of print].
8. He Y, Hong T, Wang M, Jiao L, Ge Y, Haacke EM, et al. Prevention and control of COVID-19 in neurointerventional surgery: expert consensus from the Chinese federation of interventional and therapeutic neuroradiology (CFITN) and the international society for neurovascular disease (ISNVD). *J Neurointerv Surg*. (2020) 12:658–63. doi: 10.1136/neurintsurg-2020-016073
9. Meyer D, Meyer BC, Rapp KS, Modir R, Agrawal K, Hailey L, et al. A stroke care model at an academic, comprehensive stroke center during the 2020 COVID-19 pandemic. *J Stroke Cerebrovasc Dis.* (2020) 29:104927. doi: 10.1016/j.jstrokecerebrovasdis.2020.104927
10. Wang X, Chen Y, Li Z, Wang D, Wang Y. Providing uninterrupted care during COVID-19 pandemic: experience from Beijing Tiantan hospital. *Stroke Vasc Neurol.* (2020) 5:180–4. doi: 10.1136/svn-2020-000400
11. Diegoli H, Magalhães PSC, Martins SCO, Moro CHC, França PHC, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke.* (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
12. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmünzer B, Barlinn K, et al. Acute stroke in times of the COVID-19 pandemic: a multicenter study. *Stroke.* (2020) 51:2224–7. doi: 10.1161/STROKEAHA.120.030395
13. Rudilosso S, Laredo C, Vera V, Vargas M, Renú A, Llull L, et al. Acute stroke care is at risk in the era of COVID-19: experience at a comprehensive stroke center in barcelona. *Stroke.* (2020) 51:1991–5. doi: 10.1161/STROKEAHA.120.030329
14. Teo KC, Leung WCY, Wong YK, Liu RKC, Chan AHY, Choi OMY, et al. Delays in stroke onset to hospital arrival time during COVID-19. *Stroke.* (2020) 51:2228–31. doi: 10.1161/STROKEAHA.120.030105
15. Venketasubramanian N. Stroke care services in singapore during COVID-19 pandemic-a national perspective. *Front Neurol.* (2020) 11:780. doi: 10.3389/fneur.2020.00780
16. Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke.* (2020) 51:1996–2001. doi: 10.1161/STROKEAHA.120.030225
17. Pop R, Quenardelle V, Hasiu A, Mihoc D, Sellal F, Dugay MH, et al. Impact of the covid-19 outbreak on acute stroke pathways - insights from the alsace region in France. *Eur J Neurol*. (2020). doi: 10.1111/ene.14316. [Epub ahead of print].
18. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral effect of covid-19 on stroke evaluation in the united states. *N Engl J Med.* (2020) 383:400–1. doi: 10.1056/NEJMc2014816
19. Sylaja PN, Srivastava MVP, Shah S, Bhatia R, Khurana D, Sharma A, et al. The SARS-CoV-2/COVID-19 pandemic and challenges in stroke care in India. *Ann N Y Acad Sci.* (2020). doi: 10.1111/nyas.14379. [Epub ahead of print].
20. Leonardi M, Padovani A, McArthur JC. Neurological manifestations associated with COVID-19: a review and a call for action. *J Neurol.* (2020) 267:1573–6. doi: 10.1007/s00415-020-09896-z
21. Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and antithrombotic treatment in coronavirus 2019: a new challenge. *Thromb Haemost.* (2020) 120:949–56. doi: 10.1055/s-0040-1710317
22. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a systematic review and current update. *Acta Neurol Scand.* (2020) 142:14–22. doi: 10.1111/ane.13266
23. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. (2018) 49:e46–e110. doi: 10.1161/STR.0000000000000158
24. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke.* (2019) 50:e344–e418. doi: 10.1161/STR.0000000000000211
25. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2019).
26. Hajdu SD, Pittet V, Puccinelli F, Ben Hassen W, Ben Maacha M, Blanc R, et al. Acute stroke management during the COVID-19 pandemic: does confinement impact eligibility for endovascular therapy? *Stroke.* (2020) 51:2593–6. doi: 10.1161/STROKEAHA.120.030794
27. Huang JF, Greenway MRF, Nasr DM, Chukwudelunzu FE, Demaerschalk BM, O'Carroll CB, et al. Telestroke in the time of COVID-19: the mayo clinic experience. *Mayo Clin Proc.* (2020) 95:1704–8. doi: 10.1016/j.mayocp.2020.06.007
28. Kerleroux B, Fabacher T, Bricout N, Moïse M, Testud B, Vingadassalom S, et al. Mechanical thrombectomy for acute ischemic stroke amid the COVID-19 outbreak: decreased activity, and increased care delays. *Stroke.* (2020) 51:2012–7. doi: 10.1161/STROKEAHA.120.030373
29. Nguyen-Huynh MN, Tang XN, Vinson DR, Flint AC, Alexander JG, Meighan M, et al. Acute stroke presentation, care, and outcomes in community hospitals in Northern California during the COVID-19 pandemic. *Stroke.* (2020) 51:2918–24. doi: 10.1161/STROKEAHA.120.031099
30. Onteddu SR, Nalleballe K, Sharma R, Brown AT. Underutilization of health care for strokes during the COVID-19 outbreak. *Int J Stroke.* (2020) 15:NP9–10. doi: 10.1177/1747493020934362
31. Tejada Meza H, Lambea Gil Á, Saldaña AS, Martínez-Zabaleta M, Juez PR, Martínez EL, et al. Impact of COVID-19 outbreak in reperfusion therapies of acute ischemic stroke in North-West Spain. *Eur J Neurol.* (2020). doi: 10.1111/ene.14467. [Epub ahead of print].
32. De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced rate of hospital admissions for ACS during covid-19 outbreak in Northern Italy. *N Engl J Med*. (2020). 383:88–9. doi: 10.1056/NEJMc2009166
33. Liu L, Wang D, Brainin M, Elkind MSV, Leira E, Wang Y. Approaches to global stroke care during the COVID-19 pandemic. *Stroke Vasc Neurol*. (2020) 5:107–9. doi: 10.1136/svn-2020-000429
34. Bersano A, Kraemer M, Touzé E, Weber R, Alamowitch S, Sibon I, et al. Stroke care during the COVID-19 pandemic: experience from three large European countries. *Eur J Neurol*. (2020). doi: 10.1111/ene.14375. [Epub ahead of print].
35. Zheng Y, Wu Y, Wang M, Wang Z, Wang S, Wang J, et al. Impact of a comprehensive tobacco control policy package on acute myocardial infarction and stroke hospital admissions in Beijing, China: interrupted time series study. *Top Control*. (2020). doi: 10.1136/tobaccocontrol-2020-055663. [Epub ahead of print].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 05 November 2020
doi: 10.3389/fneur.2020.574694

COVID-19 and Cerebrovascular Diseases: A Systematic Review and Perspectives for Stroke Management

Pedro Fraiman[1†], Clecio Godeiro Junior[1†], Elena Moro[2], Francesco Cavallieri[3,4] and Marialuisa Zedde[3]*

[1] Division of Neurology, Hospital Universitario Onofre Lopes, Universidade Federal do Rio Grande do Norte, Natal, Brazil, [2] Division of Neurology, Centre Hospitalier Universitaire of Grenoble, Grenoble Institut of Neuroscience, Grenoble Alpes University, Grenoble, France, [3] Neurology Unit, Neuromotor & Rehabilitation Department, Azienda Unitá Sanitaria Locale - Istituto di Ricovero e Cura a Carattere Scientifico di Reggio Emilia, Reggio Emilia, Italy, [4] Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy

Importance: Reported cerebrovascular events in patients with COVID-19 are mainly ischemic, but hemorrhagic strokes and cerebral venous sinus thrombosis (CSVT), especially in critically ill patients, have also been described. To date, it is still not clear whether cerebrovascular manifestations are caused by direct viral action or indirect action mediated by inflammatory hyperactivation, and in some cases, the association may be casual rather than causal.

Objective: To conduct a systematic review on the cerebrovascular events in COVID-19 infection.

Evidence review: A comprehensive literature search on PubMed was performed including articles published from January 1, 2020, to July 23, 2020, using a suitable keyword strategy. Additional sources were added by the authors by reviewing related references. The systematic review was conducted in accordance with the PRISMA guidelines. Only articles reporting individual data on stroke mechanism and etiology, sex, age, past cardiovascular risk factors, COVID symptoms, admission NIHSS, D-dimer levels, and acute stroke treatment were selected for the review. Articles that did not report the clinical description of the cases were excluded. A descriptive statistical analysis of the data collected was performed.

Finding: From a total of 1,210 articles published from January 1, 2020, to July 23, 2020, 80 articles (275 patients), which satisfied the abovementioned criteria, were included in this review. A total of 226 cases of ischemic stroke (IS), 35 cases of intracranial bleeding, and 14 cases of CVST were found. Among patients with IS, the mean age was 64.16 ±14.73 years (range 27–92 years) and 53.5% were male. The mean NIHSS score reported at the onset of stroke was 15.23 ±9.72 (range 0–40). Primary endovascular thrombectomy (EVT) was performed in 24/168 patients (14.29%), intravenous thrombolysis (IVT) was performed in 17/168 patients (10.12%), and combined IVT+EVT was performed in 11/168 patients (6.55%). According to the reported presence of large vessel occlusion (LVO) (105 patients), 31 patients (29.52%) underwent primary EVT or bridging. Acute intracranial bleeding was reported in 35 patients: 24 patients (68.57%) had intracerebral hemorrhage (ICH), 4 patients (11.43%)

OPEN ACCESS

Edited by:
Beom Joon Kim, Seoul National University Bundang Hospital, South Korea

Reviewed by:
Apostolos Safouris, Metropolitan Hospital, Greece
Adam Denes, Institute of Experimental Medicine (MTA), Hungary

****Correspondence:***
Marialuisa Zedde
marialuisa.zedde@gmail.com

† These authors share first authorship

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *20 June 2020*
Accepted: *27 August 2020*
Published: *05 November 2020*

Citation:
Fraiman P, Godeiro Junior C, Moro E, Cavallieri F and Zedde M (2020) COVID-19 and Cerebrovascular Diseases: A Systematic Review and Perspectives for Stroke Management. Front. Neurol. 11:574694. doi: 10.3389/fneur.2020.574694

had non-traumatic subarachnoid hemorrhage (SAH), and the remaining 7 patients (20%) had the simultaneous presence of SAH and ICH. Fourteen cases of CVST were reported in the literature (50% males), mean age 42.8 years ±15.47 (range 23–72). Treatment was reported only in nine patients; seven were treated with anticoagulant therapy; one with acetazolamide, and one underwent venous mechanical thrombectomy.

Conclusion: Cerebrovascular events are relatively common findings in COVID-19 infection, and they could have a multifactorial etiology. More accurate and prospective data are needed to better understand the impact of cerebrovascular events in COVID-19 infection.

Keywords: COVID-19, coronavirus, cerebrovascular, intracranial hemorrhage, SARS-CoV-2, stroke

INTRODUCTION

In early December 2019, several cases of unknown origin pneumonia were described in Wuhan, the capital of Hubei Province in China (1). In less than a 4 month interval, a novel coronavirus, SARS-CoV-2 (COVID-19), was identified as the causative agent, and the infection quickly spread from China to the rest of the world, becoming a pandemic by March 2020. Since then, healthcare workers around the world have been facing a new disease with complex clinical features, far beyond the pneumonia cases that were first described in Wuhan. Indeed, the clinical syndrome of COVID-19 has shown evidence of multiorgan involvement: hematological (2), renal (3), cardiovascular (4), gastroenterological (5), dermatological (6), and neurological (7). The infection pathway of SARS-CoV-2 is mediated through angiotensin-converting enzyme 2 (ACE2), which functions as a receptor for viral infection (8). Beyond lung alveolar cells, ACE2 receptors have a wide tissue distribution in humans, including expression in the endothelium and vascular smooth muscle cells of the brain (9, 10). The full mechanism of neurologic involvement in COVID-19 remains unclear.

Reported cerebrovascular complications of COVID-19 infection—ischemic, hemorrhagic strokes, and cerebral venous sinus thrombosis (CSVT)—have been most commonly described in critically ill patients (7). It is still not clear whether cerebrovascular manifestations are caused by a direct viral action—a mechanism suggested from the retrograde brain infection from the olfactory nerve (11)—or an indirect action mediated by inflammatory hyperactivation, recognized as a cytokine storm (12), causing severe dysfunction of the immune and coagulation systems, reflected through elevated D-dimer levels and intravascular disseminated intravascular coagulation (DIC). In some patients, the presence of antibodies against cardiolipin and beta-2-glycoprotein I has been found, supporting an autoimmune mechanism (13). Another mechanism of cerebrovascular damage that has been postulated more recently, similar to what has been documented histopathologically in other organs, is through an endothelitis process (14, 15), which would account largely for the microangiopathic neuroimaging pattern described recently in a case series (16–18) and case report (19). The final cerebrovascular damage would have a neuroimaging pattern suggestive of a vasculitic process affecting the central nervous system (20, 21).

Data from postmortem brain magnetic resonance imaging (MRI) showed extensive signs of cerebrovascular involvement, including microbleeds with subcortical and posterior predominance (19). This multifocal pattern of hemorrhagic lesions could also be evocative of DIC-related lesions, leading to generalized endothelialitis (14), as also observed in ischemic stroke (IS) patients. The previously described prothrombotic scenario is at least partially correlated with the occurrence of IS and CVST. On the other hand, hemorrhagic strokes are less common but still relevant. Low platelet levels are found in patients with severe SARS-CoV-2, which may have triggered intracranial bleeding. Case reports of stroke syndromes during the COVID-19 pandemic (22–31) are heterogeneous. Most cases reveal a higher incidence of large artery atherosclerosis (LAA) stroke—indicated by greater morbidity—but also reported cases of cardioembolism (CE) and small vessel disease (SVD) (22, 28), intracranial hemorrhage, and CVST (28). The reported cases are commonly associated with comorbidities—diabetes mellitus (DM), arterial hypertension (AH), atrial fibrillation (AF), dyslipidemia (DLP), smoking, and alcohol consumption—and older patients (usually over age 60). Nonetheless, there are reports of patients of younger ages—under 40 years old—and no comorbidities (24). There are increasing data on higher levels of D-dimer and ferritin on admission—possible biomarkers of prothrombotic and inflammatory states of the disease (2, 32, 33). However, even literature data have shown that high levels of these biomarkers (mainly D-dimer) are predictors of poor prognosis and mortality (33, 34), and studies showing correlations between high levels of these biomarkers and worse stroke outcomes are still missing.

METHODS

This systematic review was conducted in accordance with the PRISMA guidelines. A comprehensive literature search on PubMed was performed including articles published from January 1, 2020, to July 23, 2020, using different combinations of the following search terms: "COVID-19," "Coronavirus," "Sars-Cov-2" and "neurology," "stroke," "ischemic stroke," "cerebrovascular," "intracranial hemorrhage," "intracranial bleeding," "subarachnoid hemorrhage," "intracerebral hemorrhage," and "cerebral venous sinus thrombosis."

The search was performed by two independent reviewers (FC and PF), who also performed the validity assessment. Any disagreement was resolved by consensus with a senior author (MZ). Each selected full article was further checked for cross references to additional reports. Only articles published in English were reviewed. Only articles reporting data on stroke mechanism and etiology, sex, age, past cardiovascular risk factors, COVID symptoms, admission National Institutes of Health Stroke (NIHSS) score, D-dimer levels, and acute stroke treatment were selected for the review. Articles that did not report the clinical description of the cases were excluded. Relevant qualitative and quantitative data were extracted by two authors (FC and PF) and were reviewed by a senior researcher (MZ) in the form of absolute numbers when appropriate. Where available, the data included patient demographics (age, gender), main vascular risk factors and comorbidities, COVID-19 symptoms, the time interval between COVID-19 symptom onset and stroke, NIHSS scores, the presence of large vessel occlusion (LVO), patterns of stroke on neuroimaging, relevant biological markers (D-dimer, ferritin c-reactive protein, white blood cell count, platelet count), treatment (acute recanalization and antithrombotic therapy), and outcomes. Clinical and neuroimaging data reported in text or image format were reviewed by a senior stroke neurologist (MZ), who also performed the Trial of Org 10,172 in Acute Stroke Treatment (TOAST classification) (35) whenever possible. A descriptive statistical analysis of the data collected was performed using IBM SPSS Statistics for Windows version 10.0 (IBM, Armonk, NY, USA). The results are reported as the mean ± SD.

RESULTS

Figure 1 shows the study selection pathway. From a total of 1,210 articles published from January 1, 2020, to July 23, 2020, 983 articles were excluded due to no pertinent titles or abstracts. Of the remaining 227 articles, 147 were excluded because even if they were related to COVID-19 and cerebrovascular diseases, they did not report case descriptions of IS, intracranial bleeding, or CVST. Of the remaining 109 articles, 29 articles (1, 7, 36–62) were excluded from the analysis because even if they reported cases of cerebrovascular diseases in COVID-19 patients, they lacked individual clinical data. The remaining 80 articles (275 patients), which satisfied the abovementioned criteria, were included in this review. We found 226 cases of patients who developed IS during COVID-19 infection (16, 18, 20, 22–29, 63–106), 35 cases of intracranial bleeding (25, 72, 74, 100–104), and 14 cases of CVST (22, 31, 105–113). Individual case descriptions are available in the **Supplementary Material (S1, S2, S3)**.

Ischemic Stroke

IS was reported in the literature in 226 patients, and the main features are summarized in **Table 1** (full details are available in **Supplementary Table 1**). Among these patients, gender was reported in 188 (83.2%) patients, and 121 (53.5%) were male. Age was reported in 177 (78.3%) patients; in this subgroup, the mean age was 64.16 ± 14.73 years, with a median age of 65 years (range 27–92 years). Information about classic vascular risk factors (DM, AH, smoking, AF, alcohol consumption, chronic kidney disease [CKD], and DLP) and previous vascular history was available for 197 (87.2%) patients. Ninety-three (47.2%) patients had at least 2 vascular risk factors [age reported in 76 (38.6%) patients with mean age 69.7±12.9 years, range 39–90 years and median age 72 years]; 59 (29.9%) patients had only one vascular risk factor [age reported in 46 (23.4%) patients with mean age 60.7±12.87 years, range 36–88 years and median age 62 years]; 43 (21.8%) patients had no vascular risk factor [age reported in 34 (12.2%) patients with mean age 58.29 ± 19.01 years, range 31–92 years and median age 59 years]. Past medical history was significant for previous coronary artery disease (CAD) in 23 (10.2%) patients and for previous stroke or transient ischemic attack (TIA) in 13 (5.8%) patients. In 159 (70.35%) patients, characteristics of the COVID-19 condition were detailed (i.e., asymptomatic, mild/severe COVID infection), and among these, 24/159 (15.09%) patients were asymptomatic. No data are available about the remaining patients. For those with reported symptoms, fever, cough, and dyspnea were the most frequent. Only in 99/226 (43.81%) patients was the NIHSS score reported at the onset of stroke, and it ranged from 0 to 40 points with a mean value of 15.23 ± 9.72 points and a median of 14 points. In 164/226 (72.57%) patients, neuroimaging and their findings were reported: MRI/MRI angiography (MRA) in 28/164 (17.07%) patients and computed tomography (CT)/computed tomography angiography (CTA) in 139/164 (80%) patients. In 105/226 (46.5%) patients, large vessel occlusion (LVO) status was reported. In 23/226 (10.2%) patients, stroke etiology was not reported or not inferable from the description, according to the TOAST classification (35). In the remaining 203/226 (89.8%) patients, 131/203 (64.53%) cerebrovascular events were cryptogenic, 39/203 (19.21%) were cardioembolic, 15/203 (7.39%) were atherothrombotic, 13/203 (6.40%) were triggered by other causes (watershed stroke in systemic hypotension, posterior reversible encephalopathy syndrome, and genetic causes), and 5/203 (2.46%) were SVD-related. Among patients with reported acute treatment (168/226 patients, 74.34%), 92/168 patients (54.76%) were treated only by antithrombotic therapy (antiplatelets, low-molecular weight heparin [LMWH], oral anticoagulants). Primary endovascular thrombectomy (EVT) was performed in 24/168 patients (14.29%), intravenous thrombolysis (IVT) was performed in 17/168 patients (10.12%), and combined IVT + EVT was performed in 11/168 patients (6.55%). According to the reported presence of LVO (105 patients), 31 patients (29.52%) underwent primary EVT or bridging. Eight out of 168 (4.76%) patients underwent decompressive hemicraniectomy. Supportive treatment was performed in 24/168 patients (11.90%). The stroke treatment of 58 patients was not reported. D-dimer absolute levels were reported in 140/226 patients (61.95%) with mean value 9923.58 [±18,016] ng/mL (median 3,728; range 226–112,290). Among these patients, D-dimer levels were at least 4-fold (33, 114) higher than normal values in 99/128 patients (77.34%). D-dimer absolute levels were not reported in 86/226 patients (38.05%). Ferritin level was reported in 56/226 patients (24.78%) with mean value 1093.27 ± 1720.18 ng/mL. White blood cells (WBC) count

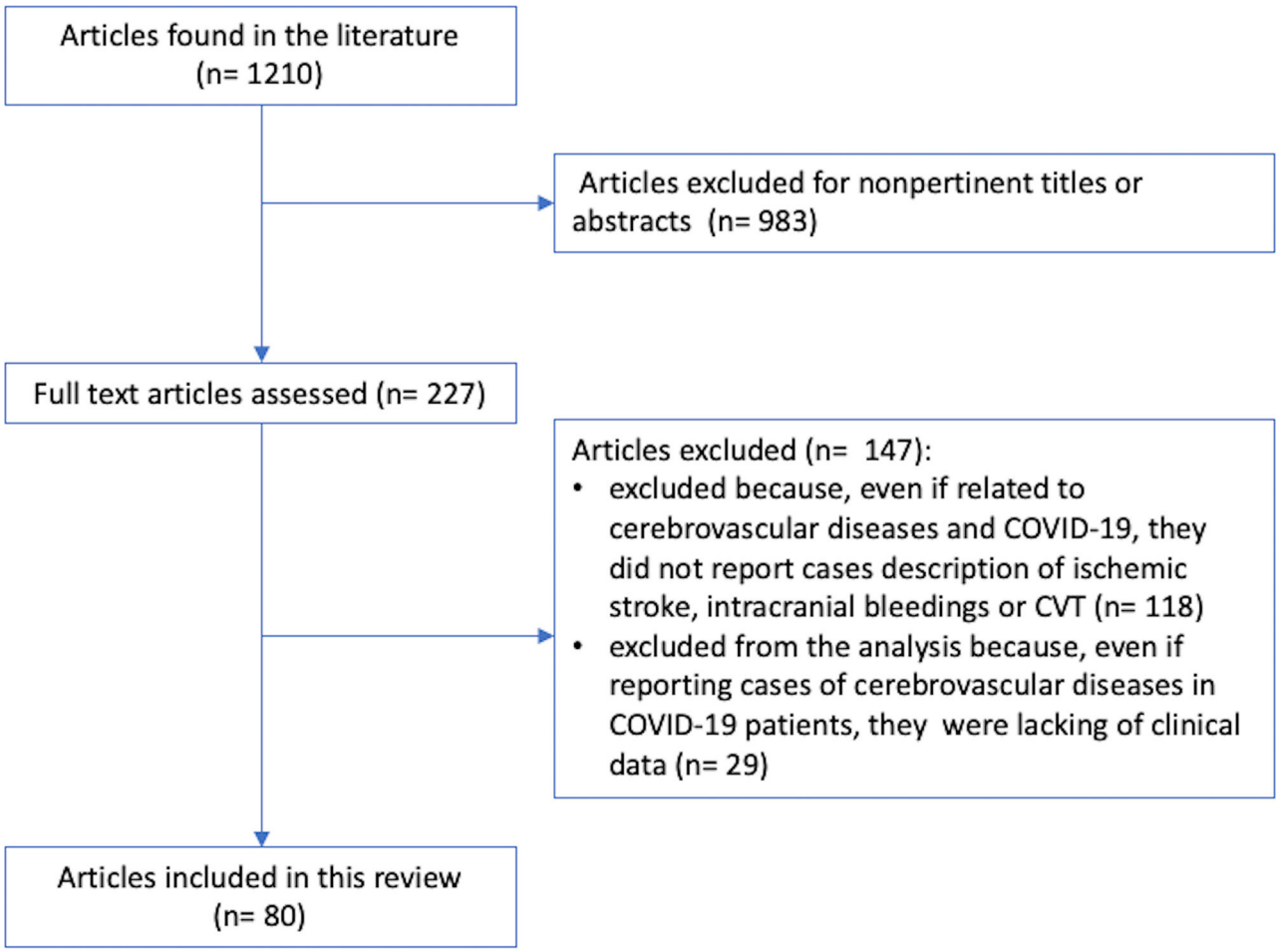


FIGURE 1 | Study selection pathway.

was reported in 66/226 patients (29.2%; mean: 11,354/mm^3; median: 8,835; SD ± 7,616; range: 100–42,900); 38/66 patients (57.6%) showed normal WBC; 25/66 patients (37.9%) showed leukocytosis and the remaining 3/66 patients showed leucopenia (4.5%). Platelet count was reported in 71/226 patients (31.4%; mean: 270,535/mm^3; median: 239,000/mm^3; SD ± 139,907; range: 78,000–76,2000). In particular, 45/71 patients (63.4%) showed normal platelet count; 18/71 patients (25.4%) were thrombocytopenic and the remaining 8/66 patients showed an excessive number of platelets in the blood (11.2%). C-reactive protein (CRP) levels were reported in 111/226 patients (49.1%; mean: 95.52 mg/L; median: 44.3; SD ± 100.77; range: 0.8–366.5); the majority of patients (98/111; 88.3%) presented high levels of CRP while the few remaining showed normal CRP levels (13/111; 11.7%).

The available outcomes are short-term and mostly related to the hospitalization phase for acute treatment, and the outcomes of 29 patients (12.83%) are not available. A total of 129 patients (65.48%) were alive; among them, 24 patients (12.18%) were critically ill, while the remaining 68 (34.52%) were dead.

Intracranial Bleeding

Acute intracranial bleeding was reported in 35 patients with COVID-19 in the literature (**Table 2**, **Supplementary Table 2**): 24 patients (68.57%) had intracerebral hemorrhage (ICH), 4 patients (11.43%) had non-traumatic subarachnoid hemorrhage (SAH), and the remaining 7 patients (20%) had the simultaneous presence of SAH and ICH. The mean age of the 35 patients with intracranial bleedings was 59.89 ± 11.91 years and 67.4% were males (16, 25, 28, 64, 71, 73, 107–121). Two of the 11 patients with non-traumatic SAH (regardless of the presence of ICH) were found to have a ruptured dissecting aneurysm (one in the posterior inferior cerebellar artery; one in the pericallosal artery). Concerning the ICH-only group ($n = 24$), most patients had a pre-existing risk factor for cardiovascular disease (CVD) (i.e., AH, immune thrombocytopenia, concomitant heparin treatment, hepatic cirrhosis). In contrast, five patients did not have known pre-existing risk factors for ICH. Five severely ill patients developed ICH during hospitalization in the intensive care unit as a consequence of a severe form of COVID-19. In most patients, neurological manifestations of ICH are represented by alterations in consciousness variably associated

TABLE 1 | Characteristics of COVID-19 patients affected by ischemic stroke (IS) ($n = 226$).

Variable	Valid *N*	Values No.–%; mean [±SD]; (range)
Age (years)	**177**	64.16 [±14.73]; (27–92)
Sex	**188**	Male 53.5%
Cardiovascular risk factors	**197**	
Arterial hypertension		102–51.78%
Diabetes mellitus		70–35.53%
Hyperlipidemia		53–26.90%
Atrial fibrillation		30–15.23%
Coronary artery disease		23–11.68%
Smoking		16–8.12%
Obesity		7–3.55%
Previous stroke or TIA	**197**	13–6.60%
NIHSS	**99**	15.23 [± 9.72]; (0–40)
COVID-19 symptoms	**159**	
Fever		81–50.94%
Cough		88–55.35%
Dyspnea		78–49.06%
Vomiting and diarrhea		3–1.89%
Body aches		9–5.66%
Asymptomatic		24–15.09%
Stroke etiology	**203**	
Cryptogenic		131–64.53%
Cardioembolic		39–19.21%
Atherothrombotic		15–7.39%
Other causes		13–6.40%
Small vessel disease		5–2.46%
Acute treatment	**168**	
Antithrombotic therapy		92–54.76%
Primary EVT		24–14.29%
Supportive treatment		20–11.90%
IVT		17–10.12%
IVT + EVT		11–14.29%
Decompressive hemicraniectomy		8–4.76%
D-Dimer (ng/mL)	**140**	9923.58 [±18,016]; (226–112,290)
Ferritin (ng/mL)	**56**	1093.27 [±1,720.18]; (7–11,062)
WBC counts (/mm3)	**66**	11,354 [±7,616]; (100–42,900)
Platelet count (/mm3)	**71**	270,535 [±139,907]; (78,000–762,000)
CRP (mg/L)	**111**	95.52 [±100.77]; (0.8–366.5)
Short-term outcome	**197**	
Survival or critically ill		129–65.48%
Death		68–34.52%

CPR, C-reactive protein; EVT, endovascular treatment; IVT, intravenous thrombolysis; NIHSS, National Institute of Health; Stroke Scale; TIA, transient ischemic attack; WBC, white blood cells. n represents the number of cases reported in the literature.

TABLE 2 | Characteristics of COVID-19 patients affected by intracranial bleeding ($n = 35$).

Variable	Valid *N*	Value No.–%; mean [±SD]; (range)
Age (years)	**35**	59.89 [±11.91]; (30–79)
Sex	**35**	Male 67.4%
Cardiovascular risk factors	**34**	
Arterial hypertension		17–50.00%
Diabetes mellitus		7–20.59%
Coronary artery disease		3–8.82%
Hyperlipidemia		2–5.88%
Smoking		2–5.88%
Obesity		1–2.94%
Type of intracranial bleeding	**35**	
ICH		24 (68.57%)
SAH		4 (11.43%)
SAH + ICH		7 (20%)
COVID-19 symptoms	**34**	
Fever		21–61.76%
Cough		15–44.12%
Dyspnea		19–55.88%
Vomiting and diarrhea		2–5.88%
Body aches		3–8.82%
Asymptomatic		5–14.71%
ICH	**24**	68,57%
SAH	**4**	11.43%
ICH+SAH	**7**	20%
D-Dimer (ng/mL)	**18**	3,380 [±2686.82]; (410–8,961)
Ferritin (ng/mL)	**6**	2969.83 [±2861.33]; (657–8,530)
WBC counts (/mm3)	**13**	12,716 [±5,908]; (590–23,320)
Platelet count (/mm3)	**18**	217,055 [±126,445]; (1,000–510,000)
CRP (mg/L)	**17**	79.15 [±100.29]; (1–330)
Short-term outcomes	**28**	
Survival or critically ill		16–57.14%
Death		12–42.86%

CPR, C-reactive protein; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; WBC, white blood cells. n represents the number of cases reported in the literature.

with focal signs or symptoms (i.e., motor or sensory deficits, aphasia, dysarthria).

CT scan/CTA and/or Brain MRI/MRA were positive in all patients showing: supratentorial lobar ICH (13 patients); deep supratentorial ICH (four patients); cerebellar and truncal ICH (four patients), extensive supra- and infratentorial ICH (three patients). D-dimer levels were reported in 18/35 patients (51.4%; mean: 3,380 ng/ml; median: 2,876; SD ± 2686.82; range: 410–8,961), while ferritin level was reported only in 6/35 patients (17.14%) with mean value 2969.83 ± 2861.33 ng/mL. WBC was reported in 13/35 patients (37.1%; mean: 12,716/mm^3; median: 13,600; SD ± 5,908; range: 590–23,320); 8/13 patients (61.5%) showed leukocytosis; 4/13 patients (30.8%) showed normal WBC, and the remaining patient showed leucopenia (7.7%). Platelet count was reported in 18/35 patients (51.4%; mean: 217,055/mm^3; median: 194,000/mm^3; SD ± 126,445; range: 1,000–510,000). In particular, 12/18 patients (66.7%) showed a normal platelet count; 5/18 patients (27.8%) were thrombocytopenic and the remaining one patient patient showed an excessive number of platelets in the blood (5.6%). CRP levels were reported in 17/35 patients (48.6%; mean: 79.15 mg/L;

TABLE 3 | Characteristics of COVID-19 patients affected by cerebral venous sinus thrombosis (CVST) ($n = 14$).

Variable	Valid *N*	Value No.–%; mean [±SD]; (range)
Age (years)	**14**	42.8 [±15.47]; (23–72)
Sex	**14**	Male 50.0%
Cardiovascular risk factor	**12**	
None		7–58.33%
Obesity		3–24.00%
Diabetes mellitus		2–15.67%
Arterial hypertension		1–8.33%
Smoking		1–8.33%
COVID-19 symptoms	**11**	
Fever		8–72.73%
Cough		7–63.64%
Dyspnea		4–36.36%
Vomiting and diarrhea		1–9.09%
Body aches		1–9.09%
Asymptomatic		1–9.09%
Sinus and vein involvement	**13**	
Transverse sinus		6–46.15%
Straight sinus		4–30.77%
Sigmoid sinus		3–23.08%
Vein of Galen		3–23.08%
Superior sagittal sinus		2–15.38%
Hemorrhagic transformation	**9**	64.29%
D-dimer (ng/mL)	**8**	4624.5 [±5,783]; (902–18,431)
Ferritin (ng/mL)	**2**	1233.5 [±238]; (1,040–1,427)
WBC counts (/mm3)	**8**	12,337 [±5,233]; (6,300–20,220)
Platelet count (/mm3)	**6**	179,500 [±109,381]; (42,000–335,000)
CRP (mg/L)	**4**	95.93 [±75.40]; (20–170.8)
Short-term outcomes	**11**	
Death		6–54.55%
Survival or critically ill		5–45,45%

CPR, C-reactive protein; WBC, white blood cells. n represents the number of cases reported in the literature.

median: 36; SD ± 100.29; range: 1–330); the majority of patients (11/17; 64.7%) presented high levels of CRP while the few remaining showed normal CRP levels (6/17; 35.3%).

Globally, 16 patients survived while 12 died. Outcome data were not available in the remain seven patients.

Cerebral Venous Sinus Thrombosis

Fourteen cases of CVST in patients with COVID-19 were reported in the literature (50% males, mean age: 42.8 years ± 15.47; median: 49; range: 23–72 years) (**Table 3**, **Supplementary Table 3**) (28, 39, 122–130). Seven patients did not have any known risk factors for CVST, three patients had obesity, two patients had DM, and one patient suffered from smoking and drinking consumption or a history of breast cancer in remission. Risk factors were not reported in two patients. The main symptoms associated with COVID-19 were fever (8 patients), cough (7 patients), dyspnea (4 patients), vomiting and diarrhea (1 patient), and body aches (1 patient). Data were not reported in three patients, while one patient did not develop any symptoms. The NIHSS was available only in two patients; in the majority of patients, neurological manifestations of CVST were headache and/or altered mental status variably associated with focal signs or symptoms (i.e., motor or sensory deficits, aphasia, altered vision) and seizures (one patient). CT scan/CTA and/or brain MRI/MRA were positive in 13 patients (in one patient, neuroimaging data were not available). In particular, venous infarction with hemorrhagic transformation was detected in 9/14 patients (64.29%), while in three patients, no parenchyma alterations were found. The transverse sinus was involved in six patients, the straight sinus in four patients, the sigmoid sinus and the vein of Galen in three patients, and the superior sagittal sinus in two patients. D-dimer levels were available in 8/14 (57.14%) and were elevated in each of them (mean value: 4624.5 ± 5783.16 ng/mL; median: 2,618 ng/mL; range: 902–18,431 ng/mL). Ferritin level was reported in 2/14 patients (14.28%) with mean value 1233.5 ± 238 ng/mL. WBC count was reported in 8/14 patients (57.14%) with mean value 12,337 ± 5,233/mm3 and platelet count was available in 6/14 patients (42.86%) with mean value of 179,500 ± 109,381/mm3. Mean CPR levels were 95.93 ± 75.40 mg/L in 4/14 patients (28.57%). Treatment was reported only in nine patients; seven of them were treated with anticoagulant therapy (LMWH, unfractionated heparin [UFH], or direct oral anticoagulants). One patient was treated only with acetazolamide, and one patient underwent venous mechanical thrombectomy. Five patients (50%) died due to complications of CVST and COVID-19 infection. Outcome data were not available for three patients.

DISCUSSION

It is well known and characterized in the literature that both acute and chronic infections and inflammatory states can be triggers of stroke (131, 132). In particular, it has been proposed that respiratory tract infection may act as a trigger and increase the risk of large vessels and/or cardioembolic IS, especially in subjects without vascular risk factors (133). In particular, influenza-like illness has previously been associated with an increased stroke risk (134). The risk of stroke during the COVID-19 outbreak was compared to the risk of stroke during the influenza outbreak in the previous year in a cohort study (135), showing that 1.6% of emergency department (ED)-admitted COVID-19 patients had acute IS vs. 0.2% of patients with influenza, reflecting an odds ratio of 7.6 (95% CI, 2.3–25.2).

Therefore, cerebrovascular events are relatively common findings in COVID-19 infection, and they could have a multifactorial etiology. The causal association with COVID-19 infection is not clearly evident or inferable in all the cases described. The manifestations are multifaceted, and the neuroimaging pattern of the patients is also consistent with different pathophysiological mechanisms, so it is difficult to identify a single pattern of cerebrovascular disease related to COVID-19.

More information is available on thrombotic events than on intracranial bleeding. IS and CVST could have a common pathophysiological path in the inflammatory and pro-coagulant state correlated with COVID-19 and is supported from the

biochemical point of view by the significantly increased values of D-dimer. In some cases of CVST, however, COVID-19 infection is explicitly reported as a possible etiological cofactor in association with known risk conditions, such as taking estrogen-progestin therapy (73, 128). Moreover, the presence of known previous risk factors for stroke (e.g., AH, AF, vascular disease, DLP, smoking) is common in reported cases of IS, but there are also reports among patients with no known risk factors (26.4%, **Supplementary Table 1**).

Ischemic Stroke

The age of IS patients on whom data are available is substantially in line with that of patients with a higher incidence of cerebrovascular events (136), also in association with multiple vascular risk factors present in the described cohort. In fact, the average age of patients with IS without any pre-existing vascular risk factor was 62.9 ± 17.2 years, with a median age of 67.5 years.

A temporal association between COVID-19 and cerebrovascular events is presented in all reported case reports; sometimes, in particular in cases of stroke caused by LVO without atherothrombosis, an etiopathogenetic association has been hypothesized between COVID-19-related coagulopathy and stroke, as in the case of CVST. Not all patients were able to collect information on the presence of an LVO, and similarly, the NIHSS score was not reported except in a limited number of patients.

Although an NIHSS score threshold has never been demonstrated that is capable of differentiation with sufficient accuracy for emergency treatment, it is nevertheless sufficiently agreed that a score >10 is associated with a greater probability of finding an LVO. Furthermore, the main limitations of this approach derive from the fact that low NIHSS scores cannot exclude LVO, not that high scores are not predictive of LVO (137). In reported patients, the NIHSS score is at least 10, and in the whole sample, a high rate of documented LVO, often in multiple vessels, was reported.

Additionally, in many of the patients for whom it was not possible to have information on the state of patency of the large cerebral vessels, ischemic lesions in multiple arterial territories have been reported, and in some of them, the etiological definition according to the TOAST classification was determined by the evidence of cardiac embolic sources (AF, endocarditis, dilated heart disease), which does not exclude the possibility that COVID-19 may have acted as a trigger on known vascular risk factors. Similar reasoning is possible for cases in which the etiological category "atherothrombosis of large vessels" is defined by the presence of a thrombotic burden, often very extensive and superimposed on an atheroma, as well as the fact that the documentation of this pattern of vascular imaging is relatively rare in acute IS treatment cases in comprehensive stroke centers (138).

Cryptogenic stroke was the most common subtype of IS in COVID-19 patients, and it is an interesting fact that can be interpreted in the context of the inflammatory and prothrombotic state characteristic of the disease, with documentation of arterial and venous thrombosis, micro- and macrovascular thrombosis, and other body areas (139–141). In fact, in many patients with COVID-19, the final cause of death has been documented to be a thrombotic complication, particularly a pulmonary embolism. Moreover, in some cases reported as cardioembolic, mostly due to the already known history of AF or hypokinetic heart disease with severe left ventricular function deficit, patients with LVO stroke have been described despite ongoing anticoagulation therapy. It is therefore possible that in this case, the prothrombotic component linked to the infection may have played a role, at least in association with the known risk factors. The cases described with ischemia in multiple vascular territories, even in the absence of LVO, could also fall within the context of cryptogenic cerebral embolism. Considering the high percentage of patients described with cryptogenic LVO, it can be speculated that the prothrombotic mechanism linked to COVID-19 can act both in isolation and in association with the classic vascular risk factors, regardless of age.

Regarding individual ischemic lesions with SVD patterns, the role of causes other than COVID-19 appears more probable, which may have played a triggering role, as is known for many systemic or localized infectious events (142).

The high percentage of patients with high D-dimer values, often >4 times the normal values, may indirectly corroborate the hypothesis of the role of the prothrombotic mechanism linked to COVID-19 in a significant proportion of patients with IS reported thus far with sufficient detail in the literature.

Tang and colleagues (34) reported that in a series of hospitalized patients with COVID-19 pneumonia 71.4% of non-survivors and 0.6% survivors met the criteria of DIC during their hospital staying and had coagulation abnormalities with markedly elevated D-dimer levels. We can therefore speculate that the occurrence of both thrombosis in cerebral large vessels, often multiple, and thrombotic microangiopathy, as neuroimaging data suggest, is one of the main mechanisms by which COVID-19 has an etiological association with stroke. It should also be considered that, even in the absence of COVID-19, among the medical emergencies associated with markedly high levels of D-dimer in ED, cerebrovascular events are second only to sepsis for D-dimer level and the D-dimer correlates with mortality (143). It is therefore possible that the diagnostic and prognostic role of D-dimer values as a coagulopathy marker in these patients should be specified by the dosage of other biomarkers (for example endothelial damage) and there is no clear information on the prognostic role of the variation of D-dimer levels over time (144).

The therapeutic approach to this mechanism is therefore mostly similar to that of stroke with LVO in revascularization strategies but more empirical in the subsequent acute and post-acute phases with a variable combination of antithrombotic drugs, often LMWH, with variable dosage.

The etiopathogenetic link appears less immediate for SVD-related cerebrovascular events. In some reported cases in patients with severe COVID-19 infection and evidence of neurological involvement after several unsuccessful attempts of extubation (27), brain MRI provided evidence of an unusual pattern of microbleeds, predominantly affecting the corpus callosum, and punctiform lesions that were DWI-positive in the centrum semiovale. Both thrombotic microangiopathy related to

direct or indirect damage by SARS-CoV-2 on the endothelium of cerebral small vessels and brain-blood-barrier injury related to hypoxemia have been hypothesized. An emblematic case of the possible causality of the association between COVID-19 and IS in a patient with CADASIL is reported (95). The few described cases of IS caused by spontaneous carotid dissection also fall into the TOAST etiopathogenetic category of "other determined etiology," which collects data on the known rare causes of IS. In this case, it is possible to postulate the role of COVID-19 infection as a dissection trigger, similar to what is known for respiratory tract infections in general (145, 146), with the possibility of two further specific elements of COVID-19 infection or the prothrombotic potential and tropism for the vascular endothelium (147). A consideration that deserves attention is that IS has been reported in patients with significant differences in the severity of COVID-19, and in some cases (90), it represented the reason for access to the hospital; that is, it is not a limited event that is more severe with severe respiratory failure and requires ventilatory support. A further element that conditions the association between COVID-19 and co-occurrent IS is that the severity of the respiratory picture and of the infection in general is widely different in various stages of the course of the disease, which can influence the prognosis of cerebrovascular events, both in the acute phase and in the post-acute phase, and the global outcome.

In a multicenter case study related to all consecutive patients hospitalized with laboratory-confirmed COVID-19 and IS in 28 sites from 16 countries (148), which collected 174 patients, it is suggested that these patients have a worse functional outcome and higher mortality than stroke patients without COVID-19 hospitalized in the same period. This worse prognosis can be correlated with the increased stroke severity at admission in COVID-19 associated stroke patients compared with the non-COVID-19 cohort and with the broad multi-system complications of COVID-19.

All these factors make it very complex to define the best IS therapy for these patients, both in the acute phase (IVT, EVT, or both) and in secondary prevention, with the need to treat the vascular complications of other organs with anti-thrombotic therapy.

Also, in the treatments described (**Table 1**, **Supplementary Table 1**), the outcome in terms of the recanalization of the previously occluded vessel is reported only occasionally, even more rarely the final outcome in terms of final brain parenchymal damage and functional outcome (e.g., modified Rankin scale). It is therefore not possible at the moment to make considerations that go beyond the individual case on this point.

Intracranial Hemorrhage

In general, there are insufficient data to be able to make etiopathogenetic hypotheses on intracranial bleeding, given the small number of cases described, the presence of an increased risk of bleeding related to the need for antithrombotic therapy (mainly anticoagulant treatment), and the different characterization of SAH and ICH. As already described for some subtypes of IS, it is possible to postulate that COVID-19 infection may in some cases have acted as a contributing cause or trigger, for example, in patients with SAH due to dissecting aneurysms, as known for endocarditis (149), but in general, the infectious hypothesis of aneurysm rupture was rejected several years ago (150). The systemic characteristics of the disease and the DIC type of multiorgan involvement pattern could, in some of the reported cases, have a close causal relationship with ICH.

Cerebral Venous Sinus Thrombosis

In CVST patients, the infectious trigger and hypercoagulability are well-known causal links. Hypercoagulability is a known complication of COVID-19 (125). Indeed, it has already been reported that COVID-19 infection may predispose patients to thrombotic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis (151). Moreover, there is also a growing understanding that antiphospholipid antibodies (anticardiolipin IgA and anti-β2-glycoprotein I IgA and IgG) may play a role in both arterial and venous infarcts in COVID-19 patients (123). Most likely, through a multifactorial process, the virus could lead to a hypercoagulable state that is responsible, at least in part, for both respiratory and cerebral involvement (152).

Limitations

This analysis has limitations, deriving primarily from the possibility that cerebrovascular events in patients with COVID-19 are underreported, especially in patients in critical clinical conditions but also in asymptomatic or paucisymptomatic patients presenting mild stroke-related symptoms and not evaluated by a neurologist. Another consideration is that many patients are expected to have remained undiagnosed because they did not have access to hospital facilities during the period of greatest pandemic burden (153).

Furthermore, the data extracted from the cases reported in the literature are often incomplete and very heterogeneous, which further limits the strength of the results of the analysis. In particular, detailed information on the diagnostic path and the treatment carried out, as well as on the evolution of the cerebrovascular event and COVID-19, are not often available. Even the patient's outcome is not always reported. Even with these limitations, the analysis of the available data shows an image of the daily clinical reality experienced in hospitals during the pandemic. The description of the cases and the reported conclusions are affected by the clear limitation of the quality of the data reported in the literature on the etiological work-up of patients with cerebrovascular events in the context of a global health crisis such as the pandemic in progress. For this reason, the data must be interpreted with caution, and what is described must be confirmed by prospective studies with greater completeness of the collected data, e.g., the European Academy of Neurology planned registry, Ean NEuro-covid ReGistrY (ENERGY) (154).

Other considerations concern the revascularization treatment of patients with IS and COVID-19. Although COVID-19 itself is not a contraindication for thrombolysis or endovascular treatment, usually worse clinical status, the unavailability of resources, and a delayed time window of intervention make these treatments impossible. It has been recently reported in the French national registry of IVT and EVT for stroke that

only 10/1,513 treated patients had biologically proven COVID-19 infection at 7/32 centers (33, 37). In the same registry (41, 45) a significant decrease in patients treated with EVT during the first stages of the COVID pandemic was reported with alarming indicators of lengthened care delays. Similar results, although with a progressive improvement in the treatment's time metrics, have been reported in the New York City series (60).

Perspectives for Stroke Management

Some lessons may be derived from the review of the case series of patients with cerebrovascular and COVID-19 events available in the literature. SARS-CoV-2 has been revealed as the "great imitator" due its variety of clinical presentations. Hence, any acute neurologic symptoms, especially cerebrovascular-related symptoms, must be considered a "potential" COVID-19 syndrome manifestation.

Firstly, we need to consider that the disease burden of cerebrovascular diseases remains even in the COVID-19 pandemic and should be addressed in a timely manner, preserving the stroke code from the extensive changes in disease management pathways seen in several countries (136, 155). Measures of social distancing or lockdown are not reasons to avoid or delay the assessment of suspected stroke patients in emergency departments. There are fewer reports from centers where there was a reduction of patients with stroke diagnosis due possible "fear of becoming infected" in the hospital and an increase in cases outside of the time window for reperfusion therapy (31, 45). These situations increase poor outcomes, disabilities, and long-term impacts on healthcare and social security.

The way stroke care has been affected during the pandemic has made it necessary to highlight the special measures of the "Protected Code Stroke" guidelines (156). These measures include crisis management resources, screening recommendations, and personal protective equipment (PPE). The COVID-19 pandemic addresses a need to go beyond normal code stroke triage, which includes information to help define reperfusion strategies (e.g., time of onset of the symptoms, presence or absence of absolute contraindications), but it now also includes new features: infection control (symptoms and clinical signs initially, as well as minimal laboratory screening) and contact with patients confirmed to have or suspected of having COVID-19.

Concurrent with required neurovascular imaging, chest CT scans add important information to infection control—findings suggestive of COVID-19 are present up to 82% of patients (1)—implicate low risk to patients and teams and add only a small amount of time to examination (e.g., minutes).

The use of PPE during the stroke code is mandatory to teams and patients. If not intubated, a surgical mask must be placed on the patient during transport and evaluations. Concerns regarding team PPE are related to the risk of aerosolization during the procedures. If not present, droplet and contact PPE are sufficient: full-sleeved gown, surgical mask, eye protection, and gloves. However, if there is a risk of aerosolization, equipment must be added to prevent airborne transmission, such as the use of N95 or PFF2 masks and face shields. It is fundamental to correctly evaluate the situation and use the proper PPE, thus avoiding the unnecessary and wasted use of equipment in the context of scarce resources or a lack of protection, if needed, revealing a false sense of security of the team.

Decisions concerning reperfusion therapy were previously discussed, but cleaning protocols must be followed in imaging and angiographic suite rooms. Thus, decontamination of the patient area and the surrounding zone and equipment between procedures may be required by specialized teams to prevent transmission to the next patient and possibly imply a delay of care for other patients (157, 158), especially in low-resource settings where usually only one piece of equipment is available. Another proposed hypothesis is to use tenecteplase instead of alteplase for IVT in some cases to reduce EC spread of COVID-19 (159).

After the decision of reperfusion therapy or conservative treatment, it is reasonable to consider the high risk of contamination of healthcare workers in stroke care units or intensive care units to reduce the exposure of the team to this avoidable risk. Then, we suggest reducing the number of health professionals in close contact with the patient and to eventually increase the intervals between the clinical revaluations after reperfusion therapy, as recommended in standard protocols.

During hospitalization, rehabilitation planning is a key part of after-stroke care. Physical therapy, occupational therapy, and speech therapy should not be withheld, but therapy services must be wisely considered when appropriate and not selected indiscriminately—alternative strategies focusing on self-exercises could increase their effectiveness and empower the patient toward their treatment. Telehealth could also be used by pharmacists, stroke education nurses, and dietary consultants and prevent unnecessary direct contact with patients (160).

Assessing stroke etiology is central to determining the best approach in the secondary prevention of new events. Due to the prothrombotic state, despite low evidence, especially with thrombotic events or high D-dimer levels, screening for lupus anticoagulant and antiphospholipid antibodies could be routinely inserted and could add information for a definition of full-intensity anticoagulation (13, 161).

However, it should be kept in mind that in patients treated in the ED due to the occurrence of stroke symptoms (and not for COVID-19 symptoms), the diagnosis of SARS-CoV-2 infection could be delayed or missed (this was particularly true during the first phases of the outbreak). Indeed, the literature cited in this review are mainly related to previously diagnosed COVID-19 patients who developed acute cerebrovascular diseases and stroke patients in whom the diagnosis of COVID-19 has been made directly in the ED. In contrast, the monitoring of stroke patients in which the diagnosis of SARS-CoV-2 infection has been carried out during the course of hospitalization may be difficult, which also leads to interpretation difficulties (i.e., hospital transmission). These challenges could be responsible for the underestimation of COVID-related strokes. Considering the abovementioned limitations, we decided to focus this review on strokes in COVID-19 patients and not to address the more complex and broad issue of the relationship between stroke and COVID-19 infection.

CONCLUSIONS

Cerebrovascular events are relatively common findings in COVID-19 infection, and they could have a multifactorial etiology. In patients directed to the ED due to the appearance of stroke symptoms (and not for COVID-19 symptoms), the diagnosis of SARS-CoV-2 infection could be delayed or missed (this was particularly true during the first phases of the outbreak). Considering the abovementioned limitations, more accurate and prospective data (such as those currently collected from many ongoing international registries) are needed to better understand the impact of cerebrovascular events in COVID-19 infection.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

DISCLOSURE

FC received personal fees from Zambon outside the submitted work. EM has received honoraria from Abbott, Medtronic, and Newronika for consulting and lecturing; she has received an educational grant from Boston Scientific. All other authors declare no financial disclosures.

AUTHOR CONTRIBUTIONS

PF, CG, and MZ were responsible for writing the manuscript. EM, FC, and MZ were responsible for its drafting. CG, EM, FC, and MZ was responsible for its revision. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.574694/full#supplementary-material

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
2. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. (2020) 95:834–47. doi: 10.1002/ajh.25829
3. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Respir Med*. (2020) 8:738–42. doi: 10.1016/S2213-2600(20)30229-0
4. Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. *Lancet*. (2020) 395:1516. doi: 10.1016/S0140-6736(20)30912-0
5. Estébanez A, Pérez-Santiago L, Silva E, Guillen-Climent S, García-Vázquez A, Ramón MD. Cutaneous manifestations in COVID-19: a new contribution. *J Eur Acad Dermatol Venereol*. (2020) 34:250–1. doi: 10.1111/jdv.16474
6. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. *Gastroenterology*. (2020) 158:1518–9. doi: 10.1053/j.gastro.2020.02.054
7. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
8. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. (2003) 426:450–4. doi: 10.1038/nature02145
9. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. (2004) 203:631–7. doi: 10.1002/path.1570
10. Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. *Eur J Neurol*. (2020) 27:1764–73. doi: 10.1111/ene.14277
11. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. *Front Cell Neurosci*. (2018) 12:386. doi: 10.3389/fncel.2018.00386
12. Vaninov N. In the eye of the COVID-19 cytokine storm. *Nat Rev Immunol*. (2020) 20:277. doi: 10.1038/s41577-020-0305-6
13. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. (2020) 382:e38. doi: 10.1056/NEJMc2007575
14. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. (2020) 383:120–8. doi: 10.1056/NEJMoa2015432
15. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5
16. Hernández-Fernández F, Valencia HS, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. *Brain*. (2020) awaa239. doi: 10.1093/brain/awaa239
17. Mahammedi A, Saba L, Vagal A, Leali M, Rossi A, Gaskill M, et al. Imaging in neurological disease of hospitalized COVID-19 patients: an italian multicenter retrospective observational study. *Radiology*. (2020) 297:E270–3. doi: 10.1148/radiol.2020201933
18. Kremer S, Lersy F, Anheim M, Merdji H, Schenck M, Oesterlé H, et al. Neurologic and neuroimaging findings in COVID-19 patients: a retrospective multicenter study. *Neurology*. (2020) 95:1868–82. doi: 10.1212/WNL.0000000000010112
19. Coolen T, Lolli V, Sadeghi N, Rovai A, Trotta N, Taccone FS, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. *Neurology*. (2020) 95:2016–27. doi: 10.1212/WNL.0000000000010116
20. Hanafi R, Roger PA, Perin B, Kuchcinski G, Deleval N, Dallery F, et al. COVID-19 neurologic complication with CNS vasculitis-like pattern. *Am J Neuroradiol*. (2020) 41:1384–7. doi: 10.3174/ajnr.A6651
21. Vaschetto R, Cena T, Sainaghi PP, Meneghetti G, Bazzano S, Vecchio D, et al. Cerebral nervous system vasculitis in a Covid-19 patient with pneumonia. *J Clin Neurosci*. (2020) 79:71–3. doi: 10.1016/j.jocn.2020.07.032
22. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586
23. González-Pinto T, Luna-Rodríguez A, Moreno-Estébanez A, Agirre-Beitia G, Rodríguez-Antigüedad A, Ruiz-Lopez M. Emergency room neurology in times of COVID-19: malignant ischaemic stroke and SARS-CoV-2 infection. *Eur J Neurol*. (2020) 27:e35–6. doi: 10.1111/ene.14286
24. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. (2020) 382:e60. doi: 10.1056/NEJMc2009787
25. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T, et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *J Neurol Neurosurg Psychiatry*. (2020) 91:846–8. doi: 10.1136/jnnp-2020-323522
26. Moshayedi P, Ryan TE, Mejia LLP, Nour M, Liebeskind DS. Triage of acute ischemic stroke in confirmed COVID-19: large vessel occlusion

associated with coronavirus infection. *Front Neurol*. (2020) 11:353. doi: 10.3389/fneur.2020.00353
27. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain Behav Immun*. (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077
28. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. (2020) 5:279–84. doi: 10.1136/svn-2020-000431
29. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. (2020) 191:9–14. doi: 10.1016/j.thromres.2020.04.024
30. Montalvan V, Toledo JD, Nugent K. Mechanisms of stroke in coronavirus disease 2019. *J Stroke*. (2020) 22:282–3. doi: 10.5853/jos.2020.01802
31. Kim JS. Coronavirus disease 2019 and stroke. *J Stroke*. (2020) 22:157–8. doi: 10.5853/jos.2020.01760
32. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost*. (2020) 120:876–8. doi: 10.1055/s-0040-1709650
33. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
34. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. (2020) 18:844–7. doi: 10.1111/jth.14768
35. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
36. Abdullahi A, Candan SA, Abba MA, Bello AH, Alshehri MA, Afamefuna Victor E, et al. Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. *Front Neurol*. (2020) 11:687. doi: 10.3389/fneur.2020.00687
37. Belani P, Schefflein J, Kihira S, Rigney B, Delman BN, Mahmoudi K, et al. COVID-19 is an independent risk factor for acute ischemic stroke. *Am J Neuroradiol*. (2020) 41:1361–4. doi: 10.3174/ajnr.A6650
38. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology*. (2020) 95:910–20. doi: 10.1212/WNL.0000000000009848
39. Chougar L, Mathon B, Weiss N, Degos V, Shor N. Atypical deep cerebral vein thrombosis with hemorrhagic venous infarction in a patient positive for COVID-19. *Am J Neuroradiol*. (2020) 41:1377–9. doi: 10.3174/ajnr.A6642
40. Dogra S, Jain R, Cao M, Bilaloglu S, Zagzag D, Hochman S, et al. Hemorrhagic stroke and anticoagulation in COVID-19. *J Stroke Cerebrovasc Dis*. (2020) 29:104984. doi: 10.1016/j.jstrokecerebrovasdis.2020.104984
41. Escalard S, Maïer B, Redjem H, Delvoye F, Hébert S, Smajda S, et al. Treatment of acute ischemic stroke due to large vessel occlusion with COVID-19: experience from Paris. *Stroke*. (2020) 51:2540–3. doi: 10.1161/STROKEAHA.120.030574
42. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
43. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet*. (2020) 395:1695–704. doi: 10.1016/S0140-6736(20)31042-4
44. Immovilli P, Terracciano C, Zaino D, Marchesi E, Morelli N, Terlizzi E, et al. Stroke in COVID-19 patients-A case series from Italy. *Int J Stroke*. (2020) 15:701–2. doi: 10.1177/1747493020938294
45. Kerleroux B, Fabacher T, Bricout N, Moïse M, Testud B, Vingadassalom S, et al. Mechanical thrombectomy for acute ischemic stroke amid the COVID-19 outbreak: decreased activity, and increased care delays. *Stroke*. (2020) 51:2012–7. doi: 10.2139/ssrn.3571545
46. Khan M, Ibrahim RH, Siddiqi SA, Kerolos Y, Al-Kaylani MM, AlRukn SA, et al. COVID-19 and acute ischemic stroke - a case series from Dubai, UAE. *Int J Stroke*. (2020) 15:699–700. doi: 10.1177/1747493020938285
47. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMP, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.013
48. Mehrpour M, Shuaib A, Farahani M, Hatamabadi HR, Fatehi Z, Ghaffari M, et al. Coronavirus disease 2019 and stroke in Iran: a case series and effects on stroke admissions. *Int J Stroke*. (2020). doi: 10.1177/1747493020937397. [Epub ahead of print].
49. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis*. (2020). doi: 10.1093/cid/ciaa270. [Epub ahead of print].
50. Piano C, Di Stasio E, Primiano G, Janiri D, Luigetti M, Frisullo G, et al. (2020). An italian neurology outpatient clinic facing SARS-CoV-2 pandemic: data from 2,167 patients. *Front Neurol*. (2020) 11:564. doi: 10.3389/fneur.2020.00564
51. Pinna P, Grewal P, Hall JP, Tavarez T, Dafer RM, Garg R, et al. Neurological manifestations and COVID-19: experiences from a tertiary care center at the Frontline. *J Neurol Sci*. (2020) 415:116969. doi: 10.1016/j.jns.2020.116969
52. Pons-Escoda A, Naval-Baudín P, Majós C, Camins A, Cardona P, Cos M, et al. Neurologic involvement in COVID-19: cause or coincidence? a neuroimaging perspective. *Am J Neuroradiol*. (2020) 41:1365–9. doi: 10.3174/ajnr.A6627
53. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. (2020) 71:762–8. doi: 10.1093/cid/ciaa248
54. Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute cerebrovascular events in hospitalized COVID-19 patients. *Stroke*. (2020) 51:219–22. doi: 10.1161/STROKEAHA.120.030995
55. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. (2020) 46:846–8. doi: 10.1007/s00134-020-05991-x
56. Rudilosso S, Laredo C, Vera V, Vargas M, Renú A, Llull L, et al. Acute stroke care is at risk in the era of COVID-19: experience at a comprehensive stroke center in Barcelona. *Stroke*. (2020) 51:1991–5. doi: 10.1161/STROKEAHA.120.030329
57. Tejada Meza H, Lambea Gil Á, Sancho Saldaña A, Villar Yus C, Pardiñas Barón B, Sagarra Mur D, et al. Ischaemic stroke in the time of coronavirus disease 2019. *Eur J Neurol*. (2020) 27:1788–92. doi: 10.1111/ene.14327
58. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
59. Xiong W, Mu J, Guo J, Lu L, Liu D, Luo J, et al. New onset neurologic events in people with COVID-19 infection in three regions in China. *Neurology*. (2020) 95:1479–87. doi: 10.1212/WNL.0000000000010034
60. Yaeger KA, Fifi JT, Lara-Reyna J, Rossitto C, Ladner T, Yim B, et al. Initial stroke thrombectomy experience in New York city during the COVID-19 pandemic. *Am J Neuroradiol*. (2020) 41:1357–60. doi: 10.3174/ajnr.A6652
61. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. (2020) 8:475–81. doi: 10.1016/S2213-2600(20)30079-5
62. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. (2020) 75:1730–41. doi: 10.1111/all.14238
63. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS2-CoV-2 and stroke in a New York healthcare system. *Stroke*. (2020) 51:e179. doi: 10.1161/STR.0000000000000342
64. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol*. (2020) 267:2185–92. doi: 10.1007/s00415-020-09885-2
65. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thromb Haemost*. (2020) 18:2031–3. doi: 10.1111/jth.14938

66. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. *Stroke*. (2020) 51:124–7. doi: 10.1161/STROKEAHA.120.030153
67. Zayet S, Klopfenstein T, Kovács R, Stancescu S, Hagenkötter B. Acute cerebral stroke with multiple infarctions and COVID-19, France, 2020. *Emerg Infect Dis*. (2020) 26:2258–60. doi: 10.3201/eid2609.201791
68. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg*. (2020) 12:648–53. doi: 10.1136/neurintsurg-2020-016220
69. Lima CFC, Holanda JLB, Pessoa MSL, Coimbra PPA. Acute ischemic stroke in a patient with COVID-19. *Arq Neuropsiquiatr*. (2020) 78:454–5. doi: 10.1590/0004-282x20200057
70. Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular disease in COVID-19. *Am J Neuroradiol*. (2020) 41:1170–2. doi: 10.3174/ajnr.A6588
71. Reddy ST, Garg T, Shah C, Nascimento FA, Imran R, Kan P, et al. Cerebrovascular disease in patients with COVID-19: a review of the literature and case series. *Case Rep Neurol*. (2020) 12:199–209. doi: 10.1159/000508958
72. Sharifi-Razavi A, Karimi N, Zarvani A, Cheraghmakani H, Baghbanian SM. Ischemic stroke associated with novel coronavirus 2019: a report of three cases. *Int J Neurosci*. (2020) 1–5. doi: 10.1080/00207454.2020.1782902
73. Franceschi AM, Arora R, Wilson R, Giliberto L, Libman RB, Castillo M. Neurovascular complications in COVID-19 infection: case series. *Am J Neuroradiol*. (2020) 41:1632–40. doi: 10.3174/ajnr.A6655
74. Gill I, Chan S, Fitzpatrick D. COVID-19-associated pulmonary and cerebral thromboembolic disease. *Radiol Case Rep*. (2020) 15:1242–9. doi: 10.1016/j.radcr.2020.05.034
75. Viguier A, Delamarre L, Duplantier J, Olivot JM, Bonneville F. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. *J Neuroradiol*. (2020) 47:393–4. doi: 10.1016/j.neurad.2020.04.003
76. Sangalli D, Polonia V, Colombo D, Mantero V, Filizzolo M, Scaccabarozzi C, et al. A single-centre experience of intravenous thrombolysis for stroke in COVID-19 patients. *Neurol Sci*. (2020) 41:2325–9. doi: 10.1007/s10072-020-04591-3
77. Sparr SA, Bieri PL. Infarction of the splenium of the corpus callosum in the age of COVID-19: a snapshot in time. *Stroke*. (2020) 51:223–6. doi: 10.1161/STROKEAHA.120.030434
78. Diaz-Segarra N, Edmond A, Kunac A, Yonclas P. COVID-19 ischemic strokes as an emerging rehabilitation population: a case series. *Am J Phys Med Rehabil*. (2020) 99:876–9. doi: 10.1097/PHM.0000000000001532
79. Chen W, Wang J, Cheng W, Li D, Zheng Y, Zhang J, Liu Y. Hidden risk of nosocomial transmission: a presymptomatic novel coronavirus disease-19 (COVID-19) case with ischemic stroke. *J Thorac Dis*. (2020) 12:3442–4. doi: 10.21037/jtd-20-1249
80. Liang JW, Reynolds AS, Reilly K, Lay C, Kellner CP, Shigematsu T, et al. COVID-19 and decompressive hemicraniectomy for acute ischemic stroke. *Stroke*. (2020) 51:215–8. doi: 10.1161/STROKEAHA.120.030804
81. Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI. Unusual microbleeds in brain MRI of Covid-19 patients. *J Neuroimaging*. (2020) 30:593–7. doi: 10.1111/jon.12755
82. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain*. (2020) awaa240. doi: 10.1093/brain/awaa240
83. Saggese CE, Del Bianco C, Di Ruzza MR, Magarelli M, Gandini R, Plocco M. (2020). COVID-19 and stroke: casual or causal role? *Cerebrovasc Dis*. (2020) 49:341–4. doi: 10.1159/000509453
84. Mahboob S, Boppana SH, Rose NB, Beutler BD, Tabaac BJ. Large vessel stroke and COVID-19: case report and literature review. *eNeurologicalSci*. (2020) 20:100250. doi: 10.1016/j.ensci.2020.100250
85. Mohamud AY, Griffith B, Rehman M, Miller D, Chebl A, Patel SC, et al. Intraluminal carotid artery thrombus in COVID-19: another danger of cytokine storm? *Am J Neuroradiol*. (2020) 41:1677–82. doi: 10.3174/ajnr.A6674
86. Gulko E, Gomes W, Ali S, Al-Mufti F, Mehta H. Acute common carotid artery bifurcation thrombus: an emerging pattern of acute strokes in patients with COVID-19? *Am J Neuroradiol*. (2020) 41:65–6. doi: 10.3174/ajnr.A6657
87. Sierra-Hidalgo F, Muñoz-Rivas N, Torres Rubio P, Chao K, Villanova Martínez M, Arranz García P, et al. Large artery ischemic stroke in severe COVID-19. *J Neurol*. (2020) 27:1–3. doi: 10.1007/s00415-020-09967-1
88. Ashrafi F, Zali A, Ommi D, Salari M, Fatemi A, Arab-Ahmadi M, et al. COVID-19-related strokes in adults below 55 years of age: a case series. *Neurol Sci*. (2020) 41:1985–9. doi: 10.1007/s10072-020-04521-3
89. D'Anna L, Kwan J, Brown Z, Halse O, Jamil S, Kalladka D, et al. Characteristics and clinical course of Covid-19 patients admitted with acute stroke. *J Neurol*. (2020) 267:3161–5. doi: 10.1007/s00415-020-10012-4
90. Cavallieri F, Marti A, Fasano A, Salda AD, Ghirarduzzi A, Moratti C, et al. Prothrombotic state induced by COVID-19 infection as trigger for stroke in young patients: a dangerous association. *eNeurologicalSci*. (2020) 20:100247. doi: 10.1016/j.ensci.2020.100247
91. Guillan M, Villacieros-Alvarez J, Bellido S, Peremarch CPJ, Suarez-Vega VM, Aragones-Garcia M, et al. Unusual simultaneous cerebral infarcts in multiple arterial territories in a COVID-19 patient. *Thromb Res*. (2020) 193:107–9. doi: 10.1016/j.thromres.2020.06.015
92. Duroi I, Van Durme F, Bruyns T, Louage S, Heyse A. Fatal ischaemic stroke during COVID-19 and acute lung injury. *Eur J Case Rep Intern Med*. (2020) 7:001732. doi: 10.12890/2020_001732
93. Doo FX, Kassim G, Lefton DR, Patterson S, Pham H, Belani P. Rare presentations of COVID-19: PRES-like leukoencephalopathy and carotid thrombosis. *Clin Imaging*. (2020) 69:94–101. doi: 10.1016/j.clinimag.2020.07.007
94. Kariyanna PT, Chandrakumar HP, Jayarangaiah A, Khan A, Vulkanov V, Ashamalla M, et al. Apical Takotsubo cardiomyopathy in a COVID-19 patient presenting with stroke: a case report and pathophysiologic insights. *Am J Med Case Rep*. (2020) 8:350–7. doi: 10.12691/ajmcr-8-10-8
95. Williams OH, Mohideen S, Sen A, Martinovic O, Hart J, Brex PA, et al. Multiple internal border zone infarcts in a patient with COVID-19 and CADASIL. *J Neurol Sci*. (2020) 416:116980. doi: 10.1016/j.jns.2020.116980
96. Zhou B, She J, Wang Y, Ma X. A case of coronavirus disease 2019 with concomitant acute cerebral infarction and deep vein thrombosis. *Front Neurol*. (2020) 11:296. doi: 10.3389/fneur.2020.00296
97. TunÇ A, ÜnlÜbaS Y, Alemdar M, AkyÜz E. Coexistence of COVID-19 and acute ischemic stroke report of four cases. *J Clin Neurosci*. (2020) 77:227–9. doi: 10.1016/j.jocn.2020.05.018
98. Morjaria JB, Omar F, Polosa R, Gulli G, Dalal PU, Kaul S. Bilateral lower limb weakness: a cerebrovascular consequence of covid-19 or a complication associated with it? *Intern Emerg Med*. (2020) 15:901–5. doi: 10.1007/s11739-020-02418-9
99. Gunasekaran K, Amoah K, Rajasurya V, Buscher MG. Stroke in a young COVID−19 patient. *QJM*. (2020) 113:573–4. doi: 10.1093/qjmed/hcaa177
100. Deliwala S, Abdulhamid S, Abusalih MF, Al-Qasmi MM, Bachuwa G. Encephalopathy as the sentinel sign of a cortical stroke in a patient infected with coronavirus disease-19 (COVID-19). *Cureus*. (2020) 12:e8121. doi: 10.7759/cureus.8121
101. Salahuddin H, Castonguay AC, Zaidi SF, Burgess R, Jadhav AP, Jumaa MA. Interventional stroke care in the era of COVID-19. *Front Neurol*. (2020) 11:468. doi: 10.3389/fneur.2020.00468
102. Zhai P, Ding Y, Li Y. The impact of COVID-19 on ischemic stroke. *Diagn Pathol*. (2020) 15:78. doi: 10.1186/s13000-020-00994-0
103. Co COC, Yu JRT, Laxamana LC, David-Ona DIA. Intravenous thrombolysis for stroke in a COVID-19 positive filipino patient, a case report. *J Clin Neurosci*. (2020) 77:234–6. doi: 10.1016/j.jocn.2020.05.006
104. Rudilosso S, Esteller D, Urra X, Chamorro Á. Thalamic perforating artery stroke on computed tomography perfusion in a patient with coronavirus disease 2019. *J Stroke Cerebrovasc Dis*. (2020) 29:104974. doi: 10.1016/j.jstrokecerebrovasdis.2020.104974
105. Papi C, Spagni G, Alexandre A, Calabresi P, Della Marca G, Broccolini A. Unprotected stroke management in an undiagnosed case of Severe Acute Respiratory Syndrome Coronavirus 2 infection. *J Stroke Cerebrovasc Dis*. (2020) 29:104981. doi: 10.1016/j.jstrokecerebrovasdis.2020.104981
106. Yeboah K, Edgell R, Conway J, Alshekhlee A. Interventional stroke management in a COVID-19 patient. *Neurol Clin Pract*. (2020). doi: 10.1212/CPJ.0000000000000884
107. Radmanesh A, Raz E, Zan E, Derman A, Kaminetzky M. (2020). Brain imaging use and findings in COVID-19: a single academic center experience

in the epicenter of disease in the United States. *Am J Neuroradiol*. (2020) 41:1179–83. doi: 10.3174/ajnr.A6610
108. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? *New Microbes New Infect*. (2020) 35:100669. doi: 10.1016/j.nmni.2020.100669
109. Zulfiqar AA, Lorenzo-Villalba N, Hassler P, Andrès E. Immune thrombocytopenic purpura in a patient with Covid-19. *N Engl J Med*. (2020) 382:e43. doi: 10.1056/NEJMc2010472
110. Hussain A, Roberts N, Oo A. Prosthetic aortic valve endocarditis complicated by COVID-19 and hemorrhage. *J Card Surg*. (2020) 35:1348–50. doi: 10.1111/jocs.14643
111. Muhammad S, Petridis A, Cornelius JF, Hänggi D. Letter to editor: severe brain haemorrhage and concomitant COVID-19 infection: a neurovascular complication of COVID-19. *Brain Behav Immun*. (2020) 87:150–1. doi: 10.1016/j.bbi.2020.05.015
112. Vu D, Ruggiero M, Choi WS, Masri D, Flyer M, Shyknevsky I, Stein EG. Three unsuspected CT diagnoses of COVID-19. *Emerg Radiol*. (2020) 27:229–32. doi: 10.1007/s10140-020-01775-4
113. Carroll E, Lewis A. Catastrophic intracranial hemorrhage in two critically ill patients with COVID-19. *Neurocrit Care*. (2020) 1–5. doi: 10.1007/s12028-020-00993-5
114. Krett JD, Jewett GAE, Elton-Lacasse C, Fonseca K, Hahn C, Au S, et al. Hemorrhagic encephalopathy associated with COVID-19. *J Neuroimmunol*. (2020) 346:577326. doi: 10.1016/j.jneuroim.2020.577326
115. Al-Olama M, Rashid A, Garozzo D. COVID-19-associated meningoencephalitis complicated with intracranial hemorrhage: a case report. *Acta Neurochir*. (2020) 162:1495–9. doi: 10.1007/s00701-020-04402-w
116. Rustemi O, Raneri F, Iannucci G, Volpin L, Segna A. Aneurysmal subarachnoid hemorrhage in a SARS-CoV-2 positive testing: casual or causal? *Br J Neurosurg*. (2020). doi: 10.1080/02688697.2020.1787343. [Epub ahead of print].
117. Agarwal A, Vishnu VY, Vibha D, Bhatia R, Gupta A, Das A, et al. Intracerebral hemorrhage and SARS-CoV-2: association or causation. *Ann Indian Acad Neurol*. (2020) 23:261–4. doi: 10.4103/aian.AIAN_362_20
118. Kim C, Kwak Y, Hwang J, Eun MY. Spontaneous intracerebral hemorrhage in a patient with asymptomatic 2019 novel coronavirus disease. *J Clin Neurol*. (2020) 16:515–7. doi: 10.3988/jcn.2020.16.3.515
119. Ghani MU, Kumar M, Ghani U, Sonia F, Abbas SA. Intracranial hemorrhage complicating anticoagulant prophylactic therapy in three hospitalized COVID-19 patients. *J Neurovirol*. (2020) 26:602–4. doi: 10.1007/s13365-020-00869-6
120. Wee NK, Fan EB, Lee KCH, Chia YW, Lim TCC. CT fluid-blood levels in COVID-19 intracranial hemorrhage. *Am J Neuroradiol*. (2020) 41:76–7. doi: 10.3174/ajnr.A6672
121. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: clinical characteristics from a case series. *Brain Behav Immun*. (2020) 88:940–4. doi: 10.1016/j.bbi.2020.06.005
122. Hughes C, Nichols T, Pike M, Subbe C, Elghenzai S. Cerebral venous sinus thrombosis as a presentation of COVID-19. *Eur J Case Rep Intern Med*. (2020) 7:001691. doi: 10.12890/2020_001691
123. Cavalcanti DD, Raz E, Shapiro M, Dehkharghani S, Yaghi S, Lillemoe K, et al. Cerebral venous thrombosis associated with COVID-19. *Am J Neuroradiol*. (2020) 41:1370–6. doi: 10.3174/ajnr.A6644
124. Poillon G, Obadia M, Perrin M, Savatovsky J, Lecler A. Cerebral venous thrombosis associated with COVID-19 infection: causality or coincidence? *J Neuroradiol*. (2020). doi: 10.1016/j.neurad.2020.05.003
125. Klein DE, Libman R, Kirsch C, Arora R. Cerebral venous thrombosis: atypical presentation of COVID-19 in the young. *J Stroke Cerebrovasc Dis*. (2020) 29:104989. doi: 10.1016/j.jstrokecerebrovasdis.2020.104989
126. Garaci F, Di Giuliano F, Picchi E, Da Ros V, Floris R. Venous cerebral thrombosis in COVID-19 patient. *J Neurol Sci*. (2020) 414:116871. doi: 10.1016/j.jns.2020.116871
127. Roy-Gash F, Marine M, Jean-Michel D, Herve V, Raphael B, Nicolas E. COVID-19-associated acute cerebral venous thrombosis: clinical, CT, MRI and EEG features. *Crit Care*. (2020) 24:419. doi: 10.1186/s13054-020-03225-6
128. Baudar C, Duprez T, Kassab A, Miller N, Rutgers MP. COVID-19 as triggering co-factor for cortical cerebral venous thrombosis? *J Neuroradiol*. (2020). doi: 10.1016/j.neurad.2020.06.008
129. Rigamonti A, Mantero V, Piamarta F, Spena G, Salmaggi A. Cerebral venous thrombosis associated with coronavirus infection: an underestimated entity? *Neurol Sci*. (2020) 1–2. doi: 10.1007/s10072-020-04539-7. [Epub ahead of print].
130. Hemasian H, Ansari B. First case of Covid-19 presented with cerebral venous thrombosis: a rare and dreaded case. *Rev Neurol*. (2020) 176:521–3. doi: 10.1016/j.neurol.2020.04.013
131. Grau AJ, Urbanek C, Palm F. Common infections and the risk of stroke. *Nat Rev Neurol*. (2010) 6:681–94. doi: 10.1038/nrneurol.2010.163
132. Miller EC, Elkind MS. Infection and stroke: an update on recent progress. *Curr Neurol Neurosci Rep*. (2016) 16:2. doi: 10.1007/s11910-015-0602-9
133. Paganini-Hill A, Lozano E, Fischberg G, Perez Barreto M, Rajamani K, Ameriso SF, et al. Infection and risk of ischemic stroke: differences among stroke subtypes. *Stroke*. (2003) 34:452–7. doi: 10.1161/01.STR.0000053451.28410.98
134. Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MSV. Influenza-like illness as a trigger for ischemic stroke. *Ann Clin Transl Neurol*. (2018) 5:456–63. doi: 10.1002/acn3.545
135. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol*. (2020) e202730. doi: 10.1001/jamaneurol.2020.2730
136. Zedde M, Pezzella FR, Paciaroni M, Corea F, Reale N, Toni D, et al. Stroke care in Italy: an overview of strategies to manage acute stroke in COVID-19 time. *Eur Stroke J*. (2020) 5:222–9. doi: 10.1177/2396987320942622
137. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, et al. Accuracy of prediction instruments for diagnosing large vessel occlusion in individuals with suspected stroke: a systematic review for the 2018 guidelines for the early management of patients with acute ischemic stroke. *Stroke*. (2018) 49:111–22. doi: 10.1161/STR.0000000000000160
138. Singh RJ, Chakraborty D, Dey S, Ganesh A, Al Sultan AS, Eesa M, et al. Intraluminal thrombi in the cervico-cephalic arteries. *Stroke*. (2019) 50:357–64. doi: 10.1161/STROKEAHA.118.023015
139. Lax SF, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med*. (2020) 173:350–61. doi: 10.7326/M20-2566
140. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, et al. Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. *Circulation*. (2020) 142:184–6. doi: 10.1161/CIRCULATIONAHA.120.047430
141. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. (2020) 18:1421–4. doi: 10.1111/jth.14830
142. Sebastian S, Stein LK, Dhamoon MS. Infection as a stroke trigger. *Stroke*. (2019) 50:2216–8. doi: 10.1161/STROKEAHA.119.025872
143. Tang N, Pan Y, Xu C, Li D. Characteristics of emergency patients with markedly elevated D-dimer levels. *Sci Rep*. (2020) 10:7784. doi: 10.1038/s41598-020-64853-0
144. Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. *J Thromb Thrombolysis*. (2020) 50:548–57. doi: 10.1007/s11239-020-02171-y
145. Grau AJ, Buggle F. A systemic review of the risk factors for cervical artery dissection. *Stroke*. (2005) 36:2340; author reply. doi: 10.1161/01.STR.0000185695.67188.f7
146. Guillon B, Berthet K, Benslamia L, Bertrand M, Bousser MG, Tzourio C. Infection and the risk of spontaneous cervical artery dissection: a case-control study. *Stroke*. (2003) 34:79–81. doi: 10.1161/01.STR.0000078309.56307.5C
147. Pfefferkorn T, Saam T, Rominger A, Habs M, Gerdes LA, Schmidt C, et al. Vessel wall inflammation in spontaneous cervical artery dissection: a prospective, observational positron emission tomography, computed

tomography, and magnetic resonance imaging study. *Stroke*. (2011) 42:1563–8. doi: 10.1161/STROKEAHA.110.599548

148. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, et al. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: the global COVID-19 stroke registry. *Stroke*. (2020) 51:254–8. doi: 10.1161/STROKEAHA.120.031208
149. Chukwudelunzu FE, Brown RD, Wijdicks EF, Steckelberg JM. Subarachnoid haemorrhage associated with infectious endocarditis: case report and literature review. *Eur J Neurol*. (2002) 9:423–7. doi: 10.1046/j.1468-1331.2002.00432.x
150. Timmons TA, Donnan GA, Whisnant JP, Shelley CD, Smith TF. Aneurysmal subarachnoid hemorrhage and viral infection. Lack of association. *Arch Neurol*. (1986) 43:376–8. doi: 10.1001/archneur.1986.00520040056019
151. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. (2020) 75:2950–73. doi: 10.1016/j.jacc.2020.04.031
152. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol*. (2020) 2:437–45. doi: 10.1016/S2665-9913(20)30121-1
153. Jasne AS, Chojecka P, Maran I, Mageid R, Eldokmak M, Zhang Q, et al. Stroke code presentations, interventions, and outcomes before and during the COVID-19 pandemic. *Stroke*. (2020) 51:2664–73. doi: 10.1161/STR.0000000000000347
154. European Academy of Neurology. *Ean NEuro-covid ReGistrY (ENERGY)*. (2020). Available online at: http://www.ern-rnd.eu/ean-sets-up-the-ean-neuro-covid-registry-energy (accessed August 2, 2020).
155. Aguiar de Sousa D, van der Worp HB, Caso V, Cordonnier C, Strbian D, Ntaios G, et al. Maintaining stroke care in Europe during the COVID-19 pandemic: results from an international survey of stroke professionals and practice recommendations from the European Stroke Organisation. *Eur Stroke J*. (2020) 5:230–6. doi: 10.1177/2396987320933746
156. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) pandemic. *Stroke*. (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.029838
157. Qureshi AI, Abd-Allah F, Alsenani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. *Int J Stroke*. (2020) 15:540–54. doi: 10.1177/1747493020923234
158. Welt FGP, Shah PB, Aronow HD, Bortnick AE, Henry TD, Sherwood MW, et al. Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from the ACC's Interventional Council and SCAI. *J Am Coll Cardiol*. (2020) 75:2372–5. doi: 10.1016/j.jacc.2020.03.021
159. Warach SJ, Saver JL. Stroke thrombolysis with tenecteplase to reduce emergency department spread of coronavirus disease 2019 and shortages of alteplase. *JAMA Neurol*. (2020) 77:1203–4. doi: 10.1001/jamaneurol.2020.2396
160. Dafer RM, Osteraas ND, Biller J. Acute stroke care in the coronavirus disease 2019 pandemic. *J Stroke Cerebrovasc Dis*. (2020) 29:104881. doi: 10.1016/j.jstrokecerebrovasdis.2020.104881
161. Aubignat M, Godefroy O. COVID-19 and ischemic stroke: should we systematically look for lupus anticoagulant and antiphospholipid antibodies? *Rev Neurol*. (2020) 176:505–6. doi: 10.1016/j.neurol.2020.05.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 09 November 2020
doi: 10.3389/fneur.2020.593520

Insights Into Neuroimaging Findings of Patients With Coronavirus Disease 2019 Presenting With Neurological Manifestations

Boran Chen[1,2†], Chaoyue Chen[1,3,4†], Junkai Zheng[1,2], Ruoyu Li[2] and Jianguo Xu[1]*

[1] Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China, [2] West China School of Medicine, Sichuan University, Chengdu, China, [3] State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [4] Collaborative Innovation Center for Biotherapy, Chengdu, China

Objective: This mini review aims to provide insight into the neurological imaging in patients with coronavirus disease 2019 (COVID-19).

Methods: PubMed, Embase, and Web of Science were searched through July 21, 2020, for relevant studies reporting the neuroimaging findings in COVID-19 patients with neurological manifestations. Proportion estimates with a 95% confidence interval (CI) were pooled after the Freeman–Tukey transformation. The heterogeneity across the included studies was also assessed.

Results: Overall, 11 studies with a total of 659 patients were included. The pooled proportion estimate of abnormal neuroimaging finding in patients who exhibited neurological manifestation and underwent brain CT or MRI was 59% (95% CI, 39–77%). The proportions of acute/subacute ischemic infarction, intracranial hemorrhage, and subcortical or deep white matter abnormalities were 22% (95% CI, 17–28%), 24% (95% CI, 17–30%), and 27% (95% CI, 12–45%), respectively.

Conclusion: This mini review comprehensively detailed neuroimaging findings of patients with COVID-19 and neurological manifestations. Clinicians should be familiar with the neuroimaging patterns to catch the sight of brain abnormalities caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Keywords: COVID-19, SARS-CoV-2, neuroimaging, CT, MRI, ischemic infarction, cerebral hemorrhage, white matter abnormality

OPEN ACCESS

Edited by:
Tomohisa Nezu, Hiroshima University, Japan

Reviewed by:
Tae Jung Kim, Seoul National University Hospital, South Korea
Hiroyuki Naito, Hiroshima City Hiroshima Citizens Hospital, Japan

***Correspondence:**
Jianguo Xu
drjianguoxu@gmail.com

† These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

Received: *10 August 2020*
Accepted: *14 October 2020*
Published: *09 November 2020*

Citation:
Chen B, Chen C, Zheng J, Li R and Xu J (2020) Insights Into Neuroimaging Findings of Patients With Coronavirus Disease 2019 Presenting With Neurological Manifestations. Front. Neurol. 11:593520. doi: 10.3389/fneur.2020.593520

INTRODUCTION

The catastrophic pandemic, coronavirus disease of 2019 (COVID-19), is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). COVID-19 has spread rapidly through countries all over the world, and the number of patients has been rising dramatically. As of October 12, 2020, over 37 million cases have been diagnosed with COVID-19 and over 1 million people have died of this disease (2).

Common symptoms caused by virus infection of the respiratory system such as fever, cough, dyspnea, and fatigue have been demonstrated by previous reports (3, 4). Most patients presented a mild course of disease and resolved without specific treatment. However, involvement

of other systems frequently happened in critically ill patients, especially the central nervous system (5). With improvement of our understanding of SARS-CoV-2, an increasing number of patients with COVID-19 who exhibited neurological manifestations have been reported. In a retrospective observational study from Wuhan, China, 36% of the 214 consecutive patients diagnosed with COVID-19 had neurological manifestations (6). Early evidence showed that muscle injury or myalgia was the most common manifestation of neurological involvement with a prevalence of 19.2%, followed by headache (10.9%), dizziness (8.7%), and nausea (10.9%) (7). Uncommon neurological manifestations included ischemic stroke, intracerebral hemorrhage, myelitis, Guillain–Barré syndrome, Bell's palsy, and rhabdomyolysis (8). Brain computed tomography (CT) and magnetic resonance imaging (MRI) are two commonly used methods and have the potential to show neurological abnormalities associated with COVID-19. Herein, we performed this mini review to provide insight into the neurological imaging in patients with COVID-19.

METHODS

This mini review was conducted and reported based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A comprehensive literature search was processed in PubMed, Embase, and Web of Science through July 21, 2020, with the following search strategy: ((COVID-19[title/abstract]) OR (COVID 19[title/abstract]) OR (SARS-Cov-2[title/abstract])) AND ((brain[title/abstract]) OR (CNS[title/abstract]) OR (central nervous system[title/abstract]) OR (neurologic[title/abstract])). We also identified potential eligible literature by screening the reference list of included studies. Two reviewers performed the literature search independently. Disagreement was arbitrated by a third reviewer.

The inclusion criteria were: (1) reporting neuroimaging findings (e.g., brain CT and MRI findings) of patients who were diagnosed with COVID-19 and had neurological manifestations; (2) documentation of the prevalence of neuroimaging findings. Studies were excluded if meeting any of the following criteria: (1) not accessible in English; (2) patients aged <18 years or >100 years; (3) total sample size of <10; (4) not peer-reviewed article; (5) review, letter, or editorial.

We applied the 11-item scale recommended by the Agency for Healthcare Research and Quality (AHRQ) to assess the quality of included studies, which were included in the quantitative analysis. Each item was scored 1 for "YES" or 0 for "NO" or "UNCLEAR." The quality of each study was graded as good (8–11), moderate (4–7), or bad (0–3).

Data collected were the first author, country, sample size, mean age, number and rate of male, neuroimaging tool, number, and proportion of positive neurological findings, as well as neurological manifestations. Data were extracted by two reviewers independently. Any discrepancy between the two reviewers was judged by a third reviewer.

STATA/SE 15.1 (Stata Corporation, College Station, TX) software was used to perform analyses. Proportion estimates with a 95% confidence interval (CI) were pooled after the Freeman–Tukey transformation (double arcsine formation) to stabilize the variances (9). We used a random-effect model to account for heterogeneity. The heterogeneity among included studies was determined by I^2 test. I^2 above 50% was considered high heterogeneity. $P < 0.05$ was considered statistically significant. Subgroup analysis was conducted by continent and neuroimaging tool to identify further potential sources of heterogeneity. We assessed publication bias by visualization of funnel plot and performing Begg's test and Egger's test (10).

RESULTS

The initial literature search involved a total of 403 records after adding additional records and removing duplicated records, with 11 records included in this mini review. **Figure 1** shows the PRISMA flow diagram of this study.

The characteristics of the included studies are presented in **Table 1**. A total of 659 patients were included in the quantitative analysis. The sample sizes ranged from 19 to 242. The mean/median age of patients in each study ranged from 58.5 to 77 years old. The male rates ranged from 46 to 81%. Most of them were of medium quality. Four studies performed brain CT as the neuroimaging tool (13, 18, 20, 21). All the studies performed MRI except the study by Xiong et al. (21), which only performed brain CT in order to reduce the exposure risk of the staff.

Among the 11 included studies, 415 out of 659 patients had abnormal brain CT or MRI findings. The overall proportion estimate of abnormal neuroimaging finding in patients who exhibited neurological manifestation and underwent brain CT or MRI was 59% (95% CI, 39–77%) with a high level of heterogeneity ($I^2 = 95.15\%$) from 10 studies (**Figure 4A**). One study excluded patients with normal imaging, ischemic infarcts, cerebral venous thrombosis (CVT), or chronic lesions unrelated to the coronavirus disease. However, detailed information of excluded patients was inaccessible except data of 37 patients with white matter abnormalities. As a result, this study was excluded from the pooled analysis of abnormal neuroimaging finding proportion estimate. The funnel plot was visually symmetric, suggesting no significant publication bias (**Figure 2**). Additionally, analyses of Egger's test ($t = -1.03$, $p = 0.335$) and Begg's test ($z = -0.09$, $p = 1.000$) yielded evidence of no significant publication bias. We performed subgroup analysis regarding different continents (Europe, North America, or Asia) and neuroimaging tool (only MRI or used CT). The pooled proportion of abnormal neuroimaging finding was 50% (95% CI, 33–66%), 82% (95% CI, 51–100%), and 32% (95% CI, 18–51%) in Europe, North America, and Asia, respectively (**Figure 3A**). The pooled proportion estimates were 68% (95% CI, 46–86%) among studies that only used MRI as the neuroimaging tool and 46% (95% CI, 11–83%) among studies that used CT (**Figure 3B**). Acute/subacute ischemic infarctions on brain CT/MRI were reported by eight studies (11, 13, 14, 16, 18–21). The pooled proportion estimate was 22% (95% CI, 17–28%) with a low level of heterogeneity ($I^2 = 46.58\%$) (**Figure 4B**). Five studies reported

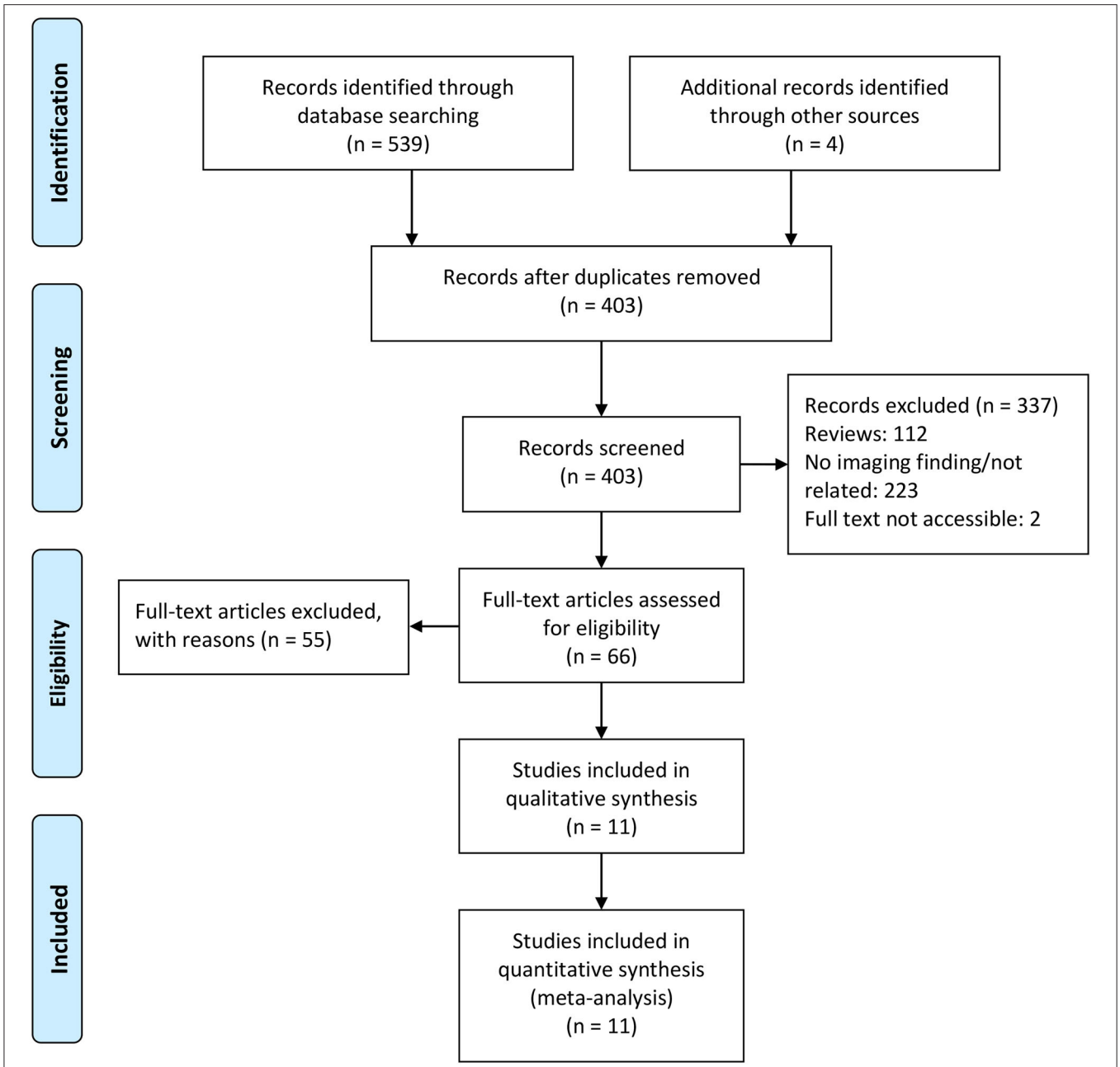


FIGURE 1 | PRISMA flow diagram of literature retrieval.

intracranial micro- or macro-hemorrhage (11–13, 17, 19). Micro-hemorrhages, best visualized by susceptibility weighted imaging (SWI) of MRI, were defined as rounded foci <5 mm in basal ganglia or subcortical white matter that result from rupture of small vessels (19, 22). Correspondingly, macro-hemorrhages were defined as foci larger than 5 mm. The pooled result showed that the proportion of intracranial hemorrhage in patients who underwent brain CT/MRI was 24% (95% CI, 17–30%) with a low level of heterogeneity ($I^2 = 0$) (**Figure 4C**). However, we were unable to perform pooled analysis on micro- and macro-hemorrhage separately due to the inconsistent reporting standards of the included studies. Six studies reported subcortical or deep white matter abnormalities (11, 12, 15, 17, 19, 20). The proportion estimate was 27% (95%CI, 12–45%) with a high level of heterogeneity ($I^2 = 93.84\%$) (**Figure 4D**). Results of quantitative analysis are presented in **Table 2**.

DISCUSSION

In this mini review, we described neuroimaging findings on brain CT/MRI in patients diagnosed with COVID-19. Neuroimaging

TABLE 1 | Characteristics of included studies for quantitative analysis.

References	Quality (score)	Country	Sample (*n*)	Age	Male, *n* (%)	Neuroimaging tool	Positive neuroimaging finding, *n* (%)	Neuroimaging findings, *n* (%)	Neurological manifestation, *n* (%)
Chougar et al. (11)	Medium (7)	France	73	58.5 ± 15.6	48/73 (66)	MRI	43/73 (59)	Ischemic lesion, 17 (23); CVT, 1 (1); micro-hemorrhage, 20 (28); perfusion abnormalities, 22 (48); multifocal white matter lesions, 4 (6); basal ganglion lesion, 4 (6); CLOCC, 3 (4); PRES, 2 (3); hypo-ischemic lesions, 3 (4); central pontine myelinolysis, 3 (4); meningeal enhancement, 2 (5); corticospinal tract FLAIR hyperintensity, 1 (1); neuritis, 2 (3)	Impaired consciousness, 39 (54); focal neurological deficit, 31 (43); seizure, 10 (14)
Collen et al. (12)	Medium (6)	Belgium	19	77 (range 49–94)	14/19 (74)	MRI	8/19 (42)	Hemorrhage, 2 (11); white matter changes, 4 (21); asymmetric olfactory bulbs, 4 (21)	Headache, 2 (10); agitation, confusion, disorientation, 5 (26); seizure, 1 (5)
Giorgianni et al. (13)	Bad (3)	Italy	26	70.6 (range 21–88)	12/26 (46)	CT/MRI	10/26 (38)	Ischemic lesions, 4 (15); hemorrhage, 5 (20); encephalitis, 1 (4)	Coma, 6 (23); confusional state, 4 (15); dizziness, 3 (12); headache, 1 (4); paresis, 6 (23); other, 6 (23)
Helms et al. (14)	Medium (4)	France	58	63[a]	NA	MRI	11/13 (84.6)	Cerebral ischemic stroke, 3 (23); leptomeningeal enhancement, 8 (62)	Agitation, 40 (69); corticospinal tract signs, 39 (67); dysexecutive syndrome, 14 (36)
Kandemirli et al. (15)	Medium (5)	The United States	27	63 (range 34–87)	21/27 (78)	MRI	12/27 (44)	Cortical FLAIR abnormality, 10 (37); white matter abnormality, 3 (11)	NA
Kremer et al. (16)	Medium (7)	France	64	65 (range 20–92)	43/64 (67)	MRI	36/64 (56)	Ischemic lesions, 17 (27); leptomeningeal enhancement, 11 (17); encephalitis, 8 (13)	Headache, 10 (16); seizure, 1 (2); anosmia, 2 (3); ageusia, 4 (6); corticospinal tract signs, 20 (31); impaired consciousness, 25 (39); confusion, 34 (53); agitation, 20 (31)
Kremer et al. (17)	Medium (6)	France	37	61 ± 12	30/37 (81)	MRI	37/37 (100)	Micro-hemorrhage, 9 (24); white matter abnormality, 37 (100)	Impaired consciousness, 27 (73); wakefulness after sedation, 15 (41); confusion, 12 (32); agitation, 7 (19); headache, 4 (11); seizure, 5 (14)
Pons-Escoda et al. (18)	Medium (4)	Spain	103	74 (50.2–90)[b]	63/103 (61)	CT/MRI	26/103 (25)	Ischemic lesions, 13 (13); hematoma, 8 (8); aneurysm, 3 (3); metastasis, 2 (2)	Headache, impaired consciousness, dysarthria, gait abnormality, 40 (39); stroke/TIA, 25 (24); traumatic brain injury, 17 (17); focal symptoms, 11 (11); post-sedation encephalopathy, 5 (5); seizure, 3 (3)

(Continued)

TABLE 1 | Continued

References	Quality (score)	Country	Sample (*n*)	Age	Male, *n* (%)	Neuroimaging tool	Positive neuroimaging finding, *n* (%)	Neuroimaging findings, *n* (%)	Neurological manifestation, *n* (%)
Radmanesh et al. (19)	Medium (5)	The United States	27	NA	NA	MRI	27/27 (100)	Ischemic lesions, 11 (41); micro-hemorrhage, 9 (33); white matter abnormality, 10 (37)	Persistently depressed mental status, 27 (100)
Radmanesh et al. (20)	Medium (6)	The United States	242	68.7 ± 16.5	150/242 (62)	CT/MRI	205/242 (85)	Chronic ischemic lesions, 47 (20); acute/subacute ischemic lesions, 13 (5); white matter abnormality, 134 (55); hemorrhage, 11 (5)	Altered mental status, 102 (42); syncope/fall, 79 (33); focal neurological deficit, 30 (12)
Xiong et al. (21)	Medium (5)	China	28	NA	NA	CT	9/28 (32)	Ischemic lesions, 6 (21); others, 3 (11)	Headache, 10 (36); stroke/history of stroke, 8 (29); occipital neuralgia, 1 (4); impaired consciousness, 1 (4); traumatic brain injury, 1 (4); syncope, 1 (4)

RT-PCR, reverse transcriptase-polymerase chain reaction; CT, computed tomography; MRI, magnetic resonance imaging; CVT, cerebral venous thrombosis; CLOCC, cytotoxic lesion of the corpus callosum; PRES, posterior reversible encephalopathy syndrome; FLAIR, fluid attenuated inversion recovery.

[a]*Median age.*

[b]*Fifth to 95th range.*

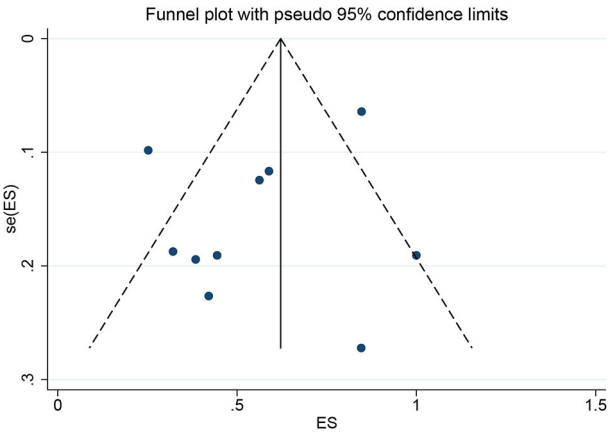


FIGURE 2 | Funnel plot for the proportion of abnormal neuroimaging finding in patients who exhibited neurological manifestation and underwent brain CT or MRI.

patterns were identified from the included studies, and their proportion was estimated. Overall, 59% of COVID-19 patients exhibited neurological manifestations and underwent brain CT or MRI had diverse neuroimaging abnormalities. Notably, about 41% of patients with COVID-19 and available neuroimaging showed normal findings. Part of the explanation was that these patients exhibited nervous system manifestations prior to detectable structural changes.

Neurovascular Event

Ischemic lesions were located in both large and small vessels, such as middle cerebral artery (23–26), anterior cerebral artery (24), posterior inferior cerebellar artery (26, 27), pericallosal artery (28), lenticulostriate artery (26), etc. Anterior circulation artery involvement accounted for 69.2% in acute/subacute infarctions according to an American study (20). The association between large vessel stroke and COVID-19 has been underlined by recent evidence. It was hypothesized that COVID-19-related hypercoagulability could cause thrombosis and embolism, thus leading to large vessel occlusion in light of the high prevalence in the young population and the absence of vessel wall disease (29, 30). However, the mechanism of small vessel occlusion remains unclear and needs further investigation. Small cortical ischemic lesions were revealed by MRI in a COVID-19 patient while neither interstitial lung involvement nor abnormal serum inflammation markers were detected (31). Furthermore, a multicenter retrospective study comparing COVID-19 patients with non-COVID-19 patients from 1 year prior found that infection with COVID-19 was the strongest independent risk factor for stroke, followed by deep vein thrombosis and male sex (32).

Micro-hemorrhages are best visualized by SWI, presenting as hypoattenuating foci. It was reported that intensive care unit (ICU) patients were more likely to experience micro-hemorrhage compared with non-ICU patients (11). De Stefano et al. (33) reported the first case of a critically ill patient

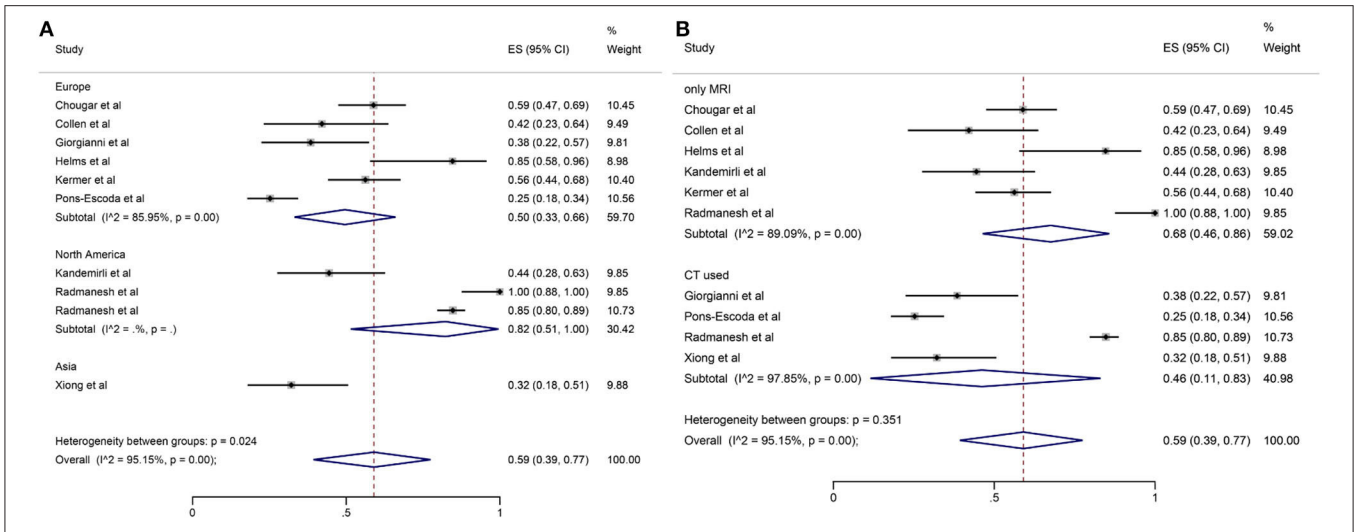


FIGURE 3 | Forest plot for subgroup analysis by **(A)** continent; **(B)** neuroimaging tool regarding the proportion of abnormal neuroimaging finding.

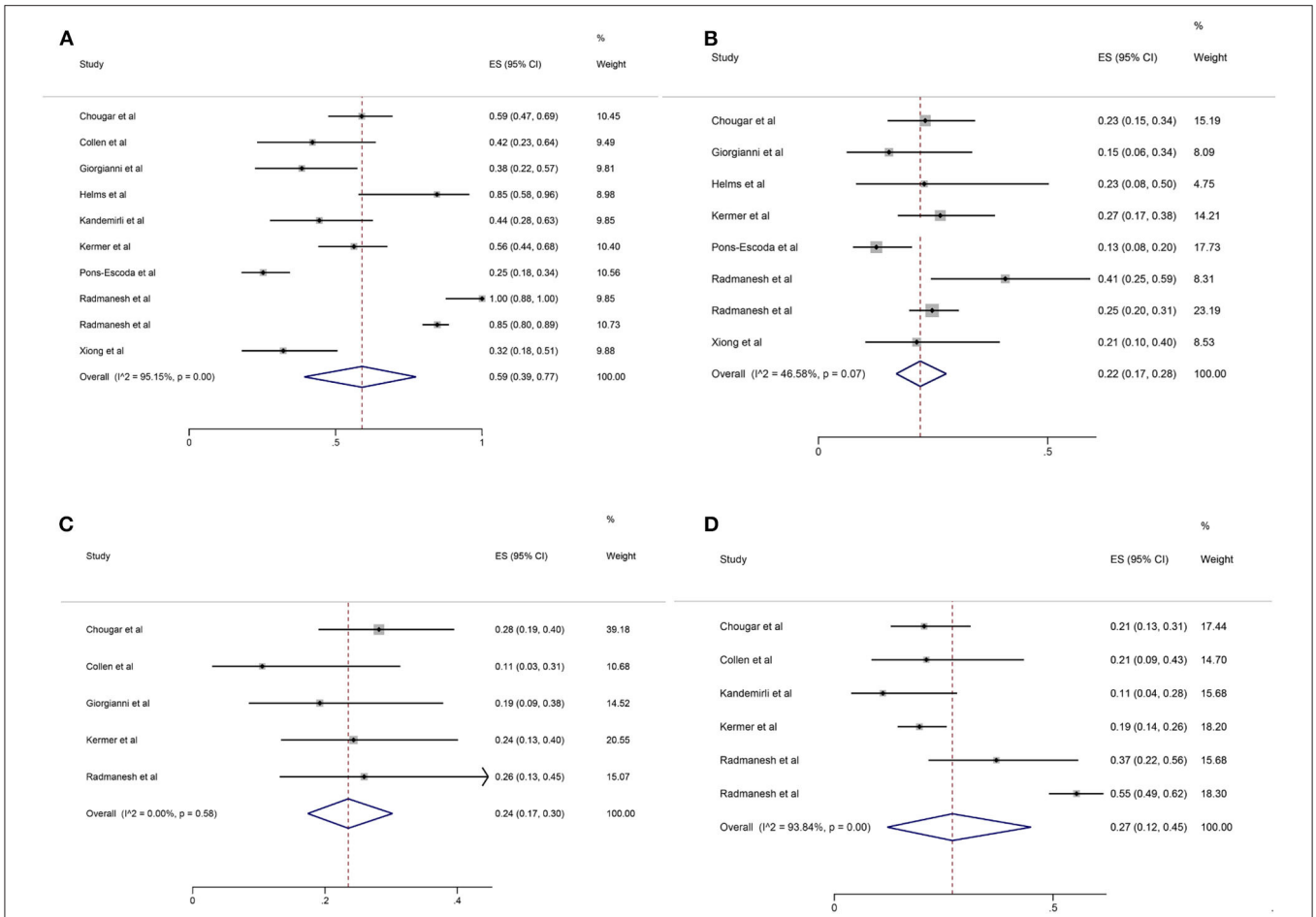


FIGURE 4 | Forest plot for the proportion of **(A)** abnormal neuroimaging finding; **(B)** acute/subacute ischemic infarction; **(C)** intracranial hemorrhage; **(D)** subcortical or deep white matter abnormalities in patients who exhibited neurological manifestation and underwent brain CT or MRI.

TABLE 2 | Summary of quantitative analysis results.

Neuroimaging finding	No. of studies	Proportion	95% CI	I^2(%)[a]	*P*-value[a]
Abnormal finding	10	0.59	0.39-0.77	95.15	<0.01
Acute/subacute ischemic lesion	8	0.22	0.17-0.28	46.58	0.07
Hemorrhage	5	0.24	0.17-0.30	0	0.58
White matter abnormality	6	0.27	0.12-0.45	93.84	<0.01

CI, confidence interval.
[a]*Indexes to evaluate heterogeneity among studies.*

with COVID-19 with massive multifocal parenchymal micro-hemorrhage on SWI while no parenchymal lesion was observed on T1- or T2-weighted imaging. A case series described unusual micro-hemorrhage distribution, which was located in the corpus callosum, internal capsule, and middle cerebellar peduncles, in nine ICU patients (34). Macro-hemorrhage was also reported. In a COVID-19 patient with altered mental status, bilateral ganglia macro-hemorrhages were observed on both CT and MRI, which was absorbed shown by a 7-day follow-up CT (35). As is known, the amount of intracranial hemorrhage has a great effect on the outcome of patients (36). However, no research has explored the effect of number or amount of intracranial hemorrhage in the setting of COVID-19.

White Matter Abnormality

We found that white matter abnormalities was the most frequent neuroimaging pattern in patients with COVID-19 and neurological manifestations, which is consistent with a previous review (37). White matter-specific injuries was presented in a case series of six COVID-19 patients who exhibited an altered mental status (38). MRI revealed FLAIR hyperintensities in bilateral deep white matter in all six patients, corpus callosum in one patient, middle cerebellar peduncles in five patients, and corticospinal tracts in three patients (38). A case series reported four children infected by SARS-Cov-2 with mild respiratory symptoms and neurological symptoms such as encephalopathy and proximal muscle weakness, and the common neuroimaging pattern was hypointensity on CT and hyperintensity with restricted diffusion on T2 MRI in the splenium of the corpus callosum, known as cytotoxic lesion of the corpus callosum (CLOCC), which is a rare but reversible lesion (39). Anzalone et al. (40) reported four COVID-19 cases with minimum involvement in the adjacent subcortical white matter, who presented neurological symptoms of agitation and spatial disorientation. However, MRI findings were predominated by multifocal cortical signal changes in this case series, which was presented as hyperintensities on T2 and FLAIR MRI (40). In summary, white matter abnormalities were presented as confluent hyperintensities on T2/FLAIR of MRI with abnormal restricted diffusion and hypointensities on CT and T1-weighted imaging in subcortical and deep white matter, as well as corpus callosum, middle cerebellar peduncles, and corticospinal tracts, causing non-specific neurological signs.

Other Abnormal Neuroimaging Findings

Other neuroimaging findings included leptomeningeal enhancement, cortical abnormalities, smaller olfactory bulb, and abnormal peripheral nerves. Leptomeningeal enhancement was depicted by post-contrast T1W1 or FLAIR images and better visualized by delayed post-contrast FLAIR (15, 16). Agitation was a frequent neurological symptom for patients with leptomeningeal enhancement (16). Like white matter signal abnormalities, cortical signal abnormalities were presented as increased FLAIR and diffusion-weighted signal (15). Additionally, the distribution of cortical abnormalities was non-specific and could affect all lobes (15). Anosmia is a common neurological symptom of COVID-19 (41). The neuroimaging findings of COVID-19 patients with anosmia involved asymmetric olfactory bulbs on spin echo MRI, hyperintensities inside bilateral olfactory bulbs on T2 MRI with fat suppression and FLAIR, as well as normal MRI images (42–44). Emerging evidence indicates that SARS-CoV-2 can trigger autoimmune neurological diseases such as Guillain–Barré syndrome (45). In a COVID-19 patient with bifacial weakness and paresthesia subtype Guillain–Barré syndrome, abnormal enhancement of oculomotor nerve, abducens nerves, and facial nerves was shown by post-contrast T1 MRI (46).

Association Between Coronavirus Disease 2019 and Abnormal Neuroimaging Findings

Evidence has shown that patients with severe COVID-19 were more likely to have abnormal neuroimaging findings. In a retrospective COVID-19 study, patients with leukoencephalopathy or cerebral micro-hemorrhages had higher peak D-dimer levels and peak international normalized ratio, lower Glasgow Coma Scale and nadir platelet count, longer ventilation time, and hospitalization, more severe acute respiratory distress syndrome, and worse functional status on discharge compared with patients who had normal brain MRI findings (47). When comparing COVID-19 patients with non-COVID-19 patients, increased frequency of in-hospital stroke onset was found in the former cohort (48 vs. 5%) (32). Results of another study revealed that patients with COVID-19-related ischemic stroke had worse functional outcome and higher mortality than patients with ischemic stroke and without COVID-19 (48). However, no study has compared the frequency or outcome of neuroimaging findings other than stroke between COVID-19 and non-COVID-19 patients.

Limitations

This study has several limitations. First, in order to accelerate the process, our initial search was restricted to [Title/Abstract] in consideration of the urgency of this pandemic. It is possible that we have left out some related literature. Nevertheless, we screened the reference list of included studies to identify potential eligible

studies. Second, our quantitative analysis included patients who only underwent brain CT. As a result, the pooled proportion of neuroimaging findings might be underestimated. Third, the studies included in this mini review were retrospective observational studies with an inherent restriction on reliability. Besides, most of the studies included in the quantitative analysis were of medium quality. However, due to the pandemic of COVID-19, high-quality researches are difficult to conduct. Fourth, we were unable to quantify the extent of white matter changes. Further studies reporting quantitative indices such as Fazekas scale are required. Fifth, neuroimaging findings may not be related to COVID-19. Aging is known to have a relationship with structural and functional brain changes. The phenomenon of frequent hyperintensities on MRI in older adults is well-established, especially in white matter (49). This change is usually caused by the loss of myelin sheets and axonal fibers resulting in impaired white matter integrity (50). As mentioned above, mean age of patients in the studies ranged from 58.5 to 77 years old. As a result, we can reckon that a large percentage of the patients included in our analysis were older patients. There is an inevitable question of whether the neuroimaging changes, especially white matter abnormalities, were COVID-19-related or age-related.

CONCLUSION

This mini review comprehensively detailed neuroimaging findings of patients with COVID-19 and neurological manifestations. Although the mechanism of neurological involvement in patients with COVID-19 has not been clearly interpreted, clinicians should be familiar with the neuroimaging patterns to catch the sight of brain abnormalities caused by SARS-CoV-2. Further research investigating the pathophysiology of neurological abnormalities, the association between abnormal neuroimages and clinical outcomes, as well as long-term follow-up of these patients is warranted to better understand the process of neuropathology and to manage patients with neurological changes in the setting of COVID-19.

AUTHOR CONTRIBUTIONS

BC and CC: study concept and design, literature review, data extraction, writing of the initial draft, and final revision. JZ: analysis, interpretation, and writing of the initial draft. RL: analysis and interpretation. JX: supervision. All authors: contributed to the article and approved the submitted version.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
2. WHO. *Coronavirus Disease (COVID-19) Dashboard*. Available online at: https://covid19.who.int/ (accessed October 12, 2020)
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
5. Nath A. Neurologic complications of coronavirus infections. *Neurology.* (2020) 94:809–10. doi: 10.1212/WNL.0000000000009455
6. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
7. Pinzon RT, Wijaya VO, Buana RB, Al Jody A, Nunsio PN. Neurologic characteristics in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Front Neurol.* (2020) 11:565. doi: 10.3389/fneur.2020.00565
8. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, et al. Neurological manifestations of COVID-19: a systematic review. *Crit Care.* (2020) 24:421. doi: 10.1186/s13054-020-03121-z
9. Nyaga VN, Arbyn M, Aerts M. Metaprop: a stata command to perform meta-analysis of binomial data. *Arch Public Health.* (2014) 72:39. doi: 10.1186/2049-3258-72-39
10. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629
11. Chougar L, Shor N, Weiss N, Galanaud D, Leclercq D, Mathon B, et al. Retrospective observational study of brain magnetic resonance imaging findings in patients with acute SARS-CoV-2 infection and neurological manifestations. *Radiology.* (2020) 17:202422. doi: 10.1148/radiol.2020202422
12. Coolen T, Lolli V, Sadeghi N, Rovaï A, Trotta N, Taccone FS, et al. Early postmortem brain MRI findings in COVID-19 non-survivors. *Neurology.* (2020) 95:e2016–27. doi: 10.1212/WNL.0000000000010116
13. Giorgianni A, Vinacci G, Agosti E, Mercuri A, Baruzzi F. Neuroradiological features in COVID-19 patients: First evidence in a complex scenario. *J Neuroradiol.* (2020) 47:474–6. doi: 10.1016/j.neurad.2020.05.005
14. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med.* (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
15. Kandemirli SG, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, et al. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. *Radiology.* (2020) 297:E232–5. doi: 10.1148/radiol.2020201697
16. Kremer S, Lersy F, Anheim M, Merdji H, Schenck M, Oesterlé H, et al. Neurologic and neuroimaging findings in COVID-19 patients: a retrospective multicenter study. *Neurology.* (2020) 95:e1868–82. doi: 10.1212/WNL.0000000000010112
17. Kremer S, Lersy F, de Sèze J, Ferré JC, Maamar A, Carsin-Nicol B, et al. Brain MRI findings in severe COVID-19: a retrospective observational study. *Radiology.* (2020) 16:202222. doi: 10.1148/radiol.2020202222
18. Pons-Escoda A, Naval-Baudín P, Majós C, Camins A, Cardona P, Cos M, et al. Neurologic involvement in COVID-19: cause or coincidence? A neuroimaging perspective. *AJNR Am J Neuroradiol.* (2020) 41:1365–9. doi: 10.3174/ajnr.A6627
19. Radmanesh A, Derman A, Lui YW, Raz E, Loh JP, Hagiwara M, et al. COVID-19 -associated diffuse leukoencephalopathy and microhemorrhages. *Radiology.* (2020) 297:E223–7. doi: 10.1148/radiol.2020202040
20. Radmanesh A, Raz E, Zan E, Derman A, Kaminetzky M. Brain imaging use and findings in COVID-19: a single academic center experience in the epicenter of disease in the United States. *AJNR Am J Neuroradiol.* (2020) 41:1179–83. doi: 10.3174/ajnr.A6610
21. Xiong W, Mu J, Guo J, Lu L, Liu D, Luo J, et al. New onset neurologic events in people with COVID-19 infection in three regions in China. *Neurology.* (2020) 95:e1479–87. doi: 10.1212/WNL.0000000000010034
22. Viswanathan A, Chabriat H. Cerebral microhemorrhage. *Stroke.* (2006) 37:550–55. doi: 10.1161/01.STR.0000199847.96188.12
23. De R, Maity A, Bhattacharya C, Das S, Krishnan P. Licking the lungs, biting the brain: malignant MCA infarct in a patient with COVID 19 infection. *Br J Neurosurg.* (2020). doi: 10.1080/02688697.2020.1769553. [Epub ahead of print].

24. Goldberg MF, Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular disease in COVID-19. *AJNR Am J Neuroradiol.* (2020) 41:1170–2. doi: 10.3174/ajnr.A6588
25. Malentacchi M, Gned D, Angelino V, Demichelis S, Perboni A, Veltri A, et al. Concomitant brain arterial and venous thrombosis in a COVID-19 patient. *Eur J Neurol*. (2020). doi: 10.1111/ene.14380. [Epub ahead of print].
26. TunÇ A, ÜnlÜbaS Y, Alemdar M, AkyÜz E. Coexistence of COVID-19 and acute ischemic stroke report of four cases. *J Clin Neurosci.* (2020) 77:227–9. doi: 10.1016/j.jocn.2020.05.018
27. Mahboob S, Boppana SH, Rose NB, Beutler BD, Tabaac BJ. Large vessel stroke and COVID-19: case report and literature review. *eNeurologicalSci.* (2020) 20:100250. doi: 10.1016/j.ensci.2020.100250
28. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol.* (2020) 267:2185–92. doi: 10.1007/s00415-020-09885-2
29. Fridman S, Bullrich MB, Jimenez-Ruiz A, Costantini P, Shah P, Just C, et al. Stroke risk, phenotypes, and death in COVID-19: systematic review and newly reported cases. *Neurology*. (2020). doi: 10.1212/WNL.0000000000010851. [Epub ahead of print].
30. Viguier A, Delamarre L, Duplantier J, Olivot JM, Bonneville F. Acute ischemic stroke complicating common carotid artery thrombosis during a severe COVID-19 infection. *J Neuroradiol.* (2020) 47:393–4. doi: 10.1016/j.neurad.2020.04.003
31. Frisullo G, Bellavia S, Scala I, Piano C, Morosetti R, Brunetti V, et al. Stroke and COVID19: not only a large-vessel disease. *J Stroke Cerebrovasc Dis.* (2020) 29:105074. doi: 10.1016/j.jstrokecerebrovasdis.2020.105074
32. Katz JM, Libman RB, Wang JJ, Sanelli P, Filippi CG, Gribko M, et al. Cerebrovascular complications of COVID-19. *Stroke.* (2020) 51:e227–e31. doi: 10.1161/STROKEAHA.120.031265
33. De Stefano P, Nencha U, De Stefano L, Mégevand P, Seeck M. Focal EEG changes indicating critical illness associated cerebral microbleeds in a covid-19 patient. *Clin Neurophysiol Pract*. (2020) 5:125–9. doi: 10.1016/j.cnp.2020.05.004
34. Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI. Unusual microbleeds in brain MRI of covid-19 patients. *J Neuroimaging.* (2020) 30:593–7. doi: 10.1111/jon.12755
35. Haddadi K, Ghasemian R, Shafizad M. Basal ganglia involvement and altered mental status: a unique neurological manifestation of coronavirus disease 2019. *Cureus.* (2020) 12:e7869. doi: 10.7759/cureus.7869
36. Roeder SS, Sprügel MI, Sembill JA, Giede-Jeppe A, Macha K, MadŽar D, et al. Influence of the extent of intraventricular hemorrhage on functional outcome and mortality in intracerebral hemorrhage. *Cerebrovasc Dis.* (2019) 47:245–52. doi: 10.1159/000501027
37. Rita Egbert A, Cankurtaran S, Karpiak S. Brain abnormalities in COVID-19 acute/subacute phase: a rapid systematic review. *Brain Behav Immun*. (2020) 89:543–54. doi: 10.1016/j.bbi.2020.07.014
38. Lang M, Buch K, Li MD, Mehan WA Jr., Lang AL, Leslie-Mazwi TM, et al. Leukoencephalopathy associated with severe COVID-19 infection: sequela of hypoxemia? *AJNR Am J Neuroradiol*. (2020) 41:1641–45. doi: 10.3174/ajnr.A6671
39. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol*. (2020). doi: 10.1001/jamaneurol.2020.2687. [Epub ahead of print].
40. Anzalone N, Castellano A, Scotti R, Scandroglio AM, Filippi M, Ciceri F, et al. Multifocal laminar cortical brain lesions: a consistent MRI finding in neuro-COVID-19 patients. *J Neurol.* (2020) 6:1–4. doi: 10.1101/2020.05.19.20103168
41. Al-Sarraj S, Troakes C, Hanley B, Osborn M, Richardson MP, Hotopf M, et al. The spectrum of neuropathology in COVID-19. *Neuropathol Appl Neurobiol*. (2020). doi: 10.1111/nan.12667. [Epub ahead of print].
42. Lee JM, Lee SJ. Olfactory and gustatory dysfunction in a COVID-19 patient with ankylosing spondylitis treated with etanercept: case report. *J Korean Med Sci.* (2020) 35:e201. doi: 10.3346/jkms.2020.35.e201
43. Li CW, Syue LS, Tsai YS, Li MC, Lo CL, Tsai CS, et al. Anosmia and olfactory tract neuropathy in a case of COVID-19. *J Microbiol Immunol Infect*. (2020). doi: 10.1016/j.jmii.2020.05.017. [Epub ahead of print].
44. Politi LS, Salsano E, Grimaldi M. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. *JAMA Neurol*. (2020) 77:1028–9. doi: 10.1001/jamaneurol.2020.2125
45. Dalakas MC. Guillain-barré syndrome: the first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm.* (2020) 7:e781. doi: 10.1212/NXI.0000000000000781
46. Hutchins KL, Jansen JH, Comer AD, Scheer RV, Zahn GS, Capps AE, et al. COVID-19-Associated bifacial weakness with paresthesia subtype of Guillain-Barré syndrome. *AJNR Am J Neuroradiol*. (2020) 41:1707–11. doi: 10.3174/ajnr.A6654
47. Agarwal S, Jain R, Dogra S, Krieger P, Lewis A, Nguyen V, et al. Cerebral microbleeds and leukoencephalopathy in critically Ill patients with COVID-19. *Stroke.* (2020) 51:2649–55. doi: 10.1161/STROKEAHA.120.030940
48. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, et al. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: the global COVID-19 stroke registry. *Stroke.* (2020) 51:e254–58. doi: 10.1161/STROKEAHA.120.031208
49. Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS. Aging of cerebral white matter: a review of MRI findings. *Int J Geriatr Psychiatry.* (2009) 24:109–17. doi: 10.1002/gps.2087
50. Farahibozorg S, Hashemi-Golpayegani SM, Ashburner J. Age- and sex-related variations in the brain white matter fractal dimension throughout adulthood: an MRI study. *Clin Neuroradiol.* (2015) 25:19–32. doi: 10.1007/s00062-013-0273-3

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 10 November 2020
doi: 10.3389/fneur.2020.597881

Investigating the Effects of COVID-19 Quarantine in Migraine: An Observational Cross-Sectional Study From the Italian National Headache Registry (RICe)

*Marianna Delussi[1], Eleonora Gentile[1], Gianluca Coppola[2], Addolorata Maria Pia Prudenzano[3], Innocenzo Rainero[4], Grazia Sances[5], Chiara Abagnale[6], Valeria Caponnetto[7], Francesco De Cesaris[8], Ilaria Frattale[7], Elena Guaschino[5], Andrea Marcinnò[4], Raffaele Ornello[7], Francesca Pistoia[7], Alessia Putortì[5], Maria Elena Roca[3], Fausto Roveta[4], Chiara Lupi[9], Maria Trojano[3], Francesco Pierelli[10], Pierangelo Geppetti[8], Simona Sacco[7] and Marina de Tommaso[1]**

[1] Applied Neurophysiology and Pain Unit, Scienze Mediche di Base, Neuroscienze e Organi di Senso Department, Bari Aldo Moro University, Bari, Italy, [2] Sapienza University of Rome Polo Pontino, Latina, Italy, [3] Headache Center, Amaducci Neurological Clinic, Policlinico General Hospital, Bari, Italy, [4] Department of Neuroscience "Rita Levi Montalcini," Headache Center, University of Torino, Turin, Italy, [5] Headache Science Centre, Istituto di Ricerca a Carattere Scientifico Mondino Foundation, Pavia, Italy, [6] Headache Center, Sapienza Rome University, Latina, Italy, [7] Headache Regional Referral Center, Azienda Sanitaria Locale 1 Abruzzo, L'Aquila University, L'Aquila, Italy, [8] Headache Center, Careggi General Hospital, Firenze, Italy, [9] University of Florence, Florence, Italy, [10] Sapienza University of Rome Polo Pontino, Latina, IRCCS - Neuromed, Pozzilli, Italy

OPEN ACCESS

Edited by:
Jesús Porta-Etessam,
Hospital Clínico San Carlos, Spain

Reviewed by:
Pablo Irimia,
University Clinic of Navarra, Spain
Yohannes W. Woldeamanuel,
Stanford University, United States

***Correspondence:**
Marina de Tommaso
marina.detommaso@uniba.it

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: 22 August 2020
Accepted: 05 October 2020
Published: 10 November 2020

Citation:
Delussi M, Gentile E, Coppola G, Prudenzano AMP, Rainero I, Sances G, Abagnale C, Caponnetto V, De Cesaris F, Frattale I, Guaschino E, Marcinnò A, Ornello R, Pistoia F, Putortì A, Roca ME, Roveta F, Lupi C, Trojano M, Pierelli F, Geppetti P, Sacco S and de Tommaso M (2020) Investigating the Effects of COVID-19 Quarantine in Migraine: An Observational Cross-Sectional Study From the Italian National Headache Registry (RICe). Front. Neurol. 11:597881. doi: 10.3389/fneur.2020.597881

Background: Previous studies during SARS and Ebola pandemics have shown that quarantine is associated with several negative psychological effects, such as post-traumatic stress symptoms, confusion, and anger. These conditions may affect the course of many diseases, including migraine. Although it is possible that the quarantine measures for the current COVID-19 pandemic affect migraine burden, no information is currently available on this issue.

Aim: In this study, we aimed to: (1) explore the possible changes in migraine frequency, severity, and days with acute medication intake during quarantine period; (2) evaluate possible differences in migraine outcomes in consideration of lifestyle changes, emotions, pandemic diffusion, and COVID-19 infection.

Methods: We interviewed patients who were included in the observational Italian Headache Registry (Registro Italiano Cefalee, RICE), retrospectively collecting information on main headache features, lifestyle factors, emotions, individual infection status, and perception of COVID-19 for 2 months before (pre-quarantine) and after the beginning of the quarantine (quarantine). Inclusion criteria were: age > 18, diagnosis of migraine without aura, migraine with aura and chronic migraine, last in-person visit more than 3 months preceding the beginning of quarantine.

Results: A total of 433 migraine subjects agreed to be interviewed. We found an overall reduction in headache frequency (9.42 ± 0.43 days with headache vs. 8.28 ± 0.41) and intensity (6.57 ± 0.19 vs. 6.59 ± 0.21) during the quarantine, compared to pre-quarantine. There was a correlation between improvement and number of days of stay-at-home. When results were stratified for geographic area, we found a tendency

toward worsening of headache frequency in northern Italy. Disgust regarding viral infection corresponded to a minor improvement in migraine.

Conclusions: Migraine patients showed a mild improvement of migraine features, probably attributable to resilient behavior toward pandemic distress. Disgust regarding the contagion whereas potentially favoring defensive behavior, could potentially worsen migraine. The spontaneous limitation of migraine burden during quarantine could favor patient follow-up via the use of telemedicine visits, reliable diaries, and frequent remote contacts.

Keywords: migraine, COVID-19, lockdown, resilience, disgust

INTRODUCTION

COVID-19 (1, 2) was declared a global pandemic on March 11, 2020 by the World Health Organization. Italy, the first European country in which there was an outbreak of the pandemic, currently records a total of ∼185,000 confirmed cases and more than 24,000 patients with severe illness. The spread of COVID-19 in the Italian territory was markedly different, with northern Italy showing a much higher number of cases compared to central and southern Italy. On March 10, the Italian government was the first in Europe to impose severe social-distancing orders. Social-distancing and mitigation strategies (3–5) aim to defer a major flow of patients and reduce the demand for hospital admissions while safeguarding the most vulnerable subjects (6).

Studies related to the 2003 outbreak of severe acute respiratory syndrome (SARS) in China and Canada, as well as the 2014 Ebola outbreak in Africa, reported that quarantine is associated with several negative psychological effects, such as post-traumatic stress symptoms, confusion, and anger (7, 8), with a potential increase in suicidal risk (9). Changes in social behavior and work activities, the unavailability of a public health system for routine medical management, and widespread fear of infection could cause important psychosocial outcomes (10–13), and could dramatically increase the burden of the disease. However, few data have been reported on the impact on migraine caused by psychosocial distress due to COVID-19 and long-term distancing measures.

In this study, we aimed to (1) explore whether the quarantine period affected the frequency and severity of migraine and days with acute medication intake, and (2) evaluate possible differences in migraine outcomes in consideration of changes in lifestyle, emotions, pandemic diffusion, and COVID-19 infection.

METHODS

Study Population and Design

This observational cross-sectional study describes the impact of the COVID-19 pandemic and social distancing measures on headache features in migraine patients. It was conducted via a structured telephone interview in a sample of patients included in the Italian Registry of Headache (Registro Italiano delle Cefalee, RICe), which enrolls patients aged ≥ 18 years who visit headache treatment centers.

RICe is an observational registry promoted and endorsed by the Italian Society for the Study of headaches (SISC), which records clinical data of consecutive patients with headache who refer to the member Headache Centers. The present ancillary sub-study is based on data from seven headache centers in northern (Pavia and Turin), central (Florence and Latina), and southern (Avezzano-L'Aquila, and two centers in Bari) that enrolled patients who had entered the RICe at least 3 months before the start of the quarantine (pre-quarantine) in Italy. The seven centers are located in geographical areas that experienced markedly different impacts of the COVID-19 outbreak: higher in the north, medium central, and lower in southern Italy (2020- http://www.protezionecivile.gov.it/attivita-rischi/rischio-sanitario/emergenze/coronavirus). All the patients admitted to the RICe study were requested to complete a headache diary, reporting the occurrence and intensity of headache (from 1 - mild to 10- the most severe headache), and use of symptomatic drugs. For the present study, the inclusion criteria were age ≥ 18 years, a diagnosis of migraine without aura, migraine with aura and chronic migraine according to the criteria of the International Classification of Headache Disorders, III edition (ICHD-III) (14), and the most recent in-person visit within the 3 months preceding the lockdown period. Exclusion criteria were ascertained comorbidity with other forms of primary headaches, psychiatric disorders according to DSMV, and liver, kidney, and heart insufficiency.

Telephone Interviews and Variables of Interest

Telephone interviews were carried out by study investigators between March 27 and April 18, 2020. The interview was a web-supported questionnaire to be completed during the telephone call. The questionnaire was administered in the Italian language (it is available in Italian and English in the **Supplementary Material**). Variables of interest included frequency of headache expressed as average number of headache days per month, calculated during the 2 months preceding the quarantine (pre-quarantine) and in the time from the beginning of the quarantine (March 8, 2020 for Northern Italy, extended on March 10, 2020 to the rest of Italy). Patients were asked to report the intensity of headache and the use of

Abbreviations: RICe, Registro Italiano Cefalee- Italian Headache Registry; SISC, Società Italiana Studio Cefalee-Italian Society for Headache Study.

symptomatic drugs during the pre-quarantine and quarantine times, according to their headache diaries. Questions included the following: number of days of staying at home, current working conditions, level of risk contacts, individual infection, personal feelings on how COVID-19 affects migraine outcomes and/or migraine as a possible risk factor for COVID-19, fear of becoming infected, possible changes in daily behaviors (food intake habits, alcohol consumption, and sleep quality) as a result of social-distancing measures, main sensations regarding the pandemic emergency (anger, fear, disgust, anxiety, sadness, happiness) on a scale from 0 (no emotion) to 10 (maximum emotion), and subjective evaluation of mood change (worsening, no change, improvement) (see the questionnaire in the **Supplementary Section**). The questionnaire was developed taking into consideration the headache features reported in the diaries. For questions related to the pandemic, we used *ad-hoc* and not previously validated scales on the possible changes of fundamental emotions, psychological reactions, and habits due to pandemic. A similar survey was used on the general Italian population during the current pandemic [(15); https://www.cnr.it/it/news/9363/risultati-dell-osservatorio-sui-mutamenti-sociali-in-atto-covid19-msa-covid19].

Study Outcomes

Study outcomes were headache frequency and intensity and days with acute medication intake during the 8 weeks preceding and during the social-distancing measures. Predictor variables were migraine severity before the quarantine, lifestyle habits, emotions, severity of pandemic diffusion, and COVID-19 infection.

Ethics

The local ethics committees of each recruiting center approved the RICe registry, and patients enrolled signed an informed consent, which included the possibility to perform sub-studies on their headache features.

Statistical Analysis

In the absence of previous similar reports and because of the descriptive nature of the study, the sample size was not calculated. The parametric distribution of the data was evaluated by the Levene test for equality of variance. As the observation period during quarantine varied across subjects, we normalized headache days for the effective period of observation (number of headache days / number of total days of observation $\times$ 30). We used ANOVA for repeated measures with condition before vs. during social distancing as factors. The effect of severity of migraine before quarantine, emotions, living behavior, and geographic area on primary outcomes was evaluated by the same repeated measures ANOVA model, introducing nominal variables as factors and quantitative variables as covariates. A complete factorial ANOVA model type III included in IBM SPSS software version 21 was used.

RESULTS

Demographic Data, Working Status, Living Conditions, and Daily Habits

General

A total of 433 migraine subjects agreed to be interviewed, while 10 patients did not give their consent. The mean interval elapsed between the start of the quarantine and the time of the interview was 31.9 $\pm$ 4.5 days without significant differences across participating centers. The baseline characteristics of the enrolled patients are presented in **Table 1**.

Most of the interviewed patients did not report changes in food intake, sleep, or alcohol consumption (**Table 1**). During quarantine, 177 subjects (55.1%) reported worsening, 42 (13.1%) no change, and 102 (31.8%) improvement in mood. Emotions scores related to pandemic are reported in **Table 1**.

Migraine During Quarantine

A reduction in the average number of days with headache (9.42 $\pm$ 0.43 before quarantine, 8.28 $\pm$ 0.41 during quarantine), days with acute medication intake (10.21 $\pm$ 0.96 before; 10.79 $\pm$ 1.02 during), and migraine intensity (6.57 $\pm$ 0.19 before; 6.59 $\pm$ 0.21 during) was observed during quarantine compared to pre-quarantine (**Table 2**). Most patients subjectively reported that their migraines did not change after the start of quarantine. Most migraine patients did not consider migraine as a facilitating factor for COVID-19 infection (**Supplemental Table 1**). Two hundred eighty-nine patients were taking preventive treatments for migraine; 88 discontinued treatment for different reasons, such as drug failure or difficulty in attaining the drugs (**Supplemental Table 2**).

Effects of Migraine Severity, Lifestyle Habits, Emotions, and Severity of Pandemic Diffusion on Headache Frequency

Before quarantine, 331 patients reported episodic migraine, while the remainder were affected by chronic migraine. Improvements in headache frequency and analgesic consumption were higher in chronic patients than in episodic migraine patients (**Table 2**). Alcohol use, smoking, eating, and subjective perception of sleep quality did not affect headache frequency and intensity, use of symptomatic drugs, and/or working conditions. The improvement of headache frequency correlated with the number of stay-at-home days (ANOVA with repeated measures with days of social distancing as covariate F 37.07 $p < 0.0001$). Changes in headache parameters were similar among patients living in different urban areas and with different levels of education. Migraine features were not significantly different among northern, central and southern Italy before the quarantine period (**Supplemental Table 3**). However, patients in northern Italy, the geographical area with the highest pandemic diffusion, showed a tendency of increased headache frequency and use of acute medication (**Table 3**; **Figure 1**). It should be noted that the number of days of effective stay-at-home was reduced in patients from northern Italy (**Supplemental Table 3**).

There was a significant relationship between disgust against COVID-19 infection and an increase in headache

TABLE 1 | Baseline characteristics of the included subjects.

	***n* = 433**
Gender, *n* (%)	
Female	333 (76.9)
Male	100 (23.1)
Age (years), mean ± SE	43.97 ± 0.63
BMI, mean ± SE	24.1 ± 0.002
Education years, *n* (%)	
0–5	16 (3.7)
6–8	84 (19.4)
9–13	175 (40.4)
>13	158 (36.5)
Days of social distancing, mean ± SE	29.27 ± 0.58
Home place, *n* (%)	
Countryside	76 (17.8)
City	183 (42.3)
Small town	174 (40.2)
No. of cohabiting family members during social distancing, mean ± SE	2.32 ± 0.13
Work, *n* (%)	
Unemployed	208 (48.0)
Employed	225 (52.0)
Employment, *n* (%)	
Work from home	89 (20.6)
At workplace	48 (11.1)
Unemployed (lost position)	88 (20.3)
Food intake, *n* (%)	
Increased	67 (15.5)
Reduced	153 (35.3)
Unchanged	213 (49.2)
Alcohol consumption, *n* (%)	
Reduced	85 (19.6)
Increased	13 (3.0)
Unchanged	344 (79.4)
Sleep quality, *n* (%)	
Improved	157 (36.3)
Worsened	45 (10.4)
Unchanged	229 (52.9)
Emotional reaction, mean ± SE	
Anger	4.15 ± 0.27
Disgust	3.39 ± 0.27
Fear	5.71 ± 0.28
Anxiety	5.86 ± 0.18
Sadness	5.40 ± 0.28
Happiness	4.67 ± 0.23

BMI indicates body mass index.
Intensity of emotions related to the COVID-19 emergency are reported on a 0–10 scale.

frequency (repeated measures ANOVA with disgust as covariate F 6.43 p 0.004).

Patients reporting mood improvement showed a tendency toward reduced headache frequency (repeated measures ANOVA with mood perception as factor: F 5.43 p 0.001). However, the Bonferroni test among the different mood perceptions did not show any significant difference. Patients who subjectively reported a worsening of their migraine showed an objective increase in headache frequency (repeated measures ANOVA with subjective impression of migraine severity as factor: F 35.58 $p < 0.0001$: Bonferroni test: got worse vs. improved $p < 0.01$). However, patients feeling migraine as a facilitating factor for infection showed a tendency toward frequency increase (ANOVA with perception of migraine as risk factor: F 3.59 p 0.012 Bonferroni test: n.s.). Emotions against pandemic and subjective perception of mood and disease severity did not influence the change in headache features in chronic migraine compared to episodic migraine.

COVID-19 Infection in Migraine Samples

In the overall sample, five patients reported having been infected by SARS-CoV-2, two patients were asymptomatic, one had recovered, and two were under treatment for mild pulmonary symptoms that did not require hospitalization (**Table 4**). These patients did not report substantial changes in their migraines after infection.

DISCUSSION

The results of the present study show that migraine patients had a mild improvement of headache frequency, days with acute medication intake, and headache intensity during the social distancing measures. Migraine improvement prevailed in chronic patients in the areas where there was the lowest prevalence of COVID-19, and was positively influenced by the number of days of stay-at-home orders. Disgust toward infection corresponded to an attenuation of headache improvement.

Migraine During Quarantine

The interview was conducted on migraine patients previously enrolled in RICe, which guaranteed the presence of accurate clinical features previously recorded. This represents a point of strength compared to interviews administered to the general population (16). The general improvement of headache frequency and intensity during lockdown confirms results obtained in smaller Italian migraine samples (17). Viral diffusion may contribute to the onset of stress-related disorders (12, 18), which may worsen migraine (19). The development of a resilient behavior associated with COVID-19 (18) may have also involved migraine patients. The American Psychological Association (2014) defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats, or even significant sources of stress." During a pandemic, resilient behavior could reduce psychological distress (20). Although we did not apply a specific questionnaire for resilience, a resilient mechanism could help to improve the main features of migraine, such as frequency in terms of days of headache per month and subjective feelings of its intensity. In fact, resilience ability is generally associated with better outcomes in patients with chronic pain (21).

TABLE 2 | Comparison of headache features before and during lockdown period.

n° 433	Before	During	*F*	*P*-value	EM before n°331	During	CM before n°102	During	*F*	*P*-value
Monthly headache days	9.42 ± 0.43	8.28 ± 0.41	60.6	<0.0001	5.10 ± 0.23	4.99 ± 0.35	21.6 ± 0.39	16.74 ± 0.59	59.6	<0.0001
Acute medication days	8.32 ± 0.51	7.19 ± 0.54	21.7	<0.0001	4.91 ± 0.46	4.2 ± 0.55	16.9 ± 0.78	13.2 ± 0.93	13.76	<0.0001
Headache intensity	6.93 ± 0.10	6.71 ± 0.11	6	0.014	6.79 ± 0.11	6.5 ± 0.12	7.25 ± 0.25	6.95 ± 0.19	0.1	n.s.

CM, Chronic Migraine patients; EM, Episodic Migraine patients. Data are reported as mean ± standard errors.

TABLE 3 | Comparison of headache features before and during lockdown period in the included patients.

	North (*n* = 105)		Center (*n* = 101)		South (*n* = 227)		*F* (geographic area)	*P*-value	*P*-value (Bonferroni)
	Before	During	Before	During	Before	During			
Monthly headache days	10.57 ± 0.81	11.03 ± 0.78	8.19 ± 0.84	6.02 ± 0.80	9.50 ± 0.56	7.78 ± 0.53	6	0.003	<0.001 (South and Center vs. North)
Acute medication days	10.21 ± 0.96	10.79 ± 1.02	7.29 ± 0.98	5.07 ± 1.04	7.46 ± 0.65	5.70 ± 0.69	3.6	0.027	<0.01 (South and Center vs. North)
Headache intensity	6.57 ± 0.19	6.59 ± 0.21	7.25 ± 0.21	7.03 ± 0.22	6.96 ± 0.21	6.50 ± 0.14	3	0.05	NS

Data are reported as mean ± standard errors.

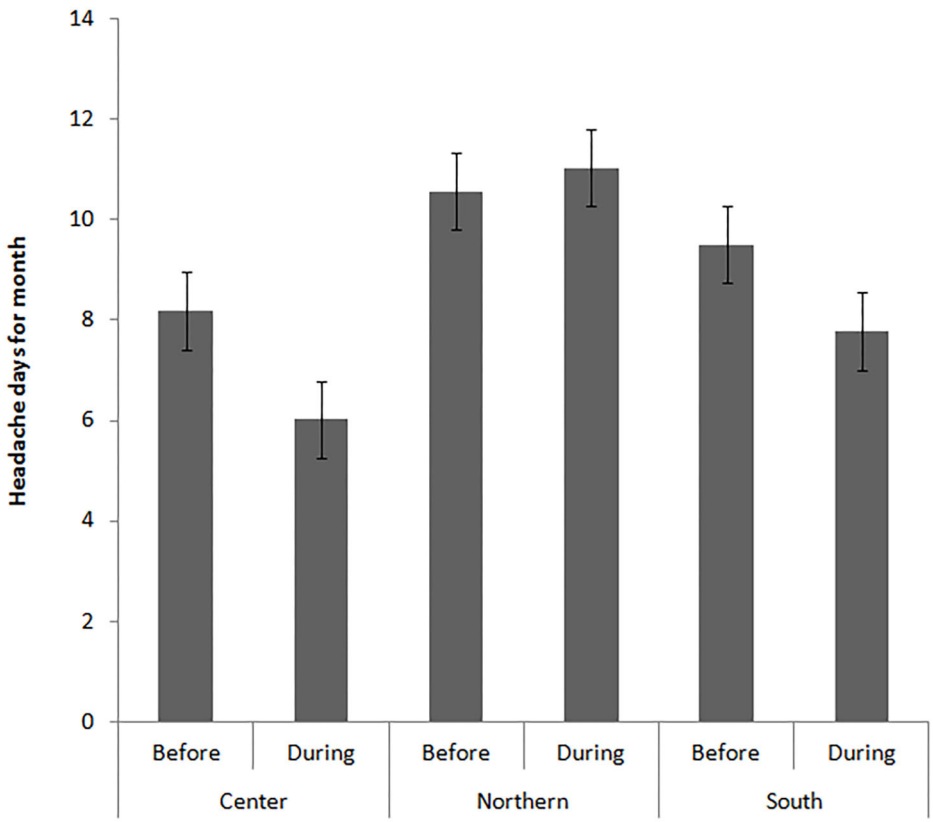


FIGURE 1 | Mean and standard errors of headache frequency, expressed in number of headache days for month, before and during the quarantine in the different Italian geographic areas. Statistical analysis is reported in **Table 3**.

TABLE 4 | Characteristics of migraine patients positive to SARS-CoV-2 infection.

Patient	Age	Sex	Geographic area	Symptomatic	COVID-19 Outcome	Migraine frequency change (%)	Mean intensity change (points)	Change in use of symptomatic drugs (%)
1	22	F	South	No		−18	0.38	−75
2	56	F	North	No		−20	1	0
3	47	F	South	Yes	Under treatment	−20	0.88	0
4	44	F	North	Yes	Recovered	−40	1	−32
5	46	F	North	Yes	Under treatment	−30	0.5	0

Changes refer to quarantine measures compared with the 2 previous months.

Effects of Migraine Severity, Lifestyle Habits, Emotions, and Severity of Pandemic Diffusion on Headache Frequency

In a previous large global cross-sectional study, patients with frequent migraine showed greater resilience in response to negative events, such as treatment failures (22). The present study suggests that mild improvement of migraine, probably attributable to a resilient behavior against the pandemic, could prevail in more severe migraines. Psychological features of migraine patients, underlying a favorable outcome under the current dramatic epidemics, were not recorded in the RICe database upon previous visits, Although this could be subject to further studies in a possible scenario of pandemic persistence (23). A correlation between the emotional impact of the pandemic situation and its effect on migraine features was not found. However, the perception that migraine could facilitate COVID-19 infection, possibly causing additional stress, negatively affected the improvement of headache frequency. The pandemic emergency did not seem to cause particular sleep disruption in our migraine sample, an effect attributable to the resilient reaction.

The improvement of headache severity was correlated with the effective number of days of stay at home (24, 25). The resilient behavior against migraine worsening for pandemic distress could thus be enhanced during effective social distancing. We did not find an association between headache improvement, work activity, and lifestyle habits. Nevertheless, staying at home, even if forced, could globally influence trigger factors and the ability to rest, possibly decreasing the risk of recurrence. Environmental factors could cause physical and psychological distress in normal daily living, which would be attenuated during the quarantine. The usual pace of life for work, exposure to weather changes, car traffic, and travel, are recognized migraine stressors, and these were obviously reduced in this unusual condition (26). This result could be taken into consideration for the social management of public health during pandemics (5).

The headache centers cooperating in data collection see patients coming from different Italian regions, so we considered the place of residence at the time of public restrictive measures. Residents in regions with higher pandemic diffusion seemed to express less resilient behavior. As an adjunctive result, we also observed that patients in northern Italy reported fewer days of social distancing, which were associated with a positive outcome of migraine. We could thus suppose that the severity of pandemic diffusion could change environmental situations and personal habits (15) and exert an influence on resilient behavior.

The expression of disgust was slightly associated with migraine frequency increase. Disgust is an emotional response of rejection or revulsion to something potentially contagious or offensive (27). It is a system that evolved to motivate infectious disease avoidance and combat the behavioral causes of infectious and chronic diseases, such as pandemic flu (28). While it could help in assessing avoidance behavior during pandemic infections, it is a cause of distress (28), which could have a negative impact on migraine frequency and attenuate the resilient reaction.

COVID-19 Infection in Migraine Samples

Although the present study was not designed to assess the frequency of infection in the migraine population, because of the relatively small sample, we did find 5 out of 433 migraine patients positive for SARS-CoV-2 infection (1.15%). At the time we collected data, there were ∼185,000 infected individuals in the general Italian population (0.3%), with a slight prevalence in males (51.7%) and a median age of 62 years (Italian Healthy System and Civil Protection report http://www.protezionecivile.gov.it/attivita-rischi/rischio-sanitario/emergenze/coronavirus). However, the percentage of asymptomatic persons among the general population is an unresolved issue, so the present data do not enable any type of speculation about the prevalence of SARS-CoV-2 infection in migraine patients. Recent reviews about the main symptoms of COVID-19 stated that headache occurs in nearly 10% of patients, while migraine is not included within the comorbidities that aggravate symptomatic patients (29). The three patients presenting with symptoms of COVID-19 had a mild form, which did not require hospitalization. They experienced the same small improvement of headache symptoms as most of the other patients. In the current literature, data on migraine patients presenting with more severe symptoms of infection are still lacking. Further studies and meta-analyses are needed to establish the prevalence and clinical aspects of COVID-19 in the migraine population.

Study Limitations

The main limitation of the present study is the small number of patients interviewed. This limitation was determined by the

restricted time window of the interview, limited to the time of the restrictive measures, also termed "phase I," enforced by the Italian Government, and by the fact that enrolled cases were solely those patients who had previously given their informed consent to the RICe study and therefore could be enrolled in the present sub-study. Additional limitations could be the scarce reliability of headache diaries during the pandemic and the short amount of time for evaluation of migraine outcome during the social and health emergency (1 month on average). In fact, the consistency of a retrospective report of headache frequency and patient habits by telephone interview could be questionable. This study was conducted in tertiary headache centers and included patients with high monthly attack frequency who were not representative of migraine in the general population. Finally, the interview text and scales for emotional and psychological impact of pandemic, were only partially validated among Italian citizens (15).

CONCLUSIONS

We found that, on average, migraine patients expressed a reduction in migraine severity indices, probably due to resilient behavior with regards to pandemic distress. The maintenance of habitual lifestyles during social distancing was less evident in people with a limited number of days of staying at home. The present data could help in the future reorganization of services, healthcare workforce, and ongoing management of migraine (30). The spontaneous limitation of migraine burden during quarantine could favor patient follow-up *via* the use of telemedicine visits (12, 31), reliable diaries, and frequent remote contacts after an initial in-person visit.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethic Committees of each recruiting center approved the RICe registry, and enrolled patients signed informed consent. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MD and EG: equally contributed, study design, interview preparation, patient selection, and study coordination. MdT: study coordination, manuscript preparation, data analysis, and manuscript editing. PG and SS: manuscript preparation, data analysis, and manuscript editing. IR, GC, GS, and AP: manuscript preparation and editing. FPie and MT: study design and manuscript editing. RO: study design and statistical analysis. CA, VC, FD, IF, EG, AM, FPis, AP, MR, and FR: patient selection, manuscript editing, preparation, and telephone interviews. CL: RICe data, patient selection, and telephone interviews. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The study was promoted by the Italian Society for Headache Study (SISC). This manuscript has been released as a pre-print at Research square: https://www.researchsquare.com/article/rs-62932/v1, https://www.researchsquare.com/article/rs-39228/v1 (32).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.597881/full#supplementary-material

REFERENCES

1. Kaur N, Gupta I, Singh H, Karia R, Ashraf A, Habib A, et al. Epidemiological and clinical characteristics of 6635 COVID-19 patients: a pooled analysis. *SN Compr Clin Med*. (2020) 2:1048–52. doi: 10.1007/s42399-020-00393-y
2. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. *J Infec*. (2020) 80:401–6. doi: 10.1016/j.jinf.2020.02.018
3. Anderson RM, Heesterbeek H, Klinkenberg D, Hollingsworth TD. How will country-based mitigation measures influence the course of the COVID-19 epidemic? *Lancet*. (2020) 395:931–4. doi: 10.1016/S0140-6736(20)30567-5
4. Nussbaumer-Streit B, Mayr V, Dobrescu AI, Chapman A, Persad E, Klerings I, et al. Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. *Cochrane Database Syst Rev*. (2020) 4:CD013574. doi: 10.1002/14651858.CD013574
5. Parodi SM, Liu VX. From containment to mitigation of COVID-19 in the, US. *JAMA*. (2020) 323:1441–2. doi: 10.1001/jama.2020.3882
6. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. WHO strategic and technical advisory group for infectious hazards. COVID-19: towards controlling of a pandemic. *Lancet*. (2020) 395:1015–8. doi: 10.1016/S0140-6736(20)30673-5
7. Hawryluck L, Gold WL, Robinson S, Pogorski S, Galea S, Styra R. SARS control and psychological effects of quarantine, Toronto, Canada. *Emerg Infect Dis*. (2004) 10:1206–12. doi: 10.3201/eid1007.030703
8. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*. (2020) 395:912–20. doi: 10.1016/S0140-6736(20)30460-8
9. De Berardis D, Fornaro M, Orsolini L, Valchera A, Carano A, Vellante F, et al. Alexithymia and suicide risk in psychiatric disorders: a mini-review. *Front Psychiatry*. (2017) 8:148. doi: 10.3389/fpsyt.2017.00148
10. Person B, Sy F, Holton K, Govert B, Liang A, National Center for Inectious Diseases/SARS Community Outreach Team. Fear and stigma: the epidemic within the SARS outbreak. *Emerg Infect Dis*. (2004) 10:358–63. doi: 10.3201/eid1002.030750
11. Shultz JM, Cooper JL, Baingana F, Oquendo MA, Espinel Z, Althouse BM, et al. The role of fear-related behaviors in the 2013–2016 West Africa Ebola virus disease outbreak. *Curr Psychiatry Rep*. (2016) 18:104. doi: 10.1007/s11920-016-0741-y
12. Szperka CL, Ailani J, Barmherzig R, Klein BC, Minen MT, Halker Singh RB. Migraine Care in the Era of COVID-19: Clinical pearls and plea to insurers. *Headache*. (2020) 60:833–42. doi: 10.1111/head.13810
13. Gautam M, Thakrar A, Akinyemi E, Mahr G. Current and future challenges in the delivery of mental healthcare during COVID-19. *SN Compr Clin Med*. (2020). doi: 10.1007/s42399-020-00348-3. [Epub ahead of print].
14. Headache Classification Committee of the International Headache Society. *The International Classification of Headache Disorders, 3rd edn*. Cephalalgia (2018) 38:1–211. doi: 10.1177/0333102417738202

15. Motta Zanin G, Gentile E, Parisi A, Spasiano DA. Preliminary evaluation of the public risk perception related to the COVID-19 health emergency in Italy. (2020). *Int J Environ Res Public Health.* 17:3024. doi: 10.3390/ijerph17093024
16. Potter R, Hee SW, Griffiths F, Dodd K, Hoverd E, Underwood M, et al. Development and validation of a telephone classification interview for common chronic headache disorders. *J Headache Pain.* (2019) 20:2. doi: 10.1186/s10194-018-0954-z
17. Parodi IC, Poeta MG, Assini A, Schirinzi E, Del Sette P. Impact of quarantine due to COVID infection on migraine: a survey in Genova, Italy. *Neurol Sci.* (2020) 41:2025–7. doi: 10.1007/s10072-020-04543-x
18. Horesh D, Brown AD. Traumatic stress in the age of COVID-19: a call to close critical gaps and adapt to new realities. *Psychol Trauma.* (2020) 12:331–5. doi: 10.1037/tra0000592
19. Peterlin BL, Katsnelson MJ, Calhoun AH. The associations between migraine, unipolar psychiatric comorbidities, and stress-related disorders and the role of estrogen. *Curr Pain Headache Rep*. (2009) 13:404–12. doi: 10.1007/s11916-009-0066-1
20. Vinkers CH, van Amelsvoort T, Bisson JI, Branchi I, Cryan JF, Domschke K, et al. Stress resilience during the coronavirus pandemic. *Eur Neuropsychopharmacol*. (2020) 35:12–6. doi: 10.1016/j.euroneuro.2020.05.003
21. France CR, Ysidron DW, Slepian PM, French DJ, Evans RT. Pain resilience and catastrophizing combine to predict functional restoration program outcomes. *Heal Psychol.* (2020) 39:573–79. doi: 10.1037/hea0000877
22. Martelletti P, Schwedt TJ, Lanteri-Minet M, Quintana R, Carboni V, Diener HC, et al. My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain.* (2018) 19:115. doi: 10.1186/s10194-018-0946-z
23. Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of Covid-19—studies needed. *N Engl J Med.* (2020) 382:1194–6. doi: 10.1056/NEJMp2002125
24. Wilkins K, Beaudet MP. Work stress and health. *Heal Rep.* (1998) 10:47–62.
25. Santos IS, Griep RH, Alves MGM, Goulart AC, Lotufo PA, Barreto SM, et al. Job stress is associated with migraine in current workers: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Eur J Pain.* (2014) 18:1290–7. doi: 10.1002/j.1532-2149.2014.489.x
26. Sauro KM, Becker WJ. The stress and migraine interaction. *Headache.* (2009) 49:1378–86. doi: 10.1111/j.1526-4610.2009.01486.x
27. Badour CL, Feldner MT. The role of disgust in posttraumatic stress. *J Exp Psychathol*. (2018) 9:pr.032813. doi: 10.5127/pr.032813
28. Curtis V. Why disgust matters. *Philos Trans R Soc Lond B Biol Sci.* (2011) 366:3478–90. doi: 10.1098/rstb.2011.0165
29. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its impact on patients with COVID-19. *SN Compr Clin Med*. (2020) 2020:1–8. doi: 10.1007/s42399-020-00363-4
30. Bhaskar S, Bradley S, Israeli-Korn S, Menon B, Chattu VK, Thomas P, et al. Chronic neurology in COVID-19 era: clinical considerations and recommendations from the reprogram consortium. *Front Neurol.* (2020) 11:664. doi: 10.3389/fneur.2020.00664
31. Giordano G, Blanchini F, Bruno R, Colaneri P, Di Filippo A, Di Matteo A, et al. Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy. *Nat Med*. (2020) 26:855–60. doi: 10.1038/s41591-020-0883-7
32. Delussi M, Gentile E, Coppola G, Prudenzano AMP, Rainero I, Sances MG, et al. Investigating the effects of COVID-19 quarantine in migraine: an observational cross-sectional study from the Italian National Headache Registry (RICe). *Res Square.* (2020). doi: 10.21203/rs.3.rs-62932/v1

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 13 November 2020
doi: 10.3389/fneur.2020.596528

Chloroquine, the Coronavirus Crisis, and Neurodegeneration: A Perspective

Giona Pedrioli[1,2], *Rickie Patani*[3,4] *and Paolo Paganetti*[1,5]*

[1] Neurodegeneration Research Group, Laboratory for Biomedical Neurosciences, Neurocenter of Southern Switzerland, Ente Ospedaliero Cantonale, Torricella-Taverne, Switzerland, [2] International PhD Program of the Biozentrum, University of Basel, Basel, Switzerland, [3] Department of Neuromuscular Disease, UCL Queen Square Institute of Neurology, London, United Kingdom, [4] The Francis Crick Institute, London, United Kingdom, [5] Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland

On the verge of the ongoing coronavirus pandemic, *in vitro* data suggested that chloroquine, and its analog hydroxychloroquine, may be useful in controlling SARS-CoV-2 infection. Efforts are ongoing in order to test this hypothesis in clinical trials. Some studies demonstrated no evidence of efficacy, whereas in some cases results were retracted after reporting. Despite the lack of scientific validation, support for the use of these compounds continues from various influencers. At the cellular level, the lysosomotropic drug chloroquine accumulates in acidic organelles where it acts as an alkalizing agent with possible downstream effects on several cellular pathways. In this perspective, we discuss a possible modulatory role of these drugs in two shared features of neurodegenerative diseases, the cellular accumulation of aberrantly folded proteins and the contribution of neuroinflammation in this pathogenic process. Certainly, the decision on the use of chloroquine must be determined by its efficacy in the specific clinical situation. However, at an unprecedented time of a potential widespread use of chloroquine, we seek to raise awareness of its potential impact in ongoing clinical trials evaluating disease-modifying therapies in neurodegeneration.

Keywords: chloroquine, COVID-19, coronavirus, neurodegeneration, clinical trials

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu, Hospital Clínico San Carlos, Spain

Reviewed by:
Ulises Gomez-Pinedo, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, Spain
Ana Laura Márquez-Aguirre, CONACYT Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco (CIATEJ), Mexico

***Correspondence:**
Paolo Paganetti
paolo.paganetti@eoc.ch

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *19 August 2020*
Accepted: *02 October 2020*
Published: *13 November 2020*

Citation:
Pedrioli G, Patani R and Paganetti P (2020) Chloroquine, the Coronavirus Crisis, and Neurodegeneration: A Perspective. Front. Neurol. 11:596528. doi: 10.3389/fneur.2020.596528

INTRODUCTION

On February 4th, 2020, at the verge of a new pandemic crisis, the anti-malarial drug chloroquine (CQ), was proposed to be highly effective in controlling SARS-CoV-2 infection *in vitro* (1). Soon after, in March 2020, the lack of specific treatments for the rising coronavirus burden induced the U. S. Food and Drug Administration (FDA) to issue an emergency use authorization (EUA) for CQ, and its (more soluble and less toxic) analog hydroxychloroquine (HCQ), as treatments for the control of SARS-CoV-2, the severe acute respiratory syndrome caused by the new coronavirus (2). On June 2020, in light of recent scientific data and analysis, the FDA revoked the EUA for CQ/HCQ, as reported side effects "no longer outweigh the known and potential risks for the authorized use" (3). The most worrisome adverse effects, also listed in the drug labels, include heart rhythm interference related to long QT syndrome, ventricular tachycardia and fibrillation, in particular

in combination with QT-prolonging drugs or pre-existing kidney or heart disorders (4–6). Likely differences in dosing regimens when using CQ/HCQ for their approved indications, which are unlikely to meet the concentrations affecting SARS-CoV-2 activity *in vitro*, may explain why the occurrence of these symptoms is uncommon in the medical practice. For instance, while safety profile of CQ in the treatment of rheumatic diseases have been reported up to 500 mg (once daily) (7), in a SARS-CoV-2 clinical trial assessing CQ efficacy a QT interval alteration was observed in patients treated with a higher dose (600 mg, twice daily) (4).

The EUA permission and revocation of the use of CQ/HCQ has caused a stir in the scientific community and beyond during this unstable and delicate pandemic situation. While we acknowledge the natural tendency to dismiss uncomfortable facts and the keenness to move away from CQ, reflecting on possible short and long-term neurological side-effects caused by its use are worthy of a more comprehensive scientific consideration. In particular considering that CQ was, and still is, used as a putative off-label drug to treat SARS-CoV-2, highlights that the response to this pandemic has not always been ruled by a rational and scientific approach. Nonetheless, the possible consequences of using CQ should instigate discussion and warrant a more cautious approach if a similar situation should arise in the future. Here we provide a perspective on the potential interaction of CQ and the neuronal dyshomeostasis observed in common degenerative disorders such as Alzheimer's or Parkinson's disease. We consider the pharmacodynamics and pharmacokinetic attributes of CQ, and its potential effects on the nervous and immune systems.

IMPAIRMENT OF THE AUTOPHAGY-LYSOSOME PATHWAY

Historically recognized for its undeniable utility in malarial prophylaxis and treatment (8), CQ is also extensively used as a cell biology research compound based on its potent inhibitory activity on autophagic and lysosomal clearance functions. The lipophilic nature of CQ enables a rapid penetration across lipid bilayer membranes. Within the cell, CQ behaves as a lysosomotropic agent, i.e., it undergoes a protonation-based trapping when it reaches the acidic environment present in the lumen of organelles such as lysosomes. Its weak base characteristics results in its accumulation as a function of the pH gradient, the neutralization of the low pH, the inhibition of acidic hydrolases and the impairment of organelle maturation (9). This has led to defining the mode of action of CQ as an inhibitor of both enzymatic activity and organelle fusion resulting in halting autophagy flux and endo-lysosomal degradative function (10).

Abbreviations: CQ, Chloroquine; FDA, U. S. Food and Drug Administration; EUA, Emergency use authorization; CNS, Central nervous system; CMA, Chaperon mediated autophagy; HSC70, Chaperone heat-shock cognate 70; LAMP2A, Lysosomal membrane associated protein 2A; MHC, Major histocompatibility complex; TLR, Toll-like receptor.

IMPAIRMENT OF THE PROTEASOME SYSTEM

Beside the autophagy-lysosome pathway, experimental evidence proposes that CQ is a weak antagonist of the proteasome system, causing accumulation of ubiquitinated proteins in mammalian cells (11, 12). Mechanistically, CQ acts as an allosteric inhibitor of the enzymatic activity of the 26S proteasome degradation system (13). Together, these studies highlight a likely dual inhibitory effect of CQ in the two major metabolic systems regulating cellular proteostasis. Moreover, the presence of CQ modify the heat-shock response regulating protein chaperons expression in mammalian cells (14) with additional consequences on the mammalian proteostasis and on the drug resistance of the malaria parasite *Plasmodium* (15).

ACCESS TO THE CENTRAL NERVOUS SYSTEM: A PHARMACOKINETIC PERSPECTIVE

CQ can be administered orally as a phosphate salt and it is efficiently absorbed by the upper intestinal tract, thus permitting a high drug bioavailability. Plasma CQ concentration peaks at 8–12 h post-administration. CQ is slowly metabolized mainly in the liver by cytochrome P450 enzymes and is converted into desethylchloroquine. Further desethylation leads to the second, less frequent, metabolite bisdesethylchloroquine. CQ and its active metabolites have a remarkably slow elimination rate, which in turns may facilitate a widespread tissue exposure, indeed reflected in a large distribution volume. Although about 70% of CQ is directly cleared by the kidneys, CQ and its metabolites are detected in blood plasma for as long as 70 days, and in the urine up to 1 year post-administration. Notably, the equally active CQ enantiomers differ in their overall elimination kinetics. In animals, the concentration of CQ reaches 10-to-700 times higher levels in the liver, spleen, kidney, and lung when taking that detected in the plasma as reference (16, 17). Despite some controversy around the efficacy of CQ to penetrate the blood-brain barrier (BBB), animal studies demonstrate that this drug and its analogs can penetrate and reach a concentration that is sufficient to exert its effects within the central nervous system (CNS) (18–20). Nonetheless, reported neurological side effects of CQ and its analogs implicate a non-yet fully confirmed CNS exposure in humans (21). In particular, CQ/HCQ can have potential adverse neuropsychiatric effects, similar to symptoms occurring in neurodegenerative disorders, such as agitation, emotional instability, anxiety, irritability and, rarely, psychosis (22, 23).

Therefore, at a time were CQ is used in clinical trials or as a self-remedy, and as long it is not excluded that the CNS is a target tissue of the drug, predicting possible consequences of CQ exposure in the brain is important in order to prevent possible neurological effects, e.g., for patients affected by neurodegenerative disorders.

MODULATION OF AUTOPHAGY

Although little is known regarding the direct effects of CQ on the CNS, the latter is particularly vulnerable to disruptions of the cellular degradative pathways. Indeed, terminally differentiated neurons rely on efficient quality control systems such as the autophagic-lysosomal pathway for maintaining their delicate proteostasis, which is gradually impaired as the brain ages (24). Autophagy is responsible for delivering cytoplasmic material to the lysosome for degradation. Autophagy is subdivided in three distinct processes that differ in their mechanism of recognition and delivery of substrates to lysosomes: chaperon mediated autophagy (CMA), macroautophagy and microautophagy (25). The selective clearance of aberrant proteins is primarily carried out by CMA and macroautophagy. In CMA, proteins that bear a pentapeptide degradation signal (KFERQ-like) are recognized by the chaperone heat-shock cognate 70 (HSC70) and delivered through the CMA adaptor lysosomal membrane associated protein 2A (LAMP2A) to the lysosomal lumen for degradation. In contrast, aberrantly folded proteins that are prone to self-aggregate into β-sheet-rich oligomers and higher order aggregates are sequestered by macroautophagy together with small portion of the cytoplasm. These substrates are encapsulated within an intermediate double lipid bilayer membrane organelle termed "autophagosome" and directed toward lysosomes, where upon membrane fusion, cargos are liberated in the hydrolases-enriched lysosomal lumen for enzymatic digestion (26) (**Figure 1A**).

Most late onset neurodegenerative disorders share the progressive deposition of aberrantly folded, β-sheet-rich protein aggregates into ubiquitinated intraneuronal inclusions. Each disorder is characterized by the aggregation of specific proteins: examples are beta-amyloid and TAU in Alzheimer's disease (27), NACP/α-synuclein in Parkinson's disease (28), huntingtin in Huntington's disease (29), TDP-43 in amyotrophic lateral sclerosis and frontotemporal lobar degeneration (30). Nevertheless, another key pathological hallmark of these otherwise clinically and etiologically diverse disorders is the progressive impairment in the autophagy-lysosome degradation pathway. This is exemplified by the fact that mutations of genes regulating autophagy and lysosome activity are associated to the most frequent late-onset forms of neurodegeneration (31). Furthermore, experimental animal models demonstrate that autophagy deficiency accelerates protein aggregation and behavioral phenotypes of neurodegeneration. Evidence that CQ exposure on neurons may lead to a similar outcome are known since long time (32). More recently the activity of CQ on the amyloidogenic processing of the amyloid precursor protein by neurons (33, 34) as well as on huntingtin accumulation in brain (20) were reported. CQ also modulates autophagic flux (35) and mitochondrial homeostasis by an autophagic process (36). CQ is also linked to neuronal death in primary cultures (37, 38). These facts are reinforced by studies demonstrating that autophagy stimulation can clear intra-neuronal insoluble protein inclusions with amelioration of behavioral phenotypes in animal models of neurodegenerative diseases (26) (**Table 1**). Nevertheless, macroautophagy may also favor seeded propagation of aberrantly folded neurodegeneration-associated TAU mediated by extracellular vesicles (39).

MODULATION OF INFLAMMATORY RESPONSE

Another increasingly documented feature of neurodegenerative disorders is the chronic inflammation of the CNS (neuroinflammation). Although a causal relationship has not yet been demonstrated, there are studies reporting a correlation between prolonged treatment with non-steroidal anti-inflammatory drugs and decreased risk for Alzheimer's and Parkinson's disease (40, 41). Activation of CNS-resident macrophages (microglia cells) around senile plaques has been documented in transgenic mouse model of Alzheimer's disease (42). These phagocytic cells actively uptake beta-amyloid and acquire an activated phenotype characterized by morphological changes and by an increased production of pro-inflammatory modulators such as the major histocompatibility complex (MHC) class II, several interleukins and tumor necrosis factor alpha. Persistent microglial activation is associated with cellular senescence, neurotoxicity and subsequent disease progression (43). Recent studies suggest that this may also involve deleterious reactive transformation in astrocytes (44). Notably, elimination of senescent glial cells, which are known to release proinflammatory modulators, is beneficial (45–47).

Against this background, HCQ's clinical efficacy in treating autoimmune inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, is well-documented (48). Current hypotheses in the field are linked to an indirect effect of HCQ in modulating the inflammatory response (**Figure 1B**). Specifically, interference of lysosomal activity might affect several immunomodulatory pathways. One intuitive mechanism is the inhibition of antigen presentation via the autophagy-lysosome pathway. As lysosomes are the main organelles for hydrolytic processing, they reside at the intersection between different pathways delivering intracellular and extracellular cargos on route to degradation (49). This context provides a unique cellular environment for the binding of antigens to MHC class II. For instance, a recent report suggests that extracellular proteins are hydrolysed in endocytic compartments and delivered to MHC class II-containing lysosomes as antigenic peptides before being presented to $CD4^+$ T cells (50). Nevertheless, functional lysosomes are required for antigenic peptide-binding to MHC class II molecules and the alkalizing properties that HCQ exerts in these organelles might impair this process. Another possibility is that HCQ interferes in Toll-like receptor (TLR) signaling. In mammals, TLRs are a group of transmembrane pattern-recognition receptors that initiate innate immune response to infection by sensing pathogen macromolecules. However, TLRs can also be activated in the absence of pathogen infection (51). Indeed, activated microglia surrounding beta-amyloid plaques in Alzheimer's disease brains display up-regulated levels of TLRs (52, 53). A recent report indicates that, in order to be functional, TLR7 requires proteolytic cleavage in lysosomes

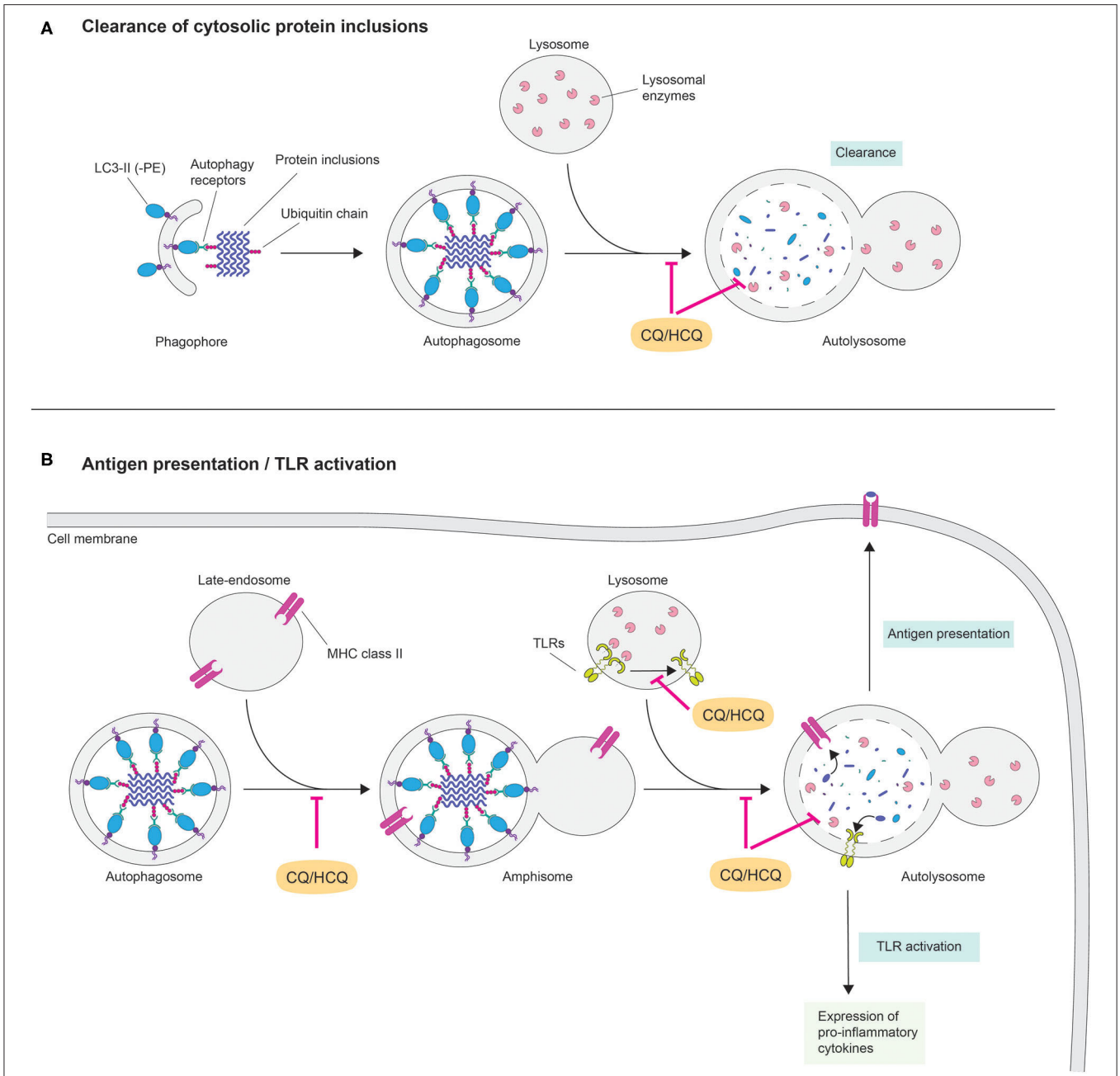


FIGURE 1 | Potential cellular and molecular mechanisms of chloroquine in neurodegeneration. The lysosomotropic agent chloroquine (CQ) rapidly penetrates across lipid bilayer membranes and following a pH gradient accumulates within lysosomes. In these acidic organelles, CQ behaves as a weak base by increasing the pH, which in turns affects the activity of lysosomal hydrolases. Disruption of lysosomal activity prevents interaction and fusion among organelles of the autophagy-lysosome and of the endocytic pathways. This cellular condition may have dichotomic effects in the pathogenesis of neurodegenerative diseases by **(A)** inhibiting cytosolic clearance of aberrantly protein fibrils and **(B)** preventing MHC class II-mediated antigen presentation and preventing the expression of pro-inflammatory cytokines *via* TLR activation.

(48). Thus, interfering with lysosomal pH via lysosomotropic agents may prevent activation of TLRs. Moreover, evidence exists for a mode of action of CQ/HCQ independently of its effect on lysosomal function, as shown for its ability to interference with interleukin-2 production (54). Although the precise mechanism(s), by which CQ/HCQ inhibits inflammatory response, requires further investigation, its potential role in disrupting the integrity of the CNS immune system in neurodegenerative disorders is an intriguing and noteworthy hypothesis. Evidence for a possible role of CQ in modulating

TABLE 1 | Examples of evidence for beneficial effect of autophagy stimulation in murine brain.

Compound	Targeted pathway	Ectopic expression	Disease model	Outcome	References
Rapamycin	Mammalian target of rapamycin (mTor)	Human TDP-43	Amyotrophic lateral sclerosis	Reduced TDP-43 inclusions and improved learning/memory impairment	(56)
Rapamycin	mTor	Human APP Human TAU Human PSEN1	Alzheimer's disease	Reduced beta-amyloid and TAU deposition and improved learning defects	(57)
Rapamycin	mTor	Human NACP	Parkinson's disease	Reduced aggregation of NACP and associated pathology	(58)
CCI-779	mTor	Human HTT	Huntington's disease	Reduced huntingtin aggregates formation and improved behavioral phenotype	(59)
Trehalose	mTor-independent	Human SOD1	Amyotrophic lateral sclerosis	Reduced accumulation of SOD1 and enhanced motoneuronal survival	(60)
Trehalose	mTor-independent	Human APP Human PSEN1	Alzheimer's disease	Reduced beta-amyloid plaque deposition and improved learning defects	(61)
Trehalose	mTor-independent	Human TAU	Alzheimer's disease	Reduced TAU inclusions and increased brain neuronal survival	(62)
Trehalose	mTor-independent	Human HTT	Huntington's disease	Reduced formation of polyglutamine aggregates and amelioration of motor dysfunction	(63)
Lithium	Inositol synthesis	Human APP Human PSEN1	Alzheimer's disease	Reduced beta-amyloid plaque formation and improved memory deficits	(64)
Lithium	Inositol synthesis	Human SOD1	Amyotrophic lateral sclerosis	Reduced SOD1 aggregates and increased brain neuronal survival	(65)
Carbamazepine	Inositol synthesis	Human APP Human PSEN1	Alzheimer's disease	Reduced beta-amyloid plaque formation and improved memory deficits	(66)
Carbamazepine	Inositol synthesis	Human TDP-43	Amyotrophic lateral sclerosis	Reduced TDP-43 inclusions and improved learning/memory impairement	(56)
Spermidine	Acetyl transferases synthesis	Human TDP-43	Amyotrophic lateral sclerosis	Reduced TDP-43 inclusions and improved learning/memory impairement	(56)
Verapamil	Ca^{2+} channel	Human SOD1	Amyotrophic lateral sclerosis	Reduced SOD1 aggregates and prolonged animal survival	(67)
Felodipine	Ca^{2+} channel	Human NACP	Parkinson's disease	Reduced aggregation of NACP and improved behavioral phenotype	(68)
Calpastatin	Calpain	Human HTT	Huntington's disease	Reduced HTT aggregates formation and improved locomotor function	(69)
Beclin-1	Beclin-1 dependent	Human NACP	Parkinson's disease	Reduced aggregation of NACP	(70)
LAMP2A	LAMP2A dependent	Human NACP	Parkinson's disease	Reduced generation of aberrant NACP species	(71)

inflammation and autophagic death of neurons in the brain exists (55).

CONCLUSIONS

Given the demographic, in particular associated to aging, of people affected by neurodegenerative disorders and patients more vulnerable to develop a serious SARS-CoV-2 disease course, the possibility that CQ, or one of its analogs, will be prescribed/self-consumed by patients enrolled in clinical trials (or outside this context and off license) is worth considering. However, the use of CQ and its analogs must be determined by clinical need, so that prescribing CQ may be opportune and take priority depending on specific clinical context. However, at a time of a potential widespread use of CQ, in order to mitigate the risk of potential misinterpretation in ongoing clinical trials evaluating disease-modifying therapies in neurodegeneration, we seek to raise awareness and caution that the use of CQ and its analogs needs to be clearly documented and carefully considered in interpreting trial outcomes in this arena and beyond.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

PP was funded by the Synapsis Foundation, the Gelu Foundation, and the Mecri Foundation. RP holds an MRC Senior Clinical Fellowship [MR/S006591/1].

ACKNOWLEDGMENTS

We thank the whole laboratory for support and advice.

REFERENCES

1. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res.* (2020) 30:269–71. doi: 10.1038/s41422-020-0282-0
2. Administration U.S.F.a.D. *Coronavirus (COVID-19) Update: Daily Roundup March 30, 2020*. (2020). Available online at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-march-30-2020 (accessed April 3, 2020).
3. Administration U.S.F.a.D. *Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine*. (2020). Available online at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and (accessed June 16, 2020).
4. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open.* (2020) 3:e208857. doi: 10.1001/jamanetworkopen.2020.8857
5. Chorin E, Dai M, Shulman E, Wadhwani L, Bar-Cohen R, Barbhaiya C, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nat Med.* (2020) 26:808–9. doi: 10.1038/s41591-020-0888-2
6. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* (2020) 5:1036–41. doi: 10.1001/jamacardio.2020.1834
7. Klinger G, Morad Y, Westall CA, Laskin C, Spitzer KA, Koren G, et al. Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. *Lancet*. (2001) 358:813–4. doi: 10.1016/S0140-6736(01)06004-4
8. Pullman TN, Craige B, Alving AS, Whorton CM, Jones R, Eichelberger L. Comparison of chloroquine, quinacrine (atabrine), and quinine in the treatment of acute attacks of sporozoite-induced vivax malaria (chesson strain). *J Clin Invest.* (1948) 27:46–50. doi: 10.1172/JCI101970
9. Al-Bari MA. Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. *J Antimicrob Chemother.* (2015) 70:1608–21. doi: 10.1093/jac/dkv018
10. Mauthe M, Orhon I, Rocchi C, Zhou X, Luhr M, Hijlkema K-J, et al. Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. *Autophagy*. (2018) 14:1435–55. doi: 10.1080/15548627.2018.1474314
11. Qiao L, Zhang J. Inhibition of lysosomal functions reduces proteasomal activity. *Neurosci Lett.* (2009) 456:15–9. doi: 10.1016/j.neulet.2009.03.085
12. Myeku N, Figueiredo-Pereira ME. Dynamics of the degradation of ubiquitinated proteins by proteasomes and autophagy: association with sequestosome 1/p62. *J Biol Chem*. (2011) 286:22426–40. doi: 10.1074/jbc.M110.149252
13. Sprangers R, Li X, Mao X, Rubinstein JL, Schimmer AD, Kay LE. TROSY-based NMR evidence for a novel class of 20S proteasome inhibitors. *Biochemistry*. (2008) 47:6727–34. doi: 10.1021/bi8005913
14. Neznanov N, Gorbachev AV, Neznanova L, Komarov AP, Gurova KV, Gasparian AV, et al. Anti-malaria drug blocks proteotoxic stress response: anti-cancer implications. *Cell Cycle.* (2009) 8:3960–70. doi: 10.4161/cc.8.23.10179
15. Daniyan MO, Przyborski JM, Shonhai A. Partners in mischief: functional networks of heat shock proteins of *Plasmodium falciparum* and their influence on parasite virulence. *Biomolecules*. (2019) 9:925. doi: 10.3390/biom9070295
16. Popert AJ. Chloroquine: a review. *Rheumatol Rehabil*. (1976) 15:235–8. doi: 10.1093/rheumatology/15.3.235
17. Adelusi SA, Salako LA. Tissue and blood concentrations of chloroquine following chronic administration in the rat. *J Pharm Pharmacol.* (1982) 34:733–5. doi: 10.1111/j.2042-7158.1982.tb06211.x
18. Osifo NG. The regional uptake of chloroquine in the rat brain. *Toxicol Appl Pharmacol*. (1979) 50:109–14. doi: 10.1016/0041-008X(79)90498-8
19. Baudry S, Pham YT, Baune B, Vidrequin S, Crevoisier C, Gimenez F, et al. Stereoselective passage of mefloquine through the blood-brain barrier in the rat. *J Pharm Pharmacol.* (1997) 49:1086–90. doi: 10.1111/j.2042-7158.1997.tb06047.x
20. Vodicka P, Lim J, Williams DT, Kegel KB, Chase K, Park H, et al. Assessment of chloroquine treatment for modulating autophagy flux in brain of WT and HD mice. *J Huntigtons Dis.* (2014) 3:159–74. doi: 10.3233/JHD-130081
21. Quinn JC. Complex membrane channel blockade: a unifying hypothesis for the prodromal and acute neuropsychiatric sequelae resulting from exposure to the antimalarial drug mefloquine. *J Parasitol Res*. (2015) 2015:368064. doi: 10.1155/2015/368064
22. Manzo C, Gareri P, Castagna A. Psychomotor agitation following treatment with hydroxychloroquine. *Drug Saf Case Rep*. (2017) 4:6. doi: 10.1007/s40800-017-0048-x
23. Ali SS, Jones H. 23. An adverse neuropsychiatric reaction following treatment with hydroxychloroquine: a case report. *Rheumatol Adv Pract*. (2018) 2:rky033.014. doi: 10.1093/rap/rky033.014
24. Son JH, Shim JH, Kim K-H, Ha J-Y, Han JY. Neuronal autophagy and neurodegenerative diseases. *Exp Mol Med.* (2012) 44:89. doi: 10.3858/emm.2012.44.2.031
25. Mizushima N, Levine B, Cuervo AM, Klionsky DJ. Autophagy fights disease through cellular self-digestion. *Nature.* (2008) 451:1069–75. doi: 10.1038/nature06639
26. Ciechanover A, Kwon YT. Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. *Exp Mol Med.* (2015) 47:e147. doi: 10.1038/emm.2014.117
27. Selkoe DJ. Alzheimer's disease. *Cold Spring Harb Perspect Biol.* (2011) 3:a004457. doi: 10.1101/cshperspect.a004457
28. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the -synuclein gene identified in families with Parkinson's disease. *Science*. (1997) 276:2045–7. doi: 10.1126/science.276.5321.2045
29. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol.* (2011) 10:83–98. doi: 10.1016/S1474-4422(10)70245-3
30. Andersen PM, Al-Chalabi A. Clinical genetics of amyotrophic lateral sclerosis: what do we really know? *Nat Rev Neurol*. (2011) 7:603–15. doi: 10.1038/nrneurol.2011.150
31. Menzies FM, Fleming A, Caricasole A, Bento CF, Andrews SP, Ashkenazi A, et al. Autophagy and neurodegeneration: pathogenic mechanisms and therapeutic opportunities. *Neuron*. (2017) 93:1015–34. doi: 10.1016/j.neuron.2017.01.022

32. Tischner K. Effects of chloroquine on neurons of long-term cultures of peripheral and central nervous system. *Acta Neuropathol.* (1974) 28:233–42. doi: 10.1007/BF00719028
33. Caporaso GL, Gandy SE, Buxbaum JD, Greengard P. Chloroquine inhibits intracellular degradation but not secretion of Alzheimer beta/A4 amyloid precursor protein. *Proc Natl Acad Sci* USA. (1992) 89:2252–6. doi: 10.1073/pnas.89.6.2252
34. Bahr BA, Abai B, Gall CM, Vanderklish PW, Hoffman KB, Lynch G. Induction of β-amyloid-containing polypeptides in hippocampus: evidence for a concomitant loss of synaptic proteins and interactions with an excitotoxin. *Exp Neurol.* (1994) 129:81–94. doi: 10.1006/exnr.1994.1149
35. Redmann M, Wani WY, Volpicelli-Daley L, Darley-Usmar V, Zhang J. Trehalose does not improve neuronal survival on exposure to alpha-synuclein pre-formed fibrils. *Redox Biol.* (2017) 11:429–37. doi: 10.1016/j.redox.2016.12.032
36. Redmann M, Benavides GA, Berryhill TF, Wani WY, Ouyang X, Johnson MS, et al. Inhibition of autophagy with bafilomycin and chloroquine decreases mitochondrial quality and bioenergetic function in primary neurons. *Redox Biol.* (2017) 11:73–81. doi: 10.1016/j.redox.2016.11.004
37. Zaidi AU, McDonough JS, Klocke BJ, Latham CB, Korsmeyer SJ, Flavell RA, et al. Chloroquine-induced neuronal cell death is p53 and bcl-2 family-dependent but caspase-independent. *J Neuropathol Exp Neurol.* (2001) 60:937–45. doi: 10.1093/jnen/60.10.937
38. Cui D, Sun D, Wang X, Yi L, Kulikowicz E, Reyes M, et al. Impaired autophagosome clearance contributes to neuronal death in a piglet model of neonatal hypoxic-ischemic encephalopathy. *Cell Death Dis.* (2017) 8:e2919. doi: 10.1038/cddis.2017.318
39. Pedrioli G, Barberis M, Molinari M, Morone D, Papin S, Paganetti P. Extracellular vesicles hijack the autophagic pathway to induce tau accumulation in endolysosomes. *bioRxiv [Preprint].* (2020). doi: 10.1101/2020.05.27.118323
40. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. *Neurology.* (1997) 48:626–32. doi: 10.1212/WNL.48.3.626
41. Chen H, Zhang SM, Hernán MA, Schwarzschild MA, Willett WC, Colditz GA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. *Arch Neurol.* (2003) 60:1059. doi: 10.1001/archneur.60.8.1059
42. Frautschy SA, Yang F, Irrizarry M, Hyman B, Saido TC, Hsiao K, et al. Microglial response to amyloid plaques in APPsw transgenic mice. *Am J Pathol.* (1998) 152:307–17.
43. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. *Nat Neurosci.* (2018) 21:1359–69. doi: 10.1038/s41593-018-0242-x
44. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature.* (2017) 541:481–7. doi: 10.1038/nature21029
45. Bussian TJ, Aziz A, Meyer CF, Swenson BL, Van Deursen JM, Baker DJ. Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. *Nature.* (2018) 562:578–82. doi: 10.1038/s41586-018-0543-y
46. Angelova DM, Brown DR. Microglia and the aging brain: are senescent microglia the key to neurodegeneration? *J Neurochem.* (2019) 151:676–88. doi: 10.1111/jnc.14860
47. Zhang P, Kishimoto Y, Grammatikakis I, Gottimukkala K, Cutler RG, Zhang S, et al. Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. *Nat Neurosci.* (2019) 22:719–28. doi: 10.1038/s41593-019-0372-9
48. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol.* (2020) 16:155–66. doi: 10.1038/s41584-020-0372-x
49. Luzio JP, Pryor PR, Bright NA. Lysosomes: fusion and function. *Nat Rev Mol Cell Biol.* (2007) 8:622–32. doi: 10.1038/nrm2217
50. Chen C, Li HQ, Liu YJ, Guo ZF, Wu HJ, Li X, et al. A novel size-based sorting mechanism of pinocytic luminal cargoes in microglia. *J Neurosci.* (2015) 35:2674–88. doi: 10.1523/JNEUROSCI.4389-14.2015
51. Zhang Z, Schluesener HJ. Mammalian toll-like receptors: from endogenous ligands to tissue regeneration. *Cell. Mol. Life Sci.* (2006) 63:2901–7. doi: 10.1007/s00018-006-6189-1
52. Letiembre M, Hao W, Liu Y, Walter S, Mihaljevic I, Rivest S, et al. Innate immune receptor expression in normal brain aging. *Neuroscience.* (2007) 146:248–54. doi: 10.1016/j.neuroscience.2007.01.004
53. Walter S, Letiembre M, Liu Y, Heine H, Penke B, Hao W, et al. Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease. *Cell. Physiol. Biochem.* (2007) 20:947–56. doi: 10.1159/000110455
54. Landewe RBM, Miltenburg AMM, Verdonk MJA, Verweij CL, Breedveld FC, Daha MR, et al. Chloroquine inhibits T cell proliferation by interfering with IL-2 production and responsiveness. *Clin Exp Immunol.* (1995) 102:144–51. doi: 10.1111/j.1365-2249.1995.tb06648.x
55. Cui CM, Gao JL, Cui Y, Sun LQ, Wang YC, Wang KJ, et al. Chloroquine exerts neuroprotection following traumatic brain injury *via* suppression of inflammation and neuronal autophagic death. *Mol Med Rep.* (2015) 12:2323–8. doi: 10.3892/mmr.2015.3611
56. Wang IF, Guo BS, Liu YC, Wu CC, Yang CH, Tsai KJ, Shen CK. Autophagy activators rescue and alleviate pathogenesis of a mouse model with proteinopathies of the TAR DNA-binding protein 43. *Proc Natl Acad Sci U S A.* (2012) 109:15024–9. doi: 10.1073/pnas.1206362109
57. Caccamo A, Majumder S, Richardson A, Strong R, Oddo S. Molecular interplay between mammalian target of rapamycin (mTOR), amyloid-beta, and Tau: effects on cognitive impairments. *J Biol Chem.* (2010) 285:13107–20. doi: 10.1074/jbc.M110.100420
58. Crews L, Spencer B, Desplats P, Patrick C, Paulino A, Rockenstein E, Hansen L, Adame A, Galasko D, Masliah E. Selective molecular alterations in the autophagy pathway in patients with Lewy body disease and in models of alpha-synucleinopathy. *PLoS One.* (2010) 5:e9313. doi: 10.1371/journal.pone.0009313
59. Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat Genet.* (2004) 36:585–95. doi: 10.1038/ng1362
60. Castillo K, Nassif M, Valenzuela V, Rojas F, Matus S, Mercado G, Court FA, van Zundert B, Hetz C. Trehalose delays the progression of amyotrophic lateral sclerosis by enhancing autophagy in motoneurons. *Autophagy.* (2013) 9:1308–20. doi: 10.4161/auto.25188
61. Du J, Liang Y, Xu F, Sun B, Wang Z. Trehalose rescues Alzheimer's disease phenotypes in APP/PS1 transgenic mice. *J Pharm Pharmacol.* (2013) 65:1753–6. doi: 10.1111/jphp.12108
62. Schaeffer V, Lavenir I, Ozcelik S, Tolnay M, Winkler DT, Goedert M. Stimulation of autophagy reduces neurodegeneration in a mouse model of human tauopathy. *Brain.* (2012) 135:2169–77. doi: 10.1093/brain/aws143
63. Tanaka M, Machida Y, Niu S, Ikeda T, Jana NR, Doi H, Kurosawa M, Nekooki M, Nukina N. Trehalose alleviates polyglutamine-mediated pathology in a mouse model of Huntington disease. *Nat Med.* (2004) 10:148–54. doi: 10.1038/nm985
64. Zhang X, Heng X, Li T, Li L, Yang D, Zhang X, Du Y, Doody RS, Le W. Long-term treatment with lithium alleviates memory deficits and reduces amyloid-β production in an aged Alzheimer's disease transgenic mouse model. *J Alzheimers Dis.* (2011) 24:739–49. doi: 10.3233/JAD-2011-101875
65. Fornai F, Longone P, Cafaro L, et al. Lithium delays progression of amyotrophic lateral sclerosis. *Proc Natl Acad Sci U S A.* (2008) 105:2052–7. doi: 10.1073/pnas.0708022105
66. Li L, Zhang S, Zhang X, Li T, Tang Y, Liu H, Yang W, Le W. Autophagy enhancer carbamazepine alleviates memory deficits and cerebral amyloid-β pathology in a mouse model of Alzheimer's disease. *Curr Alzheimer Res.* (2013) 10:433–41. doi: 10.2174/1567205011310040008
67. Zhang X, Chen S, Lu K, et al. Verapamil Ameliorates Motor Neuron Degeneration and Improves Lifespan in the SOD1^{G93A} Mouse Model of ALS by Enhancing Autophagic Flux. *Aging Dis.* (2019) 10:1159–73. doi: 10.14336/AD.2019.0228
68. Siddiqi FH, Menzies FM, Lopez A, Stamatakou E, Karabiyik C, Ureshino R, Ricketts T, Jimenez-Sanchez M, Esteban MA, Lai L, Tortorella MD, Luo Z, Liu H, Metzakopian E, Fernandes HJR, Bassett A, Karran E, Miller BL, Fleming A, Rubinsztein DC. Felodipine induces autophagy in mouse brains with

pharmacokinetics amenable to repurposing. *Nat Commun.* (2019) 10:1817. doi: 10.1038/s41467-019-09494-2

69. Menzies FM, Garcia-Arencibia M, Imarisio S, O'Sullivan NC, Ricketts T, Kent BA, Rao MV, Lam W, Green-Thompson ZW, Nixon RA, Saksida LM, Bussey TJ, O'Kane CJ, Rubinsztein DC. Calpain inhibition mediates autophagy-dependent protection against polyglutamine toxicity. *Cell Death Differ.* (2015) 22:433–44. doi: 10.1038/cdd.2014.151
70. Spencer B, Potkar R, Trejo M, Rockenstein E, Patrick C, Gindi R, Adame A, Wyss-Coray T, Masliah E. Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in alpha-synuclein models of Parkinson's and Lewy body diseases. *J Neurosci.* (2009) 29:13578–88. doi: 10.1523/JNEUROSCI.4390-09.2009
71. Xilouri M, Brekk OR, Landeck N, Pitychoutis PM, Papasilekas T, Papadopoulou-Daifoti Z, Kirik D, Stefanis L. Boosting chaperone-mediated autophagy in vivo mitigates α-synuclein-induced neurodegeneration. *Brain.* (2013) 136:2130–46. doi: 10.1093/brain/awt131

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 16 November 2020
doi: 10.3389/fneur.2020.604299

Lockdown During COVID-19 and the Increase of Frailty in People With Neurological Conditions

Paulo H. S. Pelicioni[1]*, *Jennifer S. Schulz-Moore*[2,3], *Leigh Hale*[4], *Colleen G. Canning*[5] and *Stephen R. Lord*[1,3]

[1] Neuroscience Research Australia, University of New South Wales, Sydney, NSW, Australia, [2] Faculty of Law, University of New South Wales, Sydney, NSW, Australia, [3] School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW, Australia, [4] School of Physiotherapy, University of Otago, Dunedin, New Zealand, [5] Discipline of Physiotherapy, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia

Governments around the globe have introduced quarantine, lockdown, and mandatory isolation to slow the transmission of COVID-19. These public health and policy measures aim to protect the public and vulnerable people. This perspective paper argues that the impacts of lockdown (such as social disconnection, reduced exercise, and fewer physiotherapy treatments) may be amplified for people with neurological conditions with subsequent increases in frailty. The paper outlines why this may occur, and explores how adverse impacts for these vulnerable populations may be minimized through strategies such as telehealth, exercise programs, and health policies.

Keywords: lockdown, neurological conditions, COVID-19, frailty, falls, physical inactivity, health policy

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Rupam Bhattacharyya,
University of Michigan, United States
Anna Vittoria Mattioli,
University of Modena and Reggio Emilia, Italy

****Correspondence:***
Paulo H. S. Pelicioni
p.pelicioni@neura.edu.au

Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *09 September 2020*
Accepted: *19 October 2020*
Published: *16 November 2020*

Citation:
Pelicioni PHS, Schulz-Moore JS, Hale L, Canning CG and Lord SR (2020) Lockdown During COVID-19 and the Increase of Frailty in People With Neurological Conditions. Front. Neurol. 11:604299. doi: 10.3389/fneur.2020.604299

INTRODUCTION

In March 2020, the World Health Organization declared that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, or coronavirus disease (COVID-19), is a pandemic. To reduce the spread of COVID-19 infection, most governments around the world adopted public health policies such as lockdown, isolation, and quarantine. Quarantine restricts the movement of people who may have been exposed to an infectious disease, but who are not yet symptomatic. Isolation involves separation of those who are infected. In Australia, pursuant to section 4(1) of *The Quarantine Act 1908* (Cth), quarantine includes "the examination, exclusion, detention, observation, segregation, isolation, protection, treatment and regulation of vessels, installations, human beings, plants or other goods or things." In federal jurisdictions such as Australia, the "lockdown" rules differ according to individual states and territories. Each level of lockdown is comprised of varying degrees of restrictions (such as whether non-essential services are able to operate) and lockdowns may be staged. The outcomes of these government measures may include social isolation and reduced access to health services.

Government orders such as quarantine, lockdown and mandatory isolation are primarily adopted to protect people's health, especially older people and those with chronic lung, liver, renal or heart disease, diabetes, obesity, cancer in the past 12 months, neurological conditions such as stroke or dementia and poorly controlled hypertension. Vulnerable populations and older people

have particularly poor prognoses associated with COVID-19 because of complications such as acute respiratory distress syndrome and pneumonia (1, 2). With the death of over 1 million people worldwide (at the time of writing in mid-October 2020), lockdown is a crucial measure to reduce the likelihood of death among vulnerable populations (3, 4). However, social disconnection due to lockdown during COVID-19 may increase frailty in people with neurological conditions (5, 6). For example, Helmich and Bloem (5) recently argued that there are several "hidden sorrows" and "highly disconcerting consequences" of lockdown, such as the deleterious impact on people with Parkinson's disease (PD) because of their reduction in physical activity and disengagement with physiotherapists (5).

The objectives of this perspective paper are to outline why lockdown can have negative physical, cognitive, and mental health outcomes for people with neurological conditions as well as highlight the potential of telehealth and exercise regimes to minimize such adverse health outcomes. It concludes with a discussion of a perennial problem in public health law and policy: the tension between an individual's rights and public health.

WHAT ARE THE IMPACTS OF LOCKDOWN ON PEOPLE WITH NEUROLOGICAL CONDITIONS?

The adoption of lockdown measures has saved many lives by reducing the spread of COVID-19. However, as argued elsewhere, such measures may have been a "two-edged sword" (1). While lockdown has been essential, governments and health systems have not been well-prepared to manage the consequences of social disconnection caused by this policy (2, 3). It is well-documented that social disconnection has negative health impacts (7, 8), and these negative impacts are magnified for people (such as those with neurological conditions) who need extensive care, physiotherapy, and regular activity to maintain their well-being and health. Although essential services have remained open, traditional face-to-face therapies have been modified, reduced and, sometimes, canceled. In contrast, there is evidence that physical exercise protocols for healthy people have only been slightly affected by the pandemic (2) with these individuals maintaining their exercise routines, often through the use of technology (3, 4).

However, health systems (burdened with the pandemic) have struggled to meet the needs of vulnerable people, especially people with neurological disorders (9). For example, it is known that stroke survivors need physiotherapy and stimulation upon discharge from inpatient rehabilitation, and such approaches result in better outcomes (10). People with progressive conditions such as PD and Multiple Sclerosis (MS) need maintained exercises to reduce the decline of functional capacity associated with the progressive nature of these pathologies (11–13). Exercise cessation in these groups can reduce cardiorespiratory fitness, muscle strength, muscle mass and impair cognition, leading to an "accelerated" loss of function and significantly reduced quality of life (14, 15). Consequently, a series of health and social issues are likely to arise in the forthcoming months and years (16).

LOCKDOWN AND DECLINING MENTAL HEALTH IN PEOPLE WITH NEUROLOGICAL CONDITIONS

Lockdown during the COVID-19 pandemic has caused an increase in mental health issues such as depression and anxiety (6). Previous research has reported that lack of neighborhood engagement and social connection contribute to an increased risk of mental health disorders due to loneliness (7). Researchers have also found that social disconnection remains a strong risk factor for increased mortality in older people, even after adjusting for demographic and health factors (8).

This association may be amplified for people with neurological disorders as a consequence of the pandemic for three key reasons. First, mental health conditions, particularly anxiety, and depression, are more prevalent in people with PD, people with MS, and people with cognitive impairment and dementia (17–19). These conditions may worsen during a pandemic because of the loneliness, social disconnection, and the pandemic-related uncertainties.

Second, the mental health of people with neurological conditions may decline because of the additional stressors on caregivers caused by lockdown. Caregivers experiencing multiple stressors may be unable to provide adequate care to people with neurological conditions (20). In some countries, such as Brazil and New Zealand, caregivers are not considered essential workers, thus they have had to stop "caring" for their clients. These circumstances create a troubling loop of poor health outcomes for both caregivers and care recipients.

Third, the decrease in visitors to residential facilities due to lockdown may negatively impact mental health in people with neurological conditions (21, 22). Government public health policies have meant that residents in residential care facilities either had fewer, or no, visits from people outside of the facility (23). These impacts may be amplified for people with neurological conditions, many of whom already suffer from mental health illnesses.

FALLS—FROM A CASCADE TO A LOOP EFFECT

Lockdown measures can lead to an increased risk of falls by multiple, inter-related means. First, lockdown reduces many people's physical activity levels and the negative health impacts of lack of exercise are well-documented (14, 24). Second, isolation at home can also lead to lack of exposure to sunshine, and as a result, Vitamin D deficiency (25). Consequently, the immune system can be compromised and infections can occur at a higher rate. Third, polypharmacy is a well-known risk factor for falls (26, 27), and people with neurological conditions may take more medications to cope with the negative consequences of lockdown. For example, lack of physical exercise in stroke survivors and people with MS may predispose them to joint and muscle stiffness, and increased pain, associated with an increase in pain medication usage.

Furthermore, during a pandemic, people with neurological disorders may be more inclined to stay indoors. Confined home environments can also hamper ambulation which can impair transfers and adaptive gait in people with balance and mobility impairments, as well as freezing of gait in people with PD, which can lead to falls (28–30). Declines in mental and physical health associated with sedentary behavior may increase fear of falling (31–33). Combined, these complications can result in a downward spiral adversely impacting health and increasing the likelihood of recurrent falls and serious injuries such as head trauma and fractures.

TELEHEALTH—A SOLUTION FOR ADDRESSING THE INCREASED FRAILTY IN PEOPLE WITH NEUROLOGICAL CONDITIONS DURING A PANDEMIC?

Telehealth has enormous potential for assisting people with therapies and exercise delivery (34), with many health providers now offering telehealth consultations and treatments for musculoskeletal injuries and physical exercises during COVID-19 (35, 36). Telehealth is becoming an important component of health care systems because it has the potential to address challenging issues such as access to health care and health inequalities (34). For example, telehealth has been used successfully with people living in remote areas, such as indigenous communities and rural populations (37, 38).

However, telehealth presents challenges. For example, it is not an affordable option for all patients and not all countries provide reliable internet services. In addition, using telehealth may be challenging for people with neurological disorders. Telehealth interventions involve the individual performing activities without face-to-face interaction with a therapist. During assessment and treatment without a therapist present, people with neurological conditions may present an increased risk of balance loss and, consequently, fall. Although there is some evidence that home-based protocols may be safe and suitable for individuals with mild to moderate impairments (39), previous studies have included at least one home visit to set up home-based exercises and associated technology, including virtual reality technology (40–44).

The risks are likely to be higher for individuals with more severe disease. For example, while minimally-supervised home-based exercise programs are effective in reducing falls in individuals with mild to moderate PD, they can lead to an increase in the proportion of fallers in individuals with more severe disease (45–47). This is likely due to previous multiple falls, freezing of gait, and cognitive impairment in those with more severe disease, who may require more targeted, supervised sessions to gain therapeutic benefit. Individuals with severe neurological disability or progressive or acute onset usually present with major balance impairment, or may not be able to stand without support. In a lockdown, a telehealth approach, with no supervised exercise, could be harmful to these individuals. Physiotherapy for individuals with severe neurological disorders requires careful assessment of motor, cognitive and emotional impairments. In some cases, patients are not able to perform their exercises without the therapist's assistance (48, 49).

To surmount these challenges, further research is needed to test the safety and feasibility of telehealth assessments and interventions for people with severe neurological disorders. There are information gaps around delivering physiotherapy programmes and rehabilitation for people with neurological disorders via telehealth; in particular, in relation to assessment and measurement, which are vital to appropriate delivery of rehabilitation. Telehealth is a healthcare delivery model which could improve patient care and decrease social disconnection, but validated evidence is needed to address known gaps and to correctly and effectively inform clinical practice (34).

RUNNING AGAINST THE CLOCK—HOW CAN WE MINIMIZE THE ACCELERATED PROGRESSION POTENTIALLY CAUSED BY LOCKDOWN?

Many neurological disorders (such as Alzheimer's disease, PD, MS) are progressive. The consequences of social disconnection due to lockdown (e.g., an exacerbation of inactive lifestyle and reduction in healthcare appointments) may increase the rate of progression of these neurological disorders. Therefore, with the relaxation in lockdown policies in some countries, it is time to implement clinical strategies to reduce the accelerated progression of neurological disorders. One clinical strategy, for people who are in the early stages of the disease, is multicomponent exercise. Jimenez-Pavol et al. (50), recently published an exercise recommendation for older people that may suit people in the early stages of neurological conditions. These recommendations need to be carefully tailored for individuals' conditions, symptoms, context, and preferences. For people in the more severe stages of their condition, a personalized approach is needed to identify whether new symptoms or complications have emerged since the commencement of lockdown. If therapists identify such symptoms or complications (e.g., freezing of gait in a person with PD), then specific evidence-based interventions should be initiated to address these problems.

Furthermore, physiotherapists should be considered "essential workers." Widespread use of telehealth for initial screening of people with neurological conditions would help to stratify individuals, maximize outcomes and minimize risks. Thereafter, physiotherapists could provide periodic in-person visits with the use of personal protective equipment (PPE) and precautions, to ensure safety and progression of home-based exercises. For individuals who suffer from severe gait and balance impairments, prescription of assistive devices should be considered to optimize safety, as well as occupational therapy interventions based on safe mobility training (51). Other measures, such as the installation of bars in the shower or toilet, or the removal of environmental hazards, may help to prevent falls in the home setting.

As mentioned in the section of this paper entitled "What Are the Impacts of Lockdown on People with Neurological Conditions?," caregivers may also be negatively impacted because

of social disconnection during the pandemic. Therefore, exercises and therapies may also be offered to primary caregivers to improve their mental and physical health. By caring for the caregivers, delivery of optimal care for people with neurological disorders is more likely to be achieved (52).

THE ROLE OF PUBLIC HEALTH LAW: BALANCING THE PATIENT'S RIGHTS WITH PUBLIC HEALTH DURING A PANDEMIC

According to Gostin (53), public health law is the "study of the legal powers and duties of the state to assure the conditions for people to be healthy and the limitations on the power of the state to constrain the autonomy, privacy, liberty, proprietary, or other legally protected interests of individuals for the common good." Public health laws offer essential tools for improving health and preventing illness and injury. Regulatory devices are some of the oldest and most significant tools available to public health policymakers and practitioners. The valuable role of law is evident in all of public health's greatest achievements (54). For example, the control of infectious diseases is supported by legal tools such as sanitary codes, drinking water standards, quarantine and isolation authority, building codes, pest control programmes, and inspection of food establishments (55).

Tension between policy options arose in the nineteenth and early twentieth centuries during infectious disease outbreaks and has re-emerged as health systems introduced public health laws and policies to address chronic conditions (53, 56). Infectious disease laws, introduced throughout the twentieth century, have provided extensive and coercive public health powers to prevent the spread of communicable disease. The essence of the tension is that policymakers and legislatures need to make difficult trade-offs when making determinations about the weight to give to the individual (and his/her health needs and rights), versus the public's health, or the collective good (57).

Laws authorizing the quarantine of people with certain infectious diseases are possible in jurisdictions which have legal traditions that permit limits to individual liberty to protect the common good. In doing so, there is a policy trade-off whereby other rights are given less weight. As we, and others (5, 6), have argued, the adverse impacts caused by lockdown (such as social disconnection and reduced exercise) may be magnified for people with neurological conditions. During COVID-19, policymakers have chosen to introduce measures such as lockdown to prioritize lives and the collective good. Policymakers also aimed to protect older people and vulnerable populations. However, as outlined above, these policies have been a "two-edged sword" for people with neurological conditions.

Given this outcome, this paper argues that policymakers and legislatures should consider amendments to regulations and policies to support interventions which could minimize the impact of lockdown, especially for vulnerable populations. This recalibration could be undertaken while also minimizing risks to public health. For example, as this paper has highlighted, suitable telehealth interventions could be devised to care for people with neurological conditions during a pandemic. In some jurisdictions, regulatory changes will be needed to enable the delivery of telehealth.

In addition, regulations could be amended to enable physiotherapists to undertake face-to-face care for their patients with neurological conditions. The regulations should also provide for adequate funding to maximize the likelihood that correct procedures (such as the use of PPE) will be implemented. During COVID-19, other health care provider, such as medical practitioners, have been lawfully permitted to provide care to patients while wearing PPE on the basis that such services are "essential." This paper argues that physiotherapy care for people with neurological conditions is also "essential" and that governance and regulatory structures should reflect that.

This paper recognizes that developing jurisdictions may struggle to implement applicable international health law. While international health law (such as the International Health Regulations) applies to many developing countries, the implementation challenges are well-documented (58–60). For example, developing countries that are signatories of the international regulations may not have incorporated these into their domestic regulatory framework, thereby limiting the legal impact of the regulations. Furthermore, developing countries may struggle to implement regulations into their domestic health and legal systems because of limited resources and poorly designed enforcement mechanisms. Scholars have highlighted a range of strategies to address these challenges such as public-private cooperation and negotiated rulemaking (59).

Underlying regulatory structures have a strong influence on how countries are able to respond to pandemics. Overall, public health regulatory powers should allow for flexibility and the opportunity to meet not only the public health need, but also the needs of vulnerable populations.

CONCLUSION

This perspective paper outlines how people with neurological conditions are a vulnerable population who may be adversely impacted by lockdown during COVID-19. It is well-known that social connection enhances health and well-being, while social disconnection is a powerful determinant of poor health and neurobiological changes. Researchers have found that the negative impacts of social isolation may be comparable to traditional clinical risk factors (61). These negative outcomes are amplified for people with neurological conditions because they need extensive care, physiotherapy, and regular activity to maintain their health. Additional magnification of these negative health outcomes occurs in jurisdictions which have poor integration of public health and social systems.

Given the potential burden on the healthcare system, and the policy focus on patient centered care, policymakers and practitioners around the globe should be keenly interested in investing in strategies to minimize the adverse health outcomes of social isolation on people with neurological conditions. Telehealth and appropriate exercise regimes have enormous

potential to address the challenges, but further research is needed to provide a robust evidence base, particularly for remote assessments and interventions or hybrid models including remote and face to face components. For patients in countries with limited access to technology, including telehealth, home-based exercises provide a feasible, and accessible, alternative.

COVID-19 presents policymakers with an opportunity to recalibrate the weight given to "high needs, high cost" individuals versus public health during pandemics. With such realignment, we will be better positioned to meet the needs of people with neurological disorders and to manage the impacts of social disconnection during global pandemics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

PP was responsible for the original idea, writing, and editing the manuscript. JS-M was responsible for writing, editing, and reviewing the manuscript. LH, CC, and SL were responsible for editing and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Pelicioni PHS, Lord SR. COVID-19 will severely impact older people's lives, and in many more ways than you think! *Braz J Phys Ther*. (2020) 24:293–4. doi: 10.1016/j.bjpt.2020.04.005
2. Garnier-Crussard A, Forestier E, Gilbert T, Krolak-Salmon P. Novel coronavirus (COVID-19) epidemic: what are the risks for older patients? *J Am Geristr Soc.* (2020) 68:939–40. doi: 10.1111/jgs.16407
3. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. *J Travel Med.* (2020) 27:taaa020. doi: 10.1093/jtm/taaa020
4. Salathé M, Althaus CL, Neher R, Stringhini S, Hodcroft E, Fellay J, et al. COVID-19 epidemic in Switzerland: on the importance of testing, contact tracing and isolation. *Swiss Med Wkly.* (2020) 150:w20225. doi: 10.4414/smw.2020.20225
5. Helmich RC, Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *J Parkinsons Dis.* (2020) 10:351–4. doi: 10.3233/JPD-202038
6. Shalash A, Roushdy T, Essam M, Fathy M, Dawood NL, Abushady EM, et al. Mental health, physical activity, and quality of life in Parkinson's disease during COVID-19 pandemic. *Mov Disord.* (2020) 35:1097–9. doi: 10.1002/mds.28134
7. Gyasi RM, Yeboah AA, Mensah CM, Ouedraogo R, Addae EA. Neighborhood, social isolation and mental health outcome among older people in Ghana. *J Affect Disord.* (2019) 259:154–63. doi: 10.1016/j.jad.2019.08.024
8. Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. *Proc Natl Acad Sci USA.* (2013) 110:5797–801. doi: 10.1073/pnas.1219686110
9. Zipprich HM, Teschner U, Witte OW, Schonenberg A, Prell T. Knowledge, attitudes, practices, and burden during the COVID-19 pandemic in people with Parkinson's disease in Germany. *J Clin Med.* (2020) 9:1643. doi: 10.3390/jcm9061643
10. Tanne JH, Hayasaki E, Zastrow M, Pulla P, Smith P, Rada AG. Covid-19: how doctors and healthcare systems are tachling coronavirus worldwide. *BMJ.* (2020) 368:m1090. doi: 10.1136/bmj.m1090
11. Peeri NC, Shresta N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol.* (2020) 49:717–26. doi: 10.1093/ije/dyaa033
12. Haines KJ, Berney S. Physiotherapists during COVID-19: usual business, in unusual times. *J Physiother.* (2020) 66:67–9. doi: 10.1016/j.jphys.2020.03.012
13. Ferreira MJ, Irigoyen MC, Consolim-Colombo F, Saraiva JFK, De Angelis K. Physically active lifestyle as an approach to confronting COVID-19. *Arq Bras Cardiol.* (2020) 114:601–2. doi: 10.36660/abc.20200235
14. Bowden-Davies KA, Pickles S, Sprung VS. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. *Ther Adv Endocrinol Metab.* (2019) 10:2042018819888824. doi: 10.1177/2042018819888824
15. Ellis T, Motl RW. Physical activity behavior change in persons with neurologic disorders: overviw and examples from Parkinson disease and multiple sclerosis. *J Neurol Phy Ther.* (2013) 37:85–90. doi: 10.1097/NPT.0b013e31829157c0
16. Hall G, Laddu DR, Phillips SA, Lavie CJ, Arena R. A tale of two pandemics: how will COVID-19 and global trends in physical inactivity and sedentary behavior affect one another? *Prog Cardiovasc Dis.* (2020) S0033–0620: 30077–3 doi: 10.1016/j.pcad.2020.04.005
17. Boeschoten RE, Braamse AMJ, Beekman ATF, Cuijpers P, Van Oppen P, Dekker J, et al. Prevalence of depression and anxiety and multiple sclerosis: a systematic review and meta-analysis. *J Neurol Sci.* (2017) 372:331–41. doi: 10.1016/j.jns.2016.11.067
18. Kuring JK, Mathias JL, Ward L. Prevalence of depression, anxiety and PTSD in people with dementia: a systematic review and meta-analysis. *Neuropsychol Rev.* (2018) 28:393–416. doi: 10.1007/s11065-018-9396-2
19. Salari M, Zali A, Ashrafi F, Etemadifar M, Sharma S, Hajizadeh N, et al. Incidence of anxiety in Parkinson's disease during the coronavirus disease (COVID-19) pandemic. *Mov Disord.* (2020) 35:1095–6. doi: 10.1002/mds.28116
20. Tuncay FO, Fertelli TK. Effects of the caregiver burden perceived by caregivers of patients with neurological disorders on caregiver wellbeing and caregiver stress. *Perspect Psychiatr Care.* (2019) 55:697–702. doi: 10.1111/ppc.12405
21. Cowman S, Royston M, Hickey A, Horgan F, McGee H, O'Neil D. Stroke and nursing home care: a national survey of nursing homes. *BMC Geriatr.* (2010) 10:4. doi: 10.1186/1471-2318-10-4
22. Gaugler JE, Yu F, Davila HW, Shippee T. Alzheimer's disease and nursing homes. *Health Aff.* (2014) 33:650–7. doi: 10.1377/hlthaff.2013.1268
23. Walker XJ, Walters DL, Millar N. New Zealand nursing homes (aged residential care facilities) and COVID-19 pandemic. *J Nurs Home Res.* (2020) 6:38–9. doi: 10.14283/jnhrs.2020.9
24. Esain I, Gil SM, Bidaurrazaga-Letona I, Rodriguez-Larrad A. Effects of 3 months of detraining on functional fitness and quality of life in older adults who regurlaly exercise. *Aging Clin Exp Res.* (2019) 31:503–10. doi: 10.1007/s40520-018-0990-1
25. Boucher BJ. The problems of vitamin d insufficiency in older people. *Aging Dis.* (2012) 3:313–29.
26. Morin L, Larranaga AC, Welmer A, Ruzzuto D, Wastesson JW, Johnell K. Polypharmacy and injurious falls in older adults: a nationwide nested case-control study. *Clin Epidemiol.* (2019) 11:483–93. doi: 10.2147/CLEP.S201614
27. Wilson NM, Hilmer SH, March LM, Cameron ID, Lord SR, Seibel MJ, et al. Associations between drug burden index and falls in older people in residential aged care. *J Am Geriatr Soc.* (2011) 59:875–80. doi: 10.1111/j.1532-5415.2011.03386.x
28. Pelicioni PHS, Menant JC, Latt MD, Lord SR. Falls in Parkinson's disease subtypes: risk factors, locations and circumstances. *Int J Environ Res Public Health.* (2019) 16:2216. doi: 10.3390/ijerph16122216

29. Kongwattanakul K, Hiengkaew V, Jalayondeja C, Sawangdee Y. A structural equation model of falls at home in individuals with chronic stroke, based on the international classification of function, disability, and health. *PLoS ONE.* (2020) 15:e0231491. doi: 10.1371/journal.pone.0231491
30. Rice L, Kalron A, Berkowitz SH, Backus D, Sosnoff JJ. Fall prevalence in people with multiple sclerosis who use wheelchairs and scooters. *Medicine.* (2017) 96:e7860. doi: 10.1097/MD.0000000000007860
31. Grimbergen YAM, Schrag A, Mazibrada G, Borm GF, Bloem BR. Impact of falls and fear of falling on health-related quality of life in patients with Parkinson's disease. *J Parkinsons Dis.* (2013) 3:409–13. doi: 10.3233/JPD-120113
32. Andersson AG, Kamwendo K, Appelros P. Fear of falling in stroke patients: relationship with previous falls and functional characteristics. *Int J Rehabil Res.* (2008) 31:261–4. doi: 10.1097/MRR.0b013e3282fba390
33. Mazunder R, Lambert WE, Nguyen T, Bourdette DN, Cameron MH. Fear of falling is associated with recurrent falls in people with multiple sclerosis: a longitudinal cohort study. *Int J MS Care.* (2015) 17:164–70. doi: 10.7224/1537-2073.2014-042
34. Tuckson RV, Edmunds M, Hodgkins ML. Telehealth. *N Engl J Med.* (2017) 377:1585–92. doi: 10.1056/NEJMsr1503323
35. Cottrell MA, Russel TG. Telehealth for musculoskeletal physiotherapy. *Musculoskelet Sci Pract.* (2020) 48:102193. doi: 10.1016/j.msksp.2020.102193
36. Dantas LO, Barreto RPG, Ferreira CHJ. Digital physical therapy in the COVID-19 pandemic. *Braz J Phys Ther.* (2020) 24:381–3. doi: 10.1016/j.bjpt.2020.04.006
37. Fraser S, Mackean T, Grant J, Hunter K, Ivers R. Use of telehealth for health care of indigenous peoples with chronic conditions: a systematic review. *Rural Remote Health.* (2017) 17:4205. doi: 10.22605/RRH4205
38. Caffery LJ, Bradford NK, Wickramasinghe SI, Hayman N, Smith AC. Outcomes of using telehealth for the provision of healthcare to aboriginal and Torres strait islander people: a systematic review. *Aust N Z J Public Health.* (2017) 41:48–53. doi: 10.1111/1753-6405.12600
39. Flynn A, Allen NE, Dennis S, Canning CG, Preston E. Home-based prescribed exercise improves balance-related activities in people with Parkinson's disease and has benefits similar to centre-based exercise: a systematic review. *J Physiother.* (2019) 65:188–99. doi: 10.1016/j.jphys.2019.08.003
40. Van der Kolk NM, De Vries NM, Kessels RPC, Joosten H, Zwinderman AH, Post B, et al. Effectivenes of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol.* (2019) 18:998–1008. doi: 10.1016/S1474-4422(19)30285-6
41. Taylor ME, Close JCT, Lord SR, Kurrle SE, Webster L, Savage R, et al. Pilot feasibility study of a home-based fall prevention exercise program (StandingTall) delivered through a tablet computer (iPad) in older people with dementia. *Austral J Ageing.* (2019) 39:e278-87. doi: 10.1111/ajag.12717
42. Ginis P, Nieuwboer A, Dorfman M, Ferrari A, Gazit E, Canning CG, et al. Feasibility and effects of home-based smartphone-delivered automated feedback training for gait in people with Parkinson's disease: a pilot randomized controlled trial. *Parkinsonism Relat Disord.* (2016) 22:28–34. doi: 10.1016/j.parkreldis.2015.11.004
43. Song J, Paul SS, Caetano MJD, Smith S, Dibble LE, Love R, et al. Home-based step training using videogame technology in people with Parkinson's disease: a single-blinded randomised controlled trial. *Clin Rehabil.* (2018) 32:299–311. doi: 10.1177/0269215517721593
44. Hoang P, Choene D, Gandeiva S, Smith S, Lord SR. Effects of a home-based step training programme on balance, stepping, cognition and functional performance in people with multiple sclerosis – a randomized controlled trial. *Mult Scler.* (2016) 22:94–103. doi: 10.1177/1352458515579442
45. Ashburn A, Fazakarley L, Ballinger C, Rickering R, McLellan LD, Fitton C. A randomized controlled trial of a home based exercise programme to reduce the risk of falling among people with Parkinson's disease. *J Neurol Neurosurg Psychatry.* (2007) 78:678–84. doi: 10.1136/jnnp.2006.099333
46. Canning CG, Sherrington C, Lord SR, Close JCT, Heritier S, Heller GZ, et al. Exercise for falls prevention in Parkinson disease. A randomized controlled trial. *Neurology.* (2015) 84:304–12. doi: 10.1212/WNL.0000000000001155
47. Chivers-Seymour K, Pickering R, Rochester L, Roberts HC, Ballinger C, Hulbert S, et al. Multicentre, randomized controlled trial of PDSAFE, a physiotherapist-delivered fall prevention programme for people with Parkinson's. *J Neurol Neurosurg Psychatry.* (2019) 90:774–82. doi: 10.1136/jnnp-2018-319448
48. Quinn L, Kegelmeyer D, Kloos A, Rao AK, Busse M, Fritz NE. Clinical recommendations to guide physical therapy practice for Huntington disease. *Neurology.* (2020) 94:217–28. doi: 10.1212/WNL.0000000000008887
49. Van de Weijer SCF, Hommel ALAJ, Bloem BR, Nonnekes J, De Vries NM. Promising non-pharmacological therapies in PD: targeting late stage disease and the role of computer based cognitive training. *Parkinsonism Relat Disord.* (2018) 46:S42–6. doi: 10.1016/j.parkreldis.2017.09.002
50. Jimenez-Pavon D, Carbonell-Baeza A, Lavie CJ. Physical exercise as therapy to fight against the mental and physical consequences of COVID-19 quarantine: special focus in older people. *Prog Cardiovasc Dis.* (2020) 63:386–8. doi: 10.1016/j.pcad.2020.03.009
51. Stack EL, Roberts HC. Slow down and concentrate: time for a paradigm shift in fall prevention among people with Parkinson's disease? *Parkinsons Dis.* (2013) 2013:704237. doi: 10.1155/2013/704237
52. Zacharopolou G, Zacharopolou V, Lazakidou A. Quality of life for caregivers of elderly patients with dementia and measurement tools: a review. *Int J Health Res Innov.* (2015) 3:49–64.
53. Gostin LO. *Public Health Law: Power, Duty, Restraint. Revised and Expanded.* 2nd ed. Berkeley, CA: University of California Press (2008).
54. Goodman RA, Hoffman RE, Lopez W, Matthews GW, Rothstein M, Foster K. *Law in Public Health Practice*. Oxford: Oxford University Press (2007).
55. *Public Health Act 2010* (NSW).
56. Tognotti E. Lessons from the history of quarantine, from plague to influenza A. *Emerg Infect Dis.* (2013) 19:254–9. doi: 10.3201/eid1902.120312
57. Reynolds C. Public health law: its problems and challenges. *UNSW Law J.* (1997) 20:576–93.
58. Isasi RM, Nguyen TM. The global governance of infectious diseases: the World Health Organization and the International Health Regulations. *Glob Govern Infect Dis.* (2005) 43:497–510. doi: 10.29173/alr1266
59. Mok E, Gostin LO, Das Gupta M, Levin M. Implementing public health regulations in developing countries: lessons from the OECD countries. *J Law Med Ethics.* (2010) 38:508–19. doi: 10.1111/j.1748-720X.2010.00509.x
60. Gostin LO, Mohanan JT, Kaldor J, DeBartolo M, Friedman EA, Gottschalk K, et al. The legal determinants of health: harnessing the power of law for global health and sustainable development. *Lancet.* (2019) 393:1857–910. doi: 10.1016/S0140-6736(19)30233-8
61. Pantell M, Rehkopf D, Jutte D, Syme SL, Balmes J, Adler N. Social isolation: a predictor of mortality comparable to traditional clinical risk factors. *Am J Public Health.* (2013) 103:2056–62. doi: 10.2105/AJPH.2013.301261

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 16 November 2020
doi: 10.3389/fneur.2020.591423

Change in Patient Flow in the Epilepsy Care Network Due to Novel Coronavirus Infection: An Opportunity to Strengthen Local Interdisciplinary Epilepsy Care With General Physicians

Ayataka Fujimoto[1,2]*, *Keishiro Sato*[1,3] *and Hideo Enoki*[1,4]

[1] Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, [2] Departments of Neurosurgery, Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, [3] Departments of Neurology, Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan, [4] Departments of Pediatric Neurology, Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan

OPEN ACCESS

Edited by:
Giovanni Assenza,
Campus Bio-Medico University, Italy

Reviewed by:
Jacopo Lanzone,
Policlinico Universitario Campus Bio-Medico, Italy
Tommaso Tufo,
Catholic University of the Sacred Heart, Rome, Italy

***Correspondence:**
Ayataka Fujimoto
afujimotoscienceacademy@gmail.com

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 04 August 2020
Accepted: 16 October 2020
Published: 16 November 2020

Citation:
Fujimoto A, Sato K and Enoki H (2020) Change in Patient Flow in the Epilepsy Care Network Due to Novel Coronavirus Infection: An Opportunity to Strengthen Local Interdisciplinary Epilepsy Care With General Physicians. Front. Neurol. 11:591423. doi: 10.3389/fneur.2020.591423

Introduction: Novel coronavirus disease 2019 (COVID-19) infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading worldwide. We hypothesized that patient flow in epilepsy care would change as a result of the COVID-19 pandemic. The purpose of this study was to compare the number of patients who visited our epilepsy center before and during the first peak of the pandemic.

Methods: We recorded the number of patients with epilepsy referred from general physicians (GPs) to our hospital (GP–H group), the number of patients who visited our hospital on a regular basis (R group), and the number of patients referred from our hospital to GPs (H–GP group) between July 2019 and June 2020.

Results: A total of 1,839 epilepsy patients made 4,197 visits to our hospital: 979 males and 860 females (age range, 0–94 years; mean age, 37.6 years; median age, 34 years). There were 433 patients in the GP–H group (247 before the pandemic, 186 during the first peak of the pandemic; $p = 0.008$). In the R group, 1,406 patients made 3,764 visits (1,992 visits before the pandemic, 1,772 during the first peak of the pandemic). In the H–GP group, 135 patients were referred to GPs (47 patients before the pandemic, 88 patients during the first peak of the pandemic; $p = 0.023$).

Conclusion: Patient flow in the epilepsy care network changed as a result of the COVID-19 pandemic. These changes might present an opportunity to strengthen local interdisciplinary epilepsy care.

Keywords: patient flow, local interdisciplinary epilepsy network, economic crisis, COVID-19, SARS-CoV-2

INTRODUCTION

As epilepsy is a chronic disease that requires regular medication and continuous medical oversight, it is important to have insight into the impact of the novel coronavirus disease 2019 (COVID-19) on the epilepsy care network. Currently, COVID-19 infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading worldwide and places massive strain on health services. Around the beginning of February 2020, an outbreak occurred in Japan onboard the Diamond Princess, a British-registered cruise ship that was carrying 3,711 passengers, of whom 712 were infected by SARS-CoV-2. The number of people infected in foreign countries and entering Japan increased from the beginning of March. Peak infection occurred in mid-April, mainly in urban areas, before temporarily declining in mid-May. According to the World Health Organization COVID-19 Dashboard (https://covid19.who.int/region/wpro/country/jp), the second peak period started at the beginning of July 2020, with the highest peak in August.

Daily broadcasts of medical staff in personal protective equipment made a strong impression on the public, who began to refrain from seeking medical services.

Japan has a universal health insurance system with free access and low cost (1). Before the pandemic, patients tended to visit large hospitals that are well-equipped and have full medical services. The COVID-19 mortality rate at the first peak was lower in Japan than in other countries (2–4), perhaps because the Japanese insurance system covers the majority of medical services and is available to everyone (5). However, because there is free access at low cost, it was common before the pandemic for people to demand unnecessary medical services at large hospitals (6). Thus, the ease of access by any patient to treatment at a tertiary level hospital can discourage patients from visiting their local general physician (GP). As this situation is limited to the Japanese system, most studies of the Japanese medical care system have been published in Japanese, and the Japanese situation is not widely known, although one paper sharply described this situation as a "Tragedy of the Commons" (7).

Since the pandemic, however, people have begun to consider that the risk of SARS-CoV-2 infection is higher at a tertiary hospital than at a local clinic, as the likelihood of social contact is greater at a large institution (8). In addition, negative rumors and fake information have dissuaded people from visiting hospitals (9, 10), which is the opposite of the pre-pandemic situation. As patients with epilepsy have psychological as well as physical stress (11), these patients suffer a greater negative impact compared with patients without epilepsy (12). Therefore, patients with epilepsy should be directed to the most appropriate medical service according to professional advice rather than making a subjective decision themselves based on rumors or fake information.

We hypothesized that patient flow in epilepsy care has changed in response to the COVID-19 pandemic. The purpose of this study is to compare the number of patients who visited our epilepsy center before the pandemic and during the first peak.

METHODS

Study Design and Ethics Approval

The ethics committee of Seirei Hamamatsu General Hospital, Japan, approved the protocol for this retrospective study, which was performed in accordance with the principles of the Declaration of Helsinki. The subjects of the study were identified in a review of the electronic medical records of patients who visited our epilepsy center between July 2019 and June 2020 at the Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital.

Clinical Information

We collected information from patients who had visited our epilepsy center between July 2019 and June 2020 because the first half of this period was pre-pandemic and the second half was just within the first peak of the pandemic period in Japan. Patient age was that recorded at the last visit.

Primary Outcome Measurement

We recorded the number of patients per month who were classified into each of the following three groups: (1) those referred by their GP for their first visit at our hospital (GP–H group), (2) those who visit our hospital on a regular basis (R group), and (3) those referred by our hospital to their GP (H–GP group). When we refer patients to GPs, their epilepsy information is shared between the hospital epilepsy specialists and the regional epilepsy network of GPs using the Epi Passport booklet (13).

Secondary Outcome Measurement

Type of Epilepsy, Seizure Outcome and Volume of Epilepsy Surgeries Performed

We reviewed the types of epilepsy that were referred to GPs and the outcomes of seizure control in patients in the H–GP group. We classified epilepsy type according to the International League Against Epilepsy (ILAE) 2017 (14) criteria as (1) generalized epilepsy, (2) focal epilepsy, (3) focal and generalized combined epilepsy, and (4) self-limited focal epilepsy. We classified seizure outcome into five levels using a modified version of the ILAE classification system: level 1 (seizure free); level 2 (1–3 seizure days/year); level 3 (4 seizure days/year to 50% reduction); level 4 (<50% reduction in seizures); and level 5 (uncountable due to <1 year of follow up) (13, 15). We recorded the ILAE classification for the most recent outcome at the time when they visited our clinic.

We reviewed the number of epilepsy surgeries performed per month and compared the numbers before the pandemic and during the first peak. We compared the first 6 months (July–December 2019, pre pandemic period) with the second 6 months (January–June 2020, first peak of the pandemic).

Second Peak Period

For reference, we also compared number of patients in the H-GP group, R-group, GP-H group, and epilepsy surgeries performed per month in the first 3 months (July–September 2020) of the second peak of the pandemic with those performed in the combined pre pandemic period and first peak of the pandemic.

Statistical Analysis

We used Student's *t*-test to compare the number of patients and the volume of epilepsy surgeries before the pandemic and during the first peak of the pandemic. A $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using Sigma Plot version 14 (Systat Software, San Jose, CA).

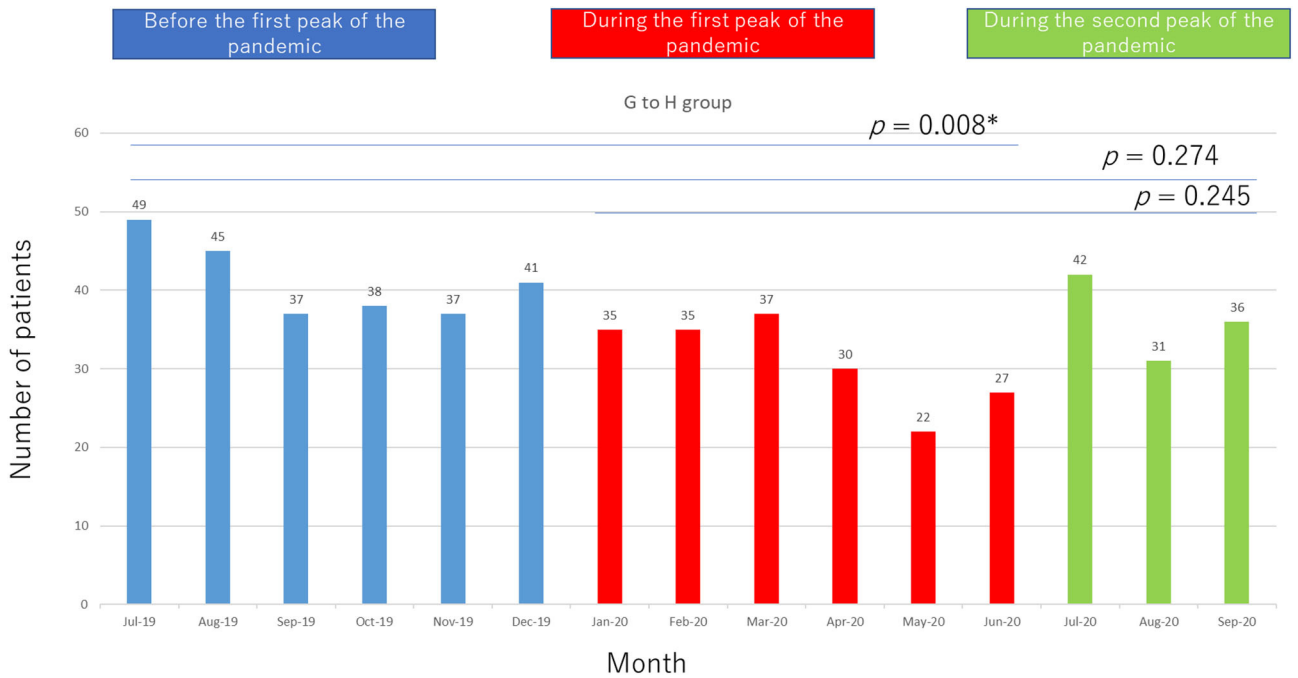


FIGURE 1 | Patient flow from general physicians to our hospital (GP–H group).

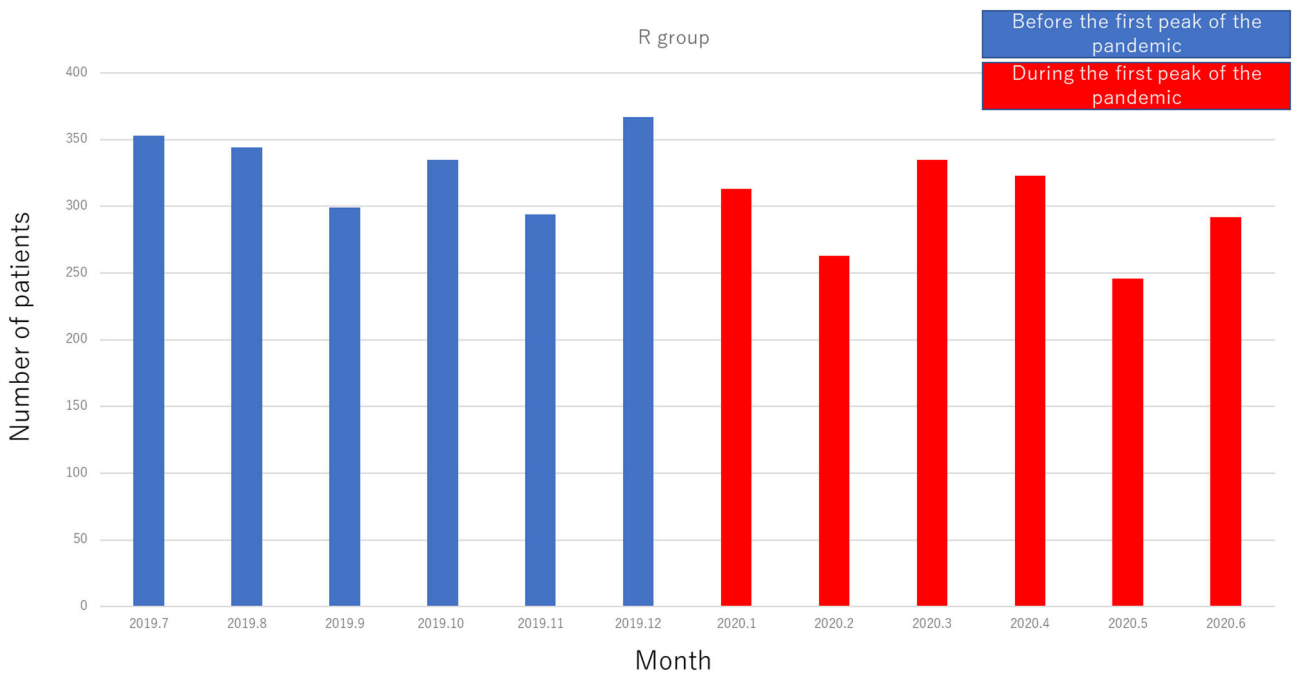


FIGURE 2 | Flow of patients who visit our hospital on a regular basis (R group).

RESULTS

Clinical Information

Between July 2019 and June 2020, 1,839 patients made 4,197 visits to our epilepsy center. There were 979 males and 860 females [age range, 0–94 years; mean age, 37.6 years; median age, 34 years; standard deviation (SD), 18.3 years].

Primary Outcome Measurement

GP–H Group

A total of 433 patients in the GP–H group first visited our epilepsy center: 247 patients before the pandemic and 186 patients during the first peak of the pandemic. The age range in this group was 0–94 years (mean age, 38.4 years; median age, 34 years; SD, 18.3 years).

The number of patients in this group per month before and during the pandemic is shown in **Figure 1** (significant difference, $p = 0.008$).

R Group

A total of 1,406 patients in the R group made 3,764 visits to our epilepsy center (age range, 1–87 years; mean age, 37.4 years; median age, 34 years; SD, 18.4 years). There were 1,992 visits before the pandemic and 1,772 visits during the pandemic.

The number of monthly visits before and during the pandemic are shown in **Figure 2** (no significant difference).

H–GP Group

A total of 135 patients were referred to GPs during the study period. There were 47 patients referred before the pandemic and 88 patients referred during the pandemic. The

TABLE 1 | Summary of epilepsy types in the H–GP group before and during the first peak of the pandemic.

	Before the pandemic	During the pandemic
Generalized epilepsy	14 (30%)	33 (37%)
Focal epilepsy	30 (64%)	52 (58%)
Focal + generalized epilepsy	2 (4%)	4 (5%)
Self-limited focal epilepsy	1 (2%)	0

TABLE 2 | Comparison of seizure control outcomes in the H–GP group before and during the first peak of the pandemic.

	Before the pandemic	During the pandemic
Level 1	42 (89%)	64 (72%)
Level 2	0	3 (3%)
Level 3	1 (2%)	7 (8%)
Level 4	2 (4%)	1 (1%)
Level 5	2 (4%)	14 (16%)

Level 1 (seizure free); level 2 (1–3 seizure days/year); level 3 (4 seizure days/year to 50% reduction); level 4 (<50% reduction in seizures) and; level 5 (uncountable due to less than a year follow up).

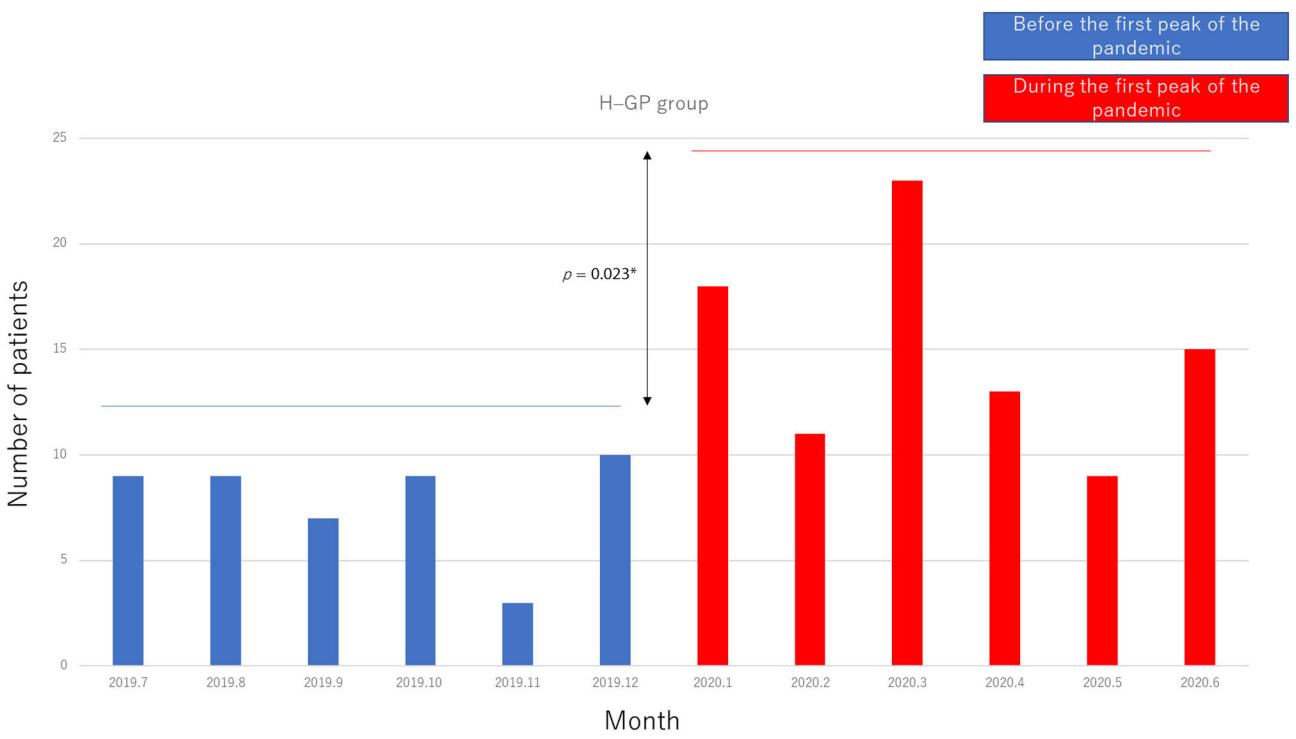


FIGURE 3 | Patient flow from our hospital to general physicians (H–GP group).

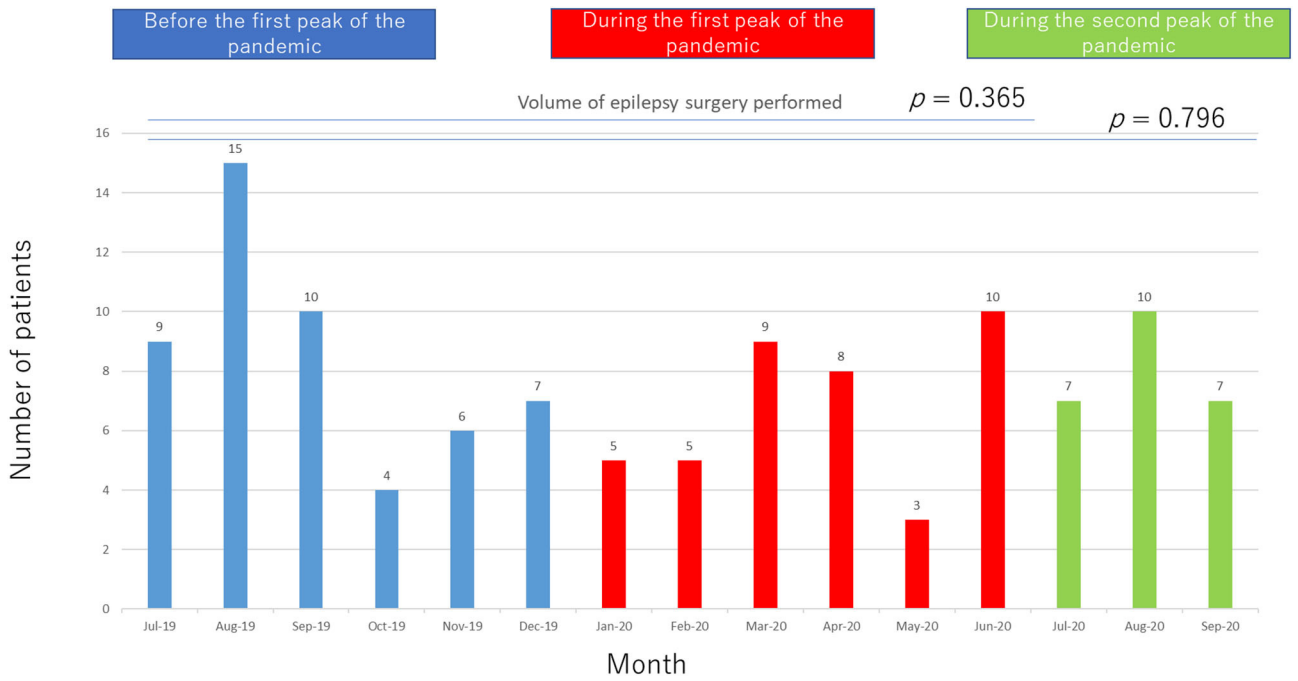


FIGURE 4 | Monthly volumes of epilepsy surgeries performed.

age range was 0–94 years (mean age, 38.4 years; median age, 34 years; SD, 18.3 years).

The numbers of referrals per month before and during the pandemic are shown in **Figure 3** (significant difference, $p = 0.023$).

Secondary Outcome Measurement

Type of Epilepsy, Seizure Outcomes and Volume of Epilepsy Surgeries Performed

There was no statistically significant difference in the H–GP group before and during the pandemic in terms of type of epilepsy (**Table 1**). In terms of seizure control outcomes, there was no statistically significant difference in the H–GP group before and during the pandemic (**Table 2**). We performed 51 epilepsy surgeries before and 40 surgeries during the pandemic (no significant significance) (**Figure 4**).

Second Peak Period

Compared with the data obtained in July 2019–June 2020, data obtained in July–September 2020 showed a greater number of patients in the R group ($p = 0.017$) and a slight increase in the number of patients in the H–GP group during the second peak, but the difference was not statistically significant ($p = 0.059$). In terms of the volume of epilepsy surgeries performed, there was no statistically significant difference among the pre pandemic, first peak, and second peak periods.

DISCUSSION

The following changes in patient flow to epilepsy care services occurred during the COVID-19 pandemic: (1) the number of patients in the GP–H group decreased, (2) the number of patients in the H–GP group increased, and (3) there was no change in the number of patients in the R group or the volume of surgeries performed for epilepsy during the first peak of the pandemic.

Compared with the first peak, the number of patients in the H–GP group showed a tendency to increase and the number of patients in the R group increased during the second peak of the pandemic.

The number of patients in the GP–H group may have decreased because fewer patients than usual visited a GP during the first peak of the pandemic in Japan, when people were advised not to leave home unless absolutely necessary. It is natural that the number of GP visits would decrease while this policy was in place. We consider that this reduction in patient flow also reduced the number of patients referred to our hospital. People with epilepsy experience social difficulties if they suffer an epileptic seizure in ordinary life; however, the shift to online delivery of many services such as telemetry (11, 16) reduced the need for people to leave their homes. An epileptic seizure is less socially disruptive if it occurs at home than in a public place (e.g., at work, school, while driving or using public transportation, eating out). The arrival of the pandemic heightened the need for streamlining patient flow to epilepsy care services (and also for other diseases); however, economic crisis due to congested patient flow was already imminent in many medical facilities (17–20).

Regional multidisciplinary epilepsy care has been established in our region (Shizuoka, Japan) (13). Although patient flow changed during the pandemic, the number of patients in the R group increased and the volume of epilepsy surgeries performed

was maintained even during the second peak, possibly because of the strength of the regional epilepsy network. The increased number of patients in the H–GP group might have contributed to the economic well-being of regional GPs; however, further study is required to prove this.

As seizure outcomes improved over the study period in the H–GP group (**Table 2**), it is natural that patients would want to reduce the risk of SARS-CoV-2 infection at a large hospital. In addition, a previous study found an increase in the income of epilepsy patients who were seen by local GPs, which was another reason for us to refer patients without seizures to GPs (13). Therefore, it could be said that patients and physicians were thinking similarly at the start of the COVID-19 pandemic. The COVID-19 situation presents an opportunity to streamline patient flow and strengthen local multidisciplinary practice in the epilepsy care network.

There was no significant change in terms of the numbers of patients who visited our department on a regular basis, or in the volumes of epilepsy surgeries. This finding indicates that patient scheduling was efficient and that there was a reduction in irrelevant services provided by our department.

As a limitation of this study, our evaluation was performed during only the first peak of the COVID-19 pandemic, and we cannot anticipate future change in patient flow as the pandemic persists. However, it is known that congested patient flow would have caused an economic crisis in the medical system at some time in the near future. As this is a serious problem facing the medical system, it is important that patient flow is activated appropriately. Whether intensive epilepsy care referral to GPs could activate patient flow and activate the medical economy of the epilepsy network is beyond the scope of the present study, but is worthy of further investigation. There could be some bias in the present study because the periods of observation do not overlap and patient visits during the year are not distributed normally.

CONCLUSION

The COVID-19 pandemic has changed patient flow in the epilepsy care network, and this situation presents an opportunity to strengthen multidisciplinary epilepsy care to include local GPs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Seirei Hamamatsu General Hospital, Japan, approved the protocol for this retrospective study, which was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

We analyzed the data of patients who visited our comprehensive epilepsy center, comprising the departments of Neurosurgery (AF), Neurology (KS), and Pediatric Neurology (HE). All authors contributed equally to data analysis, drafting, and revising the article, are accountable for all aspects of this work, and gave their approval for publication of the final version of the manuscript.

REFERENCES

1. Motomatsu K, Hirata N, Imamura T. New trends in the Japanese medical system in 2002. *Jpn Hosp.* (2002) 23–7.
2. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. *MedRxiv.* (2020). doi: 10.1101/2020.03.24.20042937
3. Shime N. Save the ICU and save lives during the COVID-19 pandemic. *J Intensive Care.* (2020) 8:1–3. doi: 10.1186/s40560-020-00456-1
4. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int J Surg.* (2020) 76:71–6. doi: 10.1016/j.ijsu.2020.02.034
5. Tashiro A, Shaw R. COVID-19 pandemic response in Japan: what is behind the initial flattening of the curve? *Sustainability.* (2020) 12:5250. doi: 10.3390/su12135250
6. Tsutsui T, Muramatsu N. Japan's universal long-term care system reform of 2005: containing costs and realizing a vision. *J Am Geriatr Soc.* (2007) 55:1458–63. doi: 10.1111/j.1532-5415.2007.01281.x
7. Nomura H, Nakayama T. The Japanese healthcare system. *Brit Med J.* (2005) 331:648–9. doi: 10.1136/bmj.331.7518.648
8. Teslya A, Pham TM, Godijk NG, Kretzschmar ME, Bootsma MCJ, Rozhnova G. Impact of self-imposed prevention measures and short-term government-imposed social distancing on mitigating and delaying a COVID-19 epidemic: a modelling study. *PLoS Med.* (2020) 17:e1003166. doi: 10.1371/journal.pmed.1003166
9. Jalali R, Mohammadi M. Rumors and incorrect reports are more deadly than the new coronavirus (SARS-CoV-2). *Antimicrob Resist Infect Control.* (2020) 9:68. doi: 10.1186/s13756-020-00738-1
10. Tasnim S, Hossain MM, Mazumder H. Impact of rumors and misinformation on COVID-19 in social media. *J Prev Med Public Health.* (2020) 53:171–4. doi: 10.3961/jpmph.20.094
11. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol.* (2020) 11:737. doi: 10.3389/fneur.2020.00737
12. Lanzone J, Cenci C, Tombini M, Ricci L, Tufo T, Piccioli M, et al. Glimpsing the impact of COVID19 lock-down on people with epilepsy: a text mining approach. *Front Neurol.* (2020) 11:870. doi: 10.3389/fneur.2020.00870
13. Fujimoto A, Ichikawa N, Sato K, Nishimura M, Enoki H, Okanishi T. Inclusion of general physicians in the multidisciplinary treatment team for epilepsy may lead to an economic benefit. *Epilepsy Behav.* (2019) 95:56–60. doi: 10.1016/j.yebeh.2019.03.041
14. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* (2017) 58:512–21. doi: 10.1111/epi.13709
15. Wieser HG, Blume WT, Fish D, Goldensohn E, Hufnagel A, King D, et al. ILAE Commission Report. Proposal for a new classification of outcome with respect

to epileptic seizures following epilepsy surgery. *Epilepsia*. (2001) 42:282–6. doi: 10.1046/j.1528-1157.2001.4220282.x
16. Kuchenbuch M, D'Onofrio G, Wirrell E, Jiang Y, Dupont S, Grinspan ZM, et al. An accelerated shift in the use of remote systems in epilepsy due to the COVID-19 pandemic. *Epilepsy Behav*. (2020) 112:107376. doi: 10.1016/j.yebeh.2020.107376
17. Ferneini EM. Corporate America's impact on our daily clinical practice. *J Oral Maxillofacial Surg*. (2019) 77:1955–7. doi: 10.1016/j.joms.2019.07.015
18. Ferneini EM. The financial impact of COVID-19 on our practice. *J Oral Maxillofacial Surg*. (2020) 78:1047–8. doi: 10.1016/j.joms.2020.03.045
19. Hussain Y, Muhammad K, Umar MF, Omerkhail A, Khan Z. COVID-19 in five neighbouring limited resources countries: a financial and health threats. *Value Health Regional Issues*. (2020). doi: 10.1016/j.vhri.2020.06.001. [Epub ahead of print].
20. Lexa FJ, Lexa FJ. Private equity-backed hospital investments and the impact of the coronavirus disease 2019 (COVID-19) epidemic. *J Am Coll Radiol*. (2020) 17:1049–52. doi: 10.1016/j.jacr.2020.05.023

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 19 November 2020
doi: 10.3389/fneur.2020.597785

Modification of Acute Stroke Pathway in Korea After the Coronavirus Disease 2019 Outbreak

*Tae Jung Kim[1,2], Beom Joon Kim[3], Dong-Seok Gwak[4,5], Ji Sung Lee[6], Jun Yup Kim[3], Keon-Joo Lee[3], Jung-A Kwon[4,5], Dong-Hyun Shim[4,5], Yong-Won Kim[4,5], Min Kyoung Kang[1], Eung-Jun Lee[1], Ki-Woong Nam[1], Jeonghoon Bae[1], Kipyoung Jeon[1], Han-Yeong Jeong[1], Keun-Hwa Jung[1], Yang-Ha Hwang[4,5], Hee-Joon Bae[3], Byung-Woo Yoon[1] and Sang-Bae Ko[1,2]**

[1] Department of Neurology, Seoul National University Hospital, Seoul, South Korea, [2] Department of Critical Care Medicine, Seoul National University Hospital, Seoul, South Korea, [3] Department of Neurology and Gyunggi Regional Cardiocerebrovascular Center, Seoul National University Bundang Hospital, Seongnam, South Korea, [4] Department of Neurology, Kyungpook National University Hospital, Daegu, South Korea, [5] Department of Neurology, School of Medicine, Kyungpook National University, Daegu, South Korea, [6] Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Po-Yu Lin,
National Cheng Kung University Hospital, Taiwan
Jiann-Shing Jeng,
National Taiwan University Hospital, Taiwan
Tsong-Hai Lee,
Linkou Chang Gung Memorial Hospital, Taiwan

***Correspondence:**
Sang-Bae Ko
sangbai1378@gmail.com
orcid.org/0000-0002-9429-9597

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 22 August 2020
Accepted: 16 October 2020
Published: 19 November 2020

Citation:
Kim TJ, Kim BJ, Gwak D-S, Lee JS, Kim JY, Lee K-J, Kwon J-A, Shim D-H, Kim Y-W, Kang MK, Lee E-J, Nam K-W, Bae J, Jeon K, Jeong H-Y, Jung K-H, Hwang Y-H, Bae H-J, Yoon B-W and Ko S-B (2020) Modification of Acute Stroke Pathway in Korea After the Coronavirus Disease 2019 Outbreak. Front. Neurol. 11:597785. doi: 10.3389/fneur.2020.597785

Background: Since the global pandemic of coronavirus disease 2019 (COVID-19), the process of emergency medical services has been modified to ensure the safety of healthcare professionals as well as patients, possibly leading to a negative impact on the timely delivery of acute stroke care. This study aimed to assess the impact of the COVID-19 pandemic on the acute stroke care processes and outcomes in tertiary COVID-19-dedicated centers in South Korea.

Methods: We included 1,213 patients with acute stroke admitted to three centers in three cities (Seoul, Seongnam, and Daegu) through the stroke critical pathway between September 2019 and May 2020 (before and during the COVID-19 pandemic). In all three centers, we collected baseline characteristics and parameters regarding the stroke critical pathway, including the number of admitted patients diagnosed with acute stroke through the stroke critical pathway, door to brain imaging time, door to intravenous recombinant tissue plasminogen activator time, door to groin puncture time, and door to admission time. We performed an interrupted time series analysis to determine the impact of the COVID-19 outbreak on outcomes and critical pathway parameters.

Results: Three centers modified the protocol of the stroke critical pathway during the COVID-19 pandemic. There was an immediate decrease in the number of patients admitted with acute ischemic stroke after the outbreak of COVID-19 in Korea, especially in the center of Daegu, an epicenter of the COVID-19 outbreak. However, the number of patients with stroke soon increased to equal that before the Covid-19 outbreak. In several critical pathway parameters, door to imaging time showed a temporary increase, and door to admission was transiently decreased after the COVID-19 outbreak. However, there was no significant effect on the timely trend. Moreover, there was no significant difference in the baseline characteristics and clinical outcomes between the periods before and during the COVID-19 pandemic.

Conclusion: This study demonstrated that the COVID-19 outbreak immediately affected the management process. However, it did not have a significant overall impact on the trends of stroke treatment processes and outcomes. The stroke management process should be modified according to changing situations for optimal acute management.

Keywords: COVID-19, stroke, critical pathway, parameters, modification

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 has greatly affected healthcare systems worldwide (1). In South Korea, the first case of COVID-19 was identified on January 19, 2020. The patient entered Korea with fever and respiratory symptoms from Wuhan, China. The number of COVID-19 cases increased rapidly since February 17, 2020, at the time of identification of case 31 in Daegu, Kyungbuk, Korea. Therefore, the Korea Disease Control and Prevention Agency raised the alert level and stepped up the social distancing strategy (2, 3). The second wave of COVID-19 spread started in Seoul in August 2020. Currently, the COVID-19 pandemic has led to delays in healthcare services for several medical emergencies, including acute stroke management (1, 4–7). To streamline the process of hyperacute stroke management during the COVID-19 pandemic, several modified recommendations have been reported (6, 8, 9). These guidelines aim to minimize the risk of exposure to COVID-19 for healthcare professionals while maintaining the quality of patient care during the COVID-19 pandemic. However, recent studies showed a reduction in the number of stroke patients requiring reperfusion therapy and those who presented with mild neurological symptoms (10–12). This study aimed to analyze the impact of the COVID-19 outbreak on the changes in acute stroke care processes and outcomes in tertiary COVID-19-dedicated centers in South Korea.

METHODS

Study Populations

We retrospectively identified consecutive patients in the stroke critical pathway from three tertiary COVID-19-dedicated centers [Center 1 (Seoul National University Hospital) in Seoul, Center 2 (Seoul National University Bundang Hospital) in Seongnam, and Center 3 (Kyungpook National University Hospital) in Daegu] in Korea between September 2019 and May 2020 (before and during the COVID-19 pandemic in Korea on February 17, 2020, identification of case 31 related to a religious group called Shincheonji in Daegu). After reporting case 31, COVID-19 rapidly spread to Daegu/Kyungbuk province and then other areas in Korea. We included 1,213 patients with acute stroke who were admitted to three centers ($n = 201$ in Center 1, $n = 548$ in Center 2, and $n = 464$ in Center 3) through the stroke critical pathway during the period mentioned earlier. This study was approved by the Institutional Review Boards (IRB number H-2007-094-114 in Seoul National University Hospital & Seoul National University Bundang Hospital and 2020-07-055 in Kyungpook National University Hospital).

Modified Acute Stroke Critical Pathway

Each center had its own protocol for the stroke critical pathway. The initiation criteria for critical pathway in Centers 1 and 2 were based on the last known well time < 24 h, and Center 3 focused on the first known abnormal time < 24 h. After the declaration of the COVID-19 pandemic, all three centers revised the triage protocol for the stroke critical pathway in the emergency department (ED) to screen for suspected or confirmed COVID-19 infection. COVID-19 diagnostic tests using real-time reverse transcription polymerase chain reaction (sensitivity 92–95% and specificity 94–97%) were performed every 6–12 h (four times per day in Center 1, twice per day in Center 2, and four times per day in Center 3), and the tests took ∼5–6 h in three centers. While treating the stoke patients with suspected or confirmed COVID-19, according to the revised stroke critical pathway, a minimum number of healthcare professionals were allowed (one ED physicians, one neurologist, one nurse, one technologist, and/or one emergency medical technician) to limit exposure to COVID-19. Moreover, all institutions were equipped with a computed tomography (CT) scanner at ED, which limited patient transfer time to the CT suite within 5 min. During the COVID-19 pandemic, all patients with suspected stroke were treated according to the modified stroke critical pathway in three centers as described:

Criteria 1

Acute stroke patients with laboratory-confirmed COVID-19. The patients are transported to the negative pressure isolation room in each center. After a neurological examination, they undergo brain CT, CT angiography, and CT perfusion in a negative pressure CT suite. Patients eligible for intravenous (IV) thrombolysis are treated according to the standard protocol in the negative pressure isolation room or the negative pressure CT room, depending on the stroke critical pathway process of each center. If a large vessel occlusion is not identified, the patients are transferred to a dedicated special ward or intensive care unit for COVID-19, as needed. If a large vessel occlusion is confirmed, stroke specialists and neuro-interventionalists decide whether to perform endovascular thrombectomy (ERT) based on multimodal CT imaging. ERT is performed in the isolated off-pressure angiography room in each center with a minimum number of healthcare professionals. It is important to ensure level D of personal protective equipment (PPE) is used by all members of staff within the angiography suite. Brain magnetic resonance

imaging (MRI) is not performed. All healthcare professionals should wear level D PPE and carried confirmed COVID-19 patients in the isolated negative pressure hood stretcher vehicle along the isolated way (4, 6, 8).

Criteria 2

Acute stroke patients with a clinical suspicion of COVID-19 (febrile or respiratory symptoms) or under quarantine due to epidemiological reasons (close contact with a confirmed case or a recent trip to COVID-19-affected regions or abroad within the previous 2 weeks). COVID-19 testing using nasopharynx swabs is performed. Subsequently, the modified stroke critical pathway follows the progress in patients with a confirmed COVID-19. As discussed, patients who needed IV thrombolysis are treated according to the standard protocol in the negative pressure isolation room or negative pressure CT room. Patients with a suspicion of COVID-19 undergo ERT in the isolated off-pressure angiography room with keeping staff to a minimum in the procedure. If IV thrombolysis or ERT is not indicated, the patients are under preemptive isolation until the laboratory diagnosis is finalized. If COVID-19 results come back negative, the patients are transferred to the Stroke Unit; otherwise, they are transferred to the negative-pressure-dedicated special medical ward or intensive care unit for COVID-19, as needed. Moreover, brain magnetic resonance imaging is not performed until the COVID-19 test is negative. All healthcare professionals should wear PPE, including disposable isolation gowns, N95 masks or KF94 (Korea Filter, equivalent to N94) masks, protective goggles, or face shields. Patients should wear a surgical mask during the entire process (4, 6, 8).

Criteria 3

Acute stroke patients not diagnosed with COVID-19 and who neither are febrile nor have respiratory symptoms. The patients follow the standard acute stroke management pathway. All staff and patients should wear a surgical face mask throughout the stroke critical pathway (4, 6, 8).

Clinical Information and Baseline Characteristics

We collected the following parameters regarding acute stroke critical pathway in all three centers: number of admitted patients diagnosed with acute stroke through the stroke critical pathway, number of reperfusion therapy (IV thrombolysis and ERT), door to first brain imaging time, door to recombinant tissue plasminogen activator (rt-PA) time, door to groin puncture time, and door to admission time. In addition, we obtained the number of admitted stroke patients after stroke critical pathway during two periods before the COVID-19 infection from September 2018 and May 2019 to evaluate the seasonal influence on the number of stroke patients. Further, baseline characteristics, vascular risk factors, and pre-stroke functional status of the included patients were obtained by reviewing electronic medical records. Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria: large-artery atherosclerosis, small-vessel occlusion, cardioembolism, or other determined and undetermined subtypes, as previously described (13). Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) and classified into NIHSS 0–7, NIHSS 8–13, and NIHSS $\geq$14 (14, 15) in all included patients at admission and discharge. Moreover, functional status at discharge was evaluated using the modified Rankin Scale (mRS). Patients were assigned to either the "favorable outcome" group (mRS score $\leq$ 2) or "unfavorable outcome" group (mRS score $\geq$ 3).

Statistics Analysis

The baseline characteristics of the included patients were presented as the number (%). Further, continuous variables with normal distributions are presented as mean $\pm$ standard deviation (SD), whereas variables that were not normally distributed are presented as median value with [interquartile range (IQR)]. Continuous variables were compared using Student's *t*-tests or the Mann–Whitney U test, whereas categorical variables (proportions) were compared using Pearson's χ^2 tests or Fisher's exact test, as appropriate, to evaluate the impact of the COVID-19 pandemic on changes in the stroke critical pathway. The association between the COVID-19 pandemic and outcomes at discharge (mRS) was analyzed using logistic regression analyses. Covariates with statistically significant differences ($P < 0.05$) by univariate analysis or clinically important factors were adjusted for multivariable analysis. We performed an interrupted time series analysis (ITSA), which implemented a segmented linear regression model, to establish whether there was an association of the COVID-19 explosive outbreak with timely changes in the stroke critical pathway, related parameters, and outcomes (16). We compared the period after February 17, 2020 (the COVID-19 pandemic period) with the pre-COVID-19 pandemic event period (16). A professional medical statistician (J. S. Lee) conducted all statistical analyses using SPSS (Version 25.0; IBM Statistics, Armonk, NY, USA) and SAS 9.4 (SAS Institute, Inc. Cary, NC, USA). Statistical significance was set at $P < 0.05$.

RESULTS

Baseline Characteristics of Included Patients

Among the included patients (n = 1,213; mean age, 67.8 years; male, 60.3%), 673 (55.5%) patients were admitted before (phase 1) and 540 (44.5%) patients were admitted after (phase 2) the declaration of COVID-19 as a national emergency on February 17, 2020. A between-period comparison of the baseline characteristics in each center revealed no significant differences in the demographic information, vascular risk factors, and pre-stroke functional status, except that hyperlipidemia increased in Center 1 and the proportion of female patients increased in Center 2 during phase 2 (**Table 1**). Stroke subtypes and mechanisms did not differ between phase 1 and phase 2 in all centers (**Table 1**). Regarding reperfusion therapy, the proportion of patients with combined IV tPA plus ERT increased in Centers 1 and 3 during phase 2, although there was no significant between-period difference in the proportion of reperfusion therapy in Center 2. Further, more patients presented with fever at $\geq$37.5°C at the ED in phase 2 in Center 2 and Center 3 (**Table 2**). During

TABLE 1 | Baseline characteristics of included patients before and after COVID-19 pandemic in each center.

	Center 1			Center 2			Center 3		
	Phase 1 (*n* = 112)	**Phase 2 (*n* = 89)**	***P*-value**	**Phase 1 (*n* = 363)**	**Phase 2 (*n* = 185)**	***P*-value**	**Phase 1 (*n* = 345)**	**Phase 2 (*n* = 119)**	***P*-value**
Age, mean (SD)	65.0 (12.4)	66.9 (14.1)	0.309	67.4 (13.8)	68.7 (13.7)	0.312	68.9 (12.9)	67.6 (14.1)	0.362
Male, *n* (%)	62 (55.4)	53 (59.6)	0.551	229 (63.1)	100 (54.1)	0.041	205 (59.4)	82 (68.9)	0.066
Hypertension, *n* (%)	79 (70.5)	63 (70.8)	0.969	250 (68.9)	126 (68.1)	0.856	198 (57.4)	71 (59.7)	0.665
Diabetes mellitus, *n* (%)	37 (33.0)	36 (40.4)	0.278	111 (30.6)	53 (28.6)	0.641	100 (29.0)	40 (33.6)	0.343
Dyslipidemia, *n* (%)	42 (37.5)	49 (55.1)	0.013	170 (46.8)	81 (43.8)	0.498	120 (34.8)	49 (41.2)	0.211
Atrial fibrillation, *n* (%)	19 (17.0)	19 (21.3)	0.430	84 (23.1)	39 (21.1)	0.585	85 (24.6)	23 (19.3)	0.237
Previous stroke/TIA, *n* (%)	13 (11.6)	26 (29.2)	0.002	95 (26.2)	39 (21.1)	0.190	85 (24.6)	29 (24.4)	0.953
Pre-stroke mRS = 0, *n* (%)	80 (71.4)	63 (70.8)	0.921	226 (62.3)	114 (61.6)	0.884	226 (65.5)	80 (67.2)	0.733
Initial NIHSS, median (IQR)	4 (1–9.75)	5 (1.5–12.5)	0.167	4 (2–10)	5 (2–11)	0.175	4 (1–9)	5 (1–9)	0.485
Initial NIHSS, *n* (%)			0.581			0.596			0.456
0–7	77 (68.8)	55 (61.8)		243 (66.9)	120 (64.9)		250 (72.5)	81 (68.1)	
8–13	14 (12.5)	13 (14.6)		58 (16.0)	27 (14.6)		40 (11.6)	19 (16.0)	
≥14	21 (18.8)	21 (23.6)		62 (17.1)	38 (20.5)		55 (15.9)	19 (16.0)	
Stroke subtypes, *n* (%)			0.109			0.081			0.320
Ischemic stroke	87 (78.4)	58 (65.2)		315 (86.8)	147 (79.5)		308 (89.3)	110 (92.4)	
TIA	9 (8.1)	13 (14.6)		19 (5.2)	14 (7.6)		37 (10.7)	9 (7.6)	
Hemorrhagic stroke	15 (13.5)	18 (20.2)		29 (8.0)	24 (13.0)		–	–	
Stroke mechanisms in ischemic stroke, *n* (%)			0.360			0.731			0.248
LAA	15 (17.2)	16 (27.6)		103 (32.7)	52 (35.4)		63 (20.5)	30 (27.3)	
SVO	18 (20.7)	8 (13.8)		48 (15.2)	20 (13.6)		101 (32.8)	31 (28.2)	
CE	21 (24.1)	12 (20.7)		86 (27.3)	33 (22.4)		91 (29.5)	36 (32.7)	
Other determined	16 (18.4)	7 (12.1)		23 (7.3)	11 (7.5)		8 (2.6)	4 (3.6)	
Undetermined	17 (19.5)	15 (25.9)		55 (17.5)	31 (21.1)		45 (14.6)	9 (8.2)	
Discharge NIHSS, median (IQR)	3 (1–5)	4 (1–10)	0.167	4 (1–7)	4 (2–8)	0.056	3 (0–6)	4 (1–8)	0.135

SD, Standard deviation; CP, critical pathway; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischemic attack; IQR, interquartile range;LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism.
Phase 1: before the declaration of COVID-19 as a national emergency on February 17, 2020.
Phase 2: after the declaration of COVID-19 as a national emergency on February 17, 2020.

the COVID-19 pandemic period, a total of 46 patients (Criteria 2) were under quarantine in the isolated negative pressure room before admission from three centers. In addition, a total of 181 COVID-19-confirmed patients were treated in three institutions ($n = 38$ in Center 1, $n = 44$ in Center 2, and $n = 99$ in Center 3) until May 2020. However, none was confirmed with COVID-19 among the stroke patients during the stroke critical pathway and after admission in all three centers.

Parameters of Stroke Critical Pathway Before and During the Coronavirus Disease 2019 Pandemic Period

In Center 3 at Daegu, fewer stroke patients were admitted in phase 2 compared with phase 1 (39.7 ± 14.4 vs. 69.0 ± 7.4, $P = 0.008$ in **Table 2**). Breakpoint analysis revealed that there was a significant decrease in the number of patients with stroke in the stroke critical pathway immediately after the COVID-19 pandemic (P for intervention = 0.0173 in **Figure 1A**). Although there was an increasing trend in the number of patients with stroke, fewer patients were admitted in phase 2 compared with phase 1 (P for time after intervention = 0.0381 in **Figure 1A**). However, in Center 1 and Center 2, there was no significant difference in the trend of the number of admitted patients (**Figure 1A**). When analyzing the trend during the same time frame in 2019, the number of admitted stroke patients was significantly decreased in February, associated with the shortest month of the year; however, there was an increase in the number of patients with stroke in other months. During the COVID-19 pandemic period, the numbers of admission were persistently lower in 2020 compared with that in 2019. Furthermore, the trend of admitted stroke patients was different compared with the same time frame in 2019 (**Supplementary Figure 1**). In Center 3, the median door to imaging time during the COVID-19 pandemic was significantly shorter than that before the COVID-19 period in univariate analysis ($P < 0.001$ in **Table 2**). However, in ITSA, there was no significant difference in the trend of the door to imaging time after the COVID-19 outbreak (**Figure 1B**). In Center 2, the door to imaging time was transiently higher after the COVID-19 outbreak, but the time trend was not significant

TABLE 2 | Parameters of acute stroke critical pathway before and after COVID-19 pandemic in each center.

	Center 1			Center 2			Center 3		
	Phase 1 (*n* = 112)	**Phase 2 (*n* = 89)**	***P*-value**	**Phase 1 (*n* = 363)**	**Phase 2 (*n* = 185)**	***P*-value**	**Phase 1 (*n* = 345)**	**Phase 2 (*n* = 119)**	***P*-value**
Number of admitted stroke patients each month through CP, mean (SD)	22.4 (5.3)	29.7 (2.1)	0.069	72.6 (8.1)	61.7 (6.7)	0.098	69.0 (7.4)	39.7 (14.4)	0.008
Fever (> 37.5°C), *n* (%)	2 (1.8)	6 (6.7)	0.142	4 (1.1)	8 (4.3)	0.026	1 (0.3)	6 (5.0)	0.001
Reperfusion therapy, *n* (%)									
IV thrombolysis only	8 (7.1)	9 (10.1)	0.452	22 (6.1)	10 (5.4)	0.757	44 (12.8)	8 (6.7)	0.072
ERT only	7 (6.3)	5 (5.6)	0.851	59 (16.3)	26 (14.1)	0.501	32 (9.3)	13 (10.9)	0.600
Combined IV thrombolysis and ERT	1 (0.9)	7 (7.9)	0.023	21 (5.8)	8 (4.3)	0.470	13 (3.8)	12 (10.1)	0.009
Door to imaging time (min), median (IQR)†	25.0 (20.0–33.0)	26.0 (20.0–34.5)	0.835	34.0 (27.0–47.0)	33.0 (24.0–43.0)	0.082	22.5 (18.0–29.0)	19.0 (15.0–24.0)	<0.001
Door to rt-PA time (min), median (IQR)‡	50.0 (37.0–71.5)	46.0 (38.8–52.5)	0.388	29.0 (23.0–40.0)	25.0 (23.0–31.0)	0.247	37.5 (30.8–49.3)	46.0 (34.0–58.0)	0.108
Door to groin puncture time (min), median (IQR)	163.5 (92.0–195.8)	110.5 (93.5–133.5)	0.208	73.0 (54.5–101.5)	70.0 (50.3–99.3)	0.490	78.0 (61.0–100.0)	74.0 (61.5–100.0)	0.878
Door to admission time (min), median (IQR)	224.5 (179.8–320.3)	298.0 (185.5–527.5)	0.007	240.5 (181.5–336.3)	195.0 (156.8–250.0)	<0.001	164.0 (113.0–268.0)	125.0 (83.0–255.0)	0.003
Good outcome (mRS 0–2) at discharge, *n* (%)	68 (60.7)	46 (51.6)	0.199	176 (48.5)	74 (40.0)	0.059	218 (63.2)	65 (54.6)	0.099

SD, Standard deviation; CP, critical pathway; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischemic attack; IQR, interquartile range; IV, intravenous; ERT, endovascular reperfusion therapy; rt-PA, recombinant tissue plasminogen activator.
Phase 1: before the declaration of COVID-19 as a national emergency on February 17, 2020.
Phase 2: after the declaration of COVID-19 as a national emergency on February 17, 2020.
Door to imaging time† Door to rt-PA time†: Center 2 is a regional comprehensive stroke center with a high volume of patients transfer from nearby primary stroke centers. Therefore, if a patient arrives at Center 2 within tPA time window with brain CT, which was undergone at primary stroke centers, then the patient may be administered with intravenous tPA. This is why door to tPA time is shorter than door to imaging time in Center 2.

($P = 0.097$, **Figure 1B**). The door to tPA time was shorter in Center 2 compared with other centers because all tPA-treated patients ($n = 61$) in Center 2 were performed in CT room during the study period, although there was no significant change in the time trend of each center during the COVID-19 pandemic. Among under quarantine patients ($n = 46$), four patients were treated with tPA according to Criteria 2. The door to tPA time was longer compared with without quarantine patients ($n = 50$), according to Criteria 3 [56.5 (IQR 34.8–64.8) vs. 36.0 (IQR 27.5–47.8) min, $P = 0.090$], although it was not statistically significant result. Compared with before the COVID-19 period, univariate analysis showed that the door to admission time after the COVID-19 period was significantly longer in Center 1 and shorter in Center 2 and Center 3. In Center 3, there was a transient decrease in the door to admission time; however, it showed an increasing time trend after the COVID-19 outbreak (**Figure 1E**). In Centers 1 and 2, the COVID-19 pandemic effect on the time trend was not significant after ITSA. Moreover, there was no significant change in parameters related to reperfusion therapy between before and after the COVID-19 pandemic in all three centers (**Figures 1C,D**). The initial stroke severity was similar between the two periods (**Table 1**). Although there was an increasing trend in the initial NIHSS (P for time after intervention $= 0.0454$ in **Figure 1F**) in Center 1, the NIHSS and mRS scores of all centers were nearly similar at discharge after the COVID-19 pandemic period compared with before the COVID-19 period (**Tables 1**, **2**, **Figures 1F,G**). In addition, the COVID-19 pandemic was not associated with discharge outcomes after adjusting for the relevant confounding variables (**Supplementary Table 1**) in the three centers. Moreover, when comparing the initial and discharge stroke severity according to the under quarantine during the COVID-19 pandemic period, there was no significant difference between under quarantine group and without quarantine group [initial NIHSS 6 (IQR, 2–19.5) vs. 5.0 (IQR 2–11), $P = 0.098$, discharge NIHSS 4 (IQR 2–22) vs. 4 (IQR 1–8), $P = 0.117$, respectively].

DISCUSSION

We found that the monthly number of admitted patients with acute stroke in the stroke critical pathway decreased immediately after the declaration of national emergency of COVID-19, especially at Center 3, which was located at the epicenter of the COVID-19 outbreak. However, there was an inconsistent and nonsignificant impact of the COVID pandemic event on the time trend of the number of patients with stroke in three centers. During the COVID-19 pandemic period, there was a transient change in the parameters of the stroke critical pathway, including door to imaging time and door to admission time. However, there was no between-period difference in the hyperacute treatment process and short-term post-stroke outcomes. Differences in stroke critical pathway parameters, including door to imaging

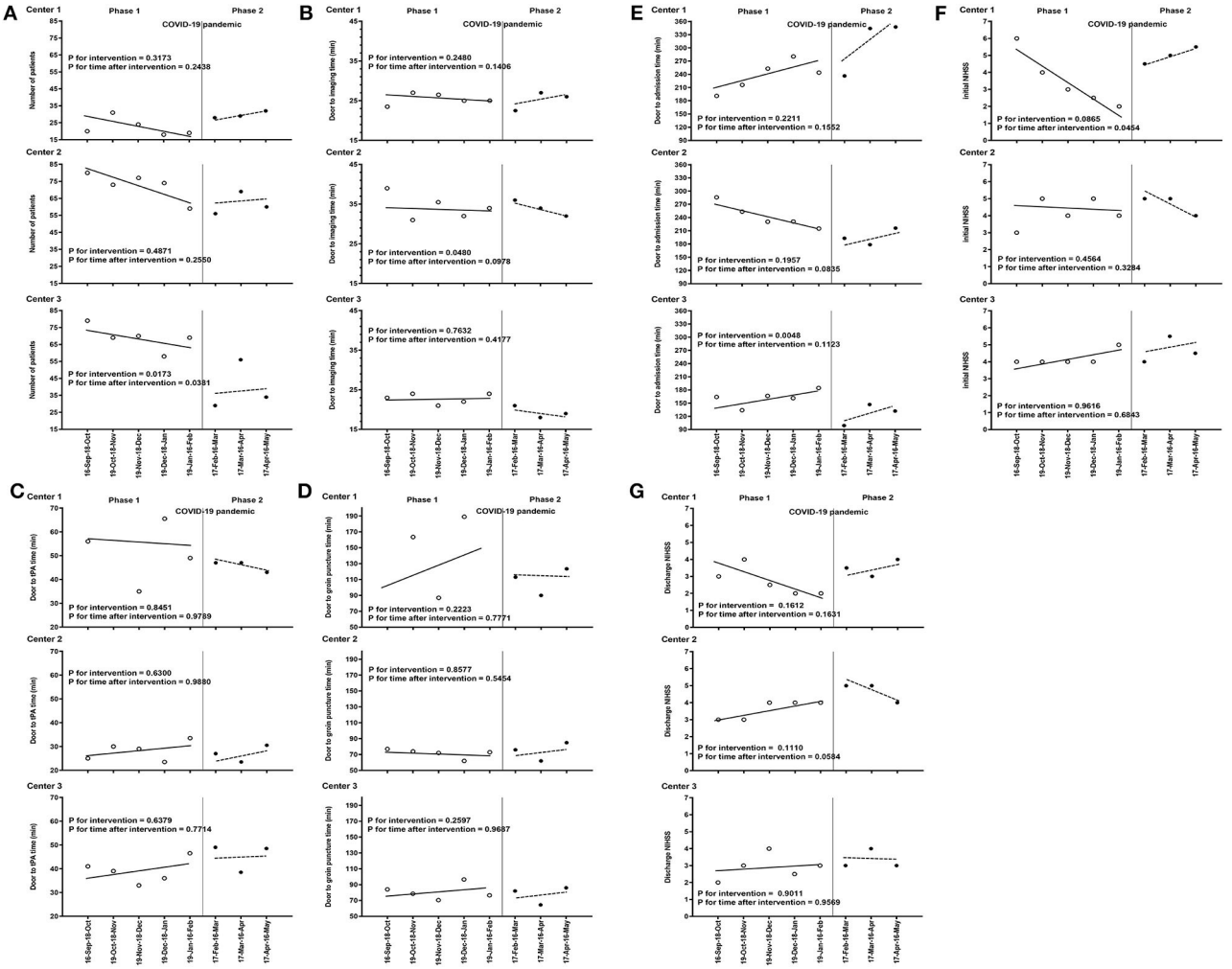


FIGURE 1 | Trends in monthly parameters of the stroke critical pathway between September 2019 and May 2020. Dashed lines represent the COVID-19 pandemic since the confirmed 31 cases related to a religious group called Shincheonji in Daegu. **(A)** Trends in the number of admitted patients in each center. **(B)** Trends in the door to imaging time in each center. **(C)** Trends in the door to rt-PA time in each center. **(D)** Trends in the door to groin puncture time in each center. **(E)** Trends in the door to admission time in each center. **(F)** Trends in initial NIHSS of patients with stroke in each center. **(G)** Trends in discharge NIHSS of patients with stroke in each center. COVID-19, coronavirus disease; rt-PA, tissue plasminogen activator; NIHSS, National Institutes of Health Stroke Scale. Phase 1: before the declaration of COVID-19 as a national emergency on February 17, 2020. Phase 2: after the declaration of COVID-19 as a national emergency on February 17, 2020.

time and door to tPA time, are related to regional differences and own stroke critical pathways of the three centers, which is not directly associated with the COVID-19 outbreak.

Previous studies have reported a reduced number of patients with a minor stroke or transient ischemic attack, as well as reperfusion therapy. Further, there could have been delayed reperfusion therapy, onset to door, and door to treatment times after the COVID-19 outbreak (4, 10, 11, 17–19). In our study, there was a temporary reduction in the number of patients with stroke in the critical pathway during the COVID-19 pandemic, which was consistent with previous studies (10–12). However, the trend subsequently recovered to the normal state-observed before the COVID-19 outbreak. In Center 3 at Daegu, which comprised 31 cases related to the Shincheonji religious group, there was a temporary decrease in the number of patients during the COVID-19 pandemic period compared with that before the COVID-19 pandemic period. However, ITSA revealed an increasing trend in the number of admitted patients after a critical pathway with the passing of time. Furthermore, the long-term COVID-19 impact on reperfusion therapy remains unclear. Regarding the door to admission time, the temporary reduction in the door to admission time in Center 3 was associated with the transient number of patients in the stroke critical pathway and stroke unit availability immediately after the COVID-19 explosive outbreak. However, there was an increasing time trend of the door to admission time in Center 3, as the time trend of the number of patients was increased after the COVID-19 explosive outbreak. During the stage after the COVID-19 outbreak, each center attempted to establish a modified protocol strategy for acute stroke management that reflected regional characteristics. Therefore, the early-stage protocol is associated with the transient change of stroke critical pathway parameters in each center. We

found that the overall characteristics and outcomes of admitted patients with stroke after the critical pathway remained stable. The strategy of hyperacute management did not significantly change during the post-COVID-19 pandemic period. In this study, four patients with clinical suspicion of COVID-19 were treated with tPA in the isolated negative pressure room or negative pressure CT room. The quarantine lengthened the door to tPA time in the quarantine group without statistical significance [56.5 (IQR 34.8–64.8) vs. 36.0 (IQR 27.5–47.8) min, $P = 0.090$], consistent with previous studies (19, 20). Their delays were attributed to when applying the PPE and additional time taken to isolate the patient. However, the initial severity [NIHSS 5.5 (IQR, 3.5–23.3) in under quarantine vs. 9 (IQR, 5–14.5) without quarantine, $P = 0.690$] and discharge outcome [NIHSS 3 (IQR, 0.5–32.5) in under quarantine vs. 4 (IQR, 1–8) in without quarantine, $P = 0.811$] were similar in two groups among all tPA-treated patients. Moreover, the COVID-19 explosive outbreak had a temporary impact on the number of admitted patients with stroke after the critical pathway and parameters associated with the critical pathway. Thus, there was no significant effect on the trends for the critical pathway parameters in this study. Moreover, the admitted COVID-19-confirmed patients were transferred through the secure pathway in each center. Therefore, the impact of the COVID-19-confirmed patients was not significant in the stroke critical pathway of each center.

These findings could be attributed to several possible explanations. Many countries, including Korea, have implemented strategies for controlling the COVID-19 spread, including social distancing; shutting down schools, churches, gyms, and bars; wearing of masks, washing of hands, and activity restrictions (10, 20). The COVID-19 is a contact-transmissible infectious disease thought to spread throughout the population via direct individual–individual contact; moreover, it is yet to have effective antiviral medications and vaccines. Consequently, some patients with stroke may refrain from visiting emergency treatment at hospitals for fear of infection, which could have attributed to the decreased number of admitted patients with stroke during the early COVID-19 periods (3, 16, 21). Most stroke centers have modified and optimized the triage protocols for acute stroke management for the prevention of COVID-19 spread with respect to regional characteristics (1, 8, 9, 22). In Korea, the spread of emerging infectious diseases was slowed down followed by a flattening of the epidemic curve after consistent implementation of government policy and strategy (10, 22). In our study, each center maintained optimism for providing effective stroke therapies after establishing modified triage protocols after the COVID-19 outbreak. Consequently, there was a transient COVID-19 impact on the critical pathway of patients with stroke, which remained nonsignificant after epidemic curve flattening and establishing the modified stroke critical pathway in each center.

This study has several limitations. First, this was a triple-center retrospective study. Therefore, there remains a possibility of selection bias, and caution should be applied when generalizing these findings to the clinical field. Second, the study period was insufficient for analyzing the impact of the COVID-19 infection breakpoint on the stroke critical pathway using ITSA. Moreover, the sample size was small to show statistical significance. Therefore, although our findings were nonsignificant in the time trend, they should be interpreted with caution. Third, the association between the severity of the COVID-19-infected patients and the admission, treatment, and outcome in patients after stroke critical pathway was not evaluated in this study because there was no admitted stroke patient with COVID-19 infection during this study period. Fourth, the change of variables related to ERT was not analyzed after the COVID-19 outbreak among the three centers. Fifth, this study might not represent the country and regions with different stroke care protocols and geographical specificities. The result of this study could be related to acute stroke treatment guidelines in South Korea. Therefore, the generalization of results could be limited in low- and middle-income developing countries because of their lack of acute stroke management systems. Thus, there is a need for these findings to be confirmed in other centers and populations. Further, our findings could be limited to community hospitals and small centers.

In conclusion, this study demonstrated that the COVID-19 explosive outbreak had an immediate acute effect on the hyperacute stroke management process within a short period. However, there was an insignificant overall impact of the COVID-19 pandemic on the trends of the stroke treatment process and outcomes. Stroke management is a dynamic process that is modifiable with changing situations. Implementation of a modified stroke pathway compatible with infection control in each stroke center ensured that the efficiency of the overall stroke management process was retained. There is a need for further large-scale studies to confirm the true relationship between the COVID-19 explosive outbreak and the long-term effect on the stroke management process.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Boards (IRB number H-2007-094-114 in Seoul National University Hospital & Seoul National University Bundang Hospital and 2020-07-055 in Kyungpook National University Hospital). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-BK, B-WY, H-JB, Y-HH, and K-HJ contributed to the study concept and design. TJK, BJK, D-SG, JYK, K-JL, J-AK, D-HS, Y-WK, MKK, E-JL, K-WN, JB, KJ, and H-YJ contributed to data collection. TJK and JSL contributed to data analysis. TJK and S-BK drafted the manuscript.

FUNDING

This study was supported in part by the National Research Foundation of Korea funded by the Ministry of Science and ICT (NRF-2020R1C1C1003249).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.597785/full#supplementary-material

REFERENCES

1. Mahase E. Covid-19: who declares pandemic because of "alarming levels" of spread, severity, and inaction. *BMJ.* (2020) 368:m1036. doi: 10.1136/bmj.m1036
2. Korean Society of Infectious Diseases, Korean Society of Pediatric Infectious Diseases, Korean Society of Epidemiology, Korean Society for Antimicrobial Therapy, Korean Society for Healthcare-associated Infection Control and Prevention, et al. Report on the epidemiological features of coronavirus disease 2019 (covid-19) outbreak in the republic of korea from January 19 to March 2, 2020. *J Korean Med Sci.* (2020) 35:e112. doi: 10.3346/jkms.2020.35.e112
3. Jang WM, Jang DH, Lee JY. Social distancing and transmission-reducing practices during the 2019 coronavirus disease and 2015 middle east respiratory syndrome coronavirus outbreaks in Korea. *J Korean Med Sci.* (2020) 35:e220. doi: 10.3346/jkms.2020.35.e220
4. Baracchini C, Pieroni A, Viaro F, Cianci V, Cattelan A, Tiberio I, et al. Acute stroke management pathway during coronavirus-19 pandemic. *Neurol Sci.* (2020) 41:1003–05. doi: 10.1007/s10072-020-04375-9
5. Ospel JM, Goyal M. Endovascular stroke treatment during the covid-19 pandemic. *Nat Rev Neurol.* (2020) 16:351–2. doi: 10.1038/s41582-020-0371-1
6. Khosravani H, Rajendram P, Notario L, Chapman M, Menon BK. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (covid-19) pandemic. *Stroke.* (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.029838
7. Moshayedi P, Ryan TE, Mejia LLP, Nour M, Liebeskind DS. Triage of acute ischemic stroke in confirmed covid-19: large vessel occlusion associated with coronavirus infection. *Front Neurol.* (2020) 11:353. doi: 10.3389/fneur.2020.00353
8. Kim BJ, Kim ES, Shin MJ, Kim HB, Lee HY, Hong K-S, et al. Management of acute stroke patients amid the coronavirus disease 2019 pandemic: Scientific statement of the Korean Stroke Society. *J Stroke.* (2020) 22:203–5. doi: 10.5853/jos.2020.01291
9. Leadership AASC. Temporary emergency guidance to us stroke centers during the coronavirus disease 2019 (covid-19) pandemic: on behalf of the american heart association/american stroke association stroke council leadership. *Stroke.* (2020) 51:1910–2. doi: 10.1161/STROKEAHA.120.030023
10. Pop R, Quenardelle V, Hasiu A, Mihoc D, Sellal F, Dugay MH, et al. Impact of the covid-19 outbreak on acute stroke pathways–insights from the alsace region in France. *Eur J Neurol.* (2020). doi: 10.1111/ene.14316. [Epub ahead of print].
11. Lin P-Y, Chang Y-M, Huang C-Y, Lin C-H, Chuang M-T, Chen P-L, et al. Management of hyperacute stroke during the coronavirus disease of 2019 pandemic: the modified code stroke in a medical center in Taiwan. *J Stroke.* (2020) 22:278–81. doi: 10.5853/jos.2020.01599
12. Roushdy TM, Nahas NME, Aref HM, Georgy SS, Zaki AS, Bedros RY, et al. Stroke in the time of coronavirus disease 2019: experience of two university stroke centers in Egypt. *J Stroke.* (2020) 22:275–7. doi: 10.5853/jos.2020.01550
13. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke.* (1993) 24:35–41. doi: 10.1161/01.STR.24.1.35
14. Fonarow GC, Saver JL, Smith EE, Broderick JP, Kleindorfer DO, Scco RL, et al. Relationship of National Institutes of Health Stroke Scale to 30-day mortality in Medicare beneficiaries with acute ischemic stroke. *J Am Heart Assoc.* (2012) 1:42–50. doi: 10.1161/xJAHA.111.000034
15. Kim TJ, Lee JS, Oh M-S, Kim J-W, Yoon JS, Lim J-S, et al. Predicting functional outcome based on linked data after acute ischemic stroke: S-SMART Score. *Transl Stroke Res.* (2020) 11:1296–305. doi: 10.1007/s12975-020-00815-y
16. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther.* (2002) 27:299–309. doi: 10.1046/j.1365-2710.2002.00430.x
17. Bhaskar S, Sharma D, Walker AH, McDonald M, Huasen B, Haridas A, et al. Acute neurological care in the covid-19 era: the pandemic health system resilience program (reprogram) consortium pathway. *Front Neurol.* (2020) 11:579. doi: 10.3389/fneur.2020.00579
18. Morelli N, Rota E, Terracciano C, Immovilli P, Spallazzi M, Colombi D, et al. The baffling case of ischemic stroke disappearance from the casualty department in the COVID-19 era. *Eur Neurol.* (2020) 83:213–5. doi: 10.1159/000507666
19. Paliwal PR, Tan B, Leow A, Sibi S, Chor DWP, Chin AXY, et al. Impact of the COVID-19 pandemic on hyperacute stroke treatment: experience from a comprehensive stroke centre in Singapore. *J Thromb Thrombolysis.* (2020) 13:1–8. doi: 10.1007/s11239-020-02225-1
20. Zhao J, Li H, Kung D, M Fisher, T Shen, R Liu. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke.* (2020) 51:1996–2001. doi: 10.1161/STROKEAHA.120.030225
21. Kim JS. Coronavirus disease 2019 and stroke. *J Stroke.* (2020) 22:157–8. doi: 10.5853/jos.2020.01760
22. Prem K, Liu Y, Russell TW, Kucharski AJ, Eggo RM, Davies N, et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: A modelling study. *Lancet Public Health.* (2020) 5:e261–70. doi: 10.1016/S2468-2667(20)30073-6

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 November 2020
doi: 10.3389/fneur.2020.589901

Effects of COVID-19 Pandemic Confinement in Patients With Cognitive Impairment

Ainara Barguilla [1], Aida Fernández-Lebrero [1,2,3], Isabel Estragués-Gázquez [1], Greta García-Escobar [3], Irene Navalpotro-Gómez [1,2,3], Rosa María Manero [2,3], Víctor Puente-Periz [1,2,3], Jaume Roquer [1] and Albert Puig-Pijoan [1,2,3]**

[1] Neurology Department, Hospital del Mar, Barcelona, Spain, [2] Cognitive Impairment and Movement Disorders Unit, Neurology Department, Hospital del Mar, Barcelona, Spain, [3] Neurofunctionality and Language Group, Neurosciences Program, Hospital del Mar Research Institute (IMIM), Barcelona, Spain

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu,
Hospital Clínico San Carlos, Spain

Reviewed by:
Magda Tsolaki,
Aristotle University of Thessaloniki, Greece
Lucia Crivelli,
Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Argentina

***Correspondence:**
Ainara Barguilla
62889@parcdesalutmar.cat
Albert Puig-Pijoan
apuig@parcdesalutmar.cat

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: 31 July 2020
Accepted: 29 October 2020
Published: 24 November 2020

Citation:
Barguilla A, Fernández-Lebrero A, Estragués-Gázquez I, García-Escobar G, Navalpotro-Gómez I, Manero RM, Puente-Periz V, Roquer J and Puig-Pijoan A (2020) Effects of COVID-19 Pandemic Confinement in Patients With Cognitive Impairment. Front. Neurol. 11:589901. doi: 10.3389/fneur.2020.589901

Introduction: State of emergency caused by COVID-19 pandemic and subsequent lockdown hit Spain on 14th March 2020 and lasted until 21st June 2020. Social isolation measures were applied. Medical attention was focused on COVID-19. Primary and social care were mainly performed by telephone. This exceptional situation may affect especially vulnerable patients such as people living with dementia. Our aim was to describe the influence of restrictive measures on patients living with mild cognitive decline and dementia evaluating SARS-CoV2 infection, changes in routines, cognitive decline stage, neuropsychiatric symptoms, delirium, falls, caregiver stress, and access to sanitary care.

Materials and Methods: We gathered MCI and dementia patients with clinical follow-up before and after confinement from DegMar registry (Hospital del Mar). A telephone *ad-hoc* questionnaire was administered. Global status was assessed using CDR scale. Changes in neuropsychiatric symptoms were assessed by Neuropsychiatric Inventory (NPI) and retrospective interview for pre-confinement base characteristics.

Results: We contacted a total of 60 patients, age 75.4 years ± 5,192. 53.3% were women. Alzheimer's Disease (41.7%) and Mild Cognitive Impairment (25%) were the most prevalent diagnosis. Remaining cases included different dementia disorders. A total of 10% of patients had been diagnosed with SARS-CoV-2. During confinement 70% of patients abandoned previous daily activities, 60% had cognitive worsening reported by relatives/caretakers, 15% presented delirium episodes, and 13% suffered increased incidence of falls. Caregivers reported an increased burden in 41% cases and burnout in 11% cases. 16% reported difficulties accessing medical care, 33% received medical phone assistance, 20% needed emergency care and 21% had changes in psychopharmacological therapies. Neuropsychiatric profile globally worsened ($p < 0.000$), also in particular items like agitation ($p = 0.003$), depression ($p < 0.000$), anxiety ($p < 0.000$) and changes in appetite ($p = 0.004$).

Conclusion: SARS-CoV2-related lockdown resulted in an important effect over social and cognitive spheres and worsening of neuropsychiatric traits in patients living with mild cognitive decline and dementia. Although the uncertainty regarding the evolution of the pandemic makes strategy difficult, we need to reach patients and caregivers and develop adequate strategies to reinforce and adapt social and health care.

Keywords: COVID- 19, SARS - CoV-2, dementia, depression, cognitive impairment, anxiety, neuropsychiatric

INTRODUCTION

The current coronavirus disease global pandemic, caused by SARS-CoV2 (Severe Acute Respiratory Syndrome Coronavirus 2), was first acknowledged in Wuhan in December 2019 (1). From then on, its high infectivity and severity collapsed the health systems of numerous countries and forced preventive measures such as social distancing and lockdown throughout the world. The World Health Organization declared the COVID-19 pandemic on 11 March 2020 (2). Measures varied hugely between countries and while social distancing has been generally the norm, there has not been a worldwide standard response.

State of emergency and subsequent lockdown started in Spain on 14 March 2020 and, through gradual de-escalation, lasted until 21st of June 2020. During the lockdown, the population was prevented from outdoor exercising and maintaining contact with friends and family. Though taking care of dependent relatives (shopping for them, medication management...) was an exception to circulation restrictions, family contact was highly discouraged. Medical attention during the state of emergency was focused on COVID-19 and primary and social care were mainly substituted by telephone visits when possible. Day centers and cognitive stimulation centers, along with outpatient care, were suspended. Only critical attention was guaranteed and even after the state of emergency ended, patient care changed: on-site interviews were reduced and telephonic attention encouraged.

Social impact of the pandemic has been huge with rising levels of poverty and unemployment affecting the care of the most vulnerable (3). Among all the population affected by the pandemic, elderly people have been in the highest risk of mortality, so far, most deaths have been over the age of 70 (4, 5).

More than 50 million people worldwide live with dementia (6). Prevalence of mild cognitive impairment in older of 60 years ranges between 16 and 20%, half of whom will develop dementia throughout their lives (7, 8). In Spain, 80% of people with dementia live at home and depend on their family as caregivers (8).

Patients living with neurodegenerative diseases are especially vulnerable to infections and changes in their routines. Social isolation has been associated with negative outcomes (9). COVID-19 pandemic and previously described restrictive measures such as social distancing may lead, thus, to a worsening of their cognitive status, functional performance, mood, behavior, and sleep (10, 11). Other complications such as falls and delirium might be favored by the lack of usual care. The difficulty to access the health care system, often magnified by the lack of an easy to use telematic platform for the elderly, may increase the anxiety and feeling of being abandoned both in patients and, very importantly, in caregivers (12).

Our aim was to make the effects of restrictive measures on patients living with dementia and cognitive impairment visible, focusing on changes in their daily routines, global cognitive/functional status, delirium, falls, caregiver stress, neuropsychiatric symptoms, and also their perception of the limitation to access to sanitary resources.

Describing the impact of this new environment over our patients is the first step toward adapting our assistance to their needs and designing new strategies in order to improve their care and therefore their quality of life.

MATERIALS AND METHODS

Subjects

In our cognitive impairment and movement disorders unit we gather patient data in the DegMar registry. Patients participating in the DegMar project sign informed consent approved by the local ethics committee (2018/7805/I) which implies the use of medical information for research purposes. Patients recruited for CogVid study and their families were asked for specific permission in order to include their clinical data in this study.

We gathered patients from DegMar registry with previous follow up within 6 months before the state of alarm in order to have the most updated previous cognitive and functional status. We excluded healthy individuals and those with subjective cognitive decline. We also excluded patients with previous comorbid psychiatric disorders or suffering from mourning deriving from family loss. From these patients, we interviewed the ones with previously programmed telephonic follow-up as a part of our daily clinical practice.

The clinical diagnosis of the subjects was stated according to clinical history. Severity of the cognitive impairment was staged by the Clinical Dementia Rating Scale (CDR) global score (13).

Assessment

We created a telephone *ad-hoc* questionnaire "CogVid Hospital del Mar questionnaire" to measure functional and neuropsychiatric changes experienced by patients and caregivers of this sample during the period of confinement (from March to May 2020). We chose an *ad-hoc* non-standarized, non-validated questionnaire in order to gather as much information as soon as possible: immediacy in our case made the information more reliable. It made a useful tool for guiding the interviewers and gather information in an homogenous way. The questionnaire

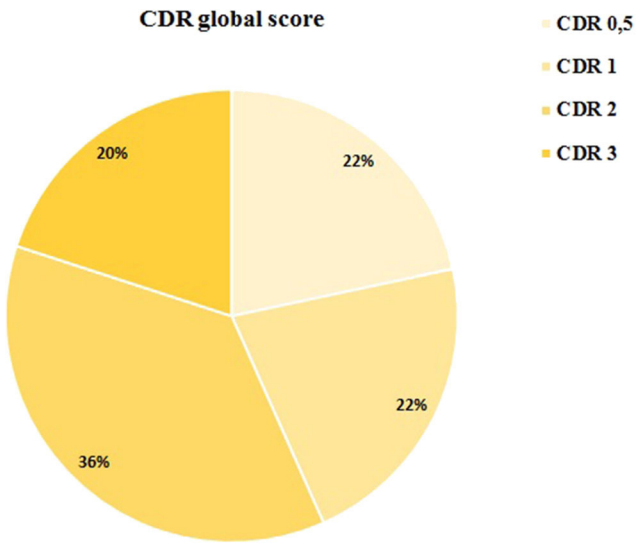


FIGURE 1 | Dementia stage distribution (CDR).

TABLE 1 | Sample characteristics according to CDR classification.

Characteristics	Sample	CDR 0.5	CDR 1	CDR 2	CDR 3	*P*
n. (%)	60 (100)	13 (21.7)	13 (21.7)	22 (36.7)	12 (20)	
Sex, *n* (% women)	32 (53.3)	7 (53.8)	7 (53.8)	10 (45.5)	8 (66.7)	NS*
Age, mean (SD)	75.4 (5.2)	77.0 (4.2)	75.5 (4.2)	75.4 (5.1)	73.58 (7.1)	NS**

*Pearson's chi-squared test, **one-way ANOVA.

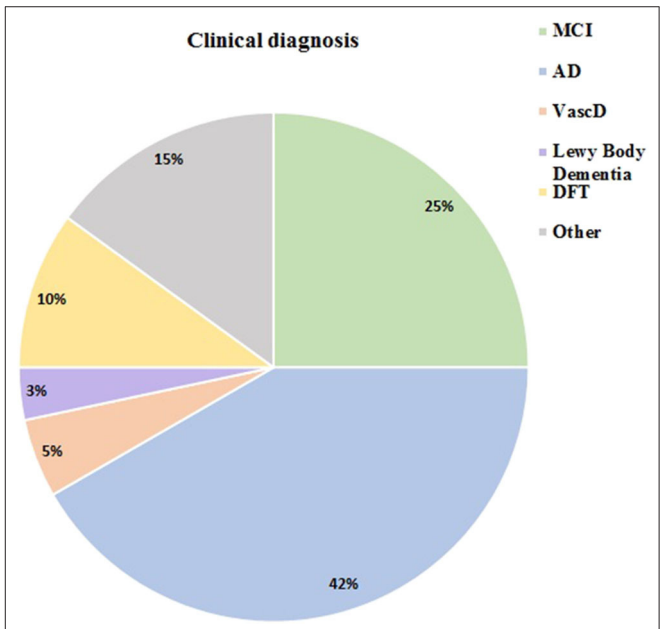


FIGURE 2 | Clinical diagnosis distribution.

included comprehension/adaptation to confinement and protective measures, change of residence, social services support loss, primary care attention, and psychopharmacological treatment adjustment during confinement period. We also registered infection symptoms, falls, interruption in cognitive stimulation programs, and loss of day to day routines (shopping, strolling…). Caregiver stress was also assessed. We registered access to institutions and professional societies' online resources and if any psychological support or relief activities (mindfulness, physical activity) were practiced. The interview was conducted with the caregiver, family, or live-in resident of the patient.

This telephone questionnaire was conducted from June to July during the programmed medical consultation, by telephone, and lasted about 20 min.

A model of the used questionnaire (CogVid Hospital del Mar Questionnaire) is attached in **Annex 1**.

In order to describe possible changes in the neuropsychiatric sphere, the Neuropsychiatric Inventory (NPI) was administered after lockdown altogether with the questionnaire. We also inquired about neuropsychiatric symptoms prior to state of alarm. This scale (14) is a structured caregiver-based interview that quantifies behavioral changes detected in the last 4 weeks and it consists on 12 items that match the following domains: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite/eating abnormalities. In addition, severity and frequency are graduated in each of them. For scoring, the severity scale is multiplied with the frequency scale and the score for each domain is obtained. The total score is the result of the sum of all the domains. The NPI is a widely used tool for measuring psychological disturbances in people with dementia (15).

The clinical diagnosis of the subjects was stated according to clinical history.

Severity of the cognitive impairment was staged by the Clinical Dementia Rating Scale (CDR) global score (13). CDR stage previous to lockdown was gathered from clinical history records from the last visit, 6 months before the state of alarm.

Statistical Analysis

Descriptive data of quantitative variables from the questionnaire are shown in mean ± (SD) when normal and median (range) when not normal.

Categorical variables were summarized using frequency counts and percentages. Absolute and relative frequencies were used for qualitative variables. For comparing quantitative continuous normal variables, we used one-way ANOVA and for categorical variables we used Pearson's chi-squared test. We used Wilcoxon test to compare midrange in paired samples both normal ordinal and not normal quantitative variables. The significance threshold was set at $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA).

TABLE 2 | Collected data from total sample and according to CDR classification.

		Sample ($n = 60$)	CDR 0.5 ($n = 13$)	CDR 1 ($n = 13$)	CDR 2 ($n = 22$)	CDR 3 ($n = 12$)
Social changes						
	Change of residence (1)	10 (16.7)	2 (15.4)	2 (15.4)	4 (18.2)	2 (15.4)
	Living alone (2)	12 (20.0)	4 (30.8)	5 (38.5)	1 (4.5)	2 (16.7)
	Loss of usual daily activities (3)	42 (70)	12 (92.3)	10 (76.9)	15 (68.2)	5 (41.7)
Clinical changes						
	Perception of cognitive worsening (4)	36 (60)	8 (61.5)	8 (61.5)	14 (63.6)	6 (50)
	Subjective mood/behavioral changes	32 (53.3)	6 (46.2)	7 (53.8)	12 (54.5)	7 (58.3)
	Mood/behavioral changes (increased NPI total score)	39 (65)	7 (53.8)	8 (61.5)	16 (72.7)	8 (66.7)
	Acute confusional state	9 (15)	0	2 (15.5)	2 (9.1)	5 (41.7)
	Increased incidence of falls	8 (13.3)	2 (15.4)	1 (7.7)	5 (22.7)	0
Covid-19 related aspects						
	Confirmed cases	6 (10)	0	0	1 (4.5)	5 (41.5)
	Oxygen therapy required	5 (8.3)	0	0	1 (4.5)	4 (33.3)
Medical care						
	Perception of difficulties in accessing care	10 (16.7)	2 (15.4)	0	4 (18.2)	4 (33.3)
	Medical phone assistance provided	20 (33.3)	3 (23.1)	4 (30.8)	10 (45.4)	3 (25)
	Standard medical consultation provided	4 (6.7)	2 (15.4)	1 (7.7)	0	1 (8.3)
	Emergency care provided	11 (18.3)	1 (7.7)	2 (15.4)	1 (4.5)	7 (58.3)
	Changes in psychopharmacological therapies	13 (21.7)	1 (7.7)	2 (15.4)	3 (13.7)	7 (58.3)
Caregiver						
	Perception of increased caregiver burden (5)	25 (41.7)	5 (38.5)	3 (23.1)	11 (50)	6 (50)
	Subjective caregiver burnout	7 (11.7)	1 (7.7)	0	2 (9.1)	4 (33.3)
	Use of support guidelines	2 (3.3)	0	1 (7.7)	1 (4.5)	0

Data are shown as number (percentage) of affirmative responses.
(1) Change of residence: referring to institutionalization or moving in with a relative.
(2) Living alone: patients living on their own without continued assistance or living in relative.
(3) Loss of usual daily activities referring to activities asked in the questionnaire: social meetings, daycare center, cognitive stimulation, visiting relative, taking care of other family members, practicing sports or strolling, shopping, reading, watching TV.
(4) Perception of cognitive worsening: asked to the interviewed caretaker as a subjective question.
(5) Perception of increased caregiver burden: asked to the interviewed caretaker as a subjective question.

RESULTS

We contacted a total of 60 patients. All the patients and families gave permission for participating in the study and answered our questionnaire without difficulties.

Mean age was 75.4 years ± 5.2. 53.3% of the patients were women 46.7%, men. Prior to the state of alarm, 13 patients had very mild dementia (CDR 0.5), 13 mild dementia (CDR 1), 22 moderate dementia (CDR 2), and 12 severe dementia CDR 3. A graphic representation of the CDR distribution is provided in **Figure 1**.

When age and sex distribution in dementia severity stages was analyzed there was no significative difference between groups (**Table 1**).

From all the interviewed patients, 25 (41.7%) had Alzheimer Disease (AD) diagnosis, 15 (25%) MCI, 6 patients were diagnosed with behavioral variant frontotemporal dementia (bvFTD) 3 patients were diagnosed with vascular dementia (VD), and 2 with Lewy body disease (LBD). Others including etiologically mixed dementias, Lewy Body disease, vascular dementia, and PSP accounted for the rest of the patients. A graphic representation of patient distribution by diagnosis is provided in **Figure 2**.

Table 2. Gathers the most important changes in our patients during the lockdown.

Before lockdown, the previous social situation of our patients was: 6 institutionalized (10%), 30 (50%) independent at home and 24 (40%) supervised at home. During the state of alarm, 10 patients (17%) changed residence. No relation between functional status (CDR) and residence change was found.

Only 12 (20%) of our patients lived alone (without additional help at home or other live-in caretaker) during lockdown, 9 in the early stages of dementia (CDR 0.5–1) but also 3 with moderate-severe dementia.

During lockdown, only 6 (10%) of our patients were infected by SARS-CoV-2. All were cases of advanced stages of dementia (CDR3). Three of the patients infected were previously institutionalized, 1 (1.3%) of them died from SARS-CoV-2 infection. Three of the patients were supervised at home and remained supervised at home after the infection. Four of the SARS-CoV-2 infected patients required urgent hospitalization. Two other patients required hospitalization but for other causes.

Forty eight (70%) of our patients abandoned previous daily activities. 43.3% of our patients, the ones previously socially active, stopped attending social reunions such as daycare centers,

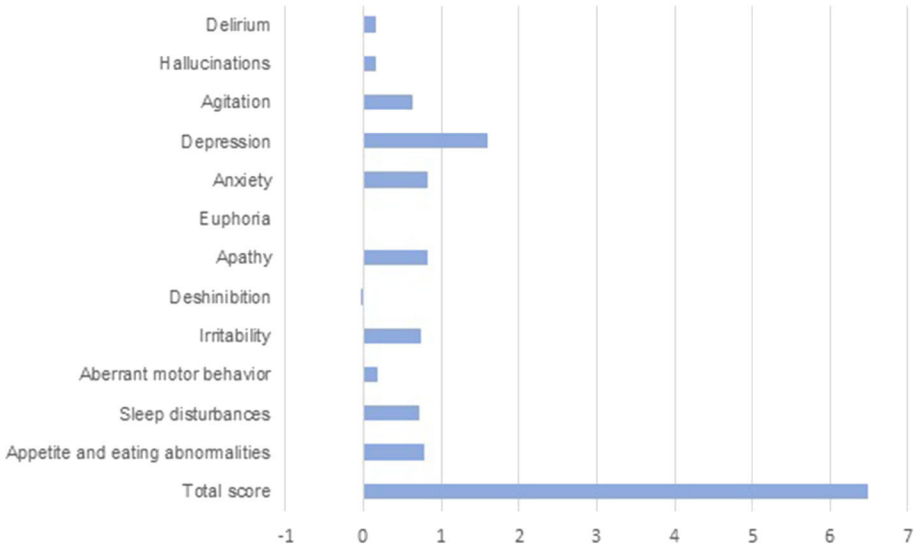


FIGURE 3 | Changes in NPI scores from baseline during lockdown.

third-age reunions, or social centers. 28.3% of our patients were previously attending cognitive stimulation in specific centers, which were closed and the activities canceled. 41.7% of our patients who previously attended gyms or went out on strolls stopped physical activity. 20% ceased to go out for daily shopping and 31% stopped visiting other family members as they did before.

In 36 (60%) patients, cognitive worsening was reported by family or caretakers, 8 among the mild cognitive decline group, 8 in the mild dementia group, and 7 in the advanced dementia group. Fourteen patients, 38% of those reported as cognitive worsening, were in dementia stage CDR2.

Functional status defined as CDR stage did not change significantly during lockdown.

When comparing prior and after lockdown CDR stages of our patients we did not find a significant difference ($p = 0.14$).

NPI score overall raised during lockdown. NPI score before lockdown was 3 (0–30). Total NPI score after lockdown was 8 (0–48). When analyzing differences between NPI before and after lockdown, we got a significant difference ($p < 0.000$).

When analyzing all the items in the NPI test, some of them revealed a significant difference before and after lockdown. These items were: agitation ($p = 0.003$), depression ($p < 0.000$), anxiety ($p < 0.000$), and changes in appetite ($p = 0.004$).

Figure 3 shows increases in most of the scores from NPI items during lockdown. An increased score means a worsening in these neuropsychiatric symptoms.

Nine (15%) of the patients presented delirium episodes, 5 of them were patients with severe dementia (CDR 3). 8 (13%) of our patients had increased incidence of falls. Most of the falls (62%) occurred to patients with moderate dementia. No falls occurred to patients with advanced dementia.

Caregivers perceived an increased burden in 25 (41%) cases independently of the dementia stage, though burnout was only reported in 7 (11%) cases, 6, nearly all of them, in cases of moderate-severe dementia. Only 2 (3%) caregivers used support guidelines during lockdown.

When asked about medical care, 10 (16%) of the patients/families interviewed reported difficulties in accessing medical resources. In 20 (33%) cases, medical phone assistance was provided. Only 4 (6%) cases required standard medical care and in 11 cases, nearly 20%, emergency care was needed. 13 (21%) patients had changes in psychopharmacological therapies during lockdown, mostly among the most advanced cases of dementia.

DISCUSSION

The COVID-19 pandemic has represented a challenge for us all, both health care professionals and patients and caretakers. Our aim in this study was to describe the influence of restrictive measures on patients living with mild cognitive decline and dementia and their caregivers, especially regarding the change in their routines and location, functional performance, neuropsychiatric symptoms, caregiver stress, and to evaluate their perception of sanitary care accessibility during the state of alarm.

Up to 10 (17%) of patients from our sample changed home in order to live with their relatives, which implies a major change for patients living with dementia *per se*. Dementia patients usually suffer from delirium when moving from location (i.e., during weekends or holidays), and usually need an adaptation period, sometimes including pharmacologic treatment adjustment. Twenty percent of our patients lived alone during lockdown which has made it challenging for families to provide optimal care. Although visits to dependent relatives were permitted, the frequency of visits might have been different during the state of alarm.

Regarding SARS-CoV2 infection, surprisingly, all of the patients from our sample who were affected by COVID-19 were also in an advanced stage of dementia. This fact makes us think that there might be a higher transmission due to ineffective isolation or institutionalization. Patients living with severe dementia have more difficulties to maintain complete isolation as they are dependent on basic activities of daily living. On the other hand, there have been multiple outbreaks in nursing homes during the state of alarm. In fact, 3 of our infected patients were institutionalized.

More than half of our patients abandoned previous activity during lockdown (60%). Among all the previously mentioned ceased activities, cognitive stimulation programs in day care centers were discontinued. This may be a step backwards for a lot of patients in early stages benefiting from this stimulation. Some of them also stopped taking care of activities that previously kept them active such as shopping or informal social meetings.

On the other hand, we have to keep in mind that 32% did not experience any change in their daily activities, which implies that there was a previous lack of cognitive and physical stimulation in most of these patients. Thus, we might acknowledge that a substantial amount of our patients is not usually taking either physical or cognitively stimulating activities.

Although no statistically significant changes in CDR were observed, caretaker-perceived cognitive worsening was reported by more than half our respondents (60%). It might be partly due to an increased observation from their caretakers (longer cohabitation) and partially influenced by caregivers' anxiety. An objective evaluation of cognitive status was not included in this assessment due to the limitations of the type of visit and the type of sample (including patients in advanced dementia stages which makes the use of telephonic versions of cognitive scales difficult to perform). We might argue that the cognitive differences sensed before may eventually surface when we get back to normal and therefore unveil as real and daily functional problems. It is important to mention that at the time this paper is written, we still haven't returned to that point of normality when our patients are able to carry their previous lives.

As discussed before, though there might also be cognitive impairment, neuropsychiatric symptoms are clearly aggravated. In our study, we found grounds to believe that the lockdown has significantly worsened this sphere globally, but even more in items such as depression, anxiety, agitation, and loss of appetite. In our view, though this might be influenced by the caregivers' observation, caregivers' own anxiety is a significant element to keep in mind. Furthermore, the fact that our patients developed more affective symptoms than psychotic symptoms during lockdown might reflect the situation of loneliness they have to face. The loss of resources, social gatherings, and institutional follow-up may make them feel forsaken.

Our results are congruent with other current studies such as the one by Lara et al. (11) which have found significant changes in NPI scores, such as agitation, apathy, and motor aberrant activity. The population analyzed in the cited study has a sample with different characteristics, with all patients in stages of mild cognitive impairment and mild dementia. This might explain the difference with our study in which different stages of dementia and etiologies are included.

Other clinical changes have also reported, such as 15% of our patients presented delirium episodes during lockdown. They were all in severe stages of dementia and, therefore, this makes us think that these patients are more fragile and vulnerable to changes. Also, falls rose over 13% in our total sample. Lack of physical stimulation may worsen motor capacities and therefore increase the risk of falls. Our results show that patients with advanced dementia had the least falls of all. This might be related to closer supervision or immobility.

Multiple studies have been conducted over anxiety among the general population in different countries. In Spain, a study by Rodriguez-Rey et al. (16) showed severe psychological impact by the pandemic in 30.4% of their sample. Hence, such psychological impact is present not only in our patients but also in their caregivers.

Our research reveals that 41% of caregivers noticed a subjective increase in stress. We need to keep in mind those figures on the overall population's psychological stress plus their particular situation hereby, taking care of their dependent relative.

In this way, most cases of burnout have been reported in severe dementia stages. This could be possibly related to limitations in outpatient health circuits, such as day-care centers shutdown, consequently reducing any assistance down to their relatives at home only. The fact that most of these challenged caregivers haven't sought help among guidelines and associations (only two of them had) is in most cases because they are not aware that such aids exist at all. That was a fact duly checked throughout our telephone interviews. In order to support these families, it will be necessary to reach out to them with wider promotion campaigns and education on virtual resources.

Medical care has also been affected during lockdown. Our results show that 16% of the families reported real obstacles accessing medical care although telephone assistance was given generally. It is important to remark how soon -within days- on-site attention turned into virtual attention to understand the general confusion of families and patients. Changes in pharmacological therapies reported by the families were made mostly by emergency clinicians and telephone calls. For instance, our data regarding NPI scores changes show higher incidence of anxiety and depression than that of pharmacological changes, which lead us to wonder if this lack of clinical follow-up or availability could have left patients unattended while symptomatic.

In conclusion, although the current uncertainty regarding the evolution of the pandemic makes strategy difficult, the reinforcement and adaptation of the care of these patients will be necessary and urgent. In our study, we exposed the influence of the lockdown in the cognitive, social, and neuropsychiatric spheres of our patients. We need to reach to the caregivers and patients and give them the education and support necessary to deal with the pandemic and social isolation. It is necessary to develop adequate strategies to restore stimulation and activity in our patients in order to improve their and their caregivers' daily life.

A multidisciplinary perspective will for sure be needed, from reinvention of current telemedicine techniques to implementation of preventive long run measures.

Limitations

All our interviews were made by telephone due to the pandemic situation even after the state of emergency was lifted. This, of course, made the clinical interview occasionally more difficult and could interfere in NPI/CDR values. An objective cognitive evaluation of patients would have been of high interest but due to the type of visit and limitations of telephonic cognitive scales on advanced dementia patients was ruled out. Other pandemic related limitations such as reaching to patients and families also influenced the sample size of our study.

Previous NPI was retrospectively based on medical records and family interviews regarding the previous state of our patients. This is of course less exact than having an actual previous NPI scale. It could magnify the difference between the already present items, for example, if a patient already affected by depression has to stay locked down, the family will magnify this during cohabitation, even if it's his/her usual state.

In some cases, through literature (17), pretest self-assessment has been considered as a valid tool. In our case the NPI retrospective items were asked to a reliable source, such as caretakers and close families.

When patients live in nursing homes or other kinds of institutions, the interview was still made with the families/caregivers. The information we have therefore relies on what the family gets from caretakers and scarce telephone conversations with the patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitè Ètic d' Investigació Clínica del Parc de Salut Mar (CEIM). The patients/participants had provided their signed informed consent to participate in DegMar registry and gived verbal informed consent to participate in this this CogVid study, which was ratified by written consent when possible, as approved by CEIM.

AUTHOR CONTRIBUTIONS

Patient recruitment was managed by AB, AF-L, and IE-G. The first draft of the manuscript was written by AB. All authors commented on previous versions of the manuscript, contributed to study conception and design, read, and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.589901/full#supplementary-material

REFERENCES

1. Lu H, Stratton CW, Tang Y-W. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol.* (2020) 92:401–2. doi: 10.1002/jmv.25678
2. World Health Organization Director-General's Opening Remarks at the Media Briefing on COVID-19–11 March (2020). Available online at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed October 06, 2020).
3. Fernandez, Rosa. Impacto del brote de coronavirus en el índice bursátil español IBEX-35 de enero a julio de 2020. *Statista.* (2020). Available online at: https://es.statista.com/estadisticas/1104248/impacto-del-coronavirus-en-el-ibex-35-en-espana-de-enero-a-marzo/ (accessed November 06, 2020).
4. Shahid Z, Kalayanamitra R, McClafferty B, Kepko D, Ramgobin D, Patel R, et al. COVID-19 and older adults: what we know. *J Am Geriatr Soc.* (2020) 68:926–9. doi: 10.1111/jgs.16472
5. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr.* (1997) 9(Suppl. 1):173–8. doi: 10.1017/S1041610297004870
6. Wang H, Li T, Barbarino P, Gauthier S, Brodaty H, Molinuevo JL, et al. Dementia care during COVID-19. *Lancet.* (2020) 395:1190–1. doi: 10.1016/S0140-6736(20)30755-8
7. Roberts R, Knopman DS. Classification and epidemiology of MCI. *Clin Geriatr Med.* (2013) 29:753–72. doi: 10.1016/j.cger.2013.07.003
8. Morley JE. An overview of cognitive impairment. *Clin Geriatr Med.* (2018) 34:505–13. doi: 10.1016/j.cger.2018.06.003
9. Grande G, Vetrano DL, Cova I, Pomati S, Mattavelli D, Maggiore L, et al. Living alone and dementia incidence: a clinical-based study in people with mild cognitive impairment. *J Geriatr Psychiatry Neurol.* (2018) 31:107–13. doi: 10.1177/0891988718774425
10. Cuffaro L, Di Lorenzo F, Bonavita S, Tedeschi G, Leocani L, Lavorgna L. Dementia care and COVID-19 pandemic: a necessary digital revolution. *Neurol Sci.* (2020) 41:1977–9. doi: 10.1007/s10072-020-04512-4
11. Lara B, Carnes A, Dakterzada F, Benitez I, Piñol-Ripoll G. Neuropsychiatric symptoms and quality of life in Spanish patients with Alzheimer's disease during the COVID-19 lockdown. *Eur J Neurol.* (2020) 27:1744–747. doi: 10.1111/ene.14339
12. Cohen G, Russo MJ, Campos JA, Allegri RF. Living with dementia: increased level of caregiver stress in times of COVID-19. *Int Psychogeriatr.* (2020). doi: 10.1017/S1041610220001593. [Epub ahead of print].
13. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* (1993) 43:2412–4. doi: 10.1212/WNL.43.11.2412-a
14. Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. *Neurology.* (1997) 48(5 Suppl. 6):S10–6. doi: 10.1212/WNL.48.5_Suppl_6.10S

15. Conn D, Thorpe L. Assessment of behavioural and psychological symptoms associated with dementia. *Can J Neurol Sci.* (2007) 34(Suppl. 1):S67–71. doi: 10.1017/S0317167100005606
16. Rodríguez-Rey R, Garrido-Hernansaiz H, Collado S. Psychological impact and associated factors during the initial stage of the coronavirus (COVID-19) pandemic among the general population in Spain. *Front Psychol.* (2020) 11:1540. doi: 10.3389/fpsyg.2020.01540
17. Nimon K. Explaining differences between retrospective and traditional pretest self-assessments: competing theories and empirical evidence. *Int J Res Method Educ.* (2013) 37:256–69. doi: 10.1080/1743727X.2013.820644

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 26 November 2020
doi: 10.3389/fneur.2020.588929

Neuromuscular Diseases Care in the Era of COVID-19

Bernat Bertran Recasens[†] *and Miguel Angel Rubio*[*†]

Neuromuscular Unit, Neurology Department, Hospital del Mar, Barcelona, Spain

The COVID-19 pandemic has pushed health systems to their limit and forced readjustment of standards of care for different pathologies. Management of neuromuscular diseases becomes a challenge since most of them are chronic, disabling, progressive, and/or require immunosuppressive drugs. There are three main aspects of COVID-19 that affect neuromuscular diseases care. The first one relates to how SARS-CoV2 directly affects different neuromuscular pathologies. Respiratory weakness, as seen in myasthenia gravis, amyotrophic lateral sclerosis, and myopathies, and the use of immunomodulatory drugs (Myasthenia Gravis and Chronic Inflammatory Demyelinating Polyneuropathy) make this group of patients potentially more vulnerable. Secondly, safety measures also affect proper care, limiting care continuity, and physical rehabilitation (one of the essential aspects of myopathies treatment). Telemedicine can partially solve the problem allowing for a continuum of close care, avoiding unnecessary visits, and even guaranteeing the attention of professionals from tertiary care centers. However, one of the crucial steps in neuromuscular diseases is diagnosis, and in most scenarios, more than one face-to-face visit is needed. Lastly, the global COVID-19 situation will also have an economic impact on patients and their families. This situation is of particular concern given that neuromuscular diseases already present difficulties due to the scarcity of resources in terms of public healthcare and research.

Keywords: neuromuscular disease (NMD), COVID-19, ALS (amyotrophic lateral sclerosis), CIDP, myasthenia gravis, telemedicine, telehealth

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu,
Hospital Clínico San Carlos, Spain

Reviewed by:
Fabiola De Marchi,
AOU Maggiore della Carità, Italy
Raffaele Dubbioso,
Federico II University Hospital, Italy
Juan Francisco Vázquez Costa,
El Instituto de Investigación Médica del Hospital La Fe (HULAFE), Spain

****Correspondence:***
Miguel Angel Rubio
marubio@parcdesalutmar.cat

[†]ORCID:
Bernat Bertran Recasens
orcid.org/0000-0002-5481-3846
Miguel Angel Rubio
orcid.org/0000-0003-0735-6854

Specialty section:
This article was submitted to Neuromuscular Diseases, a section of the journal Frontiers in Neurology

Received: *29 July 2020*
Accepted: *03 November 2020*
Published: *26 November 2020*

Citation:
Bertran Recasens B and Rubio MA (2020) Neuromuscular Diseases Care in the Era of COVID-19. Front. Neurol. 11:588929. doi: 10.3389/fneur.2020.588929

INTRODUCTION

The global pandemic situation due to COVID-19 has led to restructuring the management of different diseases. Beyond the transitory periods of total confinement that have occurred in most countries, the current situation entails a restriction of mobility due to the risk of infection of a disease for which, at the time, there is no curative treatment or vaccine. This threat has led to changes in healthcare paradigm: limited access to health centers, reconsideration of the gold standard of excellence in disease management, a thorough evaluation of the risk/benefit balance of specific interventions in the face of drug-disease interactions for a little-known infection and re-thinking of clinical trial procedures to ensure remote participation (from enrollment, dispensing of medication, and follow-up).

Neuromuscular diseases (from now on, NMD) are a heterogeneous group in terms of etiology, genetics, physiopathology, and treatments, that accounts from 2.8 to 18% of the referrals in the neurology department (1). Despite this heterogeneity, many share that they are complex, rare, chronic, disabling diseases, and can follow a progressive course. NMDs often involve the respiratory muscles or are treated with immunosuppressive treatment; which, suppose a group of potential risk

for the SARS-CoV2 infection. It is important to emphasize that patients with neuromuscular diseases should not be denied medical care on the basis of stereotypes or assessments of quality of life. Intensive care unit (ICU) doctors should contact the patient's permanent medical practitioner and/or expert center to understand the specific disease history and treatment plan of the patient.

In this paper we will review different aspects where NMDs are affected by this scenario.

NMD MANIFESTATIONS OF COVID-19 PATIENTS

In many countries, cases of neurological disease, induced by the viral infection itself or by the secondary inflammatory reaction, have been reported. These include stroke, encephalopathy, myelitis, and peripheral nervous system diseases (2). In general terms, SARS-CoV2 is believed to have neurotropism and can access the central nervous system through the olfactory nerves as well as other cranial nerves. This could explain why some patients have persistent anosmia or other cranial neuropathies (3, 4). At the level of the peripheral nerve, the mechanisms that cause its involvement are not fully understood. The nerve may be affected by direct cytotoxic damage from the virus, by systemic inflammation, or by molecular mimicry (4).

Regarding NMD, cases of isolated neuropathies of cranial nerves, acute paralysis similar to Guillain-Barré syndrome (GBS), Miller Fisher syndrome, and increased creatine kinase (CK) have been reported.

On a pathophysiological basis, GBS is considered an immune-mediated disease, but parainfectious cases have been seen during the COVID-19 pandemic. Thus, it is possible that the virus or the inflammation secondary to it damages the nerve (3) However, in most cases, the most widely accepted hypothesis is that a process of molecular mimicry occurs. SARS-CoV2, apart from binding to the angiotensin-converting enzyme 2 (ACE2), binds to glycoproteins and gangliosides on cell surfaces. This last interaction makes it plausible that a cross-reaction occurs between SARS-CoV2 spike-bearing gangliosides and sugar residues of surface peripheral nerve glycolipids (3, 4). The hypothesis of molecular mimicry is supported by the median time interval between COVID-19 symptoms and GBS onset (11.5 days), the acellular cerebrospinal fluid (CSF), and that many of them have responded favorably to IVIG (5, 6). Antiganglioside antibodies are likely not involved because it has only been reported the detection of GD1b antibodies in a patient with Miller Fisher syndrome (7). At the clinical level, the most frequent phenotype of GBS in SARS-CoV2 infection is the classical sensorimotor demyelinating GBS, but all variants and subtypes have been reported. Although one third of GBS patients have respiratory dysfunction, more than 70% have a good prognosis with immunoglobulin treatment (5, 6).

CK elevation, in some cases, appears to be secondary to myositis of probable autoimmune etiology (autoimmune necrotizing myositis: NAM), although direct damage from the virus cannot be ruled out since skeletal muscle cells also express ACE2 (4).

Due to the large number of patients requiring admission to the ICU due to COVID-19 infection, several cases of critical illness myopathy (CIM) (8) as well as compressive neuropathies or plexopathies (many of them associated with the prone position) have been reported. The early recognition of CIM is essential because it allows adaptation to a neuromotor and respiratory rehabilitation plan (9). For its diagnosis neurophysiological studies are crucial, however, sometimes, findings found can be misinterpreted as critical illness polyneuropathy or GBS. As an example, absence of F waves can be found in CIM, but reverses after 1 s burst of 20 Hz repetitive nerve stimulation (10).

Finally, to date, only 3 possible cases of myasthenia gravis debut just after COVID-19 have been described (11).

Thus, since current data seem to indicate that COVID-19 infection can induce not only GBS but also other autoimmune diseases, it is essential to pay attention to different neurological symptoms in those patients.

COVID-19 INFECTION IN NMD PATIENTS

In the literature and from our own experience, few patients with NMD have presented infection. This could be because they are aware of risks and took preventive measures, but also suggest that they are not at an increased risk of infection or severe illness. Even though certain patients with NMD who require immunosuppressive treatment or ventilatory support have a higher risk of infections, the risk of COVID-19 is not fully known and has been assumed by extrapolation. Thus, it seems logical to think that the poor prognostic factors are the same as the general population (age, obesity, cardiovascular risk factors, chronic high-dose corticosteroid treatment) (12).

There is little data regarding patients with NMD and COVID-19 infection. Cases of patients with myasthenia gravis who have had a SARS-CoV2 infection with a favorable evolution have been reported despite the fact that some have had to change their immunosuppressive treatment or have received treatment with hydroxychloroquine and/or antivirals (13–16).

There are not many reported cases of patients with other neuromuscular diseases such as immune-mediated neuropathies or ALS, and therefore, although always subject to a bias, could indicate that they do not seem to have a more severe infection or higher mortality.

Special caution must be focused in the use of certain therapies for the infection in NMD patients. During the pandemic, due to the need for urgent therapy, drugs that were believed to be effective (e.g., chloroquine or hydroxychloroquine, azithromycin, antivirals, dexamethasone and IL- inhibitors, etc.) have been administered. Actually in the first clinical studies conducted, only remdesivir and dexamethasone are effective (17, 18). In contrast, both hydroxychloroquine and azithromycin appear to be ineffective (19).

Azithromycin and chloroquine should be avoided, specifically those with MG, as both have been associated with a worsening of the disease (20). Since hydroxychloroquine additionally

supposes a risk for skeletal and cardiac muscle because with life-threatening cardiac arrhythmias is important to avoid in patients with NMD and cardiomyopathy as in DMD/BMD.

Regarding remdesivir, although some protease inhibitors had been associated with polyneuropathy, due to the short duration of treatment, only a few cases of toxic myopathy have been reported. In the case of MG, there is no evidence that remdesivir can induce clinical worsening (21).

Patients with COVID-19 have also an increased risk of thromboembolic events and therefore anticoagulant prophylaxis should be considered in patients that require also IVIG due to their underlying disease.

Finally, respiratory management has to be similar to the general population, taking into account the greater risk of respiratory muscles dysfunction.

IMPACT OF COVID-19 PANDEMIC IN THE CARE OF NMD PATIENTS

Diagnosis

One common problem of many NMD is the diagnosis delay and electrodiagnostic testing (EDX) plays an essential role. The restricted access to health centers has also limited the performance of EDX studies, as they require close contact with the patient over a prolonged period, and therefore could lead to further delay in diagnosis. Priority measures to ensure adequate safety in the studies are the use of personal protective equipment (PPE) and N95 masks, and the use of checklist of symptoms the day before the study. In cases of high-risk studies (i.e., facial studies, laryngeal electromyography), it is recommended to request polymerase chain reaction (PCR) studies on nasopharyngeal samples 24–48 h in advance (22). Follow-up EDX exams that are not urgent, do not contribute to a change in management and pose an increased risk of infection, can be postponed.

Treatment

Immunosuppressive treatment (including thymectomy in myasthenia gravis—MG) increases the risk of infections in patients with MG, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), or inflammatory myopathies. MG patients had an increased risk of infection of 39% (23), with pneumonia (especially bacterial) as the most frequent type of infection followed by sepsis, cutaneous, and soft tissue infections (24).

In the particular case of COVID-19, as mentioned above, there is little data of real risk of infection in NMD patients. However, several cohorts of patients with autoimmune diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis, or optic neuromyelitis show that treatment with immunosuppressants does not increase the risk of suffering from COVID-19 and neither present a more severe form of infection (25–28).

However, since current data corresponds to a small number of patients, it seems reasonable to continue with the indications of the expert groups; individualize decisions regarding the patient's situation or comorbidities, modify the immunosuppressive drug to one with a better safety profile (i.e., intravenous immunoglobulins, plasmapheresis, or steroids), space out the doses or even postpone the initiation of the medication in cases of stable patients or those with mild symptoms (29).

Long term corticosteroids is the drug that increase most the risk of infections (20–50%) (23, 24) and are often administered in various NMDs: MG, chronic dysimmune neuropathies, Duchenne/Becker Muscular Dystrophy (DMD/BMD) and patients with spinal muscular atrophy (SMA) treated with Onasemnogene abeparvovec-xioi (steroids must be administered for the first 2 months since the administration of the gene therapy). Although considered a risk factor given the associated immunosuppression, in general terms they should not be discontinued abruptly as they can cause a worsening of the underlying disease.

Plasmapheresis and intravenous immunoglobulins (IVIG) do not appear to increase the risk of infections, probably because they are often given in short courses, although long-term effect is unknown (30). However, a balance must always be made between the risk and benefit of each situation. For example, in CIDP patients stable for at least 6 months and treated with IVIG, the need for a new dose of IVIG could be reappraised (29, 30). Also, although plasmapheresis is not routinely used in these patients and is usually reserved for refractory cases, an US expert panel considers the inclusion of plasmapheresis as a second option over corticosteroids (31).

Prada et al., reported a cohort of 196 patients affected by immune-mediated neuromuscular diseases, with 0.6% laboratory-confirmed COVID-19 infection in those receiving IVIG or subcutaneous immunoglobulins, and 6.4% confirmed infection in those with other immunosuppressive treatment or no treatment. This could suggest a protective effect of chronic immunoglobulin therapy in the risk of COVID-19 infection. However, more studies are warranted to confirm this (32).

In patients with DMD/BMD, it is recommended to maintain the current treatment, including steroid therapy and oligonucleotide treatments (33). There have been concerns about the use of ACE inhibitors given the role of ACE2 in SARS-CoV2 infection. Numerous scientific societies such as the American Heart Association have stated that ACE inhibitors should not be withdrawn from patients as they have shown benefits in different cardiac conditions and a detrimental effect on coronavirus infection has not been yet demonstrated. Henceforth, patients with DMD/BMD who take such drugs should continue to take them (33).

Nowadays, several pharmacological treatments improve survival and motor skills of SMA patients. These treatments are nusinersen and gene therapy with Onasemnogene abeparvovec-xioi. Both have improved the quality of life, motor function and increased survival; and although these treatments are new, they should never be considered as elective or expendable. The delay of their administration should be avoided whenever possible, assessing the risks on an individual basis. In the case of nusinersen (intrathecal administration with a loading dose of 4 doses the first 2 months and then every 4 months), it has been reported that the delay of 1 month without medication leads to a 10% reduction of the drug in CSF. If there is a delay in administration, the schedule should not be readjusted, but rather

follow initial proposed calendar to ensure optimal intrathecal medication levels (34).

Regarding other immunomodulatory treatments (mycophenolate mofetil, cyclophosphamide, azathioprine, etc.), the increased risk of infection is similar to corticosteroids (35). Also, when the risk-benefit ratio of each case is considered, given the possibility of exposure to infection, it should be kept in mind that some of these drugs have no proved efficacy in some NMDs (i.e., rituximab, azathioprine, methotrexate, or mycophenolate in CIDP).

Due to the fact that patients with NMD present frequent respiratory infections, it is important to do a close follow-up (by professionals of the multidisciplinary Unit as well as from primary care). As for household measures, ventilation devices, unless equipped with bacterial/viral filters (HEPA), as well as airway clearance devices (cough assist, nebulization), increase the risk of particle dispersion into the environment. Despite this, patients and caregivers should be warned not to modify the ventilation schedule to avoid errors. If possible, it is recommended to convert the tubing and mask circuitry to a closed system by using both a double-lumen tube with a viral/bacterial filter and a non-vented full-face mask to restrict viral spread (36).

During confinement and, currently, due to social distancing measures, the population is doing less physical activity (37). This change most significantly affects patients with NMD. That is why, rehabilitation continuity must also be guaranteed, either face-to-face or by telematics communication.

A brief summary of the considerations to be taken into account in the management of the different NMDs is shown in **Table 1**.

TABLE 1 | Neuromuscular disorders management in Covid-19 era.

- Encourage telematics assessments
  - Monitoring home ventilation
  - Perform respiratory assessments if able
- Do not stop rehabilitation
- Psychological support (specially in DMD with behavioral disorders)
- Perform EDX safely and DO NOT delay diagnosis
- Consider clinical trial monitoring remotely
- Patients under steroids treatment: do not stop steroids and consider increasing the dose in ill patients
- Rationalize the use of IS agents
  - Space doses or postpone the initiation if stable (especially if the infusion is in the hospital: cyclophosphamide, rituximab, etc.)
  - Choose IS with a safer profile. Do not stop IACE drugs
  - Consider switching IVIG to subcutaneous immunoglobulins
  - Consider PLEX or IG as an alternative option instead steroids in CIDP patients
  - For maintenance rituximab therapy, consider delaying the infusion
  - even beyond 6 months, if the CD19 and CD20 lymphocytes are suppressed
- Consider anticoagulant prophylaxis in patients with COVID-19 that require also IVIG
- Continue ASO treatment as scheduled in SMA patients
- Do not stop IACE drugs (DMD/BMD)
- Avoid chloroquine, hydroxychloroquine (DMD/BMD and MG) and azithromycin (MG)

Summary of recommendations for the management of neuromuscular diseases. MG, myasthenia gravis; DMD/BMD, Duchenne/Becker muscular dystrophy; SMA, spinal muscular atrophy; ALS, amyotrophic lateral sclerosis, IS, immunosuppressants; IG, immunoglobulin; IVIG, intravenous immunoglobulin; PLEX, plasmapheresis; IACE, angiotensin-converting enzyme inhibitors; ASO, antisense oligonucleotide.

Clinical Trials

The status of clinical trials in NMD has been impaired during the pandemic situation with difficulties with new inclusions, treatment supplies and monitoring. Data reported from the NEALS (38) on the status of ALS clinical trials during the pandemic show that very few sites were able to recruit new patients and that 20% of follow-up patients withdrew from the trial. This should make us consider new approaches to clinical trials.

Thus, in a situation in which the recruitment of patients with rare diseases is already complicated (39), several strategies must be considered. Some examples are: advising the population about studies on the Internet or social network advertisements; the use of telematic consent (tele-consent) or the utilization of telephone interviews; mobile applications or other devices such as dynamometers, actigraphs, accelerometers, or remote measurements of respiratory function. Also, the need for remote dispensing and collection of medication should be addressed.

Telematic assessment of progression could evaluate more frequently and in daily environment for the patient and in turn could even reduce the duration and the number of subjects needed in clinical trials.

Finally, it is essential to prevent selection bias toward patients with ease in remote monitoring and more familiar with technology.

Socioeconomical Impact

One of many faces of catastrophic COVID-19 situation is its social, occupational and economic impact in NMD patients and their families. For example, the estimation of the annual cost of an ALS patient is approximately 50,000 euros (1), and 70,000 euros for SMA patients, being even higher in SMA type 1 (107,000 euros/year) (40). Since their essential care can be directly affected by economic situation, NMDs are at risk, in terms of personal healthcare, in a context of deterioration of the individual and global economy.

Other consequences are the increase in anxiety and feelings of loneliness that have been reported in NMD patients and their relatives/caregivers during confinement (41). In the case of ALS patients have been described worsening of depressive and anxiety symptoms, associated to altered interoceptive awareness during the outbreak (42).

It is essential not to forget the psychological support for the patient, his family and the caregivers, even if it is remotely. As an example, DMD/BMD boys may have a spectrum of behavioral disorders, including some degree of intellectual disability and anxiety problems which will require close psychological follow-up.

Finally, because research is currently focused on finding therapeutic strategies for COVID-19, there is a redirection of interest (and thus funding) which may lead to a loss of already fragile research funding in NMD.

Ethical Issues Related to NMD Patients Care

In situations with a high healthcare burden, it is important not to discriminate patients with chronic and rare diseases, from a therapeutic point of view. ICU doctors should discuss the case with the patient's permanent medical practitioner and/or expert center to understand the disease history and treatment plan of the patient (43).

FUTURE PERSPECTIVES

Vaccines

Multiple clinical trials are currently underway to develop an effective vaccine against COVID-19. There are more than 120 vaccine candidates but neither uses live attenuated virus (44), and therefore those under immunosuppressive treatment could receive it. However, it is not known whether immunomodulatory treatment can alter the efficacy of vaccines and hence, what would be the best time to vaccinate according to the immunosuppressive treatment scheme (45). Therefore, when the occasion arrives, it will be crucial for the patient to coordinate with his/her referring neurologist.

Beyond the Hospital Walls. Tele-Health in Times of COVID-19

Remote Care and Management

The current situation has pushed the limits of telehealth in NMDs, both in terms of implementation in medical centers and in terms of acceptability and skepticism by patients and health professionals. The gold standard of healthcare is multidisciplinary consultation, but this often involves drawbacks since patients and their families might spend many hours traveling and staying at the hospital with the fatigue and burden that this involves. Moreover, as the disease progresses and the problems of mobility and fatigue increase it becomes more challenging to travel and, conversely, contact with medical services becomes more necessary. Tele-health services must be conceived as an additional complimentary activity to face-to-face visits. Therefore, remote assistance is an essential opportunity for NMDs, even more so in this current pandemic situation. A survey of NEALS (North East ALS Consortium) to know the impact of the COVID-19 situation on ALS patient's healthcare and research (38) revealed that one third of the centers had not been able to visit new patients in person, more than half had visited via video-call, and only 16% of the centers were able to fully supply their patients with the basics (gastrostomy tubes, wheelchairs, medication, etc.).

In addition, the telehealth model allows the patients to hold the consultation in familiar environments, making it more comfortable to them, maintaining the link with multidisciplinary units even in more advanced stages (46).

Nowadays, we know that specific functional scales or aspects of physical examination can be performed telematically with strong correlation with their equivalents in face-to-face visits performed by health professionals (47). These methods not only can replace 'traditional' face-to-face visit but they can also be used to keep closer control of the evolution of the patients and even be essential for therapeutic decisions, such in the case of chronic dysimmune neuropathies. For this reason, it is crucial to be able to perform objective and validated measures remotely. This monitoring can be carried out through telephone interviews, questionnaires in mobile apps or even through 'user-friendly' devices, adaptation of functional scales (Inflammatory Neuropathy Cause and Treatment—INCAT disability score, Inflammatory Rasch-built Overall Disability Scale—I-RODS, ALSFR-R), by using dynamometers, through remote physical examination or by asking about activities of daily living, fatigue and falls. It is easy to imagine that a video call allows, for example, to observe the lifting capacity of the arms or the wandering. Although there may be concerns about the validity of these measurements, it should be noted that the Medical Research Council (MRC) scale also has inter- and intra-observer variability.

Respiratory function monitoring is also essential since provide prognosis information, indicates proper timing of non-invasive ventilation, and are a crucial key of inclusion criteria of most clinical trials. However, there is a risk of producing aerosols during the examination. There is evidence of viability of home respiratory screening devices with a reasonable degree of correlation with in-hospital respiratory screening and hence its use must be encouraged. Several NMD finally will require the use of home mechanical ventilation. In many cases, it is possible to control the parameters from the hospital, avoiding unnecessary displacements.

DISCUSSION

Living with a NMD is a challenge not only for patients but for their caregivers and families, and COVID-19 pandemic situation represents even a greater stress test.

NMD patients are a group at risk, either because of respiratory affectation or their condition of immunosuppression. For this reason, it is important to individualize the management of NMD patients, considering the interventions and treatments individually and taking into account the risk of going to the hospital and the risk of not receiving proper attention.

On the other hand, telemedicine has suffered an accelerated expansion, representing an opportunity to improve clinical care management and research. Ideally, a combination of telematics and face-to-face visits would create a hybrid model that would be defined depending on the evolutionary moment of each patient.

The gold standard in the management of NMDs is the attention in multidisciplinary units, where holistic and global management of the patient's needs is given, as well as research and clinical trials are performed. Multidisciplinary units must continue to commit to excellence in care, but now in a remote scenario in which the wellness of the patient must still be the focus even in these uncertain times.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. The first draft of the manuscript was written by MR and BB commented on previous versions of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Camacho A, Esteban J, Paradas C. Report by the Spanish foundation for the brain on the social impact of amyotrophic lateral sclerosis and other neuromuscular disorders. *Neurologia.* (2018) 33:35–46. doi: 10.1016/j.nrleng.2015.02.006
2. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID19: a review. *Acta Neurol Scand.* (2020) 24:1–9. doi: 10.1111/ane.13266
3. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. *Neurol Sci*. (2020) 41:3039–56. doi: 10.1007/s10072-020-04708-8
4. Dalakas MC. Guillain-barre syndrome: the first documented COVID-19– triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm.* (2020) 7:e781. doi: 10.1212/NXI.0000000000000781
5. Uncini A, Vallat JM, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. *J Neurol Neurosurg Psychiatry.* (2020) 91:1105–10. doi: 10.1136/jnnp-2020-324491
6. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol.* (2020) 25:1–38. doi: 10.1007/s00415-020-10124-x
7. Costello F, Dalakas MC. Cranial neuropathies and COVID-19: neurotropism and autoimmunity. *Neurology*. (2020) 95:195–6. doi: 10.1212/WNL.0000000000009921
8. Bagnato S, Boccagni C, Marino G, Prestandrea C, D'Agostino T, Rubino F. Critical illness myopathy after COVID-19. *Int J Infect Dis.* (2020) 99:276–8. doi: 10.1016/j.ijid.2020.07.072
9. Estraneo A, Ciapetti M, Gaudiosi C, Grippo A. Not only pulmonary rehabilitation for critically ill patients with COVID-19. *J Neurol.* (2020) 16:1–3. doi: 10.1007/s00415-020-10077-1
10. Tankisi H, Tankisi A, Harbo T, Markvardsen LK, Andersen H, Pedersen TH. Critical illness myopathy as a consequence of covid-19 infection. *Clin Neurophysiol*. (2020) 131:1931–32. doi: 10.1016/j.clinph.2020.06.003
11. Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. *Ann Intern Med*. (2020) 10:L20–0845. doi: 10.7326/L20-0845
12. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
13. Anand P, Slama MCC, Kaku M, Ong C, Cervantes-Arslanian AM, Zhou L, et al. COVID-19 in patients with myasthenia gravis. *Muscle Nerve.* (2020) 62:254–8. doi: 10.1002/mus.26918
14. Rein N, Haham N, Orenbuch-Harroch E, Romain M, Argov Z, Vaknin-Dembinsky A, et al. Description of 3 patients with myasthenia gravis and COVID-19. *J Neurol Sci.* (2020) 417:117053. doi: 10.1016/j.jns.2020.117053
15. Ramaswamy SB, Govindarajan R. COVID-19 in refractory myasthenia gravis-a case report of successful outcome. *J Neuromuscul Dis.* (2020) 7:361–4. doi: 10.3233/JND-200520
16. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol.* (2020) 19:767–83. doi: 10.1016/S1474-4422(20)30221-0
17. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 -preliminary report. *NEJM* (2020) 383:1813–26. doi: 10.1056/NEJMoa2007764
18. Johnson RM, Vinetz JM. Dexamethasone in the management of covid−19: preliminary trial results are mostly good news, but timing is everything. *BMJ.* (2020) 370:m2648. doi: 10.1136/bmj.m2648
19. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with covid-19. *NEJM.* (2020) 382:2411–18. doi: 10.1056/NEJMoa2012410
20. Sole G, Salort-Campana E, Pereon Y, Stojkovic T, Wahbi K, Cintas P, et al. Guidance for the care of neuromuscular patients during the COVID-19 pandemic outbreak from the French rare health care for neuromuscular diseases network. *Revue Neurol*. (2020) 176:507–15. doi: 10.1016/j.neurol.2020.04.004
21. Guidon A, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. (2020) 94:959–69. doi: 10.1212/WNL.0000000000009566
22. Desai U, Kassardjian CD, Del Toro D, Gleveckas-Martens N, Srinivasan J, Venesy D, et al. Guidance for resumption of routine electrodiagnostic testing during the COVID-19 pandemic. *Muscle Nerve.* (2020) 62:176–81. doi: 10.1002/mus.26990
23. Kassardjian CD, Widdifield J, Paterson JM, Kopp A, Nagamuthu C, Barnett C, et al. Serious infections in patients with myasthenia gravis: population-based cohort study. *Eur J Neurol.* (2020) 27:702–8. doi: 10.1111/ene.14153
24. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. *J Neurol.* (2018) 265:1251–8. doi: 10.1007/s00415-018-8751-9
25. Ebrahimi A, Sayad B, Rahimi Z. COVID-19 and psoriasis: biologic treatment and challenges. *J Dermatol Treat*. (2020) 6:1–5. doi: 10.1080/09546634.2020.1789051
26. Vakil-Gilani K, O'Rouke K. Are patients with rheumatologic diseases on chronic immunosuppressive therapy at lower risk of developing severe symptoms when infected with COVID-19? *Clin Rheumatol.* (2020) 39:2067–8. doi: 10.1007/s10067-020-05184-3
27. Fan M, Qui W, Bu B, Xu Y, Yang H, Huang D, et al. Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm.* (2020) 7:e787. doi: 10.1212/NXI.0000000000000787
28. Louapre C, Collongues N, Stankff B. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. *JAMA Neurol.* (2020) 77:1079–88. doi: 10.1001/jamaneurol.2020.2581
29. Dubbioso R, Nobile-Orazio E, Manganelli F, Santoro L, Briani C, Fabrizi GM. Dealing with immune-mediated neuropathies during COVID-19 in review outbreak: practical recommendations from the task force of the Italian society of neurology (SIN), the Italian society of clinical neurophysiology (SINC) and the Italian peripheral nervous system association (ASNP). *Neurol Sci*. (2020) 41:1345–8. doi: 10.1007/s10072-020-04448-9
30. Guptill JT, Juel VC, Massey JM. Effect of therapeutic plasma exchange on immunoglobulins in myasthenia gravis. *Autoimmunity.* (2016) 49:472–9. doi: 10.1080/08916934.2016.1214823
31. Rajabally YA, Goedee HS, Attarian S, Hartung HP. Management challenges for chronic dysimmune neuropathies during the COVID−19 pandemic. *Muscle and Nerve.* (2020) 62:34–40. doi: 10.1002/mus.26896
32. Prada V, Benedetti L, Cocito D, Briani C, Nobile Orazio E, Gallia F, et al. High-dose immunoglobulin pulse therapy and risk of covid19 infection. *J Neurol.* (2020) 10:1–3. doi: 10.1007/s00415-020-10146-5
33. Veerapandiyan A, Wagner KR, Apkon S, McDonald CM, Mathews KD, Parsons JA, et al. The care of patients with duchenne, becker, and other muscular dystrophies in the COVID-19 pandemic. *Muscle Nerve.* (2020) 62:41–45. doi: 10.1002/mus.26902

34. Veerapandiyan A, Connolly AM, Finkel RS, Arya K, Mathews KD, Smith EC, et al. Spinal muscular atrophy care in the COVID-19 pandemic era. *Muscle Nerve.* (2020) 62:46–49. doi: 10.1002/mus.26903
35. Feldman CH, Marty FM, Winkelmayer WC, Guan H, Franklin JM, Solomon DH, et al. Comparative rates of serious infections among patients with systemic lupus erythematosus receiving immunosuppressive medications. *Arthritis Rheumatol.* (2017) 69:387–97. doi: 10.1002/art.39849
36. Young EI, Manta D, Sah BP, Brooks BR. Modification of non-invasive ventilation for the advanced amyotrophic lateral sclerosis patient during the In review COVID-19 pandemic - do it now. *J Neurol Sci.* (2020) 414:116893. doi: 10.1016/j.jns.2020.116893
37. Di Stefano V, Battaglia G, Giustino V, Gagliardo A, D'Aleo M, Giannini O, et al. Significant reduction of physical activity in patients with neuromuscular disease during COVID-19 pandemic: the long-term consequences of quarantine. *J Neurol.* (2020) 13:1–7. doi: 10.1007/s00415-020-10064-6
38. Andrews JA, Berry JD, Baloh RH, Carberry N, Cudkowicz ME, Dedi B, et al. Amyotrophic lateral sclerosis care and research in the United States during the COVID-19 pandemic: challenges and opportunities. *Muscle Nerve.* (2020) 62:182–6. doi: 10.1002/mus.26989
39. Bedlack RS, Pastula DM, Welsh E, Pulley D, Cudkowicz ME. Scrutinizing enrollment in ALS clinical trials: room for improvement? *Amyotr Lateral Scler.* (2008) 9:257–65. doi: 10.1080/17482960802195913
40. Klug C, Schreiber-Katz O, Thiele S. Disease burden of spinal muscular atrophy in Germany. *Orphanet J Rare Dis.* (2016) 11:58. doi: 10.1186/s13023-016-0424-0
41. Consonni M, Telesca A, Dalla Bella E, Bersano E, Lauria G. Amyotrophic lateral sclerosis patients' and caregivers' distress and loneliness during COVID- 19 lockdown. *J Neurol.* (2020) 21:1–4. doi: 10.1007/s00415-020-10080-6
42. De Lucia N, Ausiello FP, Spisto M, Manganelli F, Salvatore E, Dubbioso R. The emotional impact of COVID-19 outbreak in amyotrophic lateral sclerosis patients: evaluation of depression, anxiety and interoceptive awareness. *Neurol Sci.* (2020) 41:2339–41. doi: 10.1007/s10072-020-04592-2
43. EURORDIS (Rare Diseases Europe). *Rare Disease Community Raises Alert Over Discrimination in Critical Care Guidelines During COVID-19 Pandemic.* Available online at: https://www.eurordis.org/covid19resources (accessed October 01, 2020).
44. World Health Organization. *Draft Landscape of COVID-19 Candidate Vaccines.* Available online at: https://www.who.int/who-documentsdetail/draft-landscape-of-covid-19-candidate-vaccines (accessed July 14, 2020).
45. Rondaan C, Furer V, Heijstek MW, Agmon-Levin N, Bijl M, Breedveld FC, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. *RMD Open.* (2019) 5:e001035. doi: 10.1136/rmdopen-2019-001035
46. Paganoni S, Van de Rijn M, Drake K. Adjusted cost analysis of video televisits for the care of people with amyotrophic lateral sclerosis. *Muscle Nerve.* (2019) 60:147–54. doi: 10.1002/mus.26606
47. Kelly M, Lavrov A, Garcia-Gancedo L, Parr J, Hart R, Chiwera T, et al. The use of biotelemetry to explore disease progression markers in amyotrophic lateral sclerosis. *Amyotr Lateral Scler Frontotemporal Degener.* (2020) 23:1–11. doi: 10.1080/21678421.2020.1773501

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 26 November 2020
doi: 10.3389/fneur.2020.582794

Electroencephalographic Abnormalites in SARS-CoV-2 Patients

Stephane Besnard[1], Clotilde Nardin[2], Elsa Lyon[3], Thomas Debroucker[2], Roxana Arjmand[4], Raffaella Moretti[5] and Hervé Pochat[6]*

[1] University Hospital of Caen Normandie, Explorations Fonctionnelles, CHU Caen, Caen, France, [2] Centre Hospitalier Delafontaine, Saint-Denis, France, [3] ELYOPE SAS, Paris, France, [4] Centre Hospitalier de Sens, Yonne, Sens, France, [5] Explorations Fonctionnelles Pédiatriques, CHU Armand-Trousseau, APHP, Paris, France, [6] SIGMA EEG SARL, Paris, France

Viral infection with SARS-CoV-2 has a neurological tropism that may induce an encephalopathy. In this context, electroencephalographic exploration (EEG) is indicated as a diagnostic argument correlated with lumbar puncture, biology, and imaging. We performed a retrospective analysis of 42 patients explored by EEG and infected by COVID-19, according to the EEG abnormalities and clinical signs that motivated the examination. Confusion and epileptic seizures were the most common clinical indications, with 64% of the patients displaying these symptoms. The EEG was altered in 85% of the cases of confusion, in 57% of the cases of epileptic symptoms (general or focal seizure or prolonged loss of contact) and 20% of the cases of malaise or brief loss of consciousness. Nine EEG (21%) were in favor of an encephalopathy, two had *de novo* alterations in persistent consciousness and two had alterations in general states of confusion; one was very agitated and without history of epilepsy and combined eyelids clonia while a second one exhibited unconsciousness with left hemicorpus clonus. Two were being investigated for delayed awakening without sedation for more than 24 h. All of these patients were diagnosed COVID-19, some of them with associated mild to severe respiratory disorders. This work shows the interest of the EEG in exploring COVID-19 patients suffering from neurological or general symptoms looking for cerebral alteration.

Keywords: confusion, epileptic seizure, virus, encephalopathy, electroencephalography

OPEN ACCESS

Edited by:
Giovanni Assenza, Campus Bio-Medico University, Italy

Reviewed by:
Angel Aledo-Serrano, Hospital Ruber Internacional, Spain
Beatriz Parejo-Carbonell, Hospital Clínico San Carlos, Spain

****Correspondence:***
Stephane Besnard
stephane.besnard@unicaen.fr

Specialty section:
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

Received: *13 July 2020*
Accepted: *30 September 2020*
Published: *26 November 2020*

Citation:
Besnard S, Nardin C, Lyon E, Debroucker T, Arjmand R, Moretti R and Pochat H (2020) Electroencephalographic Abnormalites in SARS-CoV-2 Patients. Front. Neurol. 11:582794. doi: 10.3389/fneur.2020.582794

INTRODUCTION

The current pandemic viral infection with coronavirus 2 (SARS-CoV-2) appears to have, as its initial target, the respiratory tract inducing acute respiratory distress syndrome, particularly in elderly subjects with certain risk factors including diabetes, immunosuppression, and chronic renal and respiratory failure. As with any severe viral infection, there is a risk of dissemination to the central nervous system with general neurological symptoms such as fatigue, headache, confusion, myalgia, and more specifically anosmia and agueusia (1). Neurological impairments may result in an encephalopathy, meningoencephalitis, necrotizing encephalitis (2) documented by imaging (3) and lumbar puncture (4) and may be accompanied by epileptic seizures or stroke (5, 6). This neurological impairment seems to be correlated with the severity of the infection (7). The underlying neurophysiopathological mechanism remains to be clarified and appears to be multimodal. The virus could cross the blood-brain barrier and bind to hACE2

receptors co-expressed with acetylcholine receptors; could induce immunological reaction; and could penetrate through the olfactory mucosa and then the receptors and olfactory nerves as entry points (1, 8, 9). Moreover, the neurological damages could be due to or aggravated by cerebral hypoxemia and metabolic acidosis induced by respiratory disorders (10, 11). Respiratory disorders could in turn be aggravated by a dysfunction of the respiratory centers, located in the brainstem, a predominant target of SARS-CoV-2 as demonstrated in a mouse model of infection (10). In total, cerebral impairments could express or combine three encephalopathic types: an infectious toxic encephalopathy, a viral encephalitis, and an anoxic encephalopathy, as described by Wu et al. (12).

The electroencephalogram (EEG), which is one of the tools for neurological explorations, could be of interest in the diagnosis of encephalopathy in the context of patients with COVID-19 and those suffering from neurological symptoms. Indeed, a clinical case has reported a man of 74 years-old suffering from respiratory distress associated with mental confusion who presented EEG abnormalities in the form of diffuse slowing and focal slowing sharply contoured waves in the left temporal region. However, while the diffuse abnormalities could be related to encephalopathy, the focal abnormalities appeared to be related to encephalomalacia secondary to a previous stroke (5).

In addition, pre-existing neurological pathology, particularly epilepsy, could be aggravated by a SARS-CoV-2 infection according to its neurological tropism. Consequently, we retrospectively analyzed and reported the EEG patterns of 42 patients infected by SARS-CoV-2.

METHODS

This is a retrospective study from an EEG database interpreted by neurophysiologists with the help of the SIGMA EEG Company, supporting facilities and administrative procedures for the transfer of medical exams whose EEG. Clinical information was collected from information sent by prescribers from Center Hospitalier Delafontaine, Center Hospitalier de Sens, Center Hospitalier Sainte Camille, Center Hospitalier de Joigny, Center Hospitalier de Brie Comte Robert, and Center Hospitalier de Coulomiers. Two EEGs were included and classified according to the indication of the exam and the electrophysiological abnormalities observed. Indications were classified as followed: (a) confusion or psychomotor retardation; b/clinical epileptic symptoms with generalized seizure or focal seizure, prolonged loss of consciousness with general hypotonia, (b) short loss of consciousness, (c) delayed awakening after reanimation, (d) hallucinations or behavioral disorders, (e) transitory ischemic stroke or suspected stroke; (f) follow-up of a meningoencephalitis. We have classified EEG abnormalities as follows: normal with somnolence, slight slowdown rhythm or poorly organized, some non-specific abnormalities, focal or diffuse epileptic pattern, encephalopathic pattern. The results are presented in a descriptive manner like a case report.

TABLE 1 | Distribution of the electroencephalographic patterns observed in patients infected by CoV-SAR-2.

EEG pattern in COVID 19 + patients	Absolute values	%
Normal with drowsiness	12	28.6
Slight slowdown rhythm or poor spatial organization	9	21.4
Unspecific anomalies	8	19
Focal or diffuse epileptic pattern (diffuse spike and polyspikes, frontal spikes, temporal, and rolandic slow sharp waves or spikes and wave spikes, and altered sharp waves	4	9.5
Encephalopathic pattern (continuous or rhythmic frontal or diffuse slow diphasic or triphasic waves or sharp waves)	9	21.4
Total	42	

RESULTS

Patients included were referred for EEG over a 2-month period between March and April 2020. Twelve EEGs were normal (21.8%), 9 showed a slight deceleration without spatial organization (21.4%), 8 some non-specific abnormalities or questionable elements (19%), 4 focal or diffuse epileptic EEG abnormalities including one related to symptomatic focal epilepsy related to stroke prior to SARS-CoV-2 infection (9.5%). Nine showed an encephalopathic pattern, one of the patients being still under sedation (21.4%) (**Table 1**).

On 33% of patients with confusion or psychomotor alterations, two EEG were normal with drowsiness, 3 EEGs were slowed but one under midazolam, 4 had some abnormal non-specific features, two had epileptic anomalies (one with rolandic epileptic abnormalities or lateralized epileptiform discharges at 1 Hz (LPDs) probably more related to a previous stroke, not fullfing criteria for non-convulsive status epilepticus; and one with a status epilepticus (fronto-temporal slow waves spikes at 2 Hz) solved with intravenous clonazepam injection) and 3 had an encephalopathic pattern. The EEG was therefore modified in 85% of the cases of confusion.

Out of 30.9% of patients with clinical epileptic symptoms, 5 EEG were normal, 1 was slowdown, 2 presented non-specific abnormalities, 2 were with comital abnormalities (one with frontal sharp-waves epileptic seizures and one with focal rolandic sharp-waves and spikes with or without slow waves) and three in favor of an encephalopathy but one remained under sedation. The EEG was then altered in 57% of cases.

Patients with epileptic symptoms expressed general tonico-clonic seizures or focal clonic seizure (limbs or jaw).

Of 12% of patients with brief loss of consciousness, three had normal EEGs, one was slightly slowdown and one showed encephalopathic pattern, so we had 20% EEG changes in case of brief loss of consciousness.

Regarding the EEG traces on hallucination, one was normal but raised doubts about pharmacological rhythms and the second one was unspecifically slowed down. The EEG for suspicion of transitory ischemic crebrovascular impairment was normal. Of

TABLE 2 | Percentage of abnormal EEGs according to their pattern and the initial indication of EEG.

Indication of the EEG and %		EEG reports (number of patients)				
	% from (the number of patients)	Normal with drowsiness	Slight slowdown, poor spatial organization	Unspecific anomalies	Focal/diffuse comitial anomalies, PLEDS or similar	Encephalopathic pattern
Confusion/psychomotor retardation	33.3 (14)	2	3	4	2	3
Epileptic seizure (general tonico-clonic or focal clonic seizure, prolonged loss of consciousness with general hypotonia)	30.9 (13)	4	1	2	2	3
Short loss of consciousness	11.9 (5)	3	1	0	0	1
Delayed awakening after reanimation	14.3 (6)	0	2	2	0	2
Hallucinations/altered behavior	4.7 (2)	1	1	0	0	0
Transitory ischemic disease	2.4 (1)	0	1	0	0	0
Follow-up of a meningoencephalitis	2.4 (1)	1	0	0	0	0
Total	42	12	9	8	4	9

the EEGs for delayed awakening, two were slightly slowed down in rhythm, three showed unspecific abnormalities, and one had a pattern of encephalopathy (**Table 2**).

Of 21.4% with an EEG in favor of encephalopathy (**Figure 1**), two had alterations without disorders of consciousness and two had alterations in general state with confusion; one was very agitated and without history of epilepsy and combined palpebral clonia after sedation had been stopped for more than 24 h while a second one exhibited unconsciouness with left clonies. Two were being investigated for delayed awakening without sedation for more than 24 h, one was being investigated for unconsciousness but his clinical condition at the time of examination had deteriorated rapidly with disturbances of consciousness, and one was being investigated for a suspicion of a state of illness in a known epileptic patient who had received anti-epileptic treatment and sedation. All of these patients were diagnosed COVID+, some of them with associated mild to severe respiratory disorders. For patients being investigated for delayed awakening, the clinical state was obviously severe as they required intensive care. Meningeal or cerebral damage remains difficult to prove and not all paraclinical elements were available at the time of the EEG.

The respective role of epilepsy and COVID-19 in neurological involvement remains subject of caution. Indeed, any infection may aggravate an existing epilepsy through hyperthermia, inflammatory syndrome, or cerebral tropism, although epileptic symptoms, with no known history of epilepsy, could be an initial expression of neurological damage.

DISCUSSION

EEG in a patient who is suspect or positive for COVID 19 was mainly prescribed from signs of encephalopathy or seizure as previously reported (13–15). Out of 42 EEGs performed, 9 were suggestive of encephalopathy. This encephalopathic aspect may be linked to viral involvement but should be discussed according to the level of sedation during the examination and also to suffering related to hypoxemia. One study reports nearly 41% of epileptiform abnormalities with 88% of frontals sharp waves. The proportion of EEG anomalies in favor of encephalopathy was 18% (14) for 21% in our study while Pellinen et al. (15) reported moderated generalized slowing for 57%. In addition, a previous spectral analysis study of the EEG confirmed the electrical changes in case of encephalopathy, even suggesting the ability to differentiate between infectious toxic encephalopathy on the one hand, and from encephalopathies in a context of severe hypoxia on the second hand (16). The proportion of altered EEG of about 85% reported here regardless the medical indication, was similar to those previously reported (15, 17). Viral infection with COVID 19 in patients with epilepsy may trigger or worse epileptic seizures more easily, particularly in the case of genetic abnormalities (18).

The EEG performed in the context of exploring delayed awakening remains difficult to date and impossible to correlate with specific central neurological damage related to COVID 19. Indeed, residual sedation, initial hypoxemic suffering and neurological damage may combine and induce EEG abnormalities of different kinds that can be assimilated to an aspect of encephalopathy.

The electroencephalographic observations confirm neurological impairment in the context of SARS-COV-2 infection, as previously shown by postmortem analysis for the mesencephalon (hypothalamus) and the cortex (19). However, electrical abnormalities on the EEG remain non-specific and cannot make the diagnosis of neurological impairment by SARS-COV-2 as previously reported (17, 20).

It remains difficult to correlate EEG abnormalities with cerebral MRI, lumbar puncture and thoracic CT since cerebral MRI and lumbar puncture were not routinely performed and the entire medical record could not be reported on the telemedicine platform on which the EEGs were interpreted. In a subgroup of 13 patients, we were able to obtain the results of the thoracic CT scan, PCR and

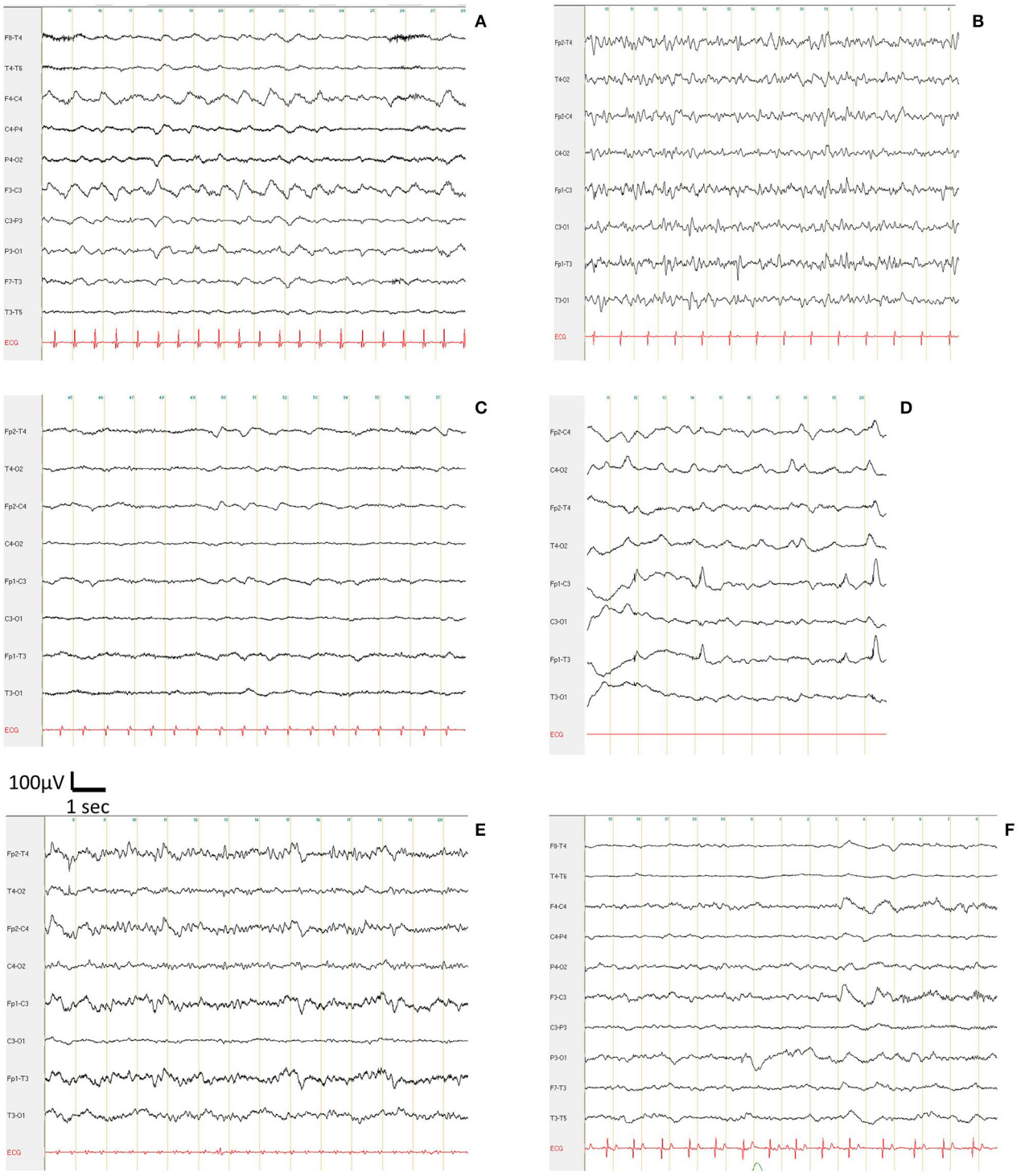


FIGURE 1 | Encephalopathic pattern with triphasic frontal waves and a frequency of the basal rhythm from 1 to 7 Hz, in COVID patients suffering from suspicion of a status epilepticus **(A)**, syncope **(B)**, delayed awakening after reanimation and being weaned off anesthetic drugs **(C)**, bilateral eyelid myoclonus during awakening following reanimation (**D**, artifacts on Fp1), altered consciousness **(E)**, and confusion for 2 days **(F)**.

lumbar puncture. We had no correlations between these items (data not shown). Moreover, the timing of EEG in the timeframe of the medical investigations remains difficult to collect as it was performed according to the onset of the neurological symptoms and not pulmonary or other first symptoms.

The pathophysiological mechanism(s) probably remain multimodal: viral encephalitis, infectious toxic encephalopathy or cerebrovascular involvement as proposed by Wu et al. (12). The encephalopathic aspect of the EEG was reported in a case report in a 74-year-old patient suffering from a SARS-COV-2 viral infection with pulmonary and neurological damage. The EEG showed electrical signs of encephalopathy and a slow temporal focus that was more likely to be related to a history of left temporal stroke with leukomalacia on imaging (5).

Damage to the olfactory nerve, thalamus and brain stem was demonstrated in a mouse model with intranasal injection of the virus (10). The brain stem appears to be the most affected site (10). Therefore, it might be relevant to systematically explore, in the case of neurological impairment, to add auditory, visual, and somatosensory evoked potentials in the assessment.

Confusion and seizure were the main indicators associated with an EEG aspect of encephalopathy. It is suspected that SARS-COV-2 infection may aggravate seizures in a patient with a history of epilepsy or being monitored for epilepsy. However, of the 13 patients with seizures, only three had a history of epilepsy and for two patients we did not have the information.

The EEG was performed at the time of onset of neurological clinical signs, but the delay between the EEG and the onset of respiratory clinical signs, for patients who had suffered from these, remains difficult to quantify. For some patients, the EEG was performed in the first few days, for others 15 days later and finally for patients with delayed recovery after resuscitation for up to 3 weeks. There was also no correlation between the degree of chest CT and encephalopathic pattern on the EEG on a subgroup of 13 patients for whom we had the imaging report. For those patients who ultimately had a negative PCR reported to us afterwards, the EEG remained normal.

Finally, given the percentage of abnormalities regardless of the initial indication, the EEG remains a useful test to explore any patient infected with COVID 19 with neurological signs.

EEG exploration after sedation remains difficult because of the pharmacological influence to discriminate the neurological damage linked to the COVID but seems interesting in some cases as previously reported (21).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SB has analyzed the EEG, data, and wrote the paper. CN, TD, RA, and RM have analyzed the EEG. EL and HP have analyzed the data and wrote the paper. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors are grateful to the EEG technicians who conducted the EEG examinations, particularly Monin C, Simonnet J, Alame K, Cote E, and Berry R and the hospital practitioners, particularly Dr. Hermann and Dr. Richelin from Creteil hospital, Dr. Lorricaud, Dr. Carreira, Dr. Renambata, Dr. Boutin, Dr. Billon, Dr. Sorial and Dr. Bernard from Sainte Camille Hospital, Dr. Wendeu from Joigny Hospital, Dr. Mielcazarek and Dr. Moro from Brie Comte Robert Hospital.

REFERENCES

1. Das G, Mukherjee N, Ghosh S. Neurological insights of COVID-19 pandemic. *ACS Chem Neurosci.* (2020) 11:1206–9. doi: 10.1021/acschemneuro.0c00201
2. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. *Neurological associations of COVID-19. Lancet Neurol.* (2020). 19:767–83. doi: 10.1016/S1474-4422(20)30221-0
3. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. *Radiology.* (2020) 31:201187. doi: 10.1148/radiol.2020201187
4. Xiang P, Xu XM, Gao LL, Wang HZ, Xiong HF, Li RH, et al. First case of 2019 novel coronavirus disease with Encephalitis. *Int J Infect Dis.* (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
5. Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological complications of coronavirus disease (COVID-19): encephalopathy. *Cureus.* (2020) 12:e7352. doi: 10.7759/cureus.7352
6. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol.* (2020) 70:311–22. doi: 10.33588/rn.7009.2020179
7. Mao L,Wang MD, Chen SH, He QW, Chang J, Hong CD, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retro-spective case series study. *medRXiv.* (2020) 77:683–90. doi: 10.2139/ssrn.3544840
8. Conde Cardona G, Quintana Pájaro LD, Quintero Marzola ID, Ramos Villegas Y, Moscote Salazar LR. Neurotropism of SARS-CoV 2: mechanisms and manifestations. *J Neurol Sci.* (2020) 412:116824. doi: 10.1016/j.jns.2020.116824
9. Tassorelli C, Mojoli F, Baldanti F, Bruno R, Benazzo M. COVID-19: what if the brain had a role in causing the deaths? *Eur. J. Neurol.* (2020). doi: 10.1111/ene.14275. [Epub ahead of print].
10. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in therespiratory failure of COVID-19 patients. *J Med Virol.* (2020) 92:552–5. doi: 10.1002/jmv.25728
11. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. *CNS Neurosci Ther.* (2020) 26:499–501. doi: 10.1111/cns.13372
12. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun.* (2020) 87:18–22. doi: 10.1016/j.bbi.2020.03.031
13. Assenza G, Lanzone J, Ricci L, Boscarino M, Tombini M, Galimberti CA, et al. Electroencephalography at the time of COVID-19 pandemic in Italy. *Neurol Sci.* (2020) 26:1–6. doi: 10.1007/s10072-020-04546-8

14. Galanopoulou AS, Ferastraoaru V, Correa DJ, Cherian K, Duberstein S, Gursky J, et al. EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: a small case series preliminary report. *Epilepsia Open.* (2020) 5:314–24. doi: 10.1002/epi4.12399
15. Pellinen J, Carroll E, Friedman D, Boffa M, Dugan P, Friedmann DE, et al. Continuous EEG findings in patients with COVID-19 infection admitted to a New York academic hospital system. *Epilepsia.* (2020). doi: 10.1111/epi.16667. [Epub ahead of print].
16. Canham LJW, Staniaszek LE, Mortimer AM, Nouri LF, Kane NM. Electroencephalographic (EEG) features of encephalopathy in the setting of COVID-19: a case series. *Clin Neurophysiol Prac.* (2020) 5:199–205. doi: 10.1016/j.cnp.2020.06.001
17. Petrescu AM, Taussig D, Bouilleret V. Electroencephalogram (EEG) in COVID-19: a systematic retrospective study. *Neurophysiol Clin.* (2020) 50:155–65. doi: 10.1016/j.neucli.2020.06.001
18. Aledo-Serrano A, Mingorance A, Jiménez-Huete A, Toledano R, García-Morales I, Anciones C, et al. Genetic epilepsies and COVID-19 pandemic: lessons from the caregiver perspective. *Epilepsia*. (2020) 61:1312–4. doi: 10.1111/epi.16537
19. Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. (2005) 202:415–24. doi: 10.1084/jem.20050828
20. Gelisse P, Rossetti AO, Genton P, Crespel A, Kaplan PW. How to carry out and interpret EEG recordings in COVID-19 patients in ICU? *Clin Neurophysiol.* (2020) 131:2023–31. doi: 10.1016/j.clinph.2020.05.006
21. De Stefano P, Nencha U, De Stefano L, Mégevand P, Seeck M. Focal EEG changes indicating critical illness associated cerebral microbleeds in a COVID-19 patient. *Clin Neurophysiol Pract.* (2020) 5:125–9. doi: 10.1016/j.cnp.2020.05.004

Conflict of Interest: SB is consultant as expert for SIGMA EEG. EL and HP were employed by company ELYOPE SAS and SigmaEEG respectively.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 27 November 2020
doi: 10.3389/fneur.2020.602114

Neurological Complications and Noninvasive Multimodal Neuromonitoring in Critically Ill Mechanically Ventilated COVID-19 Patients

Denise Battaglini[1,2], Gregorio Santori[3], Karthikka Chandraptham[1,3], Francesca Iannuzzi[1,3], Matilde Bastianello[1,3], Fabio Tarantino[1], Lorenzo Ball[1,3], Daniele Roberto Giacobbe[4], Antonio Vena[4], Matteo Bassetti[4,5], Matilde Inglese[6], Antonio Uccelli[6], Patricia Rieken Macedo Rocco[7,8,9], Nicolò Patroniti[1,3], Iole Brunetti[1], Paolo Pelosi[1,3] and Chiara Robba[1] for the GECOVID-19 Group*

[1] Anesthesia and Intensive Care, San Martino Policlinico Hospital, Istituto di Ricovero e Cura a Carattere Scientifico for Oncology and Neurosciences, Genoa, Italy, [2] Department of Medicine, University of Barcelona, Barcelona, Spain, [3] Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Genoa, Italy, [4] Department of Infectious Diseases, San Martino Policlinico Hospital - Istituto di Ricovero e Cura a Carattere Scientifico for Oncology and Neurosciences, Genoa, Italy, [5] Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy, [6] Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy, [7] Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [8] Rio de Janeiro Network on Neuroinflammation, Carlos Chagas Filho Foundation for Supporting Research in the State of Rio de Janeiro (FAPERJ), Rio de Janeiro, Brazil, [9] COVID-19 Virus Network, Ministry of Science and Technology, and Innovation, Rio de Janeiro, Brazil

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Felix Schlachetzki,
University of Regensburg, Germany
Frank Anthony Rasulo,
University of Brescia, Italy

***Correspondence:**
Chiara Robba
kiarobba@gmail.com

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care,
a section of the journal Frontiers in Neurology

Received: 02 September 2020
Accepted: 19 October 2020
Published: 27 November 2020

Citation:
Battaglini D, Santori G, Chandraptham K, Iannuzzi F, Bastianello M, Tarantino F, Ball L, Giacobbe DR, Vena A, Bassetti M, Inglese M, Uccelli A, Rocco PRM, Patroniti N, Brunetti I, Pelosi P and Robba C (2020) Neurological Complications and Noninvasive Multimodal Neuromonitoring in Critically Ill Mechanically Ventilated COVID-19 Patients. Front. Neurol. 11:602114. doi: 10.3389/fneur.2020.602114

Purpose: The incidence and the clinical presentation of neurological manifestations of coronavirus disease-2019 (COVID-19) remain unclear. No data regarding the use of neuromonitoring tools in this group of patients are available.

Methods: This is a retrospective study of prospectively collected data. The primary aim was to assess the incidence and the type of neurological complications in critically ill COVID-19 patients and their effect on survival as well as on hospital and intensive care unit (ICU) length of stay. The secondary aim was to describe cerebral hemodynamic changes detected by noninvasive neuromonitoring modalities such as transcranial Doppler, optic nerve sheath diameter (ONSD), and automated pupillometry.

Results: Ninety-four patients with COVID-19 admitted to an ICU from February 28 to June 30, 2020, were included in this study. Fifty-three patients underwent noninvasive neuromonitoring. Neurological complications were detected in 50% of patients, with delirium as the most common manifestation. Patients with neurological complications, compared to those without, had longer hospital (36.8 ± 25.1 vs. 19.4 ± 16.9 days, $p < 0.001$) and ICU (31.5 ± 22.6 vs. 11.5±10.1 days, $p < 0.001$) stay. The duration of mechanical ventilation was independently associated with the risk of developing neurological complications (odds ratio 1.100, 95% CI 1.046–1.175, $p = 0.001$). Patients with increased intracranial pressure measured by ONSD (19% of the overall population) had longer ICU stay.

Conclusions: Neurological complications are common in critically ill patients with COVID-19 receiving invasive mechanical ventilation and are associated with prolonged ICU length of stay. Multimodal noninvasive neuromonitoring systems are useful tools for the early detection of variations in cerebrovascular parameters in COVID-19.

Keywords: COVID-19, neurological complications, SARS-CoV-2, neuromonitoring, neurocritical care

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1–4), is primarily a disease of the respiratory system, leading to a variety of clinical manifestations including dry cough, fever, fatigue, and respiratory failure (4). However, recent data suggest that COVID-19 is not confined to the airways but is also responsible for a syndrome of multiorgan dysfunction, including possible neurological involvement (5, 6).

Coronaviruses may pass to the central nervous system by different routes (7, 8), including hematogenous spread from the systemic to the cerebral circulation and lymphocyte invasion or dissemination from the cribriform plate and olfactory bulb to the brain (9, 10). These hypothesis seem to be consistent with the loss of smell and taste described as—first atypical, then quite prevalent—presentations of COVID-19 (11). However, the neurologic manifestations of COVID-19 are highly variable and can occur prior to diagnosis or as a complication late in the course of infection (7, 8).

A recent systematic review of 37 articles revealed that 20% of COVID-19 patients present with headache, 60% with anosmia/ageusia, 25% with myalgia/myositis, 8.8% with encephalopathy, 2.8% with ischemic stroke, and 0.45% with intracerebral hemorrhage (12). Other neurological symptoms include impaired consciousness, ataxia, seizures, and neuralgia (13–17). SARS-CoV-2 has also been reported to trigger autoimmune diseases such as multiple sclerosis, acute disseminated encephalomyelitis, acute encephalitis, acute autoimmune polyneuropathy, and critical illness polyneuropathy (13, 18) as well as cerebrovascular events (19, 20). However, recent reports suggest that hypoxic–ischemic damage could be the main driver of neurological symptoms in COVID-19 patients (21).

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CPP, cerebral perfusion pressure; dFV, diastolic flow velocity; ESM, electronic supplemental material; FiO_2, fraction of inspired oxygen; ICP, intracranial pressure; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MAP, mean arterial pressure; MCA, middle cerebral artery; MERS, Middle East respiratory syndrome; mFV, mean flow velocity; nICP, noninvasive intracranial pressure; $nICP_{ONSD}$, noninvasive intracranial pressure measured by optic nerve sheath diameter; $nICP_{TCD}$, noninvasive intracranial pressure measured by transcranial Doppler; ONSD, optic nerve sheath diameter; OR, odds ratio; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PcPs, pressure control or pressure support; PEEP, positive end-expiratory pressure; PI, pulsatility index; q1, 1st quartile; q3, 3rd quartile; ROC, receiver operating characteristic; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SARS, severe acute respiratory syndrome; sFV, systolic flow velocity; SMPH, San Martino Policlinico Hospital; TCD, transcranial Doppler.

Noninvasive neuromonitoring systems are widely used in neurointensive care settings for patients with primary cerebral damage; more recently, they are also being employed in critically ill patients in general as useful tools to detect neurological complications (22, 23). In particular, transcranial Doppler (TCD) ultrasonography, optic nerve sheath diameter (ONSD) measurement, and quantitative automated pupillometry are safe, useful methods that can be applied at the patient's bedside to assess cerebral hemodynamics as well as to monitor cerebral perfusion pressure and intracranial pressure noninvasively (22, 23). To date, no studies have investigated cerebral hemodynamics in patients with COVID-19.

The primary aim of our study was to describe the type and the frequency of neurological complications in a cohort of critically ill patients with COVID-19 receiving invasive mechanical ventilation in an intensive care unit (ICU) and the effects of these complications on outcome. As a secondary aim, we sought to assess changes in cerebral hemodynamics, their effects on outcome, and their role as potential predictors of neurological complications in a subgroup of patients who underwent noninvasive neuromonitoring (ONSD, TCD, and automated pupillometry).

MATERIALS AND METHODS

Study Design

This is a single-center, retrospective, observational study of prospectively collected data. The study was carried out during the COVID-19 pandemic, from February 28 through June 30, 2020, at the ICU of the San Martino Policlinico Hospital (SMPH) IRCCS for Oncology and Neurosciences, Genoa, Italy. The SMPH is the main hospital serving both the metropolitan area of Genoa (approximate population of 840,000) and the wider Liguria Region (approximate population of 1,543,000). The usual ICU capacity is 52 adult beds, increased to 74 during the peak of the SARS-CoV-2 outbreak in Italy. The study protocol followed good clinical practice principles in compliance with the Declaration of Helsinki, and the Ethics Committee of Liguria, Italy (registry number 163/2020), approved the study and waived the informed consent for participation because of the retrospective nature of the study.

Study Population

Patients aged ≥18 years, confirmed positive for SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swab specimens at the moment of ICU admission, and who were critically ill, requiring invasive mechanical ventilation, were eligible for inclusion. Patients who

were not neurologically evaluable due to deep sedation for life-threatening respiratory failure were excluded.

Data Collection

Overall Population

The following data were collected from the patients' electronic records at the time of ICU admission: age in years, gender, body mass index (in kg/m^2), sequential organ failure assessment score (24), and a series of comorbidities, namely, hypertension, diabetes mellitus, respiratory disease (defined as asthma or chronic obstructive pulmonary disease), end-stage renal disease (defined as estimated glomerular filtration rate <15 ml/min/1.73 m^2), moderate/severe liver disease (defined as compensated/decompensated liver cirrhosis) (25), and cancer. The highest C-reactive protein (normal range 0–5 mg/L) and D-dimer (normal range 0–500 mcg/L) as well as the lowest partial pressure of oxygen (PaO_2) (normal range 72–104 mmHg) were collected from daily test results throughout each patient's ICU stay. At the time of ICU and hospital discharge, data on ICU length of stay (ICU-LOS) (days), overall hospital LOS (days), duration of mechanical ventilation (days), neurological complications (type and number), and mortality were collected.

Neuromonitoring Cohort

The following data were collected from patients who underwent noninvasive neuromonitoring during the day of assessment and throughout their ICU stay: ventilatory parameters [type of ventilation, positive end-expiratory pressure (PEEP) in cmH_2O, pressure control or pressure support in cmH_2O, respiratory rate in breaths per minute, tidal volume in mL, and fraction of inspired oxygen (FiO_2)], arterial blood gas values [PaO_2 in mmHg, partial pressure of carbon dioxide ($PaCO_2$) in mmHg, pH], vital signs [mean arterial pressure (MAP) in mmHg, heart rate in beats per minute], sedation (including type of sedative), analgesia (including analgesic agent), and neuromuscular blockade. The neurological complications and scales used for outcome measures are defined in the **Supplementary Tables 1–4**.

Noninvasive Neuromonitoring Systems

Ultrasound measurements were performed by two experienced operators (defined as having received more than 5 years of training and performing more than 70 examinations/year) (DB, CR) and three mentored trainees in anesthesia and intensive care (KC, FI, MB). MAP, heart rate, mean cerebral artery (MCA) flow velocities (diastolic, mean, and systolic), and ONSD were recorded during ICU stay, according to the clinical context and need (availability of personal protective equipment and clinical rationale).

Transcranial Doppler

A low-frequency (2 MHz) microconvex transducer (Philips SparQ®) was used to investigate intracranial vessels. The temporal window was preferred for passage of the Doppler signal for MCA assessment. Systolic (sFV), diastolic (dFV), and mean flow velocity (mFV) in the MCA were collected. MAP was also measured. The pulsatility index (PI) was calculated as the mean value between the right and the left MCA flow velocities using the following formula (13):

$$PI = \frac{(sFV - dFV)}{mFV}$$

Noninvasive ICP ($nICP_{TCD}$) was calculated according to the formula:

$$nICP_{TCD} = MAP - CPPe$$

where cerebral perfusion pressure (CPPe) was calculated as follows (26):

$$CPPe = \frac{MAP * dFV}{mFV} + 14$$

Intracranial pressure (ICP) values >20 mmHg were considered indicative of intracranial hypertension (26).

Optic Nerve Sheath Diameter

A linear probe (Philips SparQ®) was used for ONSD evaluation. The probe was placed on the closed upper eyelid, and ONSD was evaluated 3 mm behind the retinal papilla. Two measurements were obtained from each optic nerve: the first in the transverse plane and the second in the sagittal plane (27). Noninvasive intracranial pressure measured by ONSD ($nICP_{ONSD}$) was derived from a mathematic formula described elsewhere in the literature (28, 29). ICP values >20 mmHg were again considered indicative of intracranial hypertension (26).

Automated Pupillometry

Pupillary light reactivity was measured by a handheld quantitative automated pupillometer (Neurolight Algiscan®, ID-MED, Marseille, France) in both eyes. This device measures quantitative variation in pupillary light reactivity by using an infrared camera to record a video footage of the changes in the pupillary surface. Pupillary light reactivity was assessed by a calibrated light stimulation (320 lux for 1 s) with a precision limit of 0.05 mm. Quantitative reactivity was expressed as the percentage of pupillary light response, and baseline pupil size was expressed in millimeters. The pupillary constriction velocity (mm/s) was also reported (30–32). Abnormal pupillary reactivity was defined as an abnormal pupillary light reflex as reported by the pupillometer (e.g., a weaker than normal or "sluggish" pupil response) (33).

Statistical Analysis

The results are expressed as mean ± standard deviation, median, 1st quartile (q1), 3rd quartile (q3), interquartile range, count, and percentage frequency. No sample size calculation was performed due to the retrospective design of this study. Shapiro–Wilk test was used to assess the normal distribution of continuous variables. The null hypothesis of the Shapiro-Wilk test is that the population is normally distributed. For a P value less than the conventional alpha level (alpha = 0.05), the null hypothesis is rejected, and the data tested are assumed as not normally distributed. In this case, a

non-parametric test for comparison should be used. Mann–Whitney *U*-test was used to compare continuous variables, while categorical variables were compared with Fisher's exact test. Patient survival was evaluated by using the Kaplan–Meier estimator. Log-rank test was used to compare the survival curves. Continuous and categorical variables were entered into univariate Cox proportional hazard regression models. Efron approximation was used for each Cox model. The proportional hazards assumption for each significant Cox regression model was evaluated using correlation coefficients between transformed survival times and scaled Schoenfeld residuals. Significant variables to univariate Cox regression were entered in the multivariate model, with regression coefficient and hazard ratio (HR) with the 95% confidence interval (CI) as the main outputs. A forest plot and a rank-hazard plot were provided for multivariate Cox regression. The rank-hazard plot is able to visualize the relationship between the relative hazard of variables entered in the multivariate Cox regression model (34). Logistic regression was performed to assess the risk factors associated with neurological complications. The Hosmer–Lemeshow omnibus test was used for goodness-of-fit evaluation of each significant logistic regression model. Only logistic regression models that passed the goodness-of-fit test ($P > 0.05$) were presented. Significant variables to univariate logistic regression were entered in the multivariate model, with regression coefficient and odds ratio with the 95% confidence interval as the main outputs. A receiver operating characteristic curve was calculated for the multivariate logistic regression model as well as sensibility and specificity. Statistical significance was assumed in each test directly related to the study outcomes with a two-tailed *P*-value < 0.05. Statistical analysis was carried out by using the R software/environment (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 116 patients with COVID-19 were admitted to the SMPH ICU. Twenty-two patients were excluded because they did not meet the inclusion criteria. Thus, 94 patients were included in the final analysis, of whom 53 underwent noninvasive neuromonitoring. Thirty patients (56.6%) underwent repeated measures on different days during their ICU stay period. The whole repeated measurements ranged from 2 to 10 (4.86 ± 2.22 measurements), while the first and the

TABLE 1 | Demographic and clinical characteristics of the COVID-19 patients included in the study.

Characteristics	All patients (*n* = 94)	Patients with neurological complications (*n* = 47)	Patients without neurological complications (*n* = 47)
Gender [male, *n* (%)]	74 (78.7%)	41 (87.2)	33 (70.2)
Age (y/o, mean ± SD)	61.6 ± 11.1	62.4 ± 8.3	60.8 ± 13.3
Weight (kg, mean ± SD)	90.0 ± 13.6	82.9 ± 14.2	80.5 ± 13.0
Height (cm, mean ± SD)	176.0 ± 7.9	171.7 ± 7.5	171.8 ± 8.3
BMI (kg/m^2, mean ± SD)	29.9 ± 4.2	28.1 ± 4.2	27.3 ± 4.1
Comorbidities [*n*, (%)]			
Hypertension	49 (52.1)	27 (57.4)	22 (46.8)
Chronic renal disease	5 (5.3)	5 (10.6)	0 (0.0)
Diabetes	14 (14. 9)	6 (12.8)	8 (17.0)
Chronic respiratory disease	0 (0.0)	0 (0.0)	0 (0.0)
Chronic liver disease	3 (3.2)	1 (2.1)	2 (4.3)
Cancer	6 (6.4)	3 (6.4)	3 (6.4)
Cardiac failure	8 (8.5)	5 (10.6)	3 (6.4)
Neurological disease	0 (0.0)	0 (0.0)	0 (0.0)
Hospital length of stay (days, mean ± SD)	28.10 ± 23.00	36.77 ± 25.14	19.43 ± 16.86
ICU length of stay (days, mean ± SD)	21.51 ± 20.14	31.51 ± 22.64	11.51 ± 10.14
ICU outcome [*n*, (%)]			
Alive	61 (64.90)	31 (65.95)	30 (63.83)
Critical	2 (2.10)	2 (4.25)	0 (0.00)
Death	31 (33)	14 (29.78)	17 (36.17)
Days of mechanical ventilation (days, mean ± SD)	20.00 ± 16.33	22.93 ± 19.62	8.85 ± 7.75
Days from symptoms to hospital admission (days, mean ± SD)	3.98 ± 10.11	3.81 ± 7.16	4.14 ± 12.42
Days from symptoms to ICU admission (days, mean ± SD)	10.92 ± 6.84	9.51 ± 6.73	12.30 ± 6.74
Higher D-dimer during ICU stay (ng/ml, mean ± SD)	17.636 ± 26.631	14.067 ± 21.401	17.878 ± 31.310
Higher CRP during ICU stay (mg/L, mean ± SD)	266.25 ± 120.88	232.78 ± 127.49	161.47 ± 102.81
Lower PaO_2 during ICU stay (mmHg, mean ± SD)	60 ± 10.92	52.97 ± 7.80	57.96 ± 13.03

n, number; SD, standard deviation; y/o, years old; BMI, body mass index; ICU, intensive care unit; PaO_2, partial pressure of oxygen; CRP, C-reactive protein.

last measurements were performed between the 1st and 33rd ICU day (mean delta: 14.8 ± 9.22 days).

TABLE 2 | Type and incidence of neurological complications in the overall intensive care unit population.

Neurological complications	Number of patients (%)
Overall	47 (50)
Delirium	34 (36.17)
Critical illness neuropathy	5 (5.32)
Coma	4 (4.25)
Acute ischemic stroke	3 (3.19)
Stupor	3 (3.19)
Seizures	2 (2.13)
Encephalopathy	2 (2.13)
Cognitive deficit	1 (1.06)
Depression	1 (1.06)

Overall Population

The characteristics of the 94 patients admitted to our ICU who fulfilled the inclusion criteria—with and without neurological complications—are described in **Table 1**. Neurological complications were detected in 47/94 patients (50%). Nine patients presented more than one neurological complication. The most common complications are reported in **Table 2**. The occurrence of neurological complications did not result in increased ICU mortality ($p = 0.450$) (**Figure 1**) but was associated with longer hospital (36.77 ± 25.14 vs. 19.43 ± 16.86 days, $p < 0.001$) and ICU (31.51 ± 22.64 vs. 11.51±10.14; $p < 0.001$) stay compared to the absence of neurological complications (**Table 1**).

Risk of Developing Neurological Complications

On univariate logistic regression, duration of mechanical ventilation and CRP values were associated with the risk of developing neurological complications (**Table 3**). Multivariate logistic regression demonstrated that the

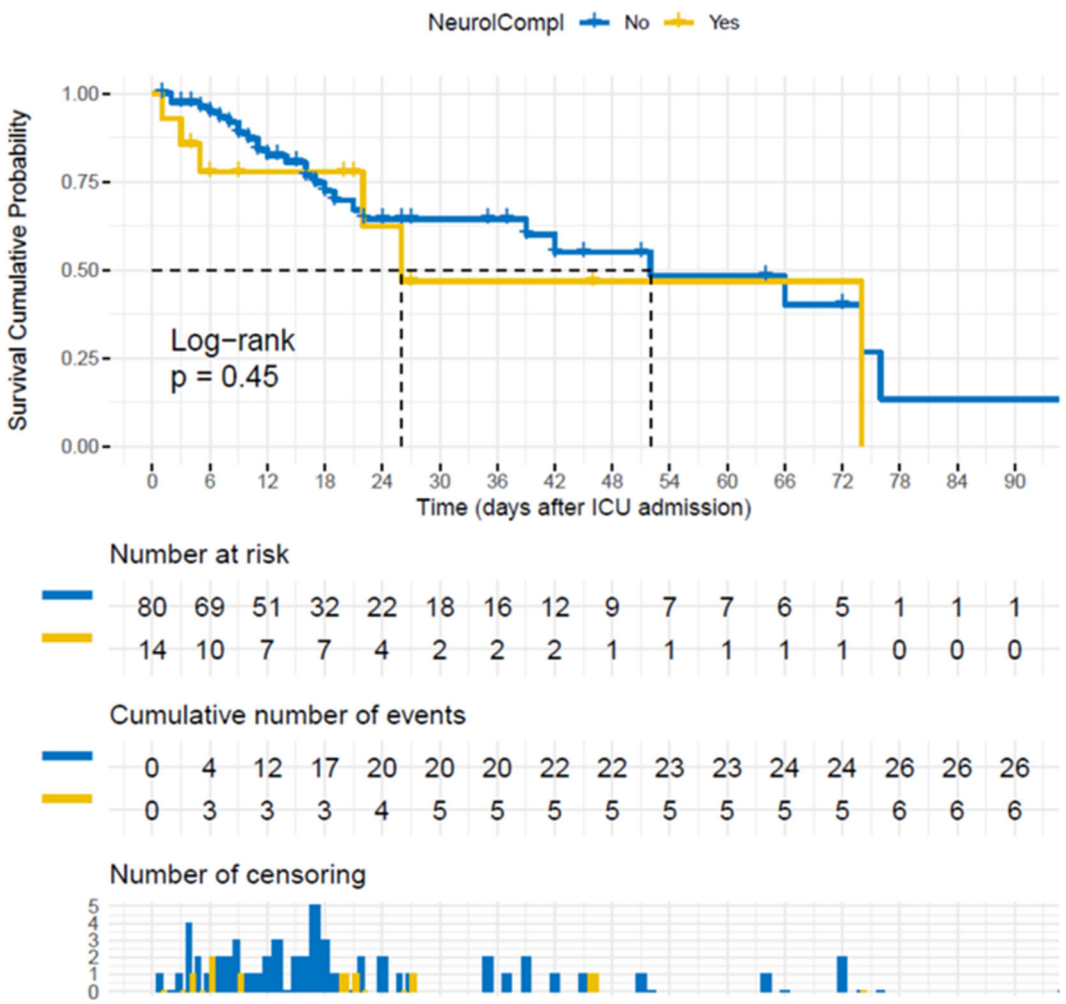


FIGURE 1 | Survival cumulative probability after intensive care unit (ICU) admission for the 94 patients included. Survival cumulative probability after ICU admission for the patients ($n = 94$) who fulfilled the inclusion criteria, stratifying for the absence/presence (no/yes) of neurological complications.

duration of mechanical ventilation was independently associated with the risk of neurological complications (OR: 1.1; 95% CI: 1.046–1.175; $p = 0.001$) (**Table 3**), with an area under the curve of 0.818, sensitivity of 0.658, and specificity of 0.786 (**Figure 2**). Additional results concerning the cumulative survival probability of the overall population after hospital and ICU admission are shown in **Supplementary Figures 1–3**.

TABLE 3 | The significant variables associated with neurological complications as assessed by univariate logistic regression and the output of the subsequent multivariate model, for the patients ($n = 94$) who fulfilled the inclusion criteria.

Variable	Univariate				Multivariate			
	RC	OR	95% CI	*P*-value	RC	OR	95% CI	*P*-value
Days of mechanical ventilation	0.088	1.092	1.046–1.154	<0.001	0.095	1.100	1.046–1.175	0.001
CRP	0.005	1.005	1.002–1.009	0.006	0.002	1.002	0.997–1.006	0.443

CRP, C-reactive protein; RC, regression coefficient; OR, odds ratio; CI, confidence interval.

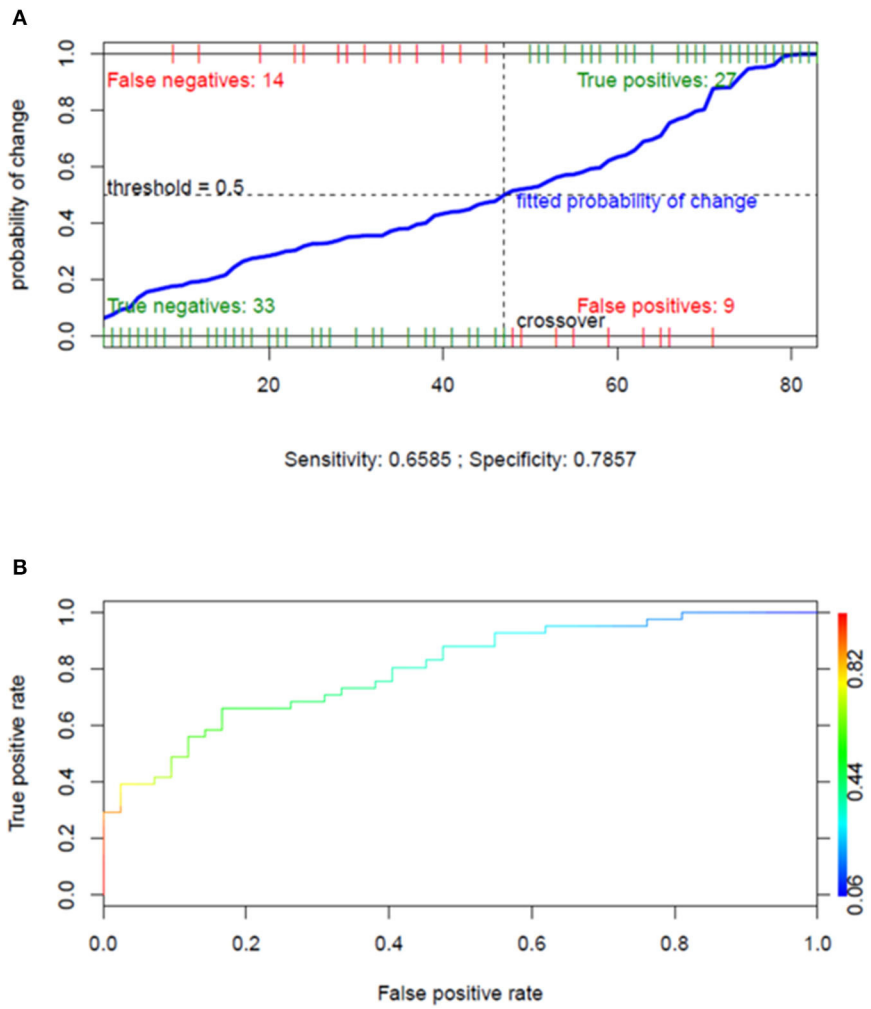


FIGURE 2 | Performance of the multivariate logistic regression model for assessing the factors independently associated with the risk of neurological complications. **(A)** Overall performance of the multivariate logistic regression model presented in **Table 3** (dependent variable: neurological complications; independent variables: days of mechanical ventilation and C-reactive protein). **(B)** Receiver operating characteristic curve of the same multivariate logistic regression model (area under the curve = 0.818).

Noninvasive Neuromonitoring Population

A total of 53 patients underwent noninvasive neuromonitoring. The characteristics of this subgroup are described in **Supplementary Table 5**. TCD was performed in 51/53 (96.23%), ONSD in 49/53 (92.45%), and automated pupillometry in 29/53 (54.72%) patients. The median sFV was 99.50 (q1: 87.00; q3: 108.75) cm/s, the median dFV was 31.59 (q1: 22.87; q3: 45.00) cm/s, and the median PI was 1.16 (q1: 0.99; q3: 1.41). The median ONSD was 5.65 (q1: 4.80; q3: 6.60) mm. The median $nICP_{TCD}$ was 17.57 (q1: 12.68; q3: 25.21) mmHg, and the median $nICP_{ONSD}$ was 14.33 (q1: 10.07; q3: 19.33) mmHg.

Effect of Altered Neuromonitoring Findings on Patients' Outcome

High ICP was found in 21 $nICP_{TCD}$ patients (39.62%) and in 10 $nICP_{ONSD}$ patients (18.87%). Among the 29 patients who

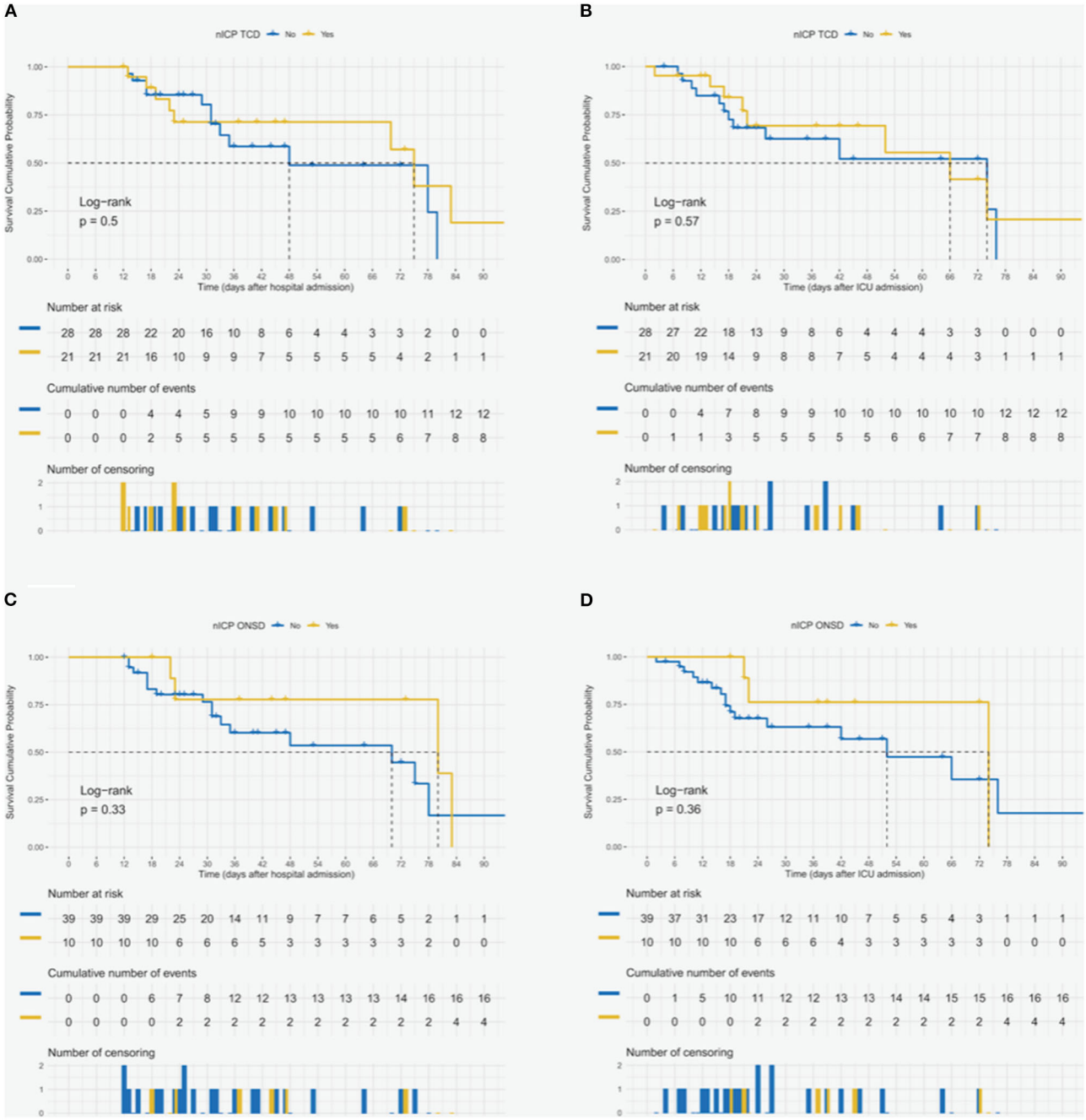


FIGURE 3 | Survival cumulative probability after hospital and intensive care unit (ICU) admission for the patients who underwent noninvasive neuromonitoring. Survival cumulative probability after hospital and ICU admission for the patients ($n = 49$) who underwent noninvasive intracranial pressure, monitoring with both transcranial Doppler **(A,B)** and optic nerve sheath diameter **(C,D)**.

underwent automated pupillometry, nine (31.03%) presented altered pupillary reactivity. Patients with increased $nICP_{ONSD}$ and $nICP_{TCD}$, compared to those with normal $nICP_{ONSD}$ and $nICP_{TCD}$, did not experience a longer hospital stay ($nICP_{ONSD}$: 45.00 ± 25.27 vs. 36.33 ± 24.70 days, $p = 0.222$; $nICP_{TCD}$: 38.90 ± 30.34 vs. 35.43 ± 19.23 days, $p = 0.691$), but patients with higher $nICP_{ONSD}$ had longer ICU stays ($nICP_{ONSD}$: 42.30 ± 23.21 vs. 28.26 ± 22.28 days, $p = 0.042$; $nICP_{TCD}$: 32.86 ± 25.55 vs. 28.61 ± 20.89 days, $p = 0.721$). Additional descriptive data on TCD are reported in **Supplementary Table 6**. Patients with increased ICP according to ONSD and TCD values compared to those with normal ICP showed no differences in hospital or ICU mortality (**Figure 3**) (**Supplementary Table 7**). The outcomes of the Cox regression models for the patients who underwent noninvasive neuromonitoring are reported in **Supplementary Table 8** and **Supplementary Figures 4, 5**. The significant variables associated with neurological complications assessed by univariate logistic regression and the output of the subsequent multivariate model, for the patients ($n = 53$) who underwent noninvasive neuromonitoring, are reported in **Table 4**. A brief case report describing the serial measurements and the course of the disease is presented in **Supplementary Case 1**.

DISCUSSION

The main findings of our study are as follows: (1) neurological complications are common in COVID-19 patients and have no effect on mortality but can be associated with increased hospital and ICU length of stay, (2) the duration of mechanical ventilation is independently associated with the development of neurological complications, and (3) increased ICP (estimated by ONSD) and pupillary abnormalities are common and associated with longer ICU length of stay.

To our knowledge, this is the first study describing cerebrovascular dynamics in mechanically ventilated COVID-19 patients, which could potentially help to elucidate the underlying pathophysiology of the neurological complications in this patient population. Moreover, to date, no studies have taken into account the possible secondary effects of mechanical ventilation and inflammation on neurological outcome.

There are several theories concerning the central and the peripheral neurological changes following a SARS-CoV-2 infection: viral neurotropism, including trans-synaptic spread, endothelial or lymphocyte invasion by SARS-CoV-2, a hyperinflammatory and hypercoagulative state, or even mechanical ventilation-associated impairment (35). In our cohort, neurological complications were detected in half of the patients admitted to our ICU with confirmed COVID-19 pneumonia who fulfilled the inclusion criteria. The most frequent complication was delirium (36.70%), followed by coma, critical illness neuropathy, ischemic stroke, stupor, encephalopathy, seizures, cognitive deficit, and depression. The frequency of delirium is in line with current COVID-19 literature, in which it has ranged from 26.80 to 73.60% (34, 36). Delirium was identified both in the acute and in the post-ICU phases during the severe acute respiratory syndrome (SARS) and Middle-East respiratory syndrome (MERS) epidemics, with a possible detrimental effect on length of stay (37). Sedatives, analgesics, pain, psychological stressors, hypoxia, metabolic and electrolyte imbalances, infection, hyperthermia, sepsis, mechanical ventilation, light, and the use of physical restraints are well-known contributors to delirium occurrence in the ICU (38, 39). Delirium is known to be associated with longer ICU stay and mechanical ventilation days as well as an increased risk of death at 6 months, disability, and long-term cognitive dysfunction (39, 40). Our results are in line with these findings; patients who developed neurological complications (mainly delirium) did not show increased ICU mortality, but they did have prolonged hospital and ICU stays, often exceeding 2 weeks, with a major impact on health expenditures and resource utilization—especially in the resource-limited setting of a pandemic.

Mechanical ventilation days and inflammation (assessed by C-reactive protein) were associated with the occurrence of neurological complications at the univariate analysis. This suggests that the magnitude of the inflammatory response and the severity of respiratory impairment may strongly affect the occurrence of neurological complications in COVID-19 (35).

Several cerebral hemodynamic changes occurred in the subpopulation undergoing neuromonitoring. First, patients with COVID-19 presented higher median ONSD values compared to the normal population [5.65 mm (4.80–6.60) vs. 4.10 mm (3.85–4.35) (41)]. As described in the literature, the threshold of increased $nICP_{ONSD}$ is 5–6 mm (27); this suggests that increased ICP is a common finding in COVID-19 patients. In fact, increased ICP measured with both ONSD and TCD was very common, and a large portion of patients (38.71%) exhibited altered pupillary reactivity.

Several factors can potentially cause increased intracranial pressure in patients with respiratory failure and pneumonia, including increased $PaCO_2$, which can cause cerebral

TABLE 4 | The significant variables associated with neurological complications as assessed by univariate logistic regression and the output of the subsequent multivariate model, for the patients ($n = 53$) who underwent noninvasive neuromonitoring.

Variable	Univariate				Multivariate			
	RC	OR	95% CI	*P*-value	RC	OR	95% CI	*P*-value
Days between hospital and ICU admission	−0.092	0.912	0.815–0.988	0.058	−0.082	0.921	0.815–1.003	0.114
dFV	−0.049	0.952	0.906–0.994	0.036	−0.044	0.956	0.909–1.001	0.069

ICU, intensive care unit; dFV, diastolic flow velocity; RC, regression coefficient; OR, odds ratio; CI, confidence interval.

vasodilatation (42, 43), or the use of high PEEP and consequently increased intrathoracic pressure (44). Indeed we found that PEEP was higher in those who showed higher nICP, whether assessed by ONSD or TCD (as we reported in the **Supplementary Material**). Although the difference was not statistically significant, it suggests that mechanical ventilation can interfere widely with cerebral hemodynamics.

Although common, the occurrence of increased ICP had no effect on cumulative probability of survival; it did prolong ICU-LOS when measured by ONSD, but not by TCD. This confirms that, in COVID-19 patients, noninvasive ICP monitoring may be essential for the early detection of patients who are at risk of longer ICU-LOS with subsequent complications and difficult recovery. The incongruity between the results of the two noninvasive methods might be explained by differences in pathophysiological sensitivity and specificity for ICP assessment between the two (26); both techniques can present important methodological limitations (intra-interobserver variability, artifacts, and low accuracy in estimating ICP as a number) (28). We therefore recommend a multimodal monitoring approach for the noninvasive measurement of intracranial pressure to predict neurological complications (28). Although we found no correlation between altered neuromonitoring findings and the occurrence of neurological complications, we strongly recommend the use of these methods in critically ill patients with COVID-19 and, in general, in ICU patients undergoing mechanical ventilation for the early detection of neurological complications. Noninvasive neuromonitoring tools are safe, quick, low-cost, and easily available and can provide relevant data at the patients' bedside.

LIMITATIONS

This study has several limitations which must be addressed. First, this was a retrospective study of prospectively collected data. Data were collected within the clinical context of the COVID-19 pandemic (limited availability of personal protective equipment, clinical reasons, and so on). Thus, neuromonitoring data are neither complete nor available for all patients. Second, TCD, ONSD, and automated pupillometer measurements were intermittent and were obtained at different stages of the patients' ICU stays. Continuous, daily, standardized monitoring would have provided more accurate data on the behavior of cerebrovascular hemodynamics in this population. Because of the critical demands of the pandemic, we were unable to obtain multiple neuromonitoring measurements to reduce intra- and inter-observer variability among the operators. However, our team consists of a group of specialized physicians with ample experience in the use of noninvasive monitoring. Third, we did not use other methods—such as neuroimaging or lumbar puncture—to confirm the findings of intracranial hypertension. Fourth, the relatively small sample size of our study, which depended on the number of COVID-19 patients admitted to our ICU and was thus beyond our control, limits the strength of our conclusions and results. Fourth, since this is not an interventional study, the sedation and analgesia protocols were not standardized but rather were based on the clinical needs of the patients, which may have had an impact on FV, ONSD, and automated pupillometer-derived values. Fifth, in this study population, ICP was only moderately elevated due to factors not related to intracranial pathologies, which might explain why the neurological complications did not lead to life-threatening complications.

CONCLUSIONS

Neurological complications, particularly delirium, are common in COVID-19 patients and are associated with longer hospital and ICU stay. The duration of mechanical ventilation is strongly associated with the development of neurological complications. Noninvasive neuromonitoring during ICU stay may be helpful to detect cerebrovascular alterations earlier. Further studies, including a larger number of patients, may provide new insights on the role of noninvasive neuromonitoring in non-COVID-19 patients admitted to ICU for different pathologies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Liguria, Italy (registry number 163/2020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DB and CR conceived the study, designed the study, acquired data, interpreted the data, and drafted the manuscript. GS analyzed and interpreted the data, critically revised the manuscript, and gave final approval. KC, FI, and MBL contributed to the acquisition of data, critical revision of the manuscript, and final approval. FT, LB, DG, AV, MBT, PR, NP, and IB contributed to the critical revision of the manuscript and final approval. PP helped with the study design, interpretation of the data, critical revision of the manuscript, and final approval. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like the names of the individual members of the *GECOVID-19 collaborators to be searchable through their individual PubMed records. This manuscript has been released as a pre-print at https://www.researchsquare.com/article/rs-57910/v1, licensed under a Creative Commons Attribution 4.0 International License.

GECOVID-19 COLLABORATORS

Chiara Berri, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Serena Cavalcoli, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy, Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Genoa, Italy; Elena Ciaravolo, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy, Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Genoa, Italy; Marcus Ferretti, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Maurizio Loconte, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Marco Sottano, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy, Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Genoa, Italy; Stefano Nogas, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy, Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Genoa, Italy; Paolo Frisoni, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Pasquale Anania, Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, (DINOGMI), University of Genoa, Genoa, Italy; Pietro Fiaschi, Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, (DINOGMI), University of Genoa, Genoa, Italy, Department of Neurosurgery, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Alessandro Prior Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, (DINOGMI), University of Genoa, Genoa, Italy; Alessandro Bertuccio, Neurosurgical Unit, Surgical Department, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; Angelo Schenone, Department of Neurosurgery, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Gianluigi Zona, Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, (DINOGMI), University of Genoa, Italy, Department of Neurosurgery, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Angelo Gratarola, Anesthesia and Intensive Care, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy; Flavio Villani, Division of Clinical Neurophysiology and Epilepsy Center, San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Genoa, Italy.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.602114/full#supplementary-material

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *NEJM.* (2020) 382:727–33. doi: 10.1056/NEJMoa2001017
2. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol.* (2020) 92:418–23. doi: 10.1002/jmv.25681
3. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance.* (2020) 25:2000045. doi: 10.2807/1560-7917.ES.2020.25.3.2000045
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:1–9. doi: 10.1001/jamaneurol.2020.1127
5. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T, et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *J Neurol Neurosurg Psichiatr.* (2020) 91:846–48. doi: 10.1136/jnnp-2020-323522
6. Robba C, Battaglini D, Pelosi P, Rocco RMP. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. *Exp Rev Respir Med.* (2020) 14:865–8. doi: 10.1080/17476348.2020.1778470
7. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol.* (2020) 77:1018–27. doi: 10.1001/jamaneurol.2020.2065
8. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5
9. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, et al. Acute-onset smell and taste disorders in the context of Covid-19: a pilot multicenter PCR-based case-control study. *Eur J Neurol.* (2020). doi: 10.1111/ene.14273
10. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* (2004) 203:631–7. doi: 10.1002/path.1570
11. Cetinkaya EA. Coincidence of COVID-19 infection and smell: taste perception disorders. *J Craniofac Surg.* (2020) 21:e625–6. doi: 10.1097/SCS.0000000000006601
12. Nepal G, Rehrig JH, Shrestha GS, Shing YK, Yadav JK, Ojha R, et al. Neurological manifestations of COVID-19: a systematic review. *Crit Care.* (2020) 24:421. doi: 10.1186/s13054-020-03121-z
13. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg.* (2020) 194:105921. doi: 10.1016/j.clineuro.2020.105921
14. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
15. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
16. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7

17. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. *BMJ*. (2020) 368:m606. doi: 10.1136/bmj.m606
18. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain Behav Immun*. (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077
19. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. *Transl Stroke Res*. (2020) 11:322–5. doi: 10.1007/s12975-020-00818-9
20. Barrios-López JM, Rego-García I, Martínez CM, Romero-Fábrega JC, Rodríguez MR, Giménez JAR, et al. Ischaemic stroke and SARS-CoV-2 infection: a causal or incidental association? *Neurología*. (2020) 35:295–302. doi: 10.1016/j.nrleng.2020.05.008
21. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. *N Engl J Med*. (2020) 383:989–92. doi: 10.1056/NEJMc2019373
22. Robba C, Goffi A, Geeraerts T, Cardim D, Via G, Czosnyka M, et al. Brain ultrasonography: methodology, basic and advanced principles and clinical applications. A narrative review. *Intensive Care Med*. (2019) 45:913–27. doi: 10.1007/s00134-019-05610-4
23. Robba C, Donnelly J, Cardim D, Tajsic T, Cabeleira M, Citerio G, et al. Optic nerve sheath diameter ultrasonography at admission as a predictor of intracranial hypertension in traumatic brain injured patients: a prospective observational study. *J Neurosurg*. (2020) 132:1279–85. doi: 10.3171/2018.11.JNS182077
24. Jones AE, Trzeciak S, Kline JA. The sequential organ failure assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Crit Care Med*. (2009) 37:1649–54. doi: 10.1097/CCM.0b013e31819def97
25. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone B, Codda G, et al. Bloodstream infections in critically ill patients with COVID-19. *Eur J Clin Invest*. (2020) 50:e13319. doi: 10.1111/eci.13319
26. Rasulo FA, Bertuetti R, Robba C, Lusenti F, Cantoni A, Bernini M, et al. The accuracy of transcranial Doppler in excluding intracranial hypertension following acute brain injury: a multicenter prospective pilot study. *Crit Care*. (2017) 21:44. doi: 10.1186/s13054-017-1632-2
27. Robba C, Santori G, Czosnyka M, Corradi F, Bragazzi N, Padayachy L, et al. Optic nerve sheath diameter measured sonographically as non-invasive estimator of intracranial pressure: a systematic review and meta-analysis. *Intensive Care Med*. (2018) 44:1284–94. doi: 10.1007/s00134-018-5305-7
28. Robba C, Cardim D, Tajsic T, Pietersen J, Bulman M, Donnelly J, et al. Ultrasound non-invasive measurement of intracranial pressure in neurointensive care: a prospective observational study. *PLoS Med*. (2017) 14:e1002356. doi: 10.1371/journal.pmed.1002356
29. Robba C, Bacigaluppi S, Cardim D, Donnelly J, Bertuccio A, Czosnyka M. Non-invasive assessment of intracranial pressure. *Acta Neurol Scand*. (2016) 134:4–21. doi: 10.1111/ane.12527
30. Robba C, Moro Salihovic B, Pozzebon S, Creteur J, Oddo M, Vincent JL, et al. Comparison of 2 automated pupillometry devices in critically Ill patients. *J Neurosurg Anesth*. (2019) 32:323–9. doi: 10.1097/ANA.0000000000000604
31. Zafar SF, Suarez JI. Automated pupillometer for monitoring the critically ill patient: a critical appraisal. *J Crit Care*. (2014) 29:599–603. doi: 10.1016/j.jcrc.2014.01.012
32. Solari D, Rossetti AO, Carteron L, Miroz J-P, Novy J, Eckert P, et al. Early prediction of coma recovery after cardiac arrest with blinded pupillometry. *Ann Neurol*. (2017) 81:804–10. doi: 10.1002/ana.24943
33. Chen J, Gombart Z, Rogers S, Gardiner S, Cecil S, Bullock R. Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the neurological pupil index. *Surg Neurol Intern*. (2011) 2:82. doi: 10.4103/2152-7806.82248
34. Khan SH, Lindroth H, Perkins AJ, Jamil Y, Wang S, Roberts S, et al. Delirium incidence, duration and severity in critically Ill patients with COVID-19. *medRxiv [Preprint]*. (2020). doi: 10.1101/2020.05.31.20118679
35. Battaglini D, Brunetti I, Anania P, Fiaschi P, Zona G, Ball L, et al. Neurological manifestations of severe SARS-CoV-2 infection: potential mechanisms and implications of individualized mechanical ventilation settings. *Front Neurol*. (2020) 11:845. doi: 10.3389/fneur.2020.00845
36. Benussi A, Pilotto A, Premi E, Libri I, Giunta M, Agosti C, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology*. (2020) 95:e910–20. doi: 10.1101/2020.04.28.20082735
37. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*. (2020) 7:611–27. doi: 10.1016/S2215-0366(20)30203-0
38. Park SY, Lee HB. Prevention and management of delirium in critically ill adult patients in the intensive care unit: a review based on the 2018 PADIS guidelines. *Acute Crit Care*. (2019) 34:117–25. doi: 10.4266/acc.2019.00451
39. Salluh JIF, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ*. (2015) 350:1–10. doi: 10.1136/bmj.h2538
40. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. (2004) 291:1753–62. doi: 10.1001/jama.291.14.1753
41. Kim DH, Jun JS, Kim R. Ultrasonographic measurement of the optic nerve sheath diameter and its association with eyeball transverse diameter in 585 healthy volunteers. *Sci Rep*. (2017) 7:1–6. doi: 10.1038/s41598-017-16173-z
42. Bhate TD, McDonald B, Sekhon MS, Griesdale DEG. Association between blood pressure and outcomes in patients after cardiac arrest: a systematic review. *Resuscitation*. (2015) 97:1–6. doi: 10.1016/j.resuscitation.2015.08.023
43. Czosnyka M, Miller C. Participants in the International Multidisciplinary Consensus Conference on multimodality monitoring. monitoring of cerebral autoregulation. *Neurocrit Care*. (2014) 21:95–102. doi: 10.1007/s12028-014-0046-0
44. Robba C, Bragazzi NL, Bertuccio A, Cardim D, Donnelly J, Sekhon M, et al. Effects of prone position and positive end-expiratory pressure on noninvasive estimators of ICP. *J Neurosurg Anesthesiol*. (2017) 29:243–50. doi: 10.1097/ANA.0000000000000295

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 27 November 2020
doi: 10.3389/fneur.2020.604907

Difficulties and Countermeasures in Hospital Emergency Management for Fast-Lane Treatment of Acute Stroke During the COVID-19 Epidemic Prevention and Control

*Haojun Yang[1], Zhuohui Chen[1], Yishu Fan[1], Lan Xiang[2], Xinhang Hu[1], Tong Wu[1], Bo Xiao[1], Li Feng[1], Zhihong Zhao[2], Yunfang Chi[3] and Mengqi Zhang[1]**

[1] Department of Neurology, Xiangya Hospital of Central South University, Changsha, China, [2] Department of Neurology, Hunan Provincial People's Hospital, Hunan Normal University, Changsha, China, [3] Laizhou People's Hospital, Yantai, China

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Tae Jung Kim,
Seoul National University Hospital,
South Korea
Adam A. Dmytriw,
Brigham and Women's Hospital and
Harvard Medical School,
United States
Zhong Wang,
Soochow University, China

***Correspondence:**
Mengqi Zhang
zhangmengqi8912@163.com

Specialty section:
This article was submitted to
Stroke,
a section of the journal
Frontiers in Neurology

Received: 11 September 2020
Accepted: 19 October 2020
Published: 27 November 2020

Citation:
Yang H, Chen Z, Fan Y, Xiang L, Hu X, Wu T, Xiao B, Feng L, Zhao Z, Chi Y and Zhang M (2020) Difficulties and Countermeasures in Hospital Emergency Management for Fast-Lane Treatment of Acute Stroke During the COVID-19 Epidemic Prevention and Control. Front. Neurol. 11:604907. doi: 10.3389/fneur.2020.604907

Background: Coronavirus disease 2019 (COVID-19) has a long incubation period and a high degree of infectivity. Patients may not show specific signs or symptoms of upper respiratory tract infection, and the age of onset is similar to that of stroke. Furthermore, an increase in neurological conditions, specifically acute cerebrovascular disease, has been detected. Providing emergency treatment for acute stroke in accordance with the strict epidemic control measures is currently one of the main challenges, as acute stroke is rapid onset and a major cause of death and disability globally. We aimed to evaluate the emergency treatment system for acute stroke during the epidemic control period to provide a reference and basis for informing government and medical institutions on improving patient treatment rates during this period.

Methods: Difficulties faced in providing emergency treatment for stroke during an epidemic were investigated and combined with medical educational resources and clinical management experiences to construct an emergency treatment framework for acute stroke during the epidemic.

Findings: Currently, emergency treatment measures for acute stroke during the epidemic control period are limited because the main focus is on identifying COVID-19 comorbidities during the critical period. Establishing standards for patients in the neurological outpatient consultation rooms and emergency observation and resuscitation zones; implementing a fast-lane system for the emergency treatment of patients with acute stroke, and strengthening ward management and medicine popularization, can improve the treatment efficiency for stroke patients during the epidemic and provide a reference for peers in clinical practice.

Interpretation: Emergency treatment for acute stroke during COVID-19 epidemic control period requires a joint promotion of clinical, popularization, and teaching resources.

Keywords: coronavirus disease 2019, epidemic control, emergency guarantee for acute stroke, medicine popularization, medical education

INTRODUCTION

In December 2019, an outbreak of a novel coronavirus pneumonia (NCP) occurred in Wuhan, Hubei province, China, and it rapidly spread to different provinces in China, as well as countries in Southeast Asia, Europe, North America, and many others (1). The Chinese National Health Commission has listed NCP as a category B infectious disease, and the management measures for category A infectious diseases were adopted, indicating that new discovered cases are required to be reported within 2 and 6 h in the city and countryside, respectively (2, 3). According to the World Health Organization (WHO), the official name of the disease is coronavirus disease 2019 (COVID-19) and according to the International Committee on Taxonomy of Viruses, the virus is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4, 5). The main clinical presentations of COVID-19 were fever, fatigue, dry cough, and other respiratory symptoms (6–8). Although the main clinical manifestations are respiratory, an increase in neurological conditions, specifically acute cerebrovascular disease, has been detected (9–11). Stroke refers to acute neurological dysfunction due to a vascular cause, which tends to occur mostly in winter and spring and is rapid onset and a major cause of death and disability globally (12, 13). People with underlying diseases such as diabetes, hypertension and cardiovascular disease, were more associated with stroke (14–16). COVID-19 patients with underlying diseases had poorer prognosis and higher mortality rates (17, 18). Identifying COVID-19 comorbidities in a patient during the critical period in acute stroke treatment is a key point and a challenge in stroke management. Herein, we evaluate and describe not only the challenges in providing emergency treatment for acute stroke but also the possible response strategies to ensure efficient operation regarding acute stroke diagnosis and treatment during the COVID-19 epidemic and provide basic ideas for clinical practice.

CHALLENGES IN PROVIDING EMERGENCY TREATMENT FOR ACUTE STROKE DURING THE COVID-19 EPIDEMIC CONTROL PERIOD

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus belonging to the Betacoronavirus genus, and its sequence is highly homologous with that of SARS-like coronaviruses in bats (19–21). The main transmission routes include infected respiratory droplets and direct contact with the infected individual. Transmission through other routes such as aerosols and fecal–oral routes is still unclear and requires validation through further studies (22, 23). Humans are generally susceptible to the disease. Compared with SARS, SARS-CoV-2 has a longer incubation period and a high degree of infectivity. Patients may not show specific upper respiratory tract signs and symptoms (24). Therefore, COVID-19 tends to cause nosocomial infection and cross-infection, which poses a great challenge in epidemic control. The construction of an emergency treatment framework and strategy is an important prerequisite for the standardization of the diagnosis and treatment process and thus improving patient treatment efficiency, thereby having direct and key effects on improving treatment rate, thereby reducing mortality rate, improving public confidence, and alleviating social panic.

Identification of COVID-19 Comorbidities During the Critical Period of Acute Stroke Treatment

Stroke, or cerebrovascular accident, involves injury to the central nervous system due to a vascular cause, which is a major cause of death and disability globally (24). Patients with COVID-19 alongside an underlying disease had poorer prognosis and higher mortality rates: the mortality rates of patients with diabetes, hypertension, and heart disease were 5.3, 2.8, and 4.2%, respectively (25). In addition to smoking, obesity, excessive alcohol consumption, and lack of exercise, hypertension and diabetes are the most important risk factors for stroke (26–28). A recent study showed ∼81% of COVID-19 patients with ischemic stroke had known vascular risk factors, the commonest being hypertension (75%) followed by diabetes (50%), coronary disease or atrial fibrillation (29). The age at onset of COVID-19 is similar to that of stroke, and all underlying comorbidities are also important risk factors for stroke. Studies have shown the possibilities of cerebrovascular diseases being the initial symptoms of COVID-19, associating with a poor prognosis. The mortality rate of COVID-19 patients with stroke was higher than that previously reported in either COVID-19 respiratory infection alone, or acute ischemic stroke alone (30). Additionally, racial disparities in COVID-19 case counts and outcomes have been highlighted, especially among African American populations (30, 31). Underlying biological, genetic, or epigenetic characteristics along with less access to healthcare, and social and economic disparities might predispose to health differences and outcomes (32, 33). 84.6% of strokes were cortical and more than 50% of patients had no identifiable source, which were categorized as embolic stroke of unknown source (ESUS) (34). The common large vessel disease with ESUS indicates an increased risk of coagulopathy and endothelial dysfunction. Several COVID-19 series pointed infarcts typically followed a subcortical or distal cortical distribution and some mechanisms for stroke, which might be associated with the infection and its complications, including either the causation of acute cardiac injury, creation of antiphospholipid antibodies or even severe hypercoagulable conditions caused by D-dimer or fibrinogen abnormalities (9, 35, 36). Consistent with the previous studies, a high rate inflammatory markers was found in stroke population, such as the neutrophil-lymphocyte ratio, ferritin, D-dimer, procalcitonin, C-reactive protein (CRP) and lactate dehydrogenase (29, 37). Therefore, attention must be paid closely to the risk of comorbidities in COVID-19 during stroke treatment. Regarding the treatment of patients with acute stroke, time is of the essence. Identifying COVID-19 comorbidities in patients with acute stroke during the critical period and reducing delays caused by COVID-19 screening is the main challenges in the emergency treatment.

Strong Popular Science Requirements for Acute Stroke

New media and we media have continuously emerged and become important sources of information for the public, which not only means that the media provides increasing popular medical knowledge, but also prompts the misinformation and rumors (38). Previous studies have shown that new media use and more media engagement was associated with negative psychological outcomes, while certain media content such as viewing heroic acts, speeches from experts, and knowledge of the disease and prevention was associated with positive psychological impact (39, 40). These studies highlighted the need for timely public health communication from official sources and debunking misinformation associated with the COVID-19 in real time by local communities and governments (41). The outline of "Healthy China 2030" highlighted that prevention was better than cure in the establishment of a healthy China and encouraged the strengthening of popular medical education and improving the public health communication (42, 43). Season type, especially winter and spring, and unhealthy lifestyles increase the risk for stroke (12, 13). How to prevent stroke at home, how to identify stroke, and the subsequent admission and treatment processes in hospitals during an epidemic are the main aspects of popular science. The deep learning of the admission and treatment processes in hospitals for patients' family members during the epidemic will not only avoid losing time due to unfamiliarity, but also strengthen their trust in the medical staff and reduce medical disputes which occur during COVID-19 screening (44, 45). However, the impact of COVID-19 on improving the doctor-patient relationship in China is still very controversial. Although the occupancy in most inpatient and outpatient clinics were reduced, the amount of work was increased by fundamental transitions of work flows, communication, staff structure and hygiene measures to cover the needs of prevention, treatment and follow-up care as well as protection of staff (46). Additionally, self-reported rates of anxiety symptoms and depression symptoms were high among medical staff under the outbreak of COVID-19 (47, 48). Therefore, how to balance the work and popular science of medical staff is another problem. How to rationally utilize the professional knowledge of medical students, combine teaching resources and medical popularization, cultivate new medical talents, and examine sustainable development mechanisms for combining social mission and the literacy training of medical students, science popularization, and public interests are problems that require crucial analytical investigation (49).

CONSTRUCTION OF AN ACUTE STROKE EMERGENCY TREATMENT FRAMEWORK UNDER EPIDEMIC CONTROL CONDITIONS

In this study, the problem of reducing the delay caused by COVID-19 screening faced during the treatment of patients with acute stroke under COVID-19 epidemic control conditions was used to propose a basic framework for fast lane treatment of acute haemorrhagic stroke and acute ischemic stroke. In this framework, the construction of a rational organizational framework is the basis for ensuring the rapid diagnosis and treatment of patients with acute stroke on the basis of COVID-19 control. The coordinated and orderly collaboration between various departments is a prerequisite for achieving resuscitation during the golden hour. Real-time standby of different teams provides important support for the emergency treatment of acute stroke. This strategy with a good response has been applied to hospitals in Changsha, China, aiming at providing a reference and basis for informing government and medical institutions on improving patient treatment rates during this period.

Strengthening Staff Control and Standardizing Admission Screening

During the treatment of patients with acute stroke, attention should be paid to the risk of COVID-19 comorbidities, which is determined by the following criteria:

Epidemiological history: ① History of travel or residence to high-risk areas within 14 days before disease onset in patients with acute stroke; ② History of contact with people from the high-risk areas within 14 days before disease onset in patients with acute stroke; ③ Presence of disease clusters; ④ Close contact with patients with fever, fatigue, or respiratory symptoms

Clinical presentation: ① Fever or respiratory symptoms including weak and dry cough; ② Classical imaging presentation of COVID-19; ③ Normal or reduced white blood cell count or lymphocytopenia during the early stages of the disease.

Patient Admission Management Process in the Neurological Outpatient Consultation Room

① Inpatient treatment should be avoided as much as possible for non-emergency outpatients, and elective admission and treatment should be carried out after the epidemic has been controlled.

② For outpatients who require hospitalization, temperature monitoring and detailed inquiry, on epidemiological contact history and clinical presentation for COVID-19 should be carried out. Lung computed tomography (CT), routine blood tests, erythrocyte sedimentation, CRP, procalcitonin, four-item pre-transfusion screening (HBsAg, HCV-Ab, TP-Ab, and HIV-Ab), and electrolyte tests should be carried out.

③ The above medical tests and relevant results are used to determine a suspected case of COVID-19 and whether the patient is admitted or entered the neurology emergency department for stroke and inpatient screening process (**Figure 1**).

④ For those who require inpatient treatment, the outpatient physician is responsible for notifying the chief resident physician in the ward.

Patient Admission Management Process in the Neurological Emergency Observation and Resuscitation Zones

The pre-screening and triage procedures are strictly complied with scientific screening and rational triaging of patients. Patients who visit the new medical emergency observation

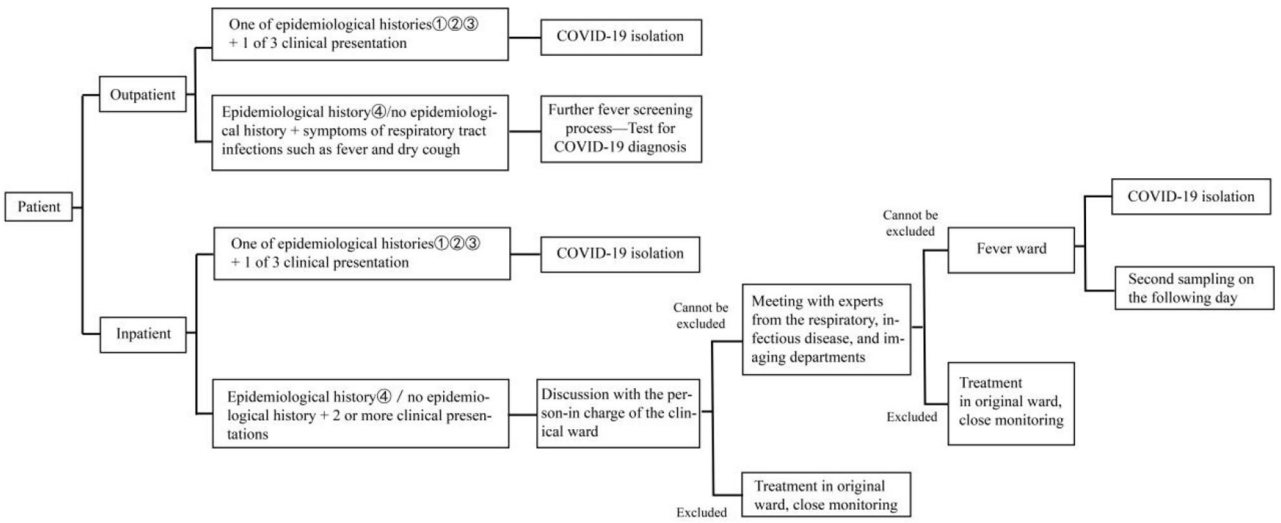


FIGURE 1 | Neurology emergency department and inpatient screening process.

or resuscitation zones after pre-screening and triage at the emergency department will be hospitalized after specialist consultation according to the routine procedures, if they do not have a fever, epidemiological history, or respiratory symptoms. If fever and respiratory symptoms are present, ① Lung CT, blood routine, ordinary CRP, erythrocyte sedimentation, procalcitonin, four-item pre-transfusion, and electrolyte tests must be performed. ② If significant imaging presentation is absent, two emergency department team members will sign and confirm, and the comments of the imaging expert will be recorded (valid within 24 h of signing). No further screening is required, and the patient can be admitted by a specialist attending physician. ③ If COVID-19 cannot be excluded according to the consultation opinions of the emergency department expert group (including imaging), the patient will be transferred to a designated fever isolation zone in the hospital for further screening. On the following day, two pharyngeal swabs will be collected for SARS-CoV-2 nucleic acid screening. ④ Patients who are positive for SARS-CoV-2 will be transferred to designated hospitals, while those who are negative will undergo consultation by the emergency department expert group (including imaging). After COVID-19 exclusion, emergency department team members will sign. Simultaneously, the comments of the imaging expert will be documented in the medical records, and the patient will be admitted to the specialist department.

Fast Lane Treatment of Emergency Department for Acute Stroke

Due to the differences in resuscitation measures during an acute haemorrhagic stroke and acute ischemic stroke, we describe the fast lane procedures for acute haemorrhagic stroke (**Figure 2**) and acute ischemic stroke (**Figure 3**) during a COVID-19 epidemic and propose the following recommendations for the consultation of patients with acute stroke in the emergency department:

① For patients with suspected or confirmed COVID-19 along with comorbid critical cerebrovascular disorder, if the disease onset occurs outside of the hospital, then they should be transferred to the nearest National Health Commission-designated hospital for treatment. Patients with acute cerebrovascular disorder who seek medical attention at our hospital should undergo scientific screening, rational triage, and timely quarantine in strict accordance with the COVID-19 emergency department pre-screening and triage procedures.

② For suspected patients who need to enter the fast lane of stroke, dedicated medical staff will accompany them to the COVID-19 screening zone, and screening will be carried out according to the fever outpatient procedure. Simultaneously, neurologists will be assigned to assist in the fast lane treatment of stroke.

③ Aggressive thrombolysis treatment should be administered simultaneously with the screening for acute ischemic stroke in patients who fulfill the criteria for a suspected COVID-19 case, within the time window for intravenous thrombolysis and if there is no contraindication for intravenous thrombolysis (50). Endovascular recanalization therapy should also be considered in suspected COVID-19 patients with acute ischemic stroke due to large artery occlusion within 6 h [or within 24 h in some cases (51)] after onset (52). Stroke team members must be careful of COVID-19 exposure during clinical evaluation and performance of imaging and laboratory procedures of stroke patients with suspected or confirmed COVID-19 infection, especially in the process of intravenous thrombolysis and mechanical thrombectomy (53). For patients with severe/critical COVID-19, the pros and cons should be

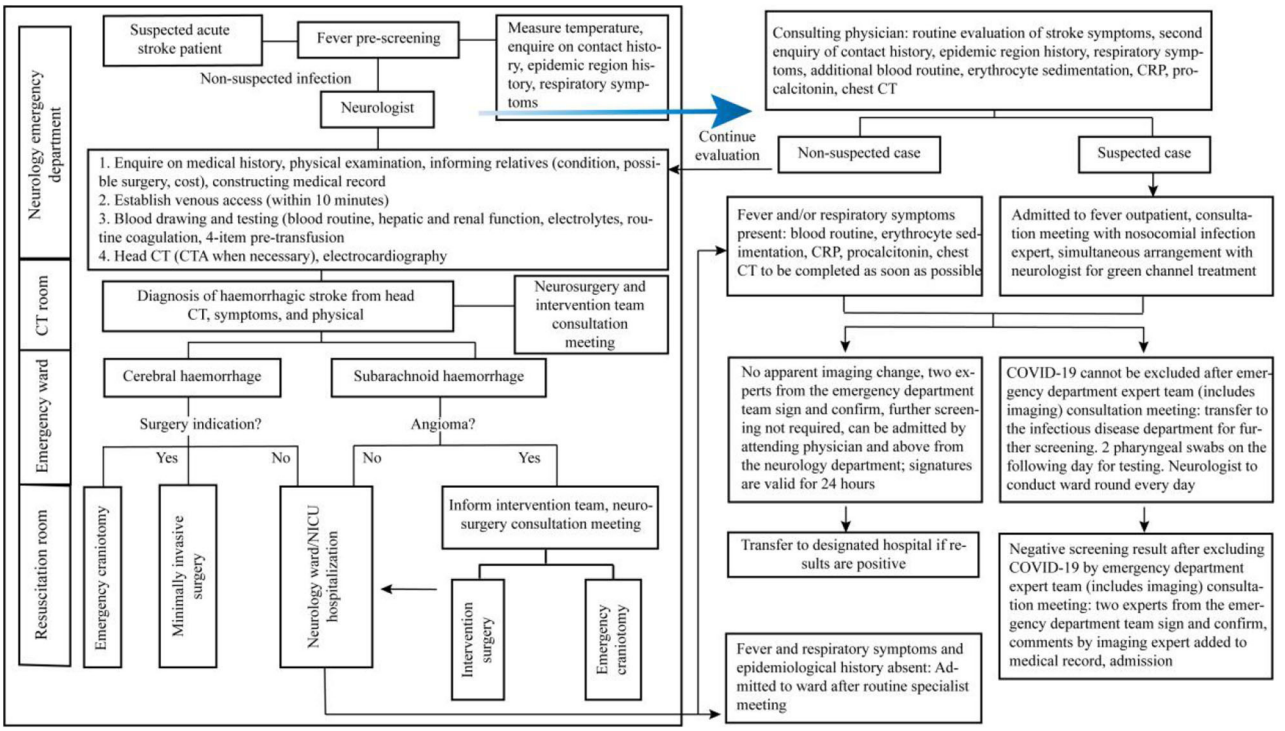


FIGURE 2 | Acute haemorrhagic stroke fast lane management procedure during the COVID-19 epidemic.

weighed. In principle, pneumonia is treated first. After completing the treatment, the patient is transferred to the isolation room, and neurologists are organized to conduct ward rounds in the isolation room daily.

④ As patients with cerebral hemorrhage or subarachnoid hemorrhage often present with fever, the procedure must be strictly followed for identification and screening. Patients suspected to have COVID-19 will not enter the catheterisation room for angiography, craniotomy, or intervention treatment for the disease. These patients should be isolated and treated with routine medical conservative treatment. Time selecting operations will be performed when COVID-19 is ruled out.

Strengthening Ward Management

Ward Control and Management

① A dedicated entrance is set up at the ordinary neurological ward for demographic information registration and temperature measurement by the staff, and it restricts access to unauthorized people. Only one caregiver can accompany every patient. In the neurological ICU ward, a telephone is used to communicate with the staff about the patient's condition. When necessary, visitation is carried out. Workers will use their staff cards, inpatients will use their wrist bands, and caregivers will use their caregiver card for access. People without their facial masks on are not allowed into the medical zone.

② Clean zones, potential contamination zones, and contamination zones are designated in the neurological ordinary and ICU wards; staff paths are set up; and bedside diagnosis, treatment, and nursing are advocated.

③ Emergency isolation wards are set up in the ward, which are equipped with sufficient disinfection and protective equipment to respond to acute respiratory infection for quarantine and treatment of suspected and confirmed patients. Work is carried out according to relevant systems and procedures to achieve isolation, disinfection, and protection requirements stipulated in the relevant guidelines.

④ The neurological ordinary and ICU wards will report data on fever in inpatients from the midnight of the previous day to the present midnight to the medical affairs department at 8 a.m. daily. The infectious disease management office of the medical affairs department will complete the summary at 8:30 a.m. daily and submit the report.

⑤ If suspected or confirmed patients are discovered in the ward, relevant emergency plans and work procedures will be activated rapidly. The suspected or confirmed patients are transferred to the emergency isolation wards [point ③], who need treatment and referral according to the requirements later. The entire ward needs to be thoroughly disinfected, and both medical staff, patients and caregivers in the ward are classified as close contacts. Medical staff and caregivers should be isolated immediately and patients should be observed and isolated while treating. Another

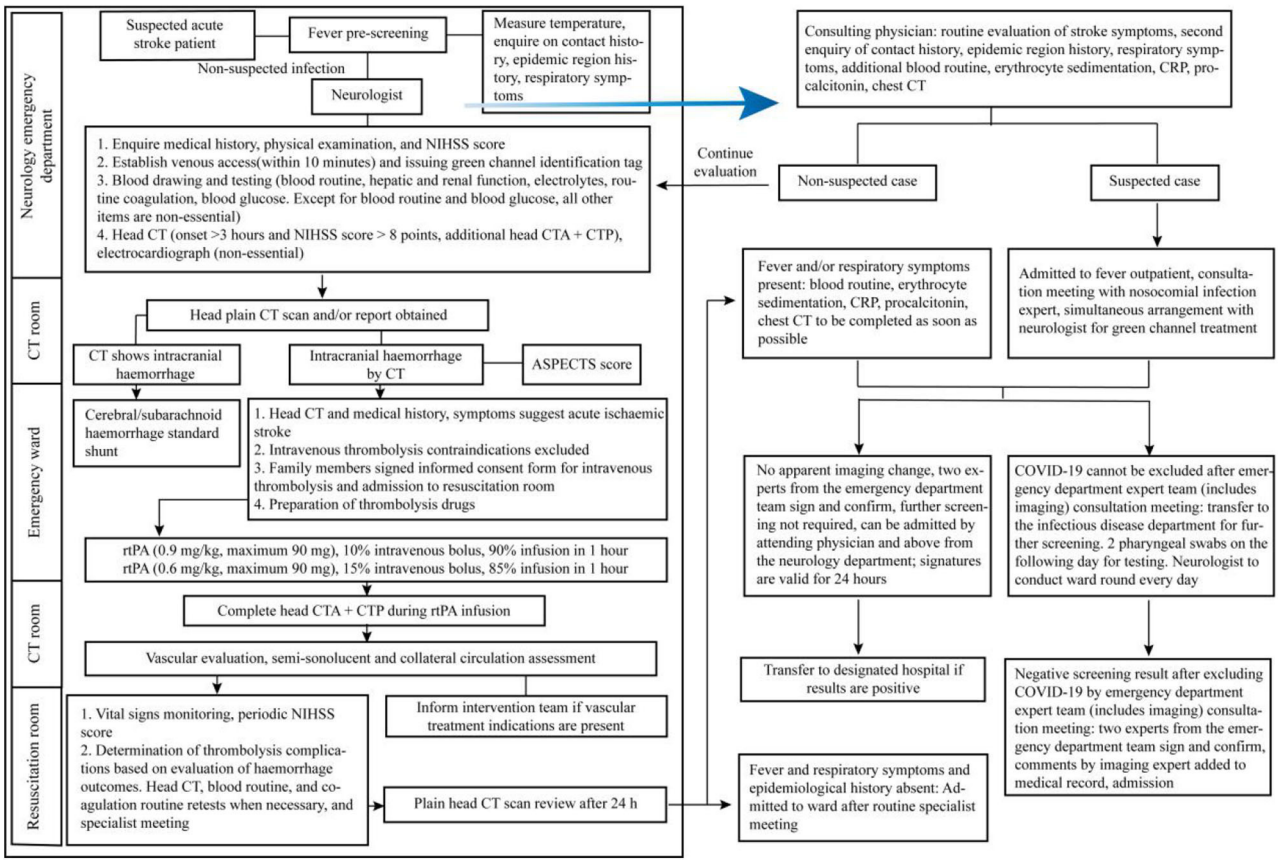


FIGURE 3 | Acute ischemic stroke fast lane management procedure during the COVID-19 epidemic.

group of medical staff will take over this ward with protection measures.

⑥ Specialist diagnosis and treatment or care of suspected or confirmed patients are carried out to ensure that medical staff achieve the corresponding protection grade in the relevant regulations. Additionally, access of non-medical staff is restricted, and visitations are not allowed according to the principle.

⑦ After patients are transferred out, the contact environment is treated according to the medical institution disinfection technical specifications (54, 55).

Medical Staff Management

Entire departmental staff training

Training on COVID-19 case discovery and reporting, epidemiological survey, sample collection, laboratory testing, medical treatment and nosocomial infection control, and personal protection will be given to all staff members in the department to make them familiar with COVID-19 control knowledge, methods, and techniques; understand laws and obligations related to epidemic control; and achieve early identification, early reporting, early quarantine, early diagnosis, and early treatment.

Overall deployment of medical resources

Overall deployment of medical resources in the department, rational establishment of medical echelons, rational scheduling, and organization of a preparatory echelon are carried out. Graded protection is carried out according to the position and zone protection standards and material allocation requirements. Department staff are supervised to ensure that they strictly comply with the medical staff protective gear gowning/degowning procedure (56), and suspected medical staff are quarantined and treated in a timely manner. The protection measures for different roles are as follows:

① Primary protection: (a) Diagnosis, treatment and nursing of ordinary inpatients; (b) Triaging, and registration of outpatients in the fever outpatient clinic and timely data reporting; (c) Cleaning and disinfection of ordinary zones; (d) Collection of medical waste from ordinary patients; (e) Ordinary cleaning work; (f) Testing ordinary patients by medical technicians; (g) While processing the samples from suspected patients in the laboratory, it is recommended that the staff wear masks (N95), protective goggles (anti-fog) or protective face shields for primary protection.

② Secondary protection: (a) Diagnosis and treatment, care, and processing medical waste from infected or suspected

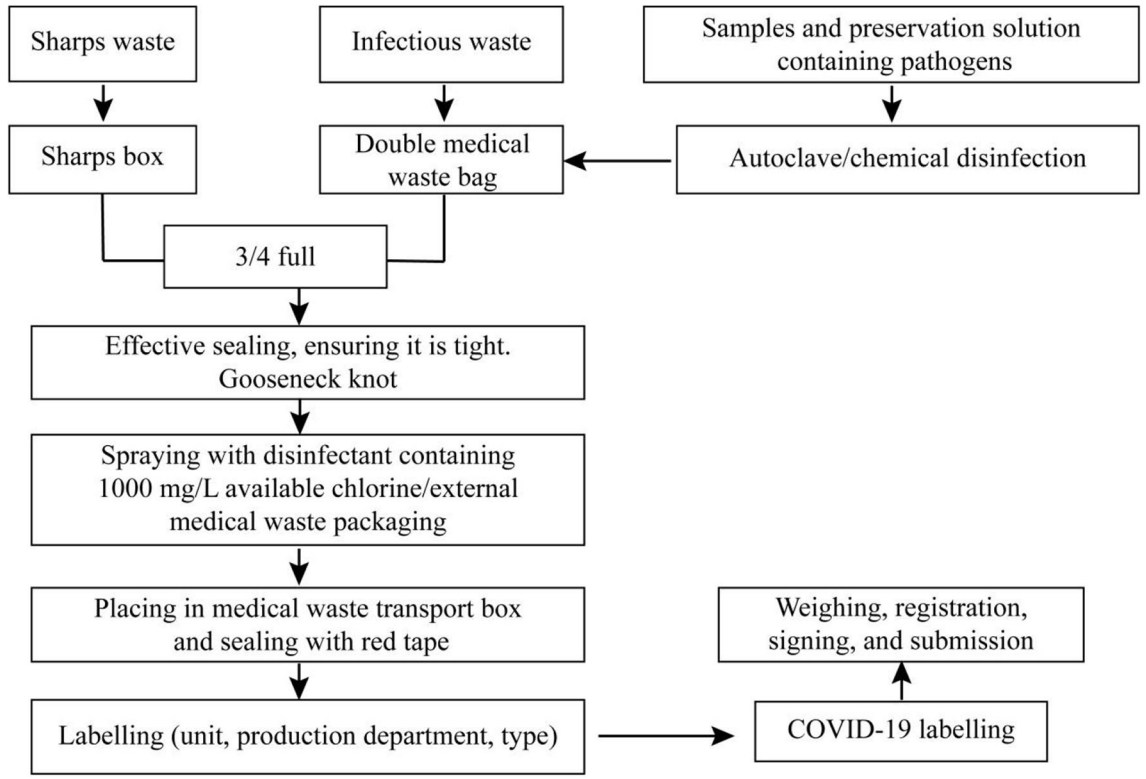


FIGURE 4 | Medical waste management and treatment flowchart.

patients; (b) Collection of medical waste from infected or suspected patients; (c) Cleaning areas that have been exposed to patients with suspected or confirmed COVID-19.

③ Tertiary protection: Diagnosis and treatment, care, and surgical operation in patients with suspected severe infections (such as tracheotomy or intubation).

Concern for the physical and mental health of medical staff

During the COVID-19 epidemic, clinical staff will face physical, intellectual, and psychological challenges, and protecting them is key to eradicating the epidemic (57, 58). Therefore, rational arrangement of manpower resources and shifts should be carried out to avoid over-exhaustion among the medical staff. Proactive health monitoring should be carried out based on the characteristics of different positions and risk assessment, and several measures should be employed to ensure good physical and mental health among the medical staff as well as the families of clinical frontline staff. If medical staff develop psychological problems and require psychological counseling and drug intervention, a psychiatrist should be asked to assist in psychological intervention when necessary.

Inpatient Management

If a suspected COVID-19 case is identified in a ward, then the patient should be quarantined in a single room, and activities and visits from family members should be restricted. Medical staff should wear protective gears (N95 mask and disposable isolation gown for primary protection), avoid contact with patients as much as possible, and avoid repeated movement in and out the ward. Emergency chest CT and routine blood tests, ordinary CRP, erythrocyte sedimentation, procalcitonin, four-item pre-transfusion, and electrolyte tests should be performed. The person in charge of the ward will examine and identify patients. For specific procedure, please refer to "neurological emergency outpatient and inpatient screening process (**Figure 1**)." Close attention must be paid to the following points during the management of inpatients:

① Quarantine should be carried out early for suspected or confirmed patients.

② Inpatients should be guided on how to correctly select and wear masks, correct cough etiquette, and hand hygiene.

③ Strengthening the management of patient visits by caregivers.

④ Proactive advocacy on epidemic control knowledge in inpatients and caregivers.

Medical Waste Management and Treatment

Different medical waste (sharps waste, infectious waste, samples, and preservation solution containing pathogens, etc.) should be collected in order (**Figure 4**). Tightness, cleanliness, color specificity, labeling, and processing registration are the most important points in the management and treatment of medical waste.

CONSTRUCTION OF AN ACUTE STROKE EMERGENCY TREATMENT TEAM DURING EPIDEMIC CONTROL

With the continuous emergence of new media, people are no longer restricted to television and newspapers to acquire information, as more information is acquired from various new media platforms (59–61). However, this increases misinformation and rumors. When faced with a public health emergency such as COVID-19, the public tended to be misinformed on the Internet when they were unable to obtain timely, authoritative, and scientific information (62, 63), which resulted in panic buying of medical supplies, increased nervousness in the public and caused severe negative social effects. This showed the importance of science popularization and the emergency treatment team. In this study, acute stroke was used as a starting point to construct science popularization and an emergency treatment team during an epidemic. First, the selection of science popularization content should include the following principles: ① Determine the target population; ② Target the current status of the epidemic; ③ Conform to actual situation; ④ Get accurate and easily understandable content. Therefore, science popularization was divided into COVID-19 epidemic and stroke modules to describe the disease characteristics, type of onset, and prevention. The connections between the contents are ensured, and long articles were avoided. This required professional knowledge and language summarisation ability of the popular science author. In addition to text, animations, comics, and videos could be combined in many ways to make popular science content more interesting and acceptable to the public. A three-layered structure is adopted for the construction of a science popularization team: ① Editorial team: consisted mainly of medical professionals with a Ph.D. degree or students with a master's or an undergraduate degree, who were responsible for selecting and compiling popular science content and submitting manuscripts to the review group. ② Review team: mainly consisted of hospital professors and physicians, who were responsible for reviewing manuscripts. ③ Publicity team: consisted of mostly the hospital publicity party committee, who were responsible for the publication of the final popular science manuscript on various major platforms such as new media platforms and WeChat accounts and for making short public interest clips and uploading to TikTok and other self-media platforms.

SUMMARY

During the COVID-19 epidemic, identifying patient with comorbid COVID-19 symptoms during the golden hour for acute stroke treatment is a challenge in stroke control. This requires an action framework and a standardized procedure. Rationally utilizing the professional knowledge of medical students and combining teaching resources will not only improve the medical knowledge of the public and reduce frontline stress in the clinical practice but also be significant in fighting against the epidemic. Moreover, promoting medical education reforms on the Internet is highly influential and should be further considered.

AUTHOR CONTRIBUTIONS

MZ conceptualized the study, acquired funding, and administered the project. HY and MZ wrote the original draft. ZC and YF provided the resources. LX, XH, TW, ZZ, and LF worked on validation. BX supervised the study. MZ, HY, and YC reviewed and edited the manuscript.

FUNDING

This study received funding from Key Program of Hunan Social Science Foundation (Grant No. 15WTB27), National Natural Science Foundation of China (Grant No. 81501025), and Hunan Natural Science Foundation (Grant No. 2020JJ4134).

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID−19 a pandemic. *Acta Biomed*. (2020) 91:157–60. doi: 10.23750/abm.v91i1.9397
2. Yang H, Chi Y, Chen Z, Fan Y, Wu H, Hu X, et al. Differential diagnosis and hospital emergency management for fastlane treatment of central nervous system infection under the COVID−19 epidemic in Changsha, China. *Front. Neurol*. (2020) 11:555202. doi: 10.3389/fneur.2020.555202
3. Society of Pathological Doctors Chinese Medical Doctors Association, Chinese Society of Pathology, Chinese Medical Association. Provisional guidelines on autopsy practice for deaths associated with COVID−19. *Zhonghua Bing Li Xue Za Zhi*. (2020) 49:406–10.
4. Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS–CoV−2 associated with the COVID−19 outbreak. *Curr. Biol*. (2020) 30:1346–51.e2. doi: 10.1016/j.cub.2020.03.022
5. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome–related coronavirus: classifying 2019-nCoV and naming it SARS–CoV−2. *Nat. Microbiol*. (2020) 5:536–44. doi: 10.1038/s41564–020–0695–z
6. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS–Cov−2) outside of Wuhan, China: retrospective case series. *BMJ*. (2020) 368:m606. doi: 10.1136/bmj.m606
7. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395:507–13. doi: 10.1016/S0140–6736(20)30211–7
8. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D–dimer as a biomarker for disease severity and mortality in COVID−19 patients: a case control study. *J. Intensive Care*. (2020) 8:49. doi: 10.1186/s40560–020–00466–z
9. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
10. Hernández–Fernández F, Valencia HS, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, et al. Cerebrovascular disease in patients with COVID−19: neuroimaging, histological and clinical description. *Brain*. (2020) 143:3089–103. doi: 10.1093/brain/awaa239
11. Fifi JT, Mocco J. COVID−19 related stroke in young individuals. *Lancet Neurol*. (2020) 19:713–15. doi: 10.1016/S1474–4422(20)30272–6

12. Liao JN, Chao TF, Liu CJ, Chen SJ, Hung CL, Lin YJ, et al. Seasonal variation in the risk of ischemic stroke in patients with atrial fibrillation: a nationwide cohort study. *Heart Rhythm*. (2018) 15:1611–6. doi: 10.1016/j.hrthm.2018.06.043
13. Turin TC, Kita Y, Murakami Y, Rumana N, Sugihara H, Morita Y, et al. Higher stroke incidence in the spring season regardless of conventional risk factors: Takashima Stroke Registry, Japan, 1988–2001. *Stroke*. (2008) 39:745–52. doi: 10.1161/STROKEAHA.107.495929
14. Cho SK, Sohn J, Cho J, Noh J, Ha KH, Choi YJ, et al. Effect of socioeconomic status and underlying disease on the association between ambient temperature and ischemic stroke. *Yonsei Med. J*. (2018) 59:686–92. doi: 10.3349/ymj.2018.59.5.686
15. Chen R, Ovbiagele B, Feng W. Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes. *Am. J. Med. Sci*. (2016) 351:380–6. doi: 10.1016/j.amjms.2016.01.011
16. Cipolla MJ, Liebeskind DS, Chan SL. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. *J. Cereb. Blood Flow Metab*. (2018) 38:2129–49. doi: 10.1177/0271678X18800589
17. Adhikari SP, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID−19) during the early outbreak period: a scoping review. *Infect. Dis. Poverty*. (2020) 9:29. doi: 10.1186/s40249–020–00646–x
18. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D. Early clinical and CT manifestations of coronavirus disease 2019 (COVID−19) pneumonia. *AJR Am. J. Roentgenol*. (2020) 215:338–43. doi: 10.2214/AJR.20.22961
19. Glass WG, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome–coronavirus (SARS–CoV) pulmonary infection of mice. *J. Immunol*. (2004) 173:4030–9. doi: 10.4049/jimmunol.173.6.4030
20. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in wuhan, china, of novel coronavirus–infected pneumonia. *N. Engl. J. Med*. (2020) 382:1199–1207. doi: 10.1056/NEJMoa2001316
21. Giovanetti M, Angeletti S, Benvenuto D, Ciccozzi M. A doubt of multiple introduction of SARS–CoV−2 in Italy: a preliminary overview. *J. Med. Virol*. (2020) 92:1634–36. doi: 10.1002/jmv.25773
22. Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY. SARS–CoV−2 and COVID−19: the most important research questions. *Cell Biosci*. (2020) 10:40. doi: 10.1186/s13578–020–00404–4
23. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS–CoV−2 infection in children. *N. Engl. J. Med*. (2020) 382:1663–5. doi: 10.1056/NEJMc2005073
24. Campbell BCV, Khatri P. Stroke. *Lancet*. (2020) 396:129–142. doi: 10.1016/S0140–6736(20)31179–X
25. Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in china. *J. Clin. Med*. (2020) 9:575. doi: 10.3390/jcm9020575
26. Zhang M, Tang M, Wu Q, Wang Z, Chen Z, Ding H, et al. LncRNA DANCR attenuates brain microvascular endothelial cell damage induced by oxygen–glucose deprivation through regulating of miR−33a−5p/XBP1s. *Aging*. (2020) 12:1778–91. doi: 10.18632/aging.102712
27. Zhang MQ, Zhou L, Deng QF, Xie YY, Xiao TQ, Cao YZ, et al. Ultra–high–resolution 3D digitalized imaging of the cerebral angioarchitecture in rats using synchrotron radiation. *Sci. Rep*. (2015) 5:14982. doi: 10.1038/srep14982
28. Li HL, Ding H, Yin XZ, Chen ZH, Tang B, Sun JY, et al. Comparison of high–resolution synchrotron–radiation–based phase–contrast imaging and absorption–contrast imaging for evaluating microstructure of vascular networks in rat brain: from 2D to 3D views. *J. Synchrotron. Radiat*. (2019) 26(Pt 6):2024–32. doi: 10.1107/S1600577519011688
29. Tiwari A, Berekashvili K, Vulkanov V, Agarwal S, Khaneja A, Turkel–Parella D, et al. Etiologic subtypes of ischemic stroke in SARS–CoV−2 patients in a cohort of New York city hospitals. *Front. Neurol*. (2020) 11:1004. doi: 10.3389/fneur.2020.01004
30. Dmytriw AA, Phan K, Schirmer C, Settecase F, Heran MKS, Efendizade A, et al. Ischaemic stroke associated with COVID-19 and racial outcome disparity in North America. *J Neurol Neurosurg Psychiatry*. (2020). doi: 10.1136/jnnp-2020-324653. [Epub ahead of print].
31. Chowkwanyun M, Reed AL, Jr. Racial health disparities and Covid−19—caution and context. *N. Engl. J. Med*. (2020) 383:201–3. doi: 10.1056/NEJMp2012910
32. Yancy CW. COVID−19 and African Americans. *JAMA*. (2020) 323:1891–2. doi: 10.1001/jama.2020.6548
33. Vepa A, Bae JP, Ahmed F, Pareek M, Khunti K. COVID−19 and ethnicity: a novel pathophysiological role for inflammation. *Diabetes Metab. Syndr*. (2020) 14:1043–51. doi: 10.1016/j.dsx.2020.06.056
34. Grewal P, Pinna P, Hall JP, Dafer RM, Tavarez T, Pellack DR, et al. Acute ischemic stroke and COVID−19: experience from a comprehensive stroke center in Midwest US. *Front. Neurol*. (2020) 11:910. doi: 10.3389/fneur.2020.00910
35. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID−19. *N. Engl. J. Med*. (2020) 382:e38. doi: 10.1056/NEJMc2007575
36. Helms J, Kremer S, Merdji H, Clere–Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS–CoV−2 Infection. *N. Engl. J. Med*. (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
37. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID−19. *J. Neurol. Neurosurg. Psychiatry*. (2020) 91:889–91. doi: 10.1136/jnnp−2020–323586
38. González–Padilla DA, Tortolero–Blanco L. Social media influence in the COVID−19 pandemic. *Int. Braz. J. Urol*. (2020) 46(Suppl. 1):120–4. doi: 10.1590/s1677–5538.ibju.2020.s121
39. Chao M, Xue D, Liu T, Yang H, Hall BJ. Media use and acute psychological outcomes during COVID−19 outbreak in China. *J. Anxiety Disord*. (2020) 74:102248. doi: 10.1016/j.janxdis.2020.102248
40. Depoux A, Martin S, Karafillakis E, Preet R, Wilder–Smith A, Larson H. The pandemic of social media panic travels faster than the COVID−19 outbreak. *J. Travel Med*. (2020) 27:taaa031. doi: 10.1093/jtm/taaa031
41. Islam MS, Sarkar T, Khan SH, Mostofa Kamal AH, Hasan SMM, Kabir A, et al. COVID−19–related infodemic and its impact on public health: a global social media analysis. *Am. J. Trop. Med. Hyg*. (2020) 103:1621–9. doi: 10.4269/ajtmh.20–0812
42. Song P, Jin C, Tang W. New medical education reform in China: towards healthy China 2030. *Biosci. Trends*. (2017) 11:366–9. doi: 10.5582/bst.2017.01198
43. Chen P, Li F, Harmer P. Healthy China 2030: moving from blueprint to action with a new focus on public health. *Lancet Public Health*. (2019) 4:e447. doi: 10.1016/S2468–2667(19)30160–4
44. Gao B, Dong J. Does the impact of COVID−19 improve the doctor–patient relationship in China? *Am. J. Med. Sci*. (2020) 360:305–6. doi: 10.1016/j.amjms.2020.05.039
45. Vallelonga F, Elia F. Doctor–patient relationship at the time of COVID−19: travel notes. *Intensive Care Med*. (2020) 46:1802. doi: 10.1007/s00134–020–06152–w
46. Härter M, Bremer D, Scherer M, von dem Knesebeck O, Koch–Gromus U. Impact of COVID−19–pandemic on clinical care, work flows and staff at a University Hospital: results of an interview–study at the UKE. *Gesundheitswesen*. (2020) 82:676–81. doi: 10.1055/a−1226–6828
47. Liu Y, Chen H, Zhang N, Wang X, Fan Q, Zhang Y, et al. Anxiety and depression symptoms of medical staff under COVID−19 epidemic in China. *J. Affect Disord*. (2020) 278:144–8. doi: 10.1016/j.jad.2020.09.004
48. Zhu J, Sun L, Zhang L, Wang H, Fan A, Yang B, et al. Prevalence and influencing factors of anxiety and depression symptoms in the first–line medical staff fighting against COVID−19 in Gansu. *Front. Psychiatry*. (2020) 11:386. doi: 10.3389/fpsyt.2020.00386
49. The Lancet. The best science for achieving Healthy China 2030. *Lancet*. (2016) 388:1851. doi: 10.1016/S0140–6736(16)31842–6
50. Lin L, Li TS. Interpretation of "guidelines for the diagnosis and treatment of novel coronavirus (2019–nCoV) infection by the National Health Commission (Trial Version 5)". *Zhonghua Yi Xue Za Zhi*. (2020) 100:805–7. doi: 10.3760/cma.j.issn.0376-2491.2020.0001
51. Ko SB, Park HK, Kim BM, Heo JH, Rha JH, Kwon SU, et al. 2019 Update of the Korean clinical practice guidelines of stroke for endovascular recanalization therapy in patients with acute ischemic stroke. *J. Stroke*. (2019) 21:231–40. doi: 10.5853/jos.2019.00024

52. Zhao J, Rudd A, Liu R. Challenges and potential solutions of stroke care during the coronavirus disease 2019 (COVID−19) outbreak. *Stroke*. (2020) 51:1356–7. doi: 10.1161/STROKEAHA.120.029701
53. Qureshi AI, Abd–Allah F, Al–Senani F, Aytac E, Borhani–Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID−19 infection: report of an international panel. *Int. J. Stroke*. (2020) 15:540–54. doi: 10.1177/1747493020923234
54. Shi XM. The critical role of environmental health and disinfection in the prevention and control of COVID−19 pandemic. *Zhonghua Yu Fang Yi Xue Za Zhi*. (2020) 54:918–22. doi: 10.3760/cma.j.cn112150-20200405-00516
55. Hernández–Navarrete MJ, Celorrio–Pascual JM, Lapresta Moros C, Solano Bernad VM. Principles of antisepsis, disinfection and sterilization. *Enferm. Infecc. Microbiol. Clin*. (2014) 32:681–8. doi: 10.1016/j.eimc.2014.04.003
56. Jin YH, Zhan QY, Peng ZY, Ren XQ, Yin XT, Cai L, et al. Chemoprophylaxis, diagnosis, treatments, and discharge management of COVID-19: an evidence-based clinical practice guideline (updated version). *Mil Med Res.* (2020) 7:41. doi: 10.1186/s40779-020-00270-8
57. Huang J, Liu F, Teng Z, Chen J, Zhao J, Wang X, et al. Care for the psychological status of frontline medical staff fighting against COVID−19. *Clin. Infect. Dis*. (2020) 3:ciaa385. doi: 10.1093/cid/ciaa385
58. Zhou Y, Wang W, Sun Y, Qian W, Liu Z, Wang R, et al. The prevalence and risk factors of psychological disturbances of frontline medical staff in china under the COVID−19 epidemic: workload should be concerned. *J. Affect Disord*. (2020) 277:510–4. doi: 10.1016/j.jad.2020.08.059
59. Jabbar A, Gasser RB, Lodge J. Can new digital technologies support parasitology teaching and learning? *Trends Parasitol*. (2016) 32:522–30. doi: 10.1016/j.pt.2016.04.004
60. Lin DJ, Cudkowicz ME, Cho TA. Opinion and Special Articles: challenges and opportunities in defining career identity in academic neurology. *Neurology*. (2018) 91:670–2. doi: 10.1212/WNL.0000000000006284
61. Chan MM, Barchino R, Medina–Merodio JA, de la Roca M, Sagastume F. MOOCs, an innovative alternative to teach first aid and emergency treatment: a practical study. *Nurse Educ. Today*. (2019) 79:92–97. doi: 10.1016/j.nedt.2019.05.008
62. Gao J, Zheng P, Jia Y, Chen H, Mao Y, Chen S, et al. Mental health problems and social media exposure during COVID−19 outbreak. *PLoS ONE*. (2020) 15:e0231924. doi: 10.1371/journal.pone.0231924
63. Ni MY, Yang L, Leung CMC, Li N, Yao XI, Wang Y, et al. Mental health, risk factors, and social media use during the COVID−19 epidemic and cordon sanitaire among the community and health professionals in Wuhan, China: cross–sectional survey. *JMIR Ment. Health*. (2020) 7:e19009. doi: 10.2196/19009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 30 November 2020
doi: 10.3389/fneur.2020.601652

Impact of COVID-19 on Stroke Admissions and the Medical Care System in the Tokyo Metropolitan Area

Takahiro Ota[1]*, *Yoshiaki Shiokawa*[2] *and Teruyuki Hirano*[3]

[1] Department of Neurosurgery, Tokyo Metropolitan Tama Medical Center, Fuchu, Japan, [2] Department of Neurosurgery, Kyorin University, Mitaka, Japan, [3] Department of Stroke and Cerebrovascular Medicine, Kyorin University, Mitaka, Japan

Aims: This study aimed to assess the number of patients with acute stroke seeking medical emergency care since the declaration of the state of emergency in the COVID-19 pandemic in the Tokyo metropolitan area of Japan.

Methods: In this combined retrospective and prospective multicenter survey, data on the numbers of hospital admissions due to acute ischemic stroke, of large vessel occlusion (LVO) cases, and of reperfusion therapies performed from February to July 2020, restrictions of the medical care system, and comprehensive stroke center (CSC) scale scores were collected in 19 stroke centers in Tokyo.

Results: In the survey period, 3,456 patients were admitted with acute stroke. There was a decrease in the number of admissions (−22%), LVO (−22%), thrombolysis (−6%), and thrombectomy (−23%) during the state of emergency, but the ratio of thrombectomy to LVO cases was not different. The acceptance of acute stroke cases by emergency transport and emergent operations in the central eastern area of Tokyo, was also significantly decreased to <50% and remains <60%. According to CSC scores, each hospital restricted their infrastructure or educational activities according to their medical resources. There was only one stroke case with COVID-19 (thrombectomy case) in all 3,456 patients in this study.

Conclusion: The COVID-19 pandemic had a major impact on stroke care in Tokyo, including stroke admissions and medical care systems, resulting in a significant reduction in thrombolysis and thrombectomy. The extent of the drop may be the result of the number of COVID-19 patients.

Keywords: care system, COVID-19, Tokyo, stroke, thrombectomy

OPEN ACCESS

Edited by:
Tomohisa Nezu,
Hiroshima University, Japan

Reviewed by:
Masahiro Uemura,
Niigata University, Japan
Mohammad Anadani,
Washington University School of Medicine in St. Louis, United States

***Correspondence:**
Takahiro Ota
toota-tky@umin.org

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *01 September 2020*
Accepted: *09 November 2020*
Published: *30 November 2020*

Citation:
Ota T, Shiokawa Y and Hirano T (2020) Impact of COVID-19 on Stroke Admissions and the Medical Care System in the Tokyo Metropolitan Area. Front. Neurol. 11:601652. doi: 10.3389/fneur.2020.601652

INTRODUCTION

The COVID-19 pandemic declared by the World Health Organization (WHO) in March 2020 has challenged healthcare systems and societies worldwide. During the pandemic, there have been many reports that the number of stroke patients seen in the emergency department has dropped considerably, with a significant reduction in both thrombolysis and mechanical thrombectomy (MT) (1, 2).

On January 16, 2020, Japan reported its first case of COVID-19. A state of emergency was declared from April 7 to May 25 with a massive increase of patients. The declaration had a great impact on the stroke management system, especially on the emergent care of acute stroke. The largest number of patients with COVID-19 is found in the Tokyo metropolitan area, which is the capital of Japan. The Tokyo metropolitan area is highly populated and consists of 23 wards (the eastern half, with a population of about 8 million in an area of 619 km^2), the Tama area (the western half, with a population of 4.3 million and an area of 1,160 km^2), and the island regions. By July 30, the total number of COVID-19 cases was 10,408 (88.3%) in the 23 wards and 1,380 (11.7%) in the Tama area.

AIMS

The objective of this study was to assess and quantify the dynamics of admission of acute stroke cases and the number of reperfusion therapies performed during the COVID-19 pandemic and to estimate the real impact of the state of emergency declaration on the emergency stroke care system in the Tokyo metropolitan area in Japan.

METHODS

This was a multicenter, combined retrospective and prospective observational study involving a questionnaire survey. The questionnaire was sent, and data were collected every 2 weeks from all the hospitals of the Tokyo/tama-Registry of Acute endovascular Thrombectomy (TREAT) (3) between February 1 and July 31, 2020 (retrospectively to March 31 and prospectively from April). The participating facilities were 11 of 13 recanalization therapy-capable stroke centers in the Tama area and 8 of about 45 recanalization therapy-capable stroke centers in the 23 wards. The cases were grouped in three periods of 2 months each, according to the declaration of the state of emergency (from April to May) in Japan. All centers were asked to answer a short questionnaire about the following items: the number of acute stroke admissions, the number of patients with large vessel occlusion (LVO), the mean (2 weeks) number of MT and thrombolysis cases, the change in the comprehensive stroke center (CSC) score (4), and the quantitative restrictions of the medical care system (outpatient department, emergency visits, elective operations, emergent operations).

STATISTICS

Descriptive statistics were used to compare the incidence of stroke admissions before and after the declaration of the state of emergency in Japan. Comparisons between groups were made using chi-squared tests for categorical variables, with p-values < 0.05 considered significant. Categorical data are expressed as the number of stroke admission, LVO cases, thrombolysis cases, and thrombectomy cases. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (5).

RESULTS

In total, 3,456 patients with acute stroke (2,354 in Tama and 1,102 in the 23 wards) presented to the participating hospitals (**Table 1**). Drops in the numbers of stroke cases, LVO, thrombolysis, and MT occurred during the state of emergency, but they did not occur homogeneously across the areas. The decreases in LVO and MT were greater in the 23 wards, but there were no significant differences in the decreases in the numbers of stroke admissions and LVO, thrombolysis, and MT cases compared to the pre-2 months before declaration of the state of emergency. One finding particularly worth mentioning is that there was only one stroke case (0.03%) with COVID-19 (an MT case) in all 3,456 patients in this study.

QUANTITATIVE RESTRICTIONS OF THE MEDICAL CARE SYSTEM

Restrictions of the outpatient department, emergency visits, elective operations, and emergent operations are shown in **Table 2**.

TABLE 1 | Numbers of acute stroke admissions and large vessel occlusion, thrombolysis, and mechanical thrombectomy cases.

	Pre (February, March)	Period of the state of emergency (April, May)	Post (June, July)	*p*
Acute stroke				n.s.
Total	329	259 (78.7%)	276 (83.9%)	
Tama area	218	180 (82.6%)	191 (87.6%)	
23 wards	112	79 (70.5%)	86 (76.8%)	
Large vessel occlusion				n.s.
Total	45	35 (77.8%)	32 (71.1%)	
Tama area	28	24 (85.7%)	22 (78.6%)	
23 wards	18	11 (61.1%)	10 (55.6%)	
Thrombolysis				n.s.
Total	17	16 (94.1%)	16 (94.1%)	
Tama area	13	13 (100.0%)	11 (84.6%)	
23 wards	4	3 (75.0%)	5 (125%)	
Thrombectomy				n.s.
Total	26	20 (76.9%)	20 (76.9%)	
Tama area	14	13 (92.9%)	13 (92.9%)	
23 wards	13	7 (53.8%)	7 (53.8%)	
Ratio of thrombectomy to total large vessel occlusion cases, %				<0.05
Total	57.8	57.1	62.5	
Tama area	50	54.2	59.1	
23 wards	72.2	63.6	70	

Values are mean numbers of admissions /2 weeks, n.s., not significant.
The radio of period of the state of emergency and Post to Pre are shown (%).

TABLE 2 | The mean number and percentage of hospitals with normal medical care systems.

	Pre (February, March)	Period of the state of emergency (April, May)	Post (June, July)	*p*
Outpatient department				not significant
Tama area	9.7 (88.6%)	3.0 (27.2%)	10.0 (91%)	
23 wards	7.2 (90.6%)	3.8 (46.9%)	7.0 (87.5%)	
Elective operations				$p < 0.05$
Tama area	9.5 (86.4%)	1.5 (13.6%)	8.0 (72.7%)	
23 wards	7.5 (93.8%)	2.0 (25%)	5.8 (71.9%)	
Emergent operations				$p < 0.05$
Tama area	11.0 (100%)	9.5 (86.4%)	10.3 (93.2%)	
23 wards	7.8 (96.9%)	4.5 (56.3%)	4.8 (59.4%)	
Emergent transfer of acute stroke cases				$p < 0.05$
Tama area	11.0 (100%)	9.0 (81.8%)	10.3 (93.2%)	
23 wards	7.8 (96.9%)	3.5 (43.8%)	4.8 (59.4%)	

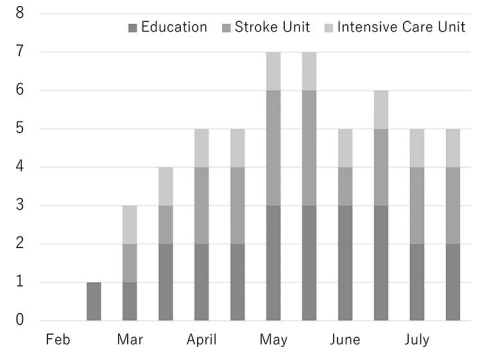


FIGURE 1 | Accumulated number of items of comprehensive stroke center scores with deficits.

During the state of emergency, each hospital restricted regular medical care systems to maintain their capability to treat COVID-19 cases. There was a major restriction of the number of outpatient departments in both the Tama area (−61.4%) and the 23 wards (−43.7%), and significant reductions of elective operations in the Tama area (−72.8%) and the 23 wards (−68.8%). After the lifting of the state of emergency, both numbers recovered quickly ($p < 0.05$). There was a rapid decrease in emergent stroke care. Compared to the Tama area, there were significant decreases in emergent operations in the 23 wards (−40.6%), and the trend of the restrictions continued to last. In particular, the acceptance of acute stroke cases by emergency transport in the 23 wards was also significantly decreased to <50% and remains <60%. In the Tama area, emergent operations and the acceptance of emergent acute stroke cases recovered to almost normal after the declaration was lifted.

COMPREHENSIVE STROKE CENTER SCORE

This score was assessed using 25 items divided into 5 components specifically recommended for CSCs. Personnel, diagnostic techniques, and specific expertise were not affected throughout this study. Infrastructure, including stroke units (maximum 3 hospitals) and intensive care units (1 hospital), was closed during this survey. Educational meetings were also not held (maximum 3 hospitals) (**Figure 1**).

DISCUSSION

The available preliminary data show lower volumes of acute stroke admissions, thrombolysis and MT cases in Tokyo over the first 6 months of the epidemic, including during the state of emergency. Each hospital restricted its medical care system, especially emergent operations and the acceptance of emergent acute stroke cases. The two main parts of the Tokyo metropolitan area, the Tama area and the 23 wards, were affected differently, probably due to the different numbers of COVID-19 cases.

Prior studies reported fewer thrombolysis and MT cases during the COVID-19 pandemic (6, 7), consistent with the present results in Japan. Fewer patients with TIAs sought hospital care, and the proportion of patients arriving within the therapeutic time window of thrombolysis was significantly lower (8). There are no reasons to assume that the incidence of stroke is decreasing. Some suggest the reason is that patients' fear of in-hospital infection causes avoidance behavior (1, 6, 8). In the present survey in Tokyo, it is noteworthy that MT rates, reflecting severe strokes, remained largely unaffected. This indicates that both patients and pre-hospital medical staff correctly recognize the need for urgent assessment and treatment despite the threat of COVID-19 infection.

The other findings of the present survey show the concrete restrictions of the medical care system in each hospital. Each hospital limited the acceptance of patients in the outpatient department and for elective operations first. With the increase in the number of COVID-19 patients, emergent operations and emergent stroke care systems were restricted to a major extent. The reason for the decrease of MT cases is not clear, whether it was a decrease in onset, the reluctance of patients, or a decrease in secondary transfer from regional stroke centers. The hospitals in the 23 wards were where the pandemic hit early and more severely (about 90% of the COVID cases in Tokyo), whereas the hospitals in the Tama area felt less impact of the COVID-19 pandemic, so that the difference in the extent of the effect may be mainly attributable to the lower number of COVID-19 cases in the Tama area. If an explosive increase of COVID-19 patients were to occur in the Tama area, an effect on the acute stroke care system similar to that seen in the 23 wards could easily occur.

Comprehensive stroke center score data were also collected. To the best of our knowledge, this is the first report of changes in CSC scores during the COVID-19 pandemic. It was found that some centers changed the structure of in-hospital stroke care during this pandemic. Resource management is critical during a pandemic. To date, there has been no explosive

increase of COVID-19 patients in Japan. Each hospital restricted their infrastructure or educational activity according to their medical resources.

LIMITATIONS

This was partly a retrospective study and not all thrombectomy-capable hospitals in the 23 wards cooperated. Data about stroke type, the delay to admission, time metrics from arrival to the hospital to the start of thrombolysis or to recanalization, and outcomes after reperfusion therapy were not collected. Whether the morbidity/mortality of stroke was increased in pandemic of COVID-19 as compared with normal situation has not become clear. Finally, one might not be able to extrapolate the results to other countries or regions with different stroke care protocols and different social and healthcare responses to the COVID-19 pandemic. The strength of the present survey is that it provides real-world information about stroke quality metrics in stroke centers in Japan.

CONCLUSIONS

The COVID-19 pandemic has had a marked impact on stroke care in Tokyo, Japan. With various timely and appropriate changes to an institution's acute stroke care system, the medical care system must maintain its capacity to treat acute stroke patients to a similar extent as pre-pandemic. Further studies will need to confirm recent findings with a larger cohort, comparing stroke treatment time metrics and long-term outcomes between pre-pandemic and pandemic acute stroke patients.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Boar of each participating institute. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TO collected, analyzed, interpreted the data, and wrote the manuscript. YS and TH were major contributions in the study design and editing of the manuscript. All authors read and approved the final manuscript.

FUNDING

This study was partially supported by Taiju Life Social Welfare Foundation.

REFERENCES

1. Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke.* (2020) 51:1996–2001. doi: 10.1161/STROKEAHA.120.030225
2. Markus HS, Brainin M. COVID-19 and stroke—A Global World Stroke Organization perspective. *Int J Stroke.* (2020) 15:361–4. doi: 10.1177/1747493020923472
3. Ota T, Shigeta K, Amano T, Ueda M, Hirano T, Matsumaru Y, et al. Regionwide retrospective survey of acute mechanical thrombectomy in Tama, Suburban Tokyo: a preliminary report. *J Stroke Cerebrovasc Dis.* (2018) 27:3350–5. doi: 10.1016/j.jstrokecerebrovasdis.2018.07.044
4. Iihara K, Nishimura K, Kada A, Nakagawara J, Ogasawara K, Ono J, et al. Effects of comprehensive stroke care capabilities on in-hospital mortality of patients with ischemic and hemorrhagic stroke: J-ASPECT study. *PLoS ONE.* (2014) 9:e96819. doi: 10.1371/journal.pone.0096819
5. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transpl.* (2013) 48:452–8. doi: 10.1038/bmt.2012.244
6. Agarwal S, Scher E, Rossan-Raghunath N, Marolia D, Butnar M, Torres J, et al. Acute stroke care in a New York city comprehensive stroke center during the COVID-19 pandemic. *J Stroke Cerebrovasc Dis.* (2020) 29:1–6. doi: 10.1016/j.jstrokecerebrovasdis.2020.105068
7. Kerleroux B, Fabacher T, Bricout N, Moïse M, Testud B, Vingadassalom S, et al. Mechanical thrombectomy for acute ischemic stroke amid the COVID-19 outbreak: decreased activity, and increased care delays. *Stroke.* (2020) 51:2012–7. doi: 10.2139/ssrn.3571545
8. Teo KC, Leung WCY, Wong YK, Liu RKC, Chan AHY, Choi OMY, et al. Delays in stroke onset to hospital arrival time during COVID-19. *Stroke.* (2020) 51:2228–31. doi: 10.1161/STROKEAHA.120.030105

Conflict of Interest: TH received honoraria from Daiichi-Sankyo, Nippon Boehringer Ingelheim, Bayer, Pfizer, Bristol Myers Squibb, and Medtronic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

OPINION
published: 30 November 2020
doi: 10.3389/fneur.2020.579079

Challenges in Neuroimaging in COVID-19 Pandemia

Sofía González-Ortiz, Santiago Medrano, José María Maiques and Jaume Capellades*

Neuroradiology Section, Radiology Department, Hospital del Mar, Barcelona, Spain

Keywords: neuroradiology, radiology, tele-radiology, personal protective equipment, COVID-19

OPEN ACCESS

Edited by:
Ricardo F. Allegri, Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI), Argentina

Reviewed by:
Manuela Jorquera, San Carlos University Clinical Hospital, Spain
Alessandra Splendiani, University of L'Aquila, Italy

****Correspondence:***
Sofía González-Ortiz
sofia.gonzalezortiz@gmail.com

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: *02 July 2020*
Accepted: *14 October 2020*
Published: *30 November 2020*

Citation:
González-Ortiz S, Medrano S, Maiques JM and Capellades J (2020) Challenges in Neuroimaging in COVID-19 Pandemia. Front. Neurol. 11:579079. doi: 10.3389/fneur.2020.579079

INTRODUCTION

Since the first case of infection was reported in December 2019, in Wuhan, China, SARS CoV 2 has spread all over the world, and was declared as a pandemia on the 11th of March by the WHO. The reported mortality rate is between 0.3 and 1% in the general population, rising to 14% in hospitalized cases (1). Even though Covid-19 infection causes a predominantly respiratory disease, its explosive eruption worldwide has affected all medical specialties.

Health care systems and workers have had to react rapidly. Each region and hospital has adapted differently depending on their specific characteristics, the prevalence of the infection and the recommendations of governments and preventative medical services. The practice of Neuroradiology, along with Radiology departments, have not escaped the effects and have had to face up to the new circumstances (2). Some works (articles, webinars and guidelines) have appeared giving recommendations and sharing their experience to face the challenge that the Covid-19 pandemia implies for the Neuroradiology. In this article, we present and discuss these recommendations in the different phases of the pandemia.

BEFORE THE PEAK OF THE PANDEMIA

In the early stages of the pandemia, crisis committees, connected with the local, regional and state public institutions, were created to establish new guidelines and protocols for each center (3–7). A general practice adopted in Radiology and Neuroradiology, was the creation of departmental co-ordination groups (typically comprising a radiologist/neuroradiologist, a radiographer and a secretary), to work in conjunction with these committees (8–10). In addition, general measures were implemented to limit the exposure of healthcare workers and patients and for early viral detection. Securing the supply of medical material and personal protective equipment (PPE) was also a priority (6).

As the rapid and explosive spread of the Covid-19 infection required a rapid response, this coordination and reorganization of Radiology departments, a common strategy followed in hospitals, was, in our opinion, key to achieving this. The supply of PPE for staff, another critical point during the early stages of the pandemia, was a great challenge, due to the high worldwide demand (11).

THE PEAK OF THE PANDEMIA

In this phase various measures have been recommended.

One of these is the strict selection of neuroimaging tests. Although each center has had to set their own criteria depending on their particular idiosyncrasies, there have been some general recommendations (4, 5, 12, 13). In the case of critical examinations, where the neuroimaging could impact the immediate management of patients, the recommendation has been to perform the test despite the pandemic situation, subject to a risk/benefit analysis. In the case of non-critical

neuroradiological examinations, the recommendation has been to postpone them and establish levels of priority (13–16). In some cases, examinations could even be canceled (15).

In this phase, the increased pressure on hospitals due to the number of Covid patients, with the consequent lack of material and human resources, and the need for social distancing, has made it impossible to carry out the usual volume of examinations. For this reason, even if there have been no specific recommendations on which particular neuroradiological examinations to maintain, we believe that the prioritization of tests during the peak of the pandemia has been key to ensure that the most critical patients received an optimal radiological diagnosis. The establishment of different priority levels in the elective tests has been essential for their orderly rescheduling. To give an objective view of the impact, neuroradiological examinations during the pandemic peak decreased by almost 50% (17, 18). We think it has also been important, as emphasized in some articles, the need of a fluid communication between neurologists, neurosurgeons and other clinicians, to highlight any special situations arising in particular cases.

Special mention should be made of patients with acute stroke, who present a particular challenge for neuroradiology departments, due to the existing relationship reported between patients with severe coronavirus infection and cerebrovascular stroke disease (19). As these patients usually undergo a brain CT and angio-CT scan, some studies have recommended the incorporation of a chest CT to rule out the possible existence of a concomitant pneumonia due to Covid-19, which would require isolation of the patient (20, 21). It seems a sensible recommendation when the prevalence of the infection in the population is high.

In terms of patient protection, the first step has been to detect potential cases in patients coming for a neuroradiological test. To this end screening questionnaires (3–5, 9) have been carried out, often even conducted by telephone before the arrival of the patient, followed by PCR tests if necessary and available. Specific circuits have been established within Neuroradiology departments to avoid contact between infected and uninfected patients. "Clean" radiological equipment has been kept for uninfected patients and "dirty" for infected patients (5, 13, 22–25). Social distancing has been enforced in waiting rooms and masks made mandatory for all patients (5, 13, 26). Cleaning, disinfection and air purification frequency have also been increased (5, 13, 22–25).

These are reasonable measures which are recommended in guidelines and have been adopted generally in hospitals and imaging centers. We think it is important that each hospital establishes their own protocols, as these recommendations can be carried out in different ways according to particular characteristics. For example, in relation to air purification, some of the recommended measures have been the use of a high-efficiency particulate air (HEPA) filter, ultraviolet irradiation or simply lengthening the time between two patients. The choice as to which to use is a decision that depends on multiple factors. In relation to the use of masks or other medical devices, such as ventilators, in Neuroradiology departments, we think it is important to highlight that they need to be compatible with the MRI environment, for both safety and image quality reasons. In the case of CT examinations, they must not contain metallic elements which could distort the image (26–29).

In terms of healthcare staff protection, education about security measures, the provision of PPE and the establishment of physical barriers, such as plastic screens and equipment covers, have been some of the more extensively adopted precautionary measures (5, 13, 14). Tele-neuroradiology has been another widely adopted practice to reduce the exposure of departmental staff, with the use of "Picture Archiving and Communication System" PACS. Where telematic work has not been possible, the establishment of groups, working different hours or days, has been an extensively used option, along with the use of individual workstations and maintaining social distancing in the work-space (7, 26, 29). In order to maintain clinical and educational communication, the use of phone calls (instead of personal interactions) and teleconference applications for virtual sessions has been widespread, especially for essential clinical care meetings (30). These applications allow communication from workstations or even phones, and also screen sharing to show neuro-radiological images (25).

Probably one of the most specific challenge for Neuroradiology, related to the staff protection, has been the rapid deployment of Home PACS Workstations and the expansion of teleradiology (31–33).

AFTER THE PEAK OF THE PANDEMIA

Once the peak of the pandemic has passed, the most emphasized recommendation for Radiology departments has been to recover activity in a tiered manner (13–15, 34–36). The postponed examinations should be re-scheduled following the degrees of priority established during the peak of the pandemia (13–15). The new petitions generated by the recovery of activity in hospitals also need to be taken into account. We think that all these common measures to recover radiological activity, have to be adapted to each situation, as the prevalence of the pandemia and the resources of health care systems could be very variable. In this regard we found the work of Madhuripan et a. (17) interesting, which related the radiology volume recovery after the pandemia to different variants, such as regional pandemic severity, the lifting of government restrictions, patient Covid-19 infection concern, management during the pandemic peak, impact of the economic recession and Radiology practice profile.

General measures to avoid the transmission of Covid-19 have still been recommended in this phase and are likely to be necessary for some time (35). For example, the obligatory use of masks and enforcing of social distancing in the hospital, the use of PPE for health workers and the increased disinfection and ventilation of imaging suites. As a result of these measures, Radiology departments still need to allow for longer times between patient examinations. Many hospitals have responded to this by increasing the hours of radiological assistance, extending the activity of the MRI and CT scans during the night and weekend shifts (34, 35). We think this may be necessary to re-schedule all the postponed activity, but hospital management

must take into account that it may mean hiring more staff or agreeing new shifts with workers.

The continued use of tele-radiology, at least partially, is still recommended at this stage (13, 34, 35). This has been one of the most widespread measures adopted in neuroradiology and has generally been implemented successfully (31–33). After these experiences and in line with other articles (37), we believe that for neuroradiologists, the coronavirus pandemic may contribute to the permanent establishment of tele-neuroradiology, or at least to a mixed model with part of the time physically present and part of the time reporting remotely.

CONCLUSION

The particular challenges for the practice of Neuroradiology during the Covid pandemia have been different during the distinct phases. In the early stage, the main challenge was the need for a rapid response. During the peak of the pandemia, the challenge was to maintain critical neuroimaging assistance, whilst preventing the spread of the infection amongst patients and healthcare workers. After the peak of the pandemia the challenge has been to recover neuroradiological activity while maintaining some Covid-19 measures, which seem likely to continue for a while. Some of the strategies with which Neuroradiology has faced the challenges of each phase have been general, and others more specific to the specialty. Broadly they have been quite consistent throughout the different articles and guidelines published.

After the peak of the Covid-19 pandemia we have to stay alert and know how to react on time to possible next waves, using what we have already learnt during these months. Neuroradiology assistance should be maintained taking into account the general care of the patients and the global health situation.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

REFERENCES

1. World Health Organization. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 COVID-19*. (2020). Available online at: https://www.who.int/docs/defaultsource/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
2. Mahajan A, Hirsch JA. Novel coronavirus: what neuroradiologists as citizens of the world need to know. *Am J Neuroradiol.* (2020) 41:552–4. doi: 10.3174/ajnr.A6526
3. Chen RC, Tan TT, Chan LP. Adapting to a new normal? 5 key operational principles for a radiology service facing the COVID-19 pandemic. *Eur Radiol.* (2020) 30:4964-7. doi: 10.1007/s00330-020-06862-1
4. Mossa-Basha M, Azadi J, Ko J, Klein J, Meltzer C, COVID-19 Task Force. *RSNA COVID-19 Task Force: Best Practices for Radiology Departments during COVID-19*. (2020). Available online at: https://www.rsna.org/-/media/Files/RSNA/Covid-19/RSNA-COVID-19-bestpractices.ashx?la=en&hash=58700DDDEDB3E5A9C8EDE80BE534B4ABB10291B7
5. Mossa-Basha M, Linnau KF, Sahani DV. Radiology Department preparedness in the coronavirus disease 2019 (COVID-19) postshutdown environment. *J Am Coll Radiol.* (2020) 17:890–93. doi: 10.1016/j.jacr.2020.05.017
6. Wong ASK, Ooi CC, Leow MQH, Kiew YS, Yeo KCW, Tan SG, et al. Adapting lessons from SARS for the COVID-19 pandemic-perspectives from radiology nursing in Singapore. *J Radiol Nurs.* (2020) 39:164–7. doi: 10.1016/j.jradnu.2020.06.008
7. Myers L, Balakrishnan S, Reddy S, Gholamrezanezhad A. Coronavirus outbreak: is radiology ready? Mass casualty incident planning. *J Am Coll Radiol.* (2020) 17:724–9. doi: 10.1016/j.jacr.2020.03.025
8. Schnal MD, Meltzer CC, Oleaga L, Soo Tan B, Mahoney MC, Mossa-Basha M, et al. Crisis leadership during COVID-19. *RSNA Webinar.* (2020). Available online at: https://www.youtube.com/watch?v=cP-IIHRD5BU (accessed July 13, 2020).
9. Iglesias B, Maiques JM, Martinez C, Rovira M, Valdés P. Radiology in the era of Covid-19 infection. *SERAM Webinars.* (2020). Available online at: https://www.seram.es/index.php/seram-rss/1490-tercer-webinar-seram-radiologia-en-la-era-de-la-infeccion-covid19 (accessed May 28, 2020).
10. Tay KH, Ooi CC, Mahmood MIB, Aw LP, Chan LP, Ng DCE, et al. Reconfiguring the radiology leadership team for crisis management during the COVID-19 pandemic in a large tertiary hospital in Singapore. *Eur Radiol.* (2020) 11:1-7. doi: 10.1007/s00330-020-07116-w
11. Albano D, Bruno A, Bruno F, Calandri M, Caruso D, Clemente A, et al. Impact of coronavirus disease 2019 (COVID-19) emergency on Italian radiologists: a national survey. *Eur Radiol.* (2020) 30:6635–44. doi: 10.1007/s00330-020-07046-7
12. Davenport MS, Bruno MA, Iyer RS, Johnson AM, Herrera R, Nicola GN, et al. ACR statement on safe resumption of routine radiology care during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Radiol.* (2020) 17:839–44. doi: 10.1016/j.jacr.2020.05.001
13. Valdés P, Rovira A, Guerrero J, Morales A, Rovira M, Martinez C. *The Radiology From the Onset of COVID-19 Infection. SERAM Guidelines.* (2020). Available online at: https://seram.es/images/site/Futuro_Radiologia_COVID_SERAM_2.pdf
14. Prosch H, Ginsberg M, Odink AE. *Radiology Fighting COVID-19 | Maintaining Quality Imaging - Developing Guidelines and Protocols in Times of Crisis*. ESR Connect (2020). Available online at: https://vimeo.com/415429281
15. Valdés P, Rovira A, Guerrero J, Morales A, Rovira M, Martinez C. *Proposals for the Citation of Radiology Studies in the post-COVID-19 era. SERAM Guidelines.* (2020). Available online at: https://seram.es/index.php/informacion-coronavirus (accessed March 21, 2020).
16. Vagal A, Mahoney M, Allen B, Kapur S, Udstuen G, Wang L, et al. Rescheduling nonurgent care in radiology: implementation during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Radiol.* (2020) 17:882–9. doi: 10.1016/j.jacr.2020.05.010
17. Madhuripan N, Cheung HMC, Alicia Cheong LH, Jawahar A, Willis MH, Larson DB. Variables influencing radiology volume recovery during the next phase of the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Radiol.* (2020) 17:855–64. doi: 10.1016/j.jacr.2020.05.026
18. Parikh KD, Ramaiya NH, Kikano EG, Tirumani SH, Pandya H, Stovicek B, et al. COVID-19 pandemic impact on decreased imaging utilization: a single institutional experience. *Acad Radiol.* (2020) 27:1204–13. doi: 10.1016/j.acra.2020.06.024
19. Goldberg MF, Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular disease in COVID-19. *Am J Neuroradiol.* (2020) 41:1170–72. doi: 10.3174/ajnr.A6588
20. Qureshi AI, French BR, Siddiq F, Arora NA, Nattanmai P, Gomez CR. COVID-19 screening with chest CT in acute stroke imaging: a clinical decision model. *J Neuroimaging.* (2020) 30:617–24. doi: 10.1111/jon.12746
21. Rodríguez-Pardo J, Fuentes B, Alonso de Leciñana M, Campollo J, Calleja Castaño P, Carneado Ruiz J, et al. Acute stroke care during the COVID-19 pandemic. Ictus Madrid Program recommendations [Atención al ictus agudo durante la pandemia por COVID-19. Recomendaciones Plan Ictus Madrid]. *Neurología.* (2020) 35:258–63. doi: 10.1016/j.nrl.2020.04.008
22. Sim WY, Chen RC, Aw LP, Abu Bakar R, Tan CC, Heng AL, et al. How to safely and sustainably reorganise a large general radiography

service facing the COVID-19 pandemic. *Radiography*. (2020) 26:e303–11. doi: 10.1016/j.radi.2020.05.001
23. Ding J, Fu H, Liu Y, Gao J, Li Z, Zhao X, et al. Prevention and control measures in radiology department for COVID-19. *Eur Radiol*. (2020) 30:3603–8. doi: 10.1007/s00330-020-06850-5
24. Filippi CG, Gerevini S, Yao ZW, Shatzkes D, and Lim T. COVID-19 neuroimaging in real life: an international perspective from the WFNRS. *In Webinar From The World Federation of Neuroradiological Societies*. (2020). Available online at: https://www.youtube.com/watch?v=T2CJ1VID1RY&feature=youtu.be (accessed May 15, 2020).
25. Tay KH, Yee J, Rossi S. COVID-19 - radiology surge and second surge preparedness-part 1. *RSNA Webinar*. (2020). Available online at: https://www.youtube.com/watch?v=hXBdkjcg-4w&feature=youtu.be
26. Chen RC, Cheng LT, Liang Lim JL, Gogna A, Ng DCE, Yi Teo LZ, et al. Touch me not: safe distancing in radiology during coronavirus disease 2019 (COVID-19). *J Am Coll Radiol*. (2020) 17:739–42. doi: 10.1016/j.jacr.2020.04.019
27. ACR. *ACR Guidance on COVID-19 and MR Use*. Available online at: https://www.acr.org/Clinical-Resources/Radiology-Safety/MR-Safety/COVID-19-and-MR-Use
28. Kooraki S, Hosseiny M, Raman SS, Myers L, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19) precautions: what the MRI suite should know. *J Am Coll Radiol*. (2020) 17:830. doi: 10.1016/j.jacr.2020.05.018
29. Cheng LT, Heilbrun M, Sahani D. Radiology surge and second surge preparedness (Part 2). *RSNA Webinar*. (2020). Available online at: https://www.youtube.com/watch?v=IcHvxr9N_5w&t=1329s (accessed June 22, 2020).
30. D'Anna G, D'Arco F, Van Goethem J. Virtual meetings: a temporary choice or an effective opportunity for the future? *Neuroradiology*. (2020) 62:769–70. doi: 10.1007/s00234-020-02461-5
31. Tridandapani S, Holl G, Canon CL. Rapid deployment of home PACS workstations to enable social distancing in the coronavirus disease (COVID-19) *Era. Am J Roentgenol*. (2020) 20:1–3. doi: 10.2214/AJR.20.23495
32. Dick EA, Raithatha A, Musker L, Redhead J, Mehta A, Amiras D. Remote reporting in the COVID-19 era: from pilot study to practice. *Clin Radiol*. (2020) 75:710.e5-8. doi: 10.1016/j.crad.2020.06.016
33. Martín-Noguerol T, Lopez-Ortega R, Ros PR, Luna A. Teleworking beyond teleradiology: managing radiology departments during the COVID-19 outbreak. *Eur Radiol*. (2020) 2:1-4. doi: 10.1007/s00330-020-07205-w
34. Mossa-Basha M, Azadi J, Klein J, Menias C, Filippi C, Tan BS, et al. RSNA COVID-19 *Task Force: Post-COVID Surge Preparedness*. (2020). Available online at: https://www.rsna.org/-/media/Files/RSNA/covid-19/RSNA-COVID-19-PostSurgePreparedness.pd (accessed May 06, 2020).
35. Azam SA, Myers L, Fields BKK, Demirjian NL, Patel D, Roberge E, et al. Coronavirus disease 2019 (COVID-19) pandemic: review of guidelines for resuming non-urgent imaging procedures in radiology during Phase II. *Clin Imaging*. (2020) 67:30–36. doi: 10.1016/j.clinimag.2020.05.032
36. Vagal A, Mahoney M, Anderson JL, Allen B, Hudepohl J, Chadalavada S, et al. Recover wisely from COVID-19: responsible resumption of nonurgent radiology services. *Acad Radiol*. (2020) 27:1343–52. doi: 10.1016/j.acra.2020.08.002
37. Moriarity AK, Friedberg E, Pyatt RS Jr., Everett C, McAdams C. What might your practice look like post-peak COVID-19? *J Am Coll Radiol*. (2020) 17:1053–5. doi: 10.1016/j.jacr.2020.06.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 16 December 2020
doi: 10.3389/fneur.2020.616550

Effects of COVID-19 Lockdown on Movement Disorders Patients With Deep Brain Stimulation: A Multicenter Survey

Carla Piano[1], Francesco Bove[1,2], Tommaso Tufo[3], Isabella Imbimbo[1,4], Danilo Genovese[1,2], Alessandro Stefani[5], Massimo Marano[6], Antonella Peppe[7], Livia Brusa[8], Rocco Cerroni[5], Francesco Motolese[6], Enrico Di Stasio[9,10], Marianna Mazza[11], Antonio Daniele[1,2], Alessandro Olivi[2,3], Paolo Calabresi[1,2], Anna Rita Bentivoglio[1,2] and Lazio DBS Study Group*

[1] Neurology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [2] Department of Neurosciences, Università Cattolica del Sacro Cuore, Rome, Italy, [3] Neurosurgery Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [4] Fondazione Don Carlo Gnocchi Onlus, Milan, Italy, [5] Department of System Medicine, Unità Operativa Semplice Dipartimentale (UOSD) Parkinson, University of Rome Tor Vergata, Rome, Italy, [6] Neurology, Neurophysiology and Neurobiology Unit, Department of Medicine, Università Campus Bio-Medico di Roma, Rome, Italy, [7] IRCCS Santa Lucia Foundation, Rome, Italy, [8] Neurology Unit, S. Eugenio Hospital, Rome, Italy, [9] Unit of Chemistry, Biochemistry and Clinical Molecular Biology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [10] Institute of Biochemistry and Clinical Biochemistry, Università Cattolica del Sacro Cuore, Rome, Italy, [11] Department of Geriatrics, Neuroscience and Orthopedics, Institute of Psychiatry and Psychology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu,
Hospital Clínico San Carlos, Spain

Reviewed by:
Pedro Chana-Cuevas,
University of Santiago, Chile
Mariana H. G. Monje,
Centro Integral en Neurociencias A.C.
HM CINAC, Spain

***Correspondence:**
Francesco Bove
francescobove86@gmail.com

Specialty section:
This article was submitted to
Movement Disorders,
a section of the journal
Frontiers in Neurology

Received: 12 October 2020
Accepted: 16 November 2020
Published: 16 December 2020

Citation:
Piano C, Bove F, Tufo T, Imbimbo I, Genovese D, Stefani A, Marano M, Peppe A, Brusa L, Cerroni R, Motolese F, Di Stasio E, Mazza M, Daniele A, Olivi A, Calabresi P, Bentivoglio AR and Lazio DBS Study Group (2020) Effects of COVID-19 Lockdown on Movement Disorders Patients With Deep Brain Stimulation: A Multicenter Survey. Front. Neurol. 11:616550. doi: 10.3389/fneur.2020.616550

Background: The containment measures taken by Italian government authorities during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic caused the interruption of neurological activities of outpatient clinics. Vulnerable patients, as Parkinson's disease (PD) and dystonic patients with deep brain stimulation (DBS), may have an increased risk of chronic stress related to social restriction measures and may show a potential worsening of motor and psychiatric symptoms.

Methods: This cross-sectional multicenter study was carried out during the SARS-CoV-2 pandemic and was based on a structured survey administered during a telephone call. The questionnaire was designed to gather motor and/or psychiatric effects of the lockdown and coronavirus disease 2019 (COVID-19) epidemiologic information in PD and dystonic patients with a functioning DBS implant.

Results: One hundred four patients were included in the study, 90 affected by PD and 14 by dystonia. Forty-nine patients reported a subjective perception of worsening of global neurological symptoms (motor and/or psychiatric) related to the containment measures. In the multivariate analysis, having problems with the DBS device was the only independent predictor of motor worsening [odds ratio (OR) = 3.10 (1.22–7.91), $p = 0.018$]. Independent predictors of psychiatric worsening were instrumental activities of daily living (IADL) score [OR = 0.78 (0.64–0.95), $p = 0.012$] and problems with DBS [OR = 5.69 (1.95–16.62), $p = 0.001$]. Only one patient underwent nasopharyngeal swabs, both negative, and no patient received a diagnosis of COVID-19.

Conclusions: Lockdown restriction measures were associated with subjective worsening of motor and psychiatric symptoms in PD and dystonic patients treated with DBS, and they may have exacerbated the burden of neurological disease and increased the chronic stress related to the DBS management.

Keywords: COVID-19, SARS-CoV-2, deep brain stimulation, Parkinson's disease, dystonia

INTRODUCTION

In early 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread worldwide, becoming a pandemic. Coronavirus disease 2019 (COVID-19) commonly presents with fever, cough, and dyspnea; the most severe complication of the infection is the acute respiratory distress syndrome (1). Many government authorities took emergency containment measures to reduce viral transmission (2). In Italy, according to Prime Minister Decree of March 11, 2020, the containment measures recommended a reduction of routine hospital activities: activities of outpatient clinics were stopped, and admittance of patients affected by neurological disorders was allowed only for emergency conditions. Elderly individuals with preexisting comorbidities, including movement disorders, are fragile patients due to their higher risk of infections and poor outcome of disease management (3). Deep brain stimulation (DBS) is a well-established second-level treatment for patients with severe Parkinson's disease (PD) and dystonia who show poor response to pharmacological treatment (4). These patients are routinely monitored with close follow-up, given the need for periodic adjustments of stimulation parameters to optimize motor control and for periodic checks of implantable pulse generator (IPG) functionality and battery status in order to reduce the risk of device-related complications (5, 6). In addition, PD and dystonic patients treated with DBS often need a close follow-up of possible psychiatric symptoms (depression, anxiety, apathy, impulse control disorders, psychosis, disorders of sleep, and wakefulness) (7). For the aforementioned reasons, patients with movement disorders are exposed to an increased risk of chronic stress related to social restriction measures and may show a potential worsening of motor and psychiatric symptoms (8–10). Aim of the present study was to analyze the effects of the lockdown on this vulnerable category of patients affected by PD and dystonia treated with DBS and, secondarily, to investigate the prevalence of COVID-19 suggestive symptoms in this population.

PATIENTS AND METHODS

This cross-sectional multicenter study was carried out during the SARS-CoV-2 pandemic and was promoted by the Neurology Clinic of the Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome (Italy), in collaboration with other neurology clinics based in Lazio region with good expertise on the management of DBS for movement disorders.

Study Population

Inclusion Criteria

PD and dystonic patients who received a DBS implant, which was functioning during the COVID-19 lockdown, and followed in the DBS centers of Lazio region were asked to participate in a telephone survey. Patients were included regardless of the DBS target, the hospital, and the year in which implantation of the neurostimulator was carried out.

Exclusion Criteria

Patients were excluded if they were unable to provide informed and valid consent at the time of the interview, if they show cognitive decline, and if they did not speak Italian fluently.

Survey Design and Testing

The study was based on a structured survey administered during a telephone call carried out as part of the close follow-up scheduled for the included patients. Surveys started on April 28, 2020, and ended on May 12, 2020. A questionnaire was employed, aimed at gathering the following data:

- demographic and clinical data related to PD and dystonia (age, sex, age at disease onset, disease duration, presence of psychiatric symptoms prior to the lockdown, preexisting hyposmia, PD phenotype, current treatment of the neurological disorder)
- information about DBS (target, years from the DBS surgery)
- assumption of medications potentially interfering with SARS-CoV-2 infection
- concomitant diseases and disability measures [activities of daily living (ADL) and instrumental activities of daily living (IADL) scales (11, 12), Hoehn and Yahr (H&Y) scale for PD patients (13), Clinical Global Impression (CGI) Severity scale (14)]
- COVID-19-related questions [including a history of COVID-19-suggestive symptoms in the last 4 months (fever, cough, dyspnea, diarrhea, abdominal pain, pharyngodynia, worsening of hyposmia, hearing loss) and additional information related to SARS-CoV-2 pandemic (testing by nasopharyngeal swabs, COVID-19 diagnosis, contact with COVID-19+ subjects, presence in endemic areas for COVID-19, presence in residential care home, respect of social restriction measures according to Prime Minister Decree of March 11, 2020, flu vaccination)]
- effects of the lockdown (all of the following were yes/no answer questions) [discontinuation of outpatient neurological visits or physiotherapy (motor physical therapy), difficulties in finding medications, need of urgent outpatient neurological visit, difficulties in the management of the DBS device (rechargeable

systems and/or patients with handheld controller to turn the DBS system on and off), feeling of insecurity about the DBS device, worsening of the relationship with own body, subjective perception of worsening of global neurological symptoms (motor and/or psychiatric), sleep disorders, depression, panic attacks, persecutory delusions, visual hallucinations, suicidal ideation, impulsive–compulsive behaviors, increased consumption of coffee and tea]
- changes on CGI Improvement scale (14) related to the lockdown period

For patients who complained one or both "difficulties in the management of the DBS device" and "feeling of insecurity about the DBS device," the cumulative variable "problems with the DBS device" was considered.

The variables related to the effects of the lockdown were assessed to detect emergent symptoms and/or changes of preexisting symptoms after March 11, 2020.

Statistical Analysis

All statistical analyses were carried out using the Statistical Package for Social Science (SPSS) program, version 25.0 (IBM Co., Armonk, NY). Data were analyzed for normality of distribution using the Kolmogorov–Smirnov test of normality and were expressed as mean [±standard deviation (SD)] for continuous variables or as frequencies (n, %) for categorical variables according to a neurological diagnosis. The Mann–Whitney rank sum test was used to compare continuous variables between diagnostic subgroups (PD and dystonia) and between patients with or without subjective perception of worsening of neurological symptoms. The χ^2 test or Fisher's exact test was used for categorical variables. Phi coefficients were calculated to estimate correlation strengths between motor/psychiatric worsening and the other binomial variables evaluating the effects of the lockdown. Finally, multivariate binary logistic analysis was performed to evaluate the relationship between the worsening of motor or psychiatric symptoms and clinical findings. The coefficients obtained from the logistic regression were expressed in terms of odds ratio (OR) with 95% confidence intervals. All statistical tests were two-tailed; statistical significance was defined as p value < 0.05, and the effect size was also reported.

Standard Protocol Approvals, Registration, and Patient Consent

The study and the survey questions were reviewed and approved by local ethical committee. Because of the biological risks related to the pandemic, after receiving a copy of written informed consent by mail or fax, patients were asked to carefully read, sign, and send it by mail or fax to the referral hospital.

Data Availability

Anonymized data will be shared with qualified external researchers after approval of their requests.

RESULTS

One hundred four patients treated with DBS were asked to participate in the survey. Since all agreed to participate, met the inclusion criteria, and no one had exclusion criteria, all 104 patients were included in the study. Ninety patients were affected by PD and 14 patients by dystonia (including 10 patients with idiopathic dystonia and four patients with secondary dystonia). In the total sample, the male/female ratio was 64/40, the mean age was 61 years (SD ±12), and the mean disease duration was 19 years (SD ±8). All dystonic patients underwent globus pallidus internus (GPi) DBS, while the DBS target was different among PD patients: 85 patients were implanted in the subthalamic nucleus (STN), three patients in the GPi, and two patients in the thalamic ventral intermediate nucleus (Vim).

For each diagnostic group, demographic and disease clinical data, disability scales, concomitant medical conditions, and neurological medications are reported in **Table 1**. When the subgroups of PD and dystonic patients were compared for demographic and disease clinical features, significant differences were found for age (62 ± 10 vs. 53 ± 16 years, $p = 0.038$, effect size = 0.82–large), age at disease onset (44 ± 9 vs. 29 ± 19 years, $p = 0.007$, effect size = 1.39–large), disease duration (18 ± 7 vs. 24 ± 10 years, $p = 0.020$, effect size = 0.81–large), scores on ADL (4.8 ± 1.8 vs. 5.9 ± 0.5, $p = 0.012$, effect size = 0.65–medium), IADL (4.4 ± 3.0 vs. 7.1 ± 2.1, $p = 0.001$, effect size = 0.93–large), and CGI Severity scale (4.0 ± 1.3 vs. 2.9 ± 1.6, $p = 0.016$, effect size = 0.82–large).

Coronavirus Disease 2019-Related Questions

Distribution of symptoms suggestive of COVID-19 in the last 4 months, epidemiologic data, and medications potentially interfering with the SARS-CoV-2 infection are reported in **Table 2**. Twenty-six patients reported one or more symptoms suggestive of COVID-19, while only five of them referred three or more of these symptoms. The most frequent symptom was cough, reported by 17 patients. Only one patient underwent (twice) nasopharyngeal swabs, both negative, and no patient received a diagnosis of COVID-19. In our sample, there was no correlation between symptoms suggestive of SARS-CoV-2 infection and assumption of angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), or immunosuppressant therapy.

No significant differences were found between the two diagnostic subgroups (PD and dystonia) as to COVID-19-suggestive symptoms or additional information related to SARS-CoV-2 pandemic.

Effects of the Lockdown on Disease Burden

Information related to the impact of the lockdown on disease burden is reported in **Table 3**. Forty-nine patients out of 104 (47%) reported a subjective perception of worsening of global neurological symptoms related to the containment measures: 20 patients (19%) reported a worsening of motor symptoms; five patients (5%), a worsening of psychiatric symptoms; 24 patients

TABLE 1 | Demographic and disease clinical data, disability scales, concomitant medical conditions, and specific neurological medications for each diagnostic group.

	PD (*n* = 90)	Dystonia (*n* = 14)	Total (*n* = 104)
Demographic features			
Age (years)	62 ± 10	53 ± 16	61 ± 12
Male, *n* (%)	58 (64%)	6 (43%)	64 (62%)
Age at disease onset (years)	44 ± 9	29 ± 19	42 ± 12
Disease duration (years)	18 ± 7	24 ± 10	19 ± 8
Information about DBS			
DBS target (STN/GPi/Vim), *n* (%)	85/3/2 (95%/3%/2%)	0/14/0 (0%/100%/0%)	85/17/2 (82%/16%/2%)
Years from DBS surgery	7 ± 6	9 ± 7	7 ± 6
Disease clinical features			
Psychiatric symptoms, *n* (%)	58 (64%)	6 (43%)	64 (62%)
Hyposmia, *n* (%)	66 (73%)	1 (7%)	67 (64%)
Rigid-akinetic phenotype*, *n* (%)	46 (52%)	–	–
Tremor-dominant phenotype*, *n* (%)	23 (26%)	–	–
Mixed phenotype*, *n* (%)	20 (22%)	–	–
Disability scales			
ADL	4.8 ± 1.8	5.9 ± 0.5	4.9 ± 1.7
IADL	4.4 ± 3.0	7.1 ± 2.1	4.8 ± 3.0
H&Y stage	3.1 ± 0.7	–	–
CGI Severity scale	4.0 ± 1.3	2.9 ± 1.6	3.9 ± 1.4
Concomitant medical conditions			
Hypertension, *n* (%)	18 (20%)	2 (14%)	20 (19%)
Heart diseases, *n* (%)	8 (9%)	0	8 (8%)
COPD, *n* (%)	5 (6%)	0	5 (5%)
Diabetes, *n* (%)	2 (2%)	1 (7%)	3 (3%)
Cancer, *n* (%)	6 (7%)	0	6 (6%)
Chronic kidney disease, *n* (%)	2 (2%)	0	2 (2%)
Obesity, *n* (%)	13 (14%)	1 (7%)	14 (13%)
Smoke, *n* (%)	30 (35%)	5 (38%)	35 (34%)
Neurological medications			
Levodopa, *n* (%)	84 (93%)	0	84 (78%)
MAOIs, *n* (%)	64 (71%)	0	64 (59%)
COMTIs, *n* (%)	36 (40%)	0	36 (35%)
Dopamine agonists, *n* (%)	42 (47%)	0	42 (40%)
Amantadine, *n* (%)	18 (20%)	0	18 (17%)
Anticholinergics, *n* (%)	4 (4%)	3 (21%)	7 (7%)
BoNT *n* (%)	1 (1%)	2 (14%)	3 (3%)
Benzodiazepines, *n* (%)	27 (30%)	5 (36%)	32 (31%)
Antidepressants, *n* (%)	33 (37%)	5 (36%)	38 (37%)
Antipsychotics, *n* (%)	30 (33%)	2 (14%)	32 (31%)
Mood stabilizers, *n* (%)	15 (17%)	3 (21%)	18 (17%)

**The classification in the three different phenotypes of PD (rigid-akinetic, tremor-dominant, and mixed) was made according the tremor/akinetic-rigid (T/AR) ratio (15).*
PD, Parkinson's disease; DBS, deep brain stimulation; STN, subthalamic nucleus; GPi, globus pallidus internus; Vim, ventral intermediate nucleus; ADL, activities of daily living; IADL, instrumental activities of daily living; H&Y, Hoehn and Yahr; COPD, chronic obstructive pulmonary disease; MAOIs, monoamine oxidase inhibitors; COMTIs, catechol-O-methyltransferase inhibitors; BoNT, botulinum neurotoxin.

TABLE 2 | Symptoms suggestive of COVID-19 in the last 4 months, epidemiologic data, and medications potentially interfering with SARS-CoV-2 infection for each diagnostic group.

	PD (*n* = 90)	Dystonia (*n* = 14)	Total (*n* = 104)
Symptoms suggestive of COVID-19			
Fever, *n* (%)	5 (6%)	1 (7%)	6 (6%)
Cough *n* (%)	15 (17%)	2 (14%)	17 (16%)
Dyspnea, *n* (%)	3 (3%)	0	3 (3%)
Diarrhea, *n* (%)	5 (6%)	0	5 (5%)
Abdominal pain, *n* (%)	5 (6%)	0	5 (5%)
Pharyngodynia, *n* (%)	5 (6%)	1 (7%)	6 (6%)
Hyposmia worsening, *n* (%)	2 (2%)	0	2 (2%)
Hearing loss, *n* (%)	2 (2%)	0	2 (2%)
Additional information related to SARS-CoV-2 pandemic			
Testing by nasopharyngeal swabs	1 (1%)	0	1 (1%)
COVID-19 diagnosis	0	0	0
Contact with COVID-19+ subjects	3 (3%)	0	3 (3%)
Presence in endemic areas for COVID-19, *n* (%)	2 (2%)	0	2 (2%)
Presence in residential care home, *n* (%)	1 (1%)	0	1 (1%)
Respect of social restriction measures, *n* (%)	84 (93%)	13 (93%)	97 (93%)
Flu vaccination, *n* (%)	26 (29%)	2 (14%)	28 (27%)
Medications potentially interfering with SARS-CoV-2 infection			
ACE inhibitors, *n* (%)	2 (2%)	2 (14%)	4 (4%)
NSAIDs, *n* (%)	3 (4%)	0	3 (3%)
Immunosuppressants, *n* (%)	3 (4%)	0	3 (3%)

PD, Parkinson's disease; NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(23%), a worsening of both motor and psychiatric symptoms. The overall worsening of the health status was also confirmed by the mean score on the CGI Improvement scale (4.6 ± 1.3). Ninety-two patients (88%) lost the scheduled follow-up visit, 60 (58%) discontinued physiotherapy, and 18 (17%) needed urgent outpatient neurological visit. Eighteen patients (17%) reported difficulties in the management of the DBS device, 26 (25%) reported feeling of insecurity about the DBS device, while 28 (27%) reported a worsening in the relationship with their own body as compared to the period immediately preceding the lockdown. Thirty-four patients (33%) complained of sleep disorders, 39 (37%) depression, 13 (12%) panic attacks, nine (9%) persecutory delusions, 13 (12%) visual hallucinations, and eight (8%) suicidal ideation. Moreover, 21 patients (20%) reported impulsive–compulsive behaviors as increase of shopping online, video game playing, and punding. Thirty-five patients (34%) reported an increased coffee and tea consumption. Among the 21 patients who complained worsening of impulsive–compulsive behaviors, 10 were on treatment with dopamine agonists. The

TABLE 3 | Effects of the lockdown on disease burden for each diagnostic group.

	PD (*n* = 90)	Dystonia (*n* = 14)	Total (*n* = 104)
Effects of the lockdown			
Perception of global neurological worsening, *n* (%)	44 (49%)	5 (36%)	49 (47%)
Perception of motor worsening, *n* (%)	39 (43%)	5 (36%)	44 (42%)
Perception of psychiatric worsening, *n* (%)	25 (28%)	4 (29%)	29 (28%)
Discontinuation of outpatient neurological visits, *n* (%)	78 (87%)	14 (100%)	92 (88%)
Discontinuation of physiotherapy, *n* (%)	55 (61%)	5 (36%)	60 (58%)
Need for urgent outpatient neurological visit, *n* (%)	16 (18%)	2 (14%)	18 (17%)
Difficulties in finding medications, *n* (%)	3 (3%)	0	3 (3%)
Difficulties in the management of the DBS device, *n* (%)	13 (14%)	5 (36%)	18 (17%)
Feeling of insecurity about the DBS device, *n* (%)	21 (23%)	5 (36%)	26 (25%)
Problems with the DBS device, *n* (%)	27 (30%)	7 (50%)	34 (33%)
Worsening of the relationship with own body, *n* (%)	24 (27%)	4 (29%)	28 (27%)
Sleep disorders, *n* (%)	29 (32%)	5 (36%)	34 (33%)
Mood impairment, *n* (%)	38 (42%)	7 (50%)	45 (43%)
Depression, *n* (%)	37 (41%)	2 (14%)	39 (37%)
Panic attacks, *n* (%)	11 (12%)	2 (14%)	13 (12%)
Persecutory delusions, *n* (%)	7 (8%)	2 (14%)	9 (9%)
Visual hallucinations, *n* (%)	12 (13%)	1 (7%)	13 (12%)
Suicidal ideation, *n* (%)	7 (8%)	1 (7%)	8 (8%)
Impulsive–compulsive behaviors, *n* (%)	18 (20%)	3 (21%)	21 (20%)
Shopping online, *n* (%)	4 (4%)	1 (7%)	5 (5%)
Video game playing, *n* (%)	8 (9%)	3 (21%)	11 (11%)
Punding, *n* (%)	8 (9%)	0	8 (8%)
Increased consumption of coffee and tea, *n* (%)	31 (34%)	4 (29%)	35 (34%)
CGI Improvement scale	4.6 ± 1.1	4.2 ± 1.1	4.6 ± 1.3

PD, Parkinson's disease; DBS, deep brain stimulation; CGI, Clinical Global Impression.

proportion of patients on treatment with dopamine agonists was not significantly higher in the subgroup with worsening of impulsive–compulsive behaviors than in the other subgroup of patients (48 vs. 39%, respectively, $p = 0.6$).

No significant differences were found between the two diagnostic subgroups (PD vs. dystonic patients) as to the effects of the lockdown.

Considering the subgroup of 26 patients reporting one or more symptoms suggestive of COVID-19 and comparing this one with the subgroup of patients without symptoms suggestive of COVID-19, no significant differences were found in worsening of motor or psychiatric symptoms.

Significant correlations were found between motor worsening and discontinuation of physiotherapy (phi coefficient = 0.22, $p = 0.024$, effect size = 0.45–small) and between worsening of psychiatric symptoms and chronic benzodiazepine intake (phi coefficient = 0.28, $p = 0.004$, effect size = 0.59–medium). Significant correlations were also observed between both motor and psychiatric worsening and need for urgent outpatient neurological visit (phi coefficient = 0.38, $p < 0.001$, effect size = 1.06–large and phi coefficient = 0.40, $p < 0.001$, effect size = 0.99–large, respectively), difficulties in the management of the DBS device (phi coefficient = 0.23, $p = 0.021$, effect size = 0.60–medium and phi coefficient = 0.23, $p = 0.021$, effect size = 0.60–medium, respectively), feeling of insecurity about the DBS device (phi coefficient = 0.27, $p = 0.006$, effect size = 0.63–medium and phi coefficient = 0.28, $p = 0.004$, effect size = 0.63–medium, respectively), worsening of the relationship with own body (phi coefficient = 0.45, $p < 0.001$, effect size = 1.04–large and phi coefficient = 0.40, $p < 0.001$, effect size = 0.86–large, respectively), sleep disorders (phi coefficient = 0.27, $p = 0.005$, effect size = 0.59–medium and phi coefficient = 0.44, $p < 0.001$, effect size = 0.91–large, respectively), depression (phi coefficient = 0.22, $p = 0.024$, effect size = 0.46–small and phi coefficient = 0.45, $p < 0.001$, effect size = 0.99–large, respectively).

No difference was found on disability scales between the subgroups of patients with and without worsening of motor symptoms. By contrast, the subgroup with worsening of psychiatric symptoms, as compared to the subgroup without psychiatric worsening, presented significantly lower scores on IADL (3.7 ± 3.0 vs. 5.2 ± 2.9, $p = 0.0436$, effect size = 0.50–small) and higher scores on CGI Severity scale (4.5 ± 1.0 vs. 3.7 ± 1.4, $p = 0.0081$, effect size = 0.71–medium).

In the reduced models of multivariate logistic regression analysis, having problems with the DBS device (difficulties in the management of the DBS device or feeling of insecurity about the DBS device) was the only independent predictor of motor worsening [OR = 3.10 (1.22–7.91), $p = 0.018$]. Independent

predictors of psychiatric worsening were IADL score [OR = 0.78 (0.64–0.95), $p = 0.012$] and problems with DBS [OR = 5.69 (1.95–16.62), $p = 0.001$]. Other variables included in the models were age, sex, diagnosis (PD or dystonia), and disease duration (**Table 4**).

TABLE 4 | Multivariate logistic regression models of factors predicting motor and psychiatric worsening during the lockdown.

Variable	OR	95% CI (lower–upper)	*p* value
Motor worsening			
Age	0.99	0.95–1.03	0.6
Male sex	1.51	0.60–3.77	0.4
PD diagnosis	1.40	0.31–6.23	0.7
Disease duration	0.98	0.92–1.04	0.5
IADL	0.95	0.81–1.11	0.5
Problems with DBS	3.10	1.22–7.91	0.018*
Psychiatric worsening			
Age	0.98	0.94–1.03	0.4
Male sex	0.71	0.26–1.95	0.5
PD diagnosis	0.86	0.15–4.97	0.9
Disease duration	1.00	0.93–1.07	0.9
IADL	0.78	0.64–0.95	0.012*
Problems with DBS	5.69	1.95–16.62	0.001*

*$p < 0.05$.
OR, odds ratio; CI, confidence interval; PD, Parkinson's disease; DBS, deep brain stimulation; IADL, instrumental activities daily living.

DISCUSSION

The study, based on a telephone survey administered by neurologists of the DBS movement disorders network in Lazio region, attempted to investigate the consequences of the COVID-19 lockdown on the perception of neurological status (motor and psychiatric symptoms) in patients affected by PD and dystonia treated with DBS.

The demographic and clinical characteristics between the two diagnostic subgroups differed significantly: as compared to PD patients, dystonic patients showed an earlier age at onset, a longer disease duration, and a milder disability.

Although patients with neurological disorders, especially in late disease stages, might be particularly at risk for COVID-19 complications (16–18), in our sample, only ¼ of patients reported symptoms suggestive of SARS-CoV-2 infection. One patient underwent nasopharyngeal swabs, and none received a diagnosis of COVID-19. No patient with symptoms suggestive of COVID-19 needed specific treatments, hospitalization, or respiratory assistance.

Half of the patients in our sample reported a subjective perception of global neurological worsening, which required urgent outpatient neurological visit in 18 cases. A mean CGI Improvement score >4 after the lockdown period confirmed these data. In most patients, worsening of health status seemed to result from discontinuation of neurological visits and physiotherapy, as reported for patients with chronic neurological diseases (19, 20). A significant number of patients presented a worsening of sleep quality, mood, and behavioral disturbances, including onset or worsening of impulsive–compulsive behaviors. As well as worsening of impulsive–compulsive behaviors was not related to treatment with dopamine agonists, it may be a consequence of restriction measures more than an adverse effect induced by dopamine agonists. Indeed, 13 patients reported visual hallucinations during the weeks of social isolation probably induced by a home "hospitalization" phenomenon (21) and exacerbated by sleep disturbances (22).

No significant differences were found between the two diagnostic subgroups (PD vs. dystonic patients) as to the effects of the lockdown. Furthermore, in the multivariate analysis, the specific neurological disease was not an independent predictor of motor or psychiatric worsening during the lockdown.

No significant differences were found in worsening of motor or psychiatric symptoms comparing the subgroup of patients with and without symptoms suggestive of COVID-19.

Significant correlations were found between the subjective perception of motor worsening and discontinuation of physiotherapy treatment, although with a small effect size, and between worsening of psychiatric symptoms and chronic intake of benzodiazepines, with a medium effect size. These findings point out the beneficial effects of physiotherapy in patients with movement disorders and the importance of strategies focused on remote rehabilitation treatment (23). Indeed, a closer psychiatric follow-up would be recommended for patients with chronic use of benzodiazepines, who have an increased risk of developing depressive symptoms (24).

In our study, problems with the DBS device (difficulties in the management of the DBS device and feeling of insecurity about the DBS device) were independent predictors of motor and psychiatric worsening. Such difficulties may be chronic stressful factors that induce depression, anxiety, and insomnia (25). Therefore, DBS played an important role in impairing motor and psychiatric symptoms during the lockdown, independently from the underlying neurological disease. Greater disability (lower IADL score) due to the chronic neurological disease was another independent predictor of psychiatric worsening. On the other hand, demographic factors, disease duration, and neurological diagnosis (PD or dystonia) did not contribute to the global worsening during the lockdown.

These findings suggest that the effects of social restriction measures seriously impact on patients with chronic neurological disease and, in particular, in carriers of a DBS stimulator with greater disability. They also highlight the importance of management programs in the post-epidemic phase with the implementation of telemedicine, remote rehabilitation treatment, and technologies for remote DBS monitoring and programming (9, 26, 27).

Limitations

This study has several limits. First, since data collection was carried out by means of telephone contacts and not by a

face-to-face assessment, the results of the survey might have been influenced by uncontrolled biases. Second, the effects of the lockdown were only assessed by subjective perception and not by validated scales for motor and psychiatric symptoms because of the lack of specific evaluation just before the lockdown. Furthermore, subjective perception of motor and/or psychiatric worsening may be influenced by depressive mood, which had a high prevalence in our sample and is typical of the pandemic situation. In fact, there is a positive correlation between depression and subjective perception of motor and/or psychiatric worsening, thus the patients might have overestimated the real worsening during the pandemic. Another limitation of the study is the small sample size for dystonic patients. Finally, although the multivariate analysis showed that DBS played an independent role in motor and psychiatric worsening, future comparative studies between carriers and noncarriers of DBS should be made.

CONCLUSIONS

Our findings suggest that lockdown restriction measures were associated with subjective worsening of motor and psychiatric symptoms in PD and dystonic patients treated with DBS, and that such measures may have exacerbated the burden of neurological disease and increased the chronic stress related to the DBS management.

Lazio DBS Study Group

Maria Concetta Altavista, Neurology Unit, San Filippo Neri Hospital ASL Roma 1, Roma, Italy

Marco Ciavarro, IRCCS Neuromed, Pozzilli, Italy

Francesca Cortese, Neurology Unit, San Filippo Neri Hospital ASL Roma 1, Roma, Italy

Manuela D'Ercole, Neurosurgery, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Lazzaro Di Biase, Unit of Neurology, Neurophysiology and Neurobiology, Department of Medicine, Campus Bio-Medico of Rome University, Rome, Italy

Maria Francesca De Pandis, Institute for Research and Medical Care IRCCS San Raffaele Cassino, Cassino, Italy

Daniela Di Giuda, Nuclear Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Giovanni Fabbrini, Department of Human Neurosciences, Sapienza University of Rome, Italy; IRCCS Neuromed Institute, Pozzilli, Italy

Alessandro Izzo, Neurosurgery, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Rosa Liperoti, Geriatrics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Giuseppe Marano, Institute of Psychiatry and Psychology, Department of Geriatrics, Neuroscience and Orthopedics, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Nicola Modugno, IRCCS Neuromed, Pozzilli, Italy

Michela Orsini, Clinical Psychology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Michele Paradiso, Department of Neurology, St John the Baptist Hospital, ACISMOM, Rome, Italy

Mariangela Pierantozzi, Neurology Unit, University Hospital "Tor Vergata", Rome, Italy; Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Camilla Rocchi, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Antonio Suppa, Department of Human Neurosciences, Sapienza University of Rome, Italy; IRCCS Neuromed Institute, Pozzilli, Italy

Laura Vacca, University and Institute for Research and Medical Care IRCCS San Raffaele, Rome, Italy

Rita Vadalà, NeuroRadiology, IRCCS Fondazione S Lucia, Rome, Italy

Michela Orsini, Neurology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Fabio Viselli, Department of Neurology, St John the Baptist Hospital, ACISMOM, Rome, Italy.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fondazione Policlinico Universitario A. Gemelli IRCCS ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CP, FB, and ARB designed and conceptualized the study, interpreted the data, and drafted the manuscript. EDS analyzed the data and revised the manuscript for intellectual content. TT, II, DG, AS, MMar, AP, LB, RC, FM, MMaz, AD, AO, PC, and Lazio DBS Study Group collected the data and revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med.* (2020) 180:934–43. doi: 10.1001/jamainternmed.2020.0994
2. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): A literature review. *J Infect Public Health.* (2020) 13:667–73. doi: 10.1016/j.jiph.2020.03.019
3. Clegg A, Young J, Iliffe S, Rikkert MO,Rockwood K. Frailty in elderly people. *Lancet.* (2013) 381:752–62. doi: 10.1016/S0140-6736(12)62167-9

4. Larson PS. Deep brain stimulation for movement disorders. *Neurotherapeutics.* (2014) 11:465–74. doi: 10.1007/s13311-014-0274-1
5. Deuschl G, Herzog J, Kleiner-Fisman G, Kubu C, Lozano AM, Lyons KE, et al. Deep brain stimulation: postoperative issues. *Mov Disord.* (2006) 21 (Suppl. 14):S219–37. doi: 10.1002/mds.20957
6. Holla VV, Neeraja K, Surisetti BK, Prasad S, Kamble N, Srinivas D, et al. Deep brain stimulation battery exhaustion during the COVID-19 pandemic: crisis within a crisis. *J Mov Disord.* (2020) 13:218–22. doi: 10.14802/jmd.20073
7. Lauterbach EC, Freeman A,Vogel RL. Differential DSM-III psychiatric disorder prevalence profiles in dystonia and Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* (2004) 16:29–36. doi: 10.1176/jnp.16.1.29
8. Helmich RC,Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *J Parkinsons Dis.* (2020) 10:351–4. doi: 10.3233/JPD-202038
9. Bhidayasiri R, Virameteekul S, Kim JM, Pal PK,Chung SJ. COVID-19: an early review of its global impact and considerations for Parkinson's disease patient care. *J Mov Disord.* (2020) 13:105–14. doi: 10.14802/jmd.20042
10. Salari M, Zali A, Ashrafi F, Etemadifar M, Sharma S, Hajizadeh N, et al. Incidence of anxiety in Parkinson's disease during coronavirus disease (COVID-19) pandemic. *Mov Disord.* (2020) 35:1095–6. doi: 10.1016/j.yebeh.2020.107442
11. Katz S, Ford AB, Moskowitz RW, Jackson BA,Jaffe MW. Studies of illness in the aged. The index of Adl: A standardized measure of biological and psychosocial function. *JAMA.* (1963) 185:914–9. doi: 10.1001/jama.1963.03060120024016
12. Lawton MP,Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* (1969) 9:179–86. doi: 10.1093/geront/9.3_Part_1.179
13. Hoehn MM,Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427
14. Busner J,Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry.* (2007) 4:28–37.
15. Schiess MC, Zheng H, Soukup VM, Bonnen JG,Nauta HJ. Parkinson's disease subtypes: clinical classification and ventricular cerebrospinal fluid analysis. *Parkinsonism Relat Disord.* (2000) 6:69–76. doi: 10.1016/S1353-8020(99)00051-6
16. Antonini A, Leta V, Teo J,Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. *Mov Disord.* (2020) 35:905–8. doi: 10.1002/mds.28104
17. Schirinzi T, Cerroni R, Di Lazzaro G, Liguori C, Scalise S, Bovenzi R, et al. Self-reported needs of patients with Parkinson's disease during COVID-19 emergency in Italy. *Neurol Sci.* (2020) 41:1373–5. doi: 10.1007/s10072-020-04442-1
18. Fasano A, Cereda E, Barichella M, Cassani E, Ferri V, Zecchinelli AL, et al. COVID-19 in Parkinson's disease patients living in Lombardy, Italy. *Mov Disord.* (2020) 35:1089–93. doi: 10.1002/mds.28176
19. Piano C, Di Stasio E, Primiano G, Janiri D, Luigetti M, Frisullo G, et al. An Italian neurology outpatient clinic facing SARS-CoV-2 pandemic: data from 2,167 patients. *Front Neurol.* (2020) 11:564. doi: 10.3389/fneur.2020.00564
20. Prasad S, Holla VV, Neeraja K, Surisetti BK, Kamble N, Yadav R, et al. Impact of prolonged lockdown due to COVID-19 in patients with Parkinson's disease. *Neurol India.* (2020) 68:792–5. doi: 10.4103/0028-3886.293472
21. Michalska Da Rocha B, Rhodes S, Vasilopoulou E,Hutton P. Loneliness in psychosis: a Meta-analytical review. *Schizophr Bull.* (2018) 44:114–25. doi: 10.1093/schbul/sbx036
22. Sheaves B, Bebbington PE, Goodwin GM, Harrison PJ, Espie CA, Foster RG, et al. Insomnia and hallucinations in the general population: findings from the 2000 and 2007 British Psychiatric Morbidity Surveys. *Psychiatry Res.* (2016) 241:141–6. doi: 10.1016/j.psychres.2016.03.055
23. Leocani L, Diserens K, Moccia M,Caltagirone C. Disability through COVID-19 pandemic: neurorehabilitation cannot wait. *Eur J Neurol.* (2020) 27:e50–1. doi: 10.1111/ene.14320
24. Quello SB, Brady KT,Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. *Sci Pract Perspect.* (2005) 3:13–21. doi: 10.1151/spp053113
25. Fasano A, Antonini A, Katzenschlager R, Krack P, Odin P, Evans AH, et al. Management of advanced therapies in Parkinson's disease patients in times of humanitarian crisis: The COVID-19 experience. *Mov Disord Clin Pract.* (2020) 7:361–72. doi: 10.1002/mdc3.12965
26. Miocinovic S, Ostrem JL, Okun MS, Bullinger KL, Riva-Posse P, Gross RE, et al. Recommendations for deep brain stimulation device management during a pandemic. *J Parkinsons Dis.* (2020) 10:903–10. doi: 10.3233/JPD-202072
27. Zhang J, Hu W, Chen H, Meng F, Li L,Okun MS. Implementation of a novel bluetooth technology for remote deep brain stimulation programming: the pre- and post-COVID-19 Beijing experience. *Mov Disord.* (2020) 35:909–10. doi: 10.1002/mds.28098

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 17 December 2020
doi: 10.3389/fneur.2020.583870

Deep Phenotyping of Headache in Hospitalized COVID-19 Patients *via* Principal Component Analysis

Álvaro Planchuelo-Gómez[1], Javier Trigo[2], Rodrigo de Luis-García[1], Ángel L. Guerrero[2,3,4], Jesús Porta-Etessam[5] and David García-Azorín[2,3]*

[1] Imaging Processing Laboratory, Universidad de Valladolid, Valladolid, Spain, [2] Headache Unit, Department of Neurology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain, [3] Neuroscience Research Unit, Institute for Biomedical Research of Salamanca, Salamanca, Spain, [4] Department of Medicine, Universidad de Valladolid, Valladolid, Spain, [5] Headache Unit, Department of Neurology, Hospital Clínico San Carlos, Madrid, Spain

OPEN ACCESS

Edited by:
Raquel Gil-Gouveia,
Hospital da Luz Lisboa, Portugal

Reviewed by:
Lanfranco Pellesi,
Rigshospitalet, Denmark
Elizabeth Seng,
Yeshiva University, United States

***Correspondence:**
Ángel L. Guerrero
gueneurol@gmail.com
orcid.org/0000-0001-7493-6002

Specialty section:
This article was submitted to Headache Medicine and Facial Pain, a section of the journal Frontiers in Neurology

Received: 15 July 2020
Accepted: 30 November 2020
Published: 17 December 2020

Citation:
Planchuelo-Gómez Á, Trigo J, de Luis-García R, Guerrero ÁL, Porta-Etessam J and García-Azorín D (2020) Deep Phenotyping of Headache in Hospitalized COVID-19 Patients via Principal Component Analysis. Front. Neurol. 11:583870. doi: 10.3389/fneur.2020.583870

Objectives: Headache is a common symptom in systemic infections, and one of the symptoms of the novel coronavirus disease 2019 (COVID-19). The objective of this study was to characterize the phenotype of COVID-19 headache *via* machine learning.

Methods: We performed a cross-sectional study nested in a retrospective cohort. Hospitalized patients with COVID-19 confirmed diagnosis who described headache were included in the study. Generalized Linear Models and Principal Component Analysis were employed to detect associations between intensity and self-reported disability caused by headache, quality and topography of headache, migraine features, COVID-19 symptoms, and results from laboratory tests.

Results: One hundred and six patients were included in the study, with a mean age of 56.6 ± 11.2, including 68 (64.2%) females. Higher intensity and/or disability caused by headache were associated with female sex, fever, abnormal platelet count and leukocytosis, as well as migraine symptoms such as aggravation by physical activity, pulsating pain, and simultaneous photophobia and phonophobia. Pain in the frontal area (83.0% of the sample), pulsating quality, higher intensity of pain, and presence of nausea were related to lymphopenia. Pressing pain and lack of aggravation by routine physical activity were linked to low C-reactive protein and procalcitonin levels.

Conclusion: Intensity and disability caused by headache attributed to COVID-19 are associated with the disease state and symptoms. Two distinct headache phenotypes were observed in relation with COVID-19 status. One phenotype seems to associate migraine symptoms with hematologic and inflammatory biomarkers of severe COVID-19; while another phenotype would link tension-type headache symptoms to milder COVID-19.

Keywords: COVID-19, headache disorders, migraine, tension-type headache, machine learning

INTRODUCTION

Headache is one of the most common symptoms in coronavirus disease 2019 (COVID-19) (1, 2). However, differently to other symptoms, as anosmia or myalgia, the headache phenotype appears to be non-uniform (3). The most reported phenotype is bilateral pain, pulsating or pressing quality in temporoparietal or frontal region, with moderate to severe intensity (4).

The clinical presentation of COVID-19 is linked to its pathophysiology. Interferon gamma type I-III seem related to general systemic symptoms, such as fever and myalgia, among others. The cytokine release, macrophage activation and lymphocyte depletion are related with endothelial dysfunction and micro-thrombosis (5). In addition, the downregulation of type 2 angiotensin II receptors and the upregulation of type 1 angiotensin II receptors causes vasoconstriction and a proinflammatory state (6). The laboratory correlate to COVID-19 pathophysiology is observed by lymphopenia and increased C-reactive protein (CRP), procalcitonin (PCT) and D-dimer, among others (7). In patients with COVID-19 and headache, there was at least one abnormal laboratory value in the first measure, being the most common abnormal increased CRP levels (8).

The objective of this study was to analyze whether the headache phenotype did correlate with the laboratory biomarkers that have been linked to COVID-19 pathophysiology and/or the COVID-19 clinical presentation, by performing an analysis based on machine learning techniques.

MATERIALS AND METHODS

We conducted a cross-sectional study nested in cohort of patients. The Ethics Review Board of Valladolid East health area approved the study (PI: 20-1738).

Participants

The inclusion criteria for participants were: (1) Confirmed COVID-19 diagnosis by real time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay from respiratory tract samples, or by the presence of anti-SARS-CoV-2 IgM + IgA antibodies in patients with clinical symptoms, according to the World Health Organization protocols (9, 10); (2) suffering from headache throughout the course of COVID-19; (3) hospitalization because of COVID-19; (4) agreement to participate; (5) fulfillment of criteria for acute headache attributed to systemic viral infection according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) (11).

The exclusion criteria were: (1) Acute secondary headache with better agreement for a diagnosis different to acute headache attributed to systemic viral infection according to the ICHD-3 (11); (2) death during the hospitalization; (3) previous dementia or cognitive impairment that made difficult a detailed description of the suffered headache; (4) poor medical condition that difficulted the precise description of the headache phenotype; (5) no answer to the invitation to participate in the study; (6) rejection to take part in the study.

All the patients admitted to the Hospital Clínico Universitario de Valladolid (Valladolid, Spain) from March 8th to April 11th, 2020 were screened. The information employed in this study was collected from the primary care electronic digital records, the emergency room records and the hospitalization reports. Every patient was asked about suffering from headache, and those patients who answered with a positive response were invited to take part in the study. Two neurologists with expertise in headache medicine interviewed the patients according to a pre-specified structured interview.

Variables

Six groups of variables related to headache were analyzed as variables of interest: (1) Intensity of the pain (0–10 numeric rating scale; 0: no pain, 10: maximum intensity); (2) disability caused by headache, self-rated by the patient (0–100 numeric rating scale; 0: no disability, 100: complete disability); (3) presence of typical migraine and tension-type headache (TTH) features (categorical variables showing presence of each symptom included in criteria C and D for migraine without aura from the ICHD-3, and ICHD-3 criteria C and D for TTH, analyzing if patients fulfilled the ICHD-3 criteria); (4) laterality (categorical variables indicating unilateral or bilateral pain); (5) topography (categorical variables for presence of pain in diverse areas, e.g., frontal); (6) quality of the pain (e.g., pressing). For the topography and quality of pain, patients were asked to describe the predominant one. The cranial territories or phenotypic characteristics present at least in 20% of the subjects were included, taking into account the number of possible regions, with no consideration of simultaneous pain in more than one region.

As main independent variables, diverse COVID-19 symptoms (categorical variables describing the presence of each different symptom) and results from laboratory tests were evaluated. The COVID-19 symptoms included in this study were arthralgia, chest pain, cough, diarrhea, dyspnea, expectoration, fatigue, fever, headache (100% in this sample), hyposmia or anosmia, lightheadedness, myalgia, nausea, odynophagia, rhinorrhea, skin rash, weakness, and vomiting. We gathered different laboratory parameters on admission and worst values during the stay. These values were represented as numerical variables and categorical variables indicating abnormal levels. Reference values and units are detailed in **Supplementary Table 1**. Other analyzed independent variables were demographic (age and sex), prior medical history (more details in **Supplementary Table 1**), previous history of headache (including a 0–100 rating scale to assess the level of similarity), modified Rankin scale, other symptoms associated with the headache (cranial autonomic symptoms, hypersensitivity to stimuli, vegetative symptoms, and aura), other headache features (duration, pain during sleep, worst experienced headache, aggravation by walking, head or

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; FDR, false discovery rate; GLM, generalized linear model; ICHD-3, The International Classification of Headache Disorders (3rd edition); IL-6, interleukin-6; LDH, lactate dehydrogenase; PCA, principal component analysis; CT, procalcitonin; RT-PCR, real-time reverse-transcriptase-polymerase-chain-reaction; TTH, tension-type headache.

ocular movements, and clinophilia), presence of pneumonia (either diagnosed *via* chest X-ray or computed tomography), and variables related to treatment (employed treatments and resistance to treatment).

Statistical Analysis and Principal Component Analysis

First, univariate analyses were performed. The continuous variables, intensity of pain and disability caused by headache, were analyzed using Generalized Linear Models (GLM) with a Gaussian distribution. The remaining binary variables related to headache were analyzed using GLM with a binomial family, i.e., logistic regression models. Considering the high number of possible binary variables which could be analyzed, only the most frequent topography, quality, and criteria C and D from the ICHD-3 for migraine were examined.

To detect specific patterns between the variables, a Principal Component Analysis (PCA) of mixed data (continuous and categorical) was carried out. For the main continuous variables, different PCA were performed for each group of categorical main variables. In the case of the categorical laboratory tests and COVID-19 symptoms variables, the variables with statistically significant results in the univariate analyses were introduced in the PCA. Furthermore, for the main categorical variables, PCA using the significant continuous results from laboratory tests that were statistically significant in the univariate analyses were carried out on the one hand, and CRP, PCT, lymphocytes, and D-dimer (worst and first values on admission) were analyzed on the other hand. Furthermore, the most frequent characteristics found in this sample (8, 12), i.e., hypersensitivity to stimuli, pressing and intense pain, and pain in the frontal area (which was also bilateral diffuse pain in most cases), were also assessed.

Finally, for the response variables analyzed with univariate GLM, a multivariate model was obtained. Only variables with p-value equal or lower than 0.20 in the univariate analyses and with no or very low amount of missing values (<5%) were considered to be introduced in the multivariate model. The Akaike's Information Criterion (lowest value) was used to obtain the final multivariate GLM in combination with an automatic stepwise (use of forward and backward steps) procedure. To reduce effects of overfitting related to a great number of employed variables, the variable with the highest p-value was removed from the model until the model showed no excessive overfitting effects, i.e., no exaggerated standard error values. A false discovery rate (FDR) procedure was used to correct for multiple comparisons in the multivariate models (13).

A p-value of 0.05 was considered as statistical signification threshold. Complete-case analysis was employed in situations with variables with missing values. There was no previous estimation of sample size because the initial objective of the analysis with the patients was exploratory. R statistical software version 3.5.2 was used for the analysis.

RESULTS

After the examination of inclusion and exclusion criteria, 106 patients were included in the study. The number of hospitalized patients because of COVID-19 with a positive test was 580, and among them, 136 patients described headache. A complete flow diagram is shown in **Supplementary Figure 1**.

The mean age of the sample was 56.6 ± 11.2 years, with 76 patients (71.7%) older than 49, and 68 women (64.2%) participated in the study. Regarding the previous history of headache, 61 patients presented a previous history of headache (57.5%). Among these patients, 28 suffered previously from TTH, 16 from migraine, two from both TTH and migraine, and 15 from other headache (e.g., cervicogenic headache, hypnic headache, and episodic cluster headache). Taking into account that the previous history of the diverse types of headache disorders may be related to the headache phenotype, the results associated with this variable are reported in the following subsections. In the subjects with prior history of headache, the level of similarity to prior headache (0–100 rating scale) was 32.5 ± 29.5 (median = 40, interquartile range = 0–50).

Criterion C for migraine from the ICHD-3 was fulfilled by 55 patients (51.9%), and criterion D by 40 patients (37.7%). Criterion C for TTH from the ICHD-3 was fulfilled by 90 patients (84.9%), and criterion D by 66 patients (62.3%). The most frequent quality of pain was pressing, which was present in 80 patients (75.4%), and the most frequent location was frontal, which was present in 88 patients (83.0%). Both characteristics were analyzed in uni- and multivariate GLM.

PCA and Univariate Models—Continuous Variables

Significant results from univariate models and from PCA for intensity of headache and self-reported disability are detailed in **Supplementary Tables 2**, **3**, respectively, and in the following subsections. Regarding the previous history of headache disorders, we found no significant associations with either intensity of headache or self-reported disability caused by headache. However, we found that lower values of intensity and disability scores were significantly related to higher similarity to prior headache in the univariate models (**Supplementary Table 2**).

COVID-19 Symptoms and Laboratory Tests

The variables that showed statistically significant association in the univariate disability models were lightheadedness and fever, and abnormal platelet values on admission and during hospitalization (qualitative variables), and therefore those variables were included in the PCA analysis. In the univariate models, higher disability score was associated with fever, while lower disability score was associated with lightheadedness.

The PCA showed three groups clearly differentiated, one of them composed by people with fever and lightheadedness, other by people with only fever, and the last group by people with neither fever nor lightheadedness. Regarding laboratory tests, three clearly differentiated patterns of intensity and disability were also observed. The first group exhibited low disability and low intensity of headache, that had abnormal platelet count on admission and during the hospitalization; the second group had higher intensity and disability than the former and normal platelet values on admission, but not during the hospitalization. The last group had the highest intensity and disability and

had a normal platelet count, both on admission and during hospitalization. These PCA results showing the intensity and disability differences between the abnormal and normal levels are depicted in **Figure 1A** and **Supplementary Figure 2**.

With respect to COVID-19 symptoms, people with lightheadedness and fever presented the lowest (negative mean) PCA second component values, and people with only fever exhibited medium values. Higher second PCA component values were associated with higher intensity and with lower disability. The higher disability was observed in the two groups of patients that had fever as COVID-19 symptom. The PCA results showing the intensity and disability differences between patients with and without fever and lightheadedness can be seen in **Figure 1B** and **Supplementary Figure 2**. The group with fever and lightheadedness presented the lowest headache intensity values, and the group with fever but no lightheadedness had the highest intensity values.

Migraine and TTH Symptoms

Fulfillment of criterion C of TTH was significantly associated with lower intensity and disability scores, while migraine symptoms such as pulsating pain, aggravation by routine physical activity, and simultaneous phonophobia or photophobia, were associated with higher intensity and disability scores. The last two positive associations are equivalent to a negative association with the absence of the features (e.g., no aggravation by physical activity), which is in line with lower intensity and disability values in TTH.

The PCA did not reveal clearly differentiated groups based on migraine symptoms, in contrast to the analyses with COVID-19 symptoms and laboratory tests. However, noticeable differences can be observed between people with nausea and/or aggravation caused by routine physical activity, and no unilateral pain. These differences can be appreciated in **Figure 1C** and **Supplementary Figure 3**. Better clustering was found with fulfillment of criteria for migraine and TTH from the ICHD-3 (**Supplementary Figure 4**).

Quality of Pain

Pulsating and stabbing pain were associated with higher values of intensity of headache, while pressing pain was associated with lower values of intensity and disability caused by headache. Although stabbing pain was present in $<$20% of the subjects (15 subjects, 14.2%), it was finally included in the PCA because of the significant association.

In line with the intensity and disability univariate models, people with pressing pain presented different PCA scores in comparison with people with pulsating or stabbing pain, as can be seen in **Figure 1D** and **Supplementary Figure 5**.

Laterality and Topography of Pain

A significant association was found between higher values of disability caused by headache and bilateral diffuse pain. The PCA revealed a clear separation based on frontal pain. Approximately two thirds of the subjects with frontal pain presented bilateral diffuse pain, and one third periocular pain. No clear distinctions were found for temporal pain. The results from this simultaneous analysis comparing intensity and disability between diverse areas are shown in **Figure 1E** and **Supplementary Figure 6**.

Most Frequent Characteristics

Bilateral diffuse pain was the characteristic showing the higher difference in the PCA comparing bilateral diffuse pain, pressing pain and hypersensitivity to stimuli, as can be seen in **Figure 1F** and **Supplementary Figure 7**.

PCA and Univariate Models—Categorical Main Variables

Significant univariate models and PCA results are shown in **Supplementary Tables 4–8**.

Migraine Symptoms

With respect to the univariate models analyzing criteria C and D of migraine from the ICHD-3 and their relationship with laboratory tests, a significant negative association (higher values, lower odds of presenting a phenotype with migraine features) was found with worst levels and levels on admission of lactate dehydrogenase (LDH) and glomerular filtration. There were no higher values of any continuous variable associated with higher odds of presenting headache with migraine features. No significant association was found between criteria C and D of migraine, and previous history of headache. The PCA showed that the first component, which explained higher variance, was weighted mostly by glomerular filtration (**Supplementary Table 5**).

According to the PCA with the CRP and PCT values on admission and worst levels, the symptoms with the highest differences were nausea (lower CRP-values) and aggravation by movement (higher PCT-values), as can be observed in **Figures 2A,B** and **Supplementary Figure 8**. According to the lymphocyte and D-dimer levels, patients with nausea presented lower D-dimer and lymphocyte values on admission and worst levels, and patients with pulsating pain showed lower lymphocyte count, as can be seen in **Figures 3A,B** and **Supplementary Figure 8**.

The PCA analyzing LDH and glomerular filtration (four continuous variables) and migraine symptoms, suggested that patients with headache aggravation by physical activity showed lower PC1 values (weighted mostly by glomerular filtration), as shown in **Supplementary Figure 8**.

Quality of Headache

No significant association was found between quality of headache and continuous results from laboratory tests in the univariate models. The same lack of statistically significant association was also found between pressing pain and previous history of headache. In the PCA using the CRP, PCT, lymphocyte, and D-dimer values, a clear separation was observed in patients with pressing compared to stabbing and pulsating pain based on lower values on admission and worst levels of CRP and PCT, as can be seen in **Figures 2C,D** and **Supplementary Figure 9**. Additionally, pulsating pain was associated with lower lymphocyte count on admission and worst values, as illustrated in **Figures 3C,D** and **Supplementary Figure 9**.

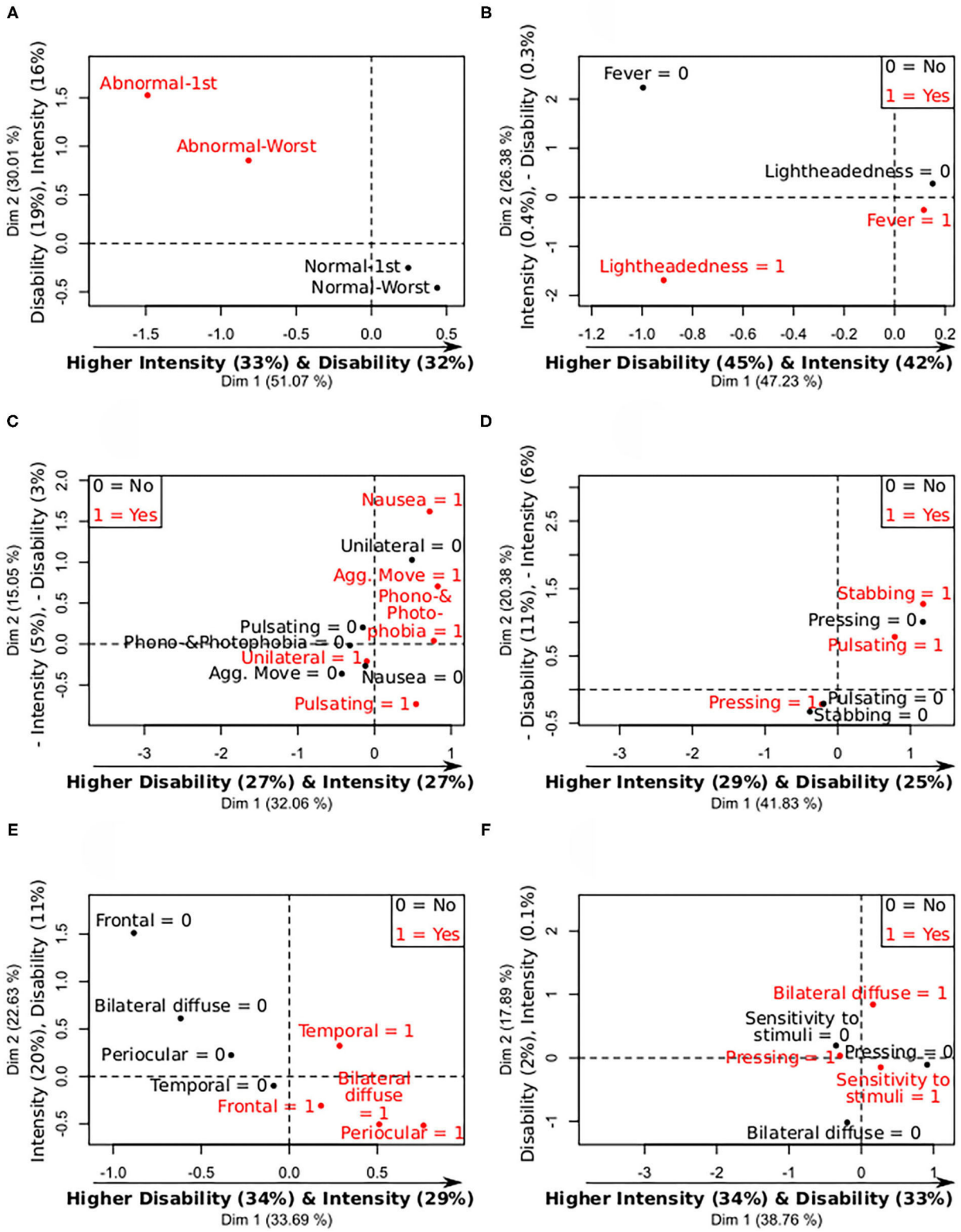


FIGURE 1 | Summary of mix PCA of headache intensity and disability caused by headache (continuous variables), and the analyzed categorical features. X- and Y-axis contain the values of the first and second principal components, and the relative contribution of each continuous variable to the component, remarking in bold the most important relationships between the continuous variables and the components. 0 = no symptom; 1 = present symptom. **(A)** Levels—Platelets intensity and disability. **(B)** Levels—COVID-19 symptoms intensity and disability. **(C)** Levels—Migraine symptoms intensity and disability. **(D)** Levels—Quality of pain intensity and disability. **(E)** Levels—Laterality and topography intensity and disability. **(F)** Levels—Most frequent symptoms intensity and disability.

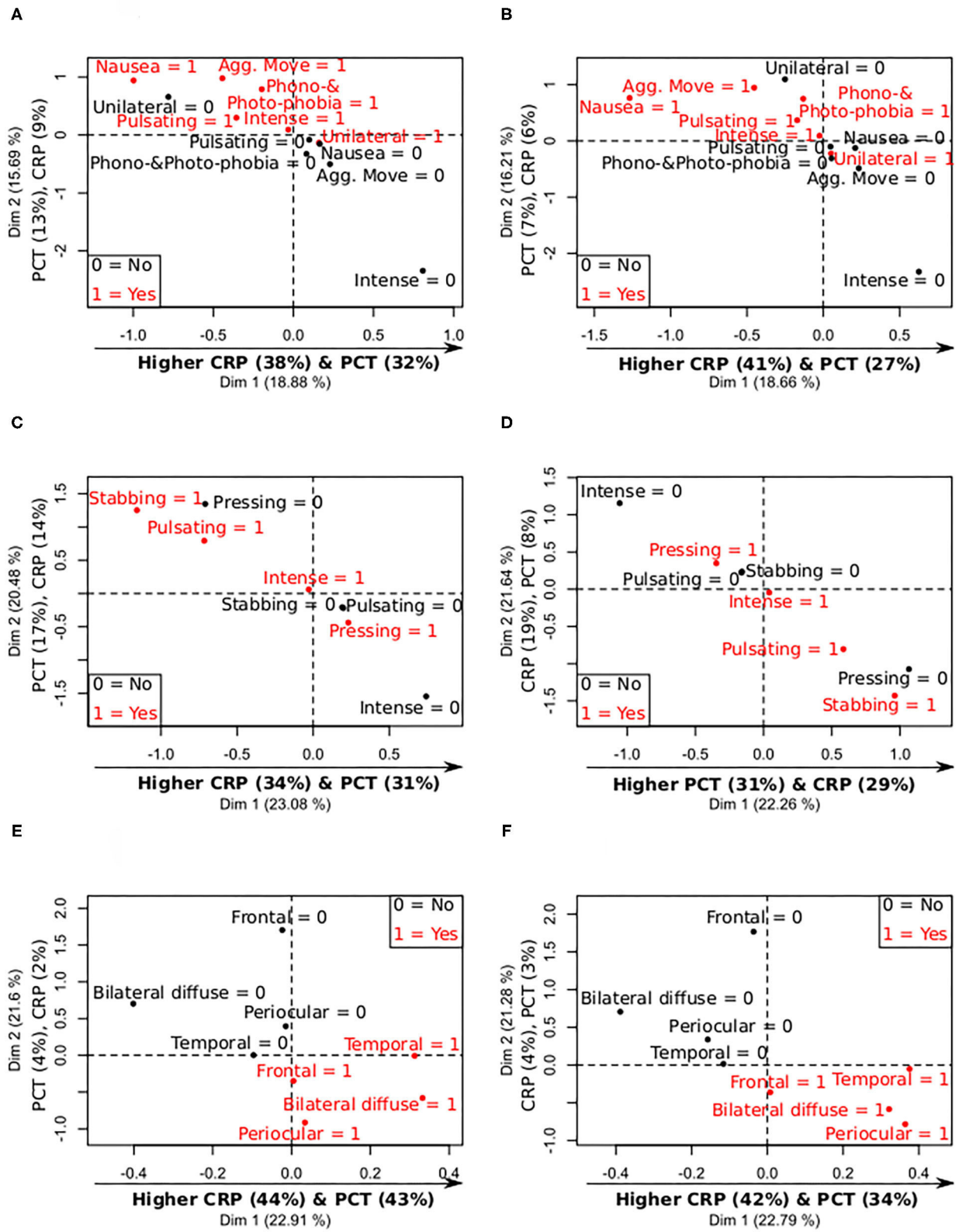


FIGURE 2 | Summary of mix PCA of CRP, PCT, D-dimer, and lymphocytes levels (continuous variables), and the analyzed categorical features, focused on CRP and PCT levels. X- and Y-axis contain the values of the first and second principal components, and the relative contribution of each continuous variable to the component, remarking in bold the most important relationships between the continuous variables and the components. 0 = no symptom; 1 = present symptom. **(A)**

(Continued)

FIGURE 2 | Levels—Migraine symptoms CRP and PCT (admission). **(B)** Levels—Migraine symptoms CRP and PCT (worst values). **(C)** Levels—Quality of pain CRP and PCT (admission). **(D)** Levels—Quality of pain CRP and PCT (worst values). **(E)** Levels—Laterality and topography CRP and PCT (admission). **(F)** Levels—Laterality and topography CRP and PCT (worst values).

Topography of Headache

Lower leukocyte, lymphocyte and platelet levels on admission, and worst platelet levels, were significantly associated with laterality-topography of the pain. The PCA with the previous variables showed differences based on frontal pain and bilateral diffuse pain, which can be seen in **Supplementary Figure 10**, obtaining similar results with respect to results shown in **Supplementary Figure 6**. No significant association was found between pain in the frontal area and previous history of headache.

In the PCA using the CRP, PCT, lymphocyte and D-dimer values, higher CRP and PCT values on admission, and worst values, were clearly differentiated in patients with temporal and bilateral diffuse pain, as shown in **Figures 2E,F** and **Supplementary Figure 11**. Lower lymphocyte count, on admission and worst values, was observed in patients with frontal and bilateral diffuse pain, and lower D-dimer values in patients with temporal pain, as can be seen in **Figures 3E,F** and **Supplementary Figure 11**. In **Figure 3F**, lymphocyte count seems higher in patients with bilateral diffuse pain, but it is worth noting that the second component (**Figure 2F**) is weighted mainly by the lymphocyte count (8% compared to 4–3% of CRP and PCT), and patients with bilateral diffuse pain presented lower PC2 values.

PCA: Most Frequent Characteristics and Laboratory Tests

As mentioned in previous subsections, PCA results showed that bilateral diffuse pain was associated with higher CRP and PCT values on admission and worst levels, and with lower values for pressing pain. Hypersensitivity to stimuli was associated with higher CRP and PCT values, as depicted in **Figures 4A,B** and **Supplementary Figures 12**, **13**. Lower lymphocyte count on admission and worst values was observed in bilateral diffuse pain, as mentioned in previous subsections, which can be also seen in **Figures 4C,D**. No other clear trend was observed.

Multivariate Models

Intensity and Disability

After correcting for multiple comparisons, lower values of intensity of headache were significantly associated with resistance to treatment. Higher intensity values were significantly associated with female sex, aggravation by physical activity, and pulsating or stabbing quality compared to pressing quality. The complete multivariate model is shown in **Table 1**. In this table, coefficients reflect that, for example, people whose headache was aggravated by physical activity, had 2.13 more intensity points (on average) that people with no aggravation.

With respect to the disability caused by headache, lower values were significantly associated with treatment resistant headache, lightheadedness, and abnormal levels of platelets on admission. Higher disability values were significantly associated with female sex, aggravation by physical activity, simultaneous photophobia and phonophobia, fever, expectoration, and abnormal leukocyte values on admission. The complete multivariate model is shown in **Table 1**. The interpretation of the coefficients is the same as for the intensity, noting that the score ranges between 0 and 100. In the case of the leukocyte levels, a value of the coefficient equal to 0.002 means that for each additional 1,000 leukocyte units (range 1,980–16,600 in this sample), the disability score is 2 points higher.

Migraine Symptoms

The multivariate logistic regression model for the migraine symptoms (criterion C from the ICHD-3) showed significantly higher odds associated with periocular pain, progressive worsening of the headache and criterion D of migraine. Lower odds were significantly associated with pressing pain and higher worst LDH levels. The complete model is shown in **Table 2**. In the logistic regression models, the Odds Ratio is employed to interpret the results. Values over 1 indicate a positive association, while values below 1 a negative association. For example, people with pressing pain presented 84% lower odds (Odds Ratio = 0.16) of developing migraine symptoms in comparison with people with no pressing pain. In the case of worst LDH values, the original coefficient from the logistic regression model was equal to −0.009 (Odds Ratio = 0.991); with an increase of 100 LDH units, the coefficient would be −0.9 and the Odds Ratio would be ∼0.40, i.e., for each additional 100 LDH units (range 130–743 in this sample), the probability of developing migraine symptoms is around 60% lower.

Lower odds in the model of criterion D of migraine were related to chest pain, remitting headache, and abnormal ferritin levels. Disability caused by headache, prior history of diabetes, diarrhea, abnormal levels of lymphocytes, and treatment-resistant headache were associated with higher odds of the fulfillment of criterion D of migraine. The complete model is shown in **Table 2**.

Topography (Frontal Region) and Quality of Pain

Higher odds of frontal pain were associated with female sex, bilateral diffuse pain, and abnormal interleukin-6 (IL-6) levels, and lower odds were related to cranial autonomic symptoms, after correcting for multiple comparisons. The complete frontal pain model is shown in **Table 3**.

Lower odds of pressing pain were associated with headache intensity, headache when sleeping (and with consequent waking-up), modified Rankin scale, abnormal PCT levels and clinophilia. Higher odds of pressing pain with diabetes and pathologic chest X-Ray were identified. The complete model is shown in **Table 3**. Anyway, the extremely high and low values represented in **Table 3** indicate overfitting, and Odds Ratios should be interpreted with high caution.

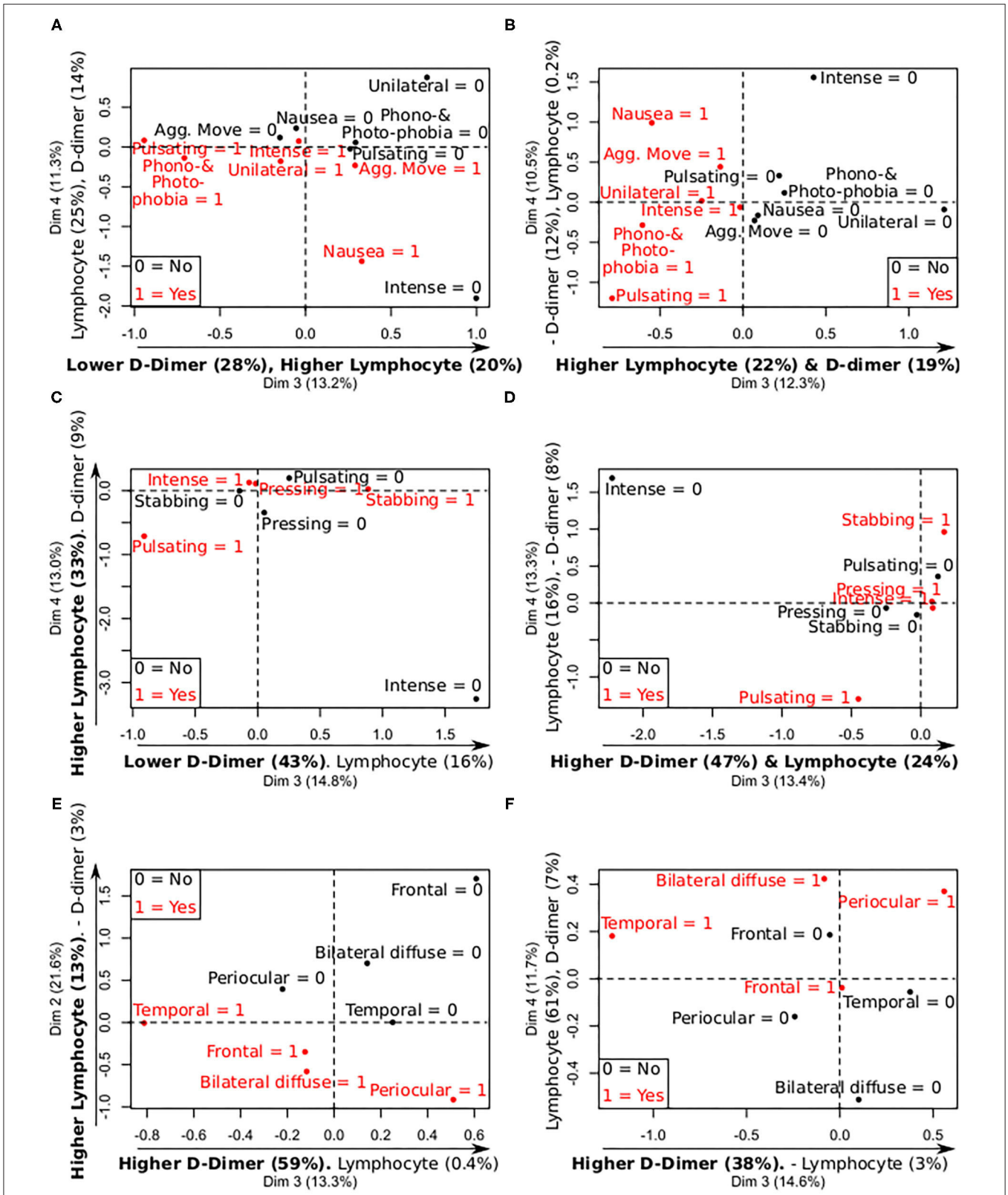


FIGURE 3 | Summary of mix PCA of CRP, PCT, D-dimer, and lymphocytes levels (continuous variables), and the analyzed categorical features, focused on D-dimer and lymphocyte levels. X- and Y-axis contain the values of two principal components, and the relative contribution of each continuous variable to the component,

(Continued)

FIGURE 3 | remarking in bold the most important relationships between the continuous variables and the components. 0 = no symptom; 1 = present symptom. **(A)** Levels—Migraine symptoms D-dimer and lymphocytes (admission). **(B)** Levels—Migraine symptoms D-dimer and lymphocytes (worst values). **(C)** Levels—Quality of pain D-dimer and lymphocytes (admission). **(D)** Levels—Quality of pain D-dimer and lymphocytes (worst values). **(E)** Levels—Laterality and topography D-dimer and lymphocytes (admission). **(F)** Levels—Laterality and topography D-dimer and lymphocytes (worst values).

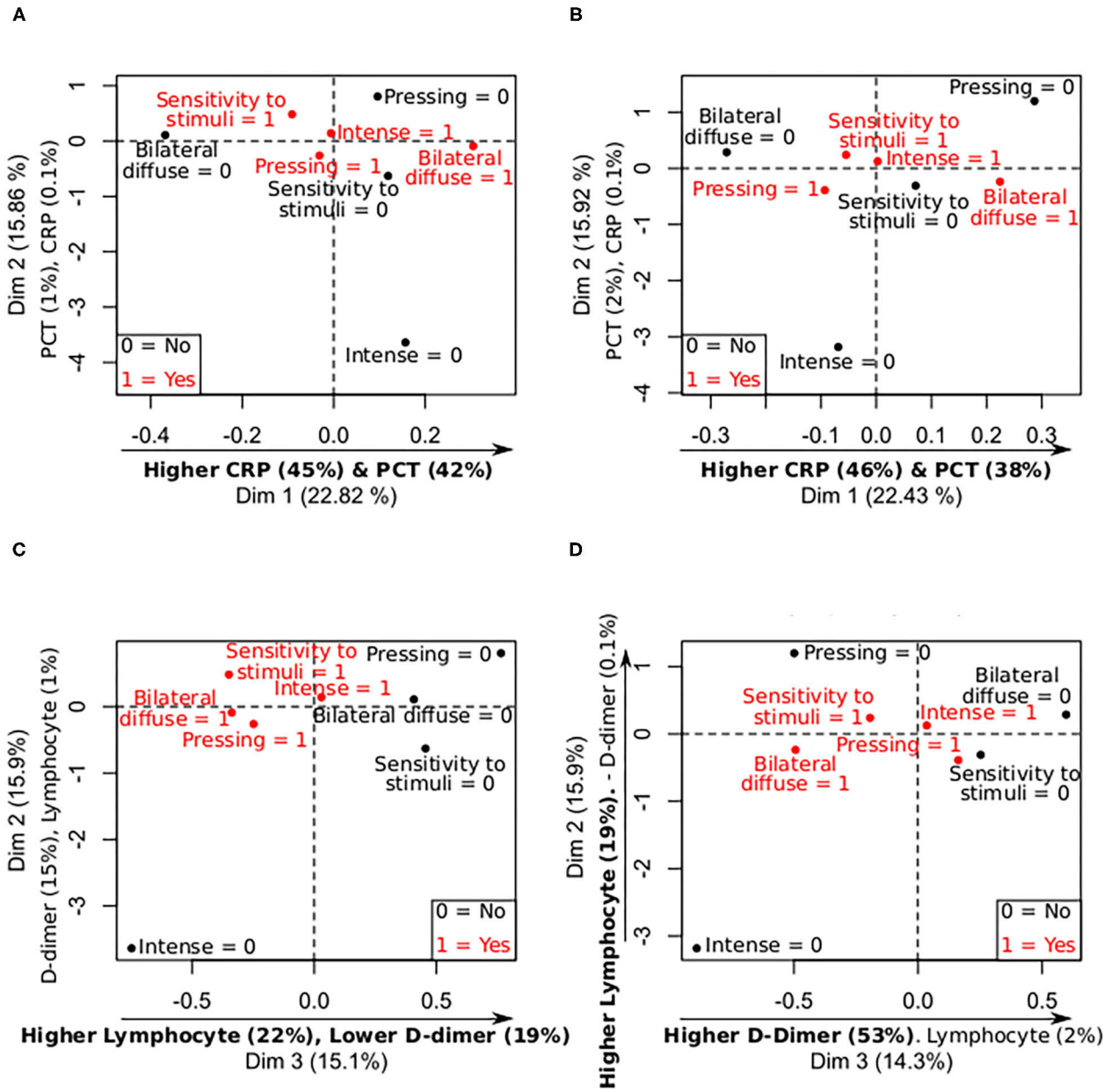


FIGURE 4 | Summary of mix PCA of CRP, PCT, D-dimer, and lymphocytes levels (continuous variables), and most frequent symptoms in the sample (categorical variables). X- and Y-axis contain the values of two principal components, and the relative contribution of each continuous variable to the component, remarking in bold the most important relationships between the continuous variables and the components. 0 = no symptom; 1 = present symptom. **(A)** Levels—Most frequent symptoms CRP and PCT (admission). **(B)** Levels—Most frequent symptoms CRP and PCT (worst values). **(C)** Levels—Most frequent symptoms D-dimer and lymphocytes (admission). **(D)** Levels—Most frequent symptoms D-dimer and lymphocytes (worst values).

DISCUSSION

The results from this study showed that intensity and disability caused by headache attributed to COVID-19 were associated with the disease state and certain symptoms, mainly fever, and two different phenotypes. The first phenotype is the headache with migraine features (specifically pulsating quality and nausea during headache), related to high intensity and

TABLE 1 | Multivariate GLM of the headache intensity in patients hospitalized because of COVID-19.

	Coefficient and 95% CI	Unadjusted *p*-value	Adjusted *p*-value (FDR)
Intensity model			
Independent term	3.70 (1.84, 5.55)	<0.001	0.001
Treatment resistant	−0.74 (−1.29, −0.19)	0.010	0.032
Sex (Female vs. Male)	1.18 (0.65, 1.72)	<0.001	<0.001
Aggravation by physical activity	2.13 (0.47, 3.79)	0.014	0.039
Quality of headache			
Pulsating vs. pressing	2.06 (1.09, 3.03)	<0.001	<0.001
Stabbing vs. pressing	1.60 (0.60, 2.59)	0.002	0.010
Aggravation by head movement	−1.37 (−2.96, 0.23)	0.096	0.11
Lightheadedness	−0.76 (−1.49, −0.03)	0.044	0.076
Abnormal platelets on admission	−0.71 (−1.44, 0.01)	0.058	0.076
High blood pressure comorbidity	−0.63 (−1.18, −0.08)	0.029	0.069
Progressive	0.54 (−0.14, 1.22)	0.12	0.13
Headache as first COVID-19 symptom	0.61 (−0.00, 1.22)	0.054	0.076
Phonophobia and photophobia	0.62 (0.02, 1.23)	0.047	0.076
Expectoration	0.82 (0.07, 1.56)	0.034	0.073
TTH—Criterion C	0.87 (−0.11, 1.85)	0.086	0.10
Pathologic chest X-Ray	1.37 (0.02, 2.73)	0.050	0.076
Disability model			
Independent term	12.36 (−9.53, 34.24)	0.27	0.27
Lightheadedness	−14.17 (−24.81, −3.53)	0.011	0.030
Abnormal platelet count on admission	−12.53 (−22.85, −0.20)	0.020	0.042
Treatment resistant	−9.99 (−17.84, −2.13)	0.015	0.036
Aggravation by physical activity	12.16 (4.26, 20.06)	0.003	0.029
Phonophobia and photophobia	12.78 (3.97, 21.60)	0.006	0.030
Sex (Female vs. Male)	14.03 (5.36, 22.70)	0.002	0.029
Fever	14.65 (2.10, 27.20)	0.025	0.047
Expectoration	14.88 (3.98, 25.79)	0.009	0.030
Leukocyte count on admission	0.0020 (0.0005, 0.0034)	0.010	0.030
Smoking (previous or current)	−10.59 (−23.49, 2.31)	0.11	0.13
Use of Angiotensin-converting-enzyme inhibitors and angiotensin II receptors	−7.66 (−16.29, 0.98)	0.086	0.11
Days from admission to worst lymphocyte count	−0.60 (−1.21, 0.01)	0.056	0.080
Neurological symptoms of headache	8.51 (−2.00, 19.01)	0.12	0.13
Bilateral diffuse pain	8.21 (0.54, 15.88)	0.039	0.060
Quality of headache			
Pulsating vs. pressing	12.93 (1.24, 24.62)	0.033	0.056
Stabbing vs. pressing	10.53 (−2.82, 23.87)	0.13	0.13

The bold terms show statiscally significant variables after the FDR correction (if a p-value is provided for the variable) or indicate a specific model.

TABLE 2 | Multivariate logistic regression model of migraine characteristics (criteria C and D) in patients hospitalized because of COVID-19.

	Odds ratio and 95% CI	Unadjusted *p*-value	Adjusted *p*-value (FDR)
Migraine—Criterion C model			
Independent term	3.68 (0.48, 34.54)	0.22	0.22
Pressing pain	0.16 (0.03, 0.64)	0.013	0.037
Migraine—Criterion D	4.24 (1.29, 15.51)	0.021	0.047
Periocular pain	4.66 (1.45, 16.37)	0.012	0.037
Progressive	9.57 (1.89, 70.04)	0.013	0.037
Worst LDH values	0.991 (0.984, 0.997)	0.006	0.037
No response to analgesics	0.29 (0.05, 1.51)	0.15	0.16
Family history of headache	2.51 (0.84, 7.96)	0.10	0.13
Worst headache experienced in life	3.05 (0.97, 10.27)	0.061	0.085
Abnormal liver enzymes	3.45 (1.15, 11.48)	0.033	0.061
Prior history of neurological disorders	3.86 (1.05, 16.55)	0.052	0.081
Migraine—Criterion D model			
Independent term	0.13 (0.01, 1.45)	0.11	0.11
Chest pain (COVID-19 symptom)	0.12 (0.02, 0.47)	0.005	0.030
Remitting headache	0.16 (0.04, 0.64)	0.013	0.047
Abnormal ferritin	0.18 (0.03, 0.79)	0.028	0.047
Disability caused by headache	1.04 (1.01, 1.07)	0.005	0.030
Diarrhea (COVID-19 symptom)	3.42 (1.14, 11.39)	0.034	0.047
Lymphopenia on admission	3.95 (1.27, 13.92)	0.023	0.047
Treatment resistant	5.07 (1.34, 22.86)	0.024	0.047
Prior history of diabetes	6.64 (1.30, 42.47)	0.030	0.047
Worst headache experienced in life	2.98 (0.93, 10.49)	0.073	0.081
Treatment resistant (analgesics)	5.23 (0.98, 33.76)	0.063	0.077

The bold terms show statiscally significant variables after the FDR correction (if a p-value is provided for the variable) or indicate a specific model or a variable with more than two categorical values.

disability caused by headache itself, to hematologic and inflammatory potential biomarkers of COVID-19 severity such as thrombocytopenia, lymphopenia, and hyperferritinemia. The second phenotype presents TTH characteristics (particularly pressing quality, not aggravated by movement and mild or moderate pain intensity) and is linked to lower PCT and CRP levels, both potential biomarkers of COVID-19 severity when high levels are present. A last possible phenotype would be a COVID-19 specific phenotype, associated with lymphopenia and high levels of PCT and CRP, and characterized by bilateral (diffuse) frontally localized, pressing, and intense pain, and hypersensitivity to stimuli. A summary of the results is shown in **Figure 5**.

PCA was employed to overcome the limitations of regression. PCA allows to analyze simultaneously a set of variables and detect specific patterns depending on predictor variables. A principal component is influenced by the effect of the variables included in the analysis, each one with a specific weight per component. In this study, for example, the PCA showed that CRP and PCT levels followed simultaneous changes in relationship with diverse headache features. The identification of concurrent changes in some variables is a key advantage of PCA in comparison with

TABLE 3 | Multivariate logistic regression model of headache in the frontal area in patients hospitalized because of COVID-19.

	Odds ratio and 95% CI	Unadjusted *p*-value	Adjusted *p*-value (FDR)
Frontal pain model			
Independent term	0.12 (0.01, 1.05)	0.076	0.087
Cranial autonomic symptoms	0.049 (0.003, 0.63)	0.026	0.042
Sex (Female vs. Male)	20.59 (3.05, 286.23)	0.007	0.018
Abnormal IL-6 levels	36.93 (5.06, 605.14)	0.002	0.009
Bilateral diffuse pain	65.53 (8.24, 1247.40)	<0.001	0.006
Modified rankin scale at discharge	0.19 (0.04, 0.62)	0.011	0.021
Glomerular filtration rate on admission (interval)	0.22 (0.03, 1.16)	0.093	0.093
Pulsating	53.15 (2.44, 10459.82)	0.053	0.070
Pressing pain model			
Independent term	383.92 (6.53, 50195.26)	0.008	0.017
Abnormal PCT on admission	0.031 (0.001, 0.381)	0.011	0.021
Modified rankin scale	0.041 (0.003, 0.466)	0.014	0.021
Clinophilia	0.06 (0.01, 0.37)	0.007	0.017
Headache when sleeping	0.18 (0.04, 0.75)	0.023	0.027
Headache intensity	0.35 (0.17, 0.61)	0.001	0.005
Prior history of diabetes	88.00 (2.95, 9378.87)	0.024	0.027
Pathologic chest X-Ray	794.78 (29.10, 68399.71)	<0.001	0.005
No response to analgesics	0.31 (0.06, 1.34)	0.12	0.12

The bold terms show statiscally significant variables after the FDR correction (if a p-value is provided for the variable) or indicate a specific model or a variable with more than two categorical values.

regression analysis, which analyzes a unique dependent variable per model.

Considering the relationship between the primary headache features, migraine and TTH in this case, and a secondary headache attributed to COVID-19, a possible explanatory mechanism would be related to pre-existing primary migraine and TTH. Schankin and Straube observed that sometimes secondary headaches are strongly related to pre-existing primary headaches (14). In our study, we found no statistically significant associations between phenotypes related to migraine and TTH characteristics, such as higher/lower intensity of pain and pulsating or pressing quality, and previous history of migraine and TTH, respectively. However, the number of patients with prior history of primary headache was relatively small in our sample, including 18 and 30 patients with previous migraine and TTH, respectively. Further studies with higher sample size should elucidate whether diverse pre-existing primary headaches, mainly migraine and prior family history of migraine, influence the different manifestations of headache attributed to COVID-19.

Concerning the identification of headache phenotypes, higher values of intensity of headache and self-rated disability were associated with symptoms related to migraine and female sex, which is substantially more common in migraine. These results suggest that phenotypic features of migraine should be monitored in COVID-19 patients in relation to the course of the disease, considering that it may affect patients' quality of life.

Furthermore, higher disability values were associated with COVID-19 symptoms and results from laboratory tests. Patients with fever presented the highest disability scores in our sample. Headache intensity has been previously associated with fever in COVID-19 (3) and non-cephalic infections, and headache has also been hypothesized as a secondary effect of fever (15). In contrast, lightheadedness was associated with lower disability according to our results (**Table 1**). However, people with lightheadedness and fever exhibited higher disability than patients with none of them, considering that almost all patients with lightheadedness also presented fever. This result is in line with reported higher dizziness in patients with migraine compared to control subjects, although the presence of migraine did not increase the risk of dizziness (16).

Regarding the relationship between disability caused by headache and laboratory tests, leukocytosis on admission was associated with higher disability, and abnormal (very high or low) platelet levels on admission with lower disability. On the one hand, thrombocytopenia has been observed in patients with headache characteristics related to migraine, with attacks occurring regularly during periods of thrombocytopenia and relieve of migraine symptoms associated with its normalization (17–19). Thrombocytopenia has also been related to increased risk of severe COVID-19 (20, 21). On the other hand, platelet-leukocyte aggregates count has been found to be higher in patients with migraine during the interictal period in comparison with control subjects (22), with a possible link to the release of IL-6 and cytokine tumoral necrosis factor-α (19). Therefore, our results suggest that higher disability caused by headache may be related to a phenotype with migraine features, with possible platelet and platelet-leukocyte complex pathophysiological underlying mechanisms.

Following laboratory tests results, we found that abnormal (higher) levels of IL-6 were associated with pain in the frontal region, the most common region with pain in our sample. IL-6 has been found to be increased in patients with TTH and migraine during headache compared to controls (23, 24). These increased levels in both primary headaches may explain the reason of the lack of association with specific migraine or TTH features. With regard to the pathophysiological mechanism of IL-6, a sensitization of the dural afferents has been suggested to contribute to migraine pathophysiology in association with IL-6 in the meninges (24). Moreover, IL-6 blood measurement has been pointed out as a potential biomarker of COVID-19 severity (25). We also identified that other laboratory results, such as lymphopenia, were also associated with migraine features. This relationship between frontal pain in headache in patients with COVID-19 and headache with migraine characteristics may reflect the connection between disability, or even severity of COVID-19, and headache in some patients with COVID-19. IL-6 may play an important role in the generation of headache attributed to COVID-19. In rat models, calcitonin gene-related peptide, strongly related to migraine headache (26), was shown to be released in heat conditions in association with IL-6 (27).

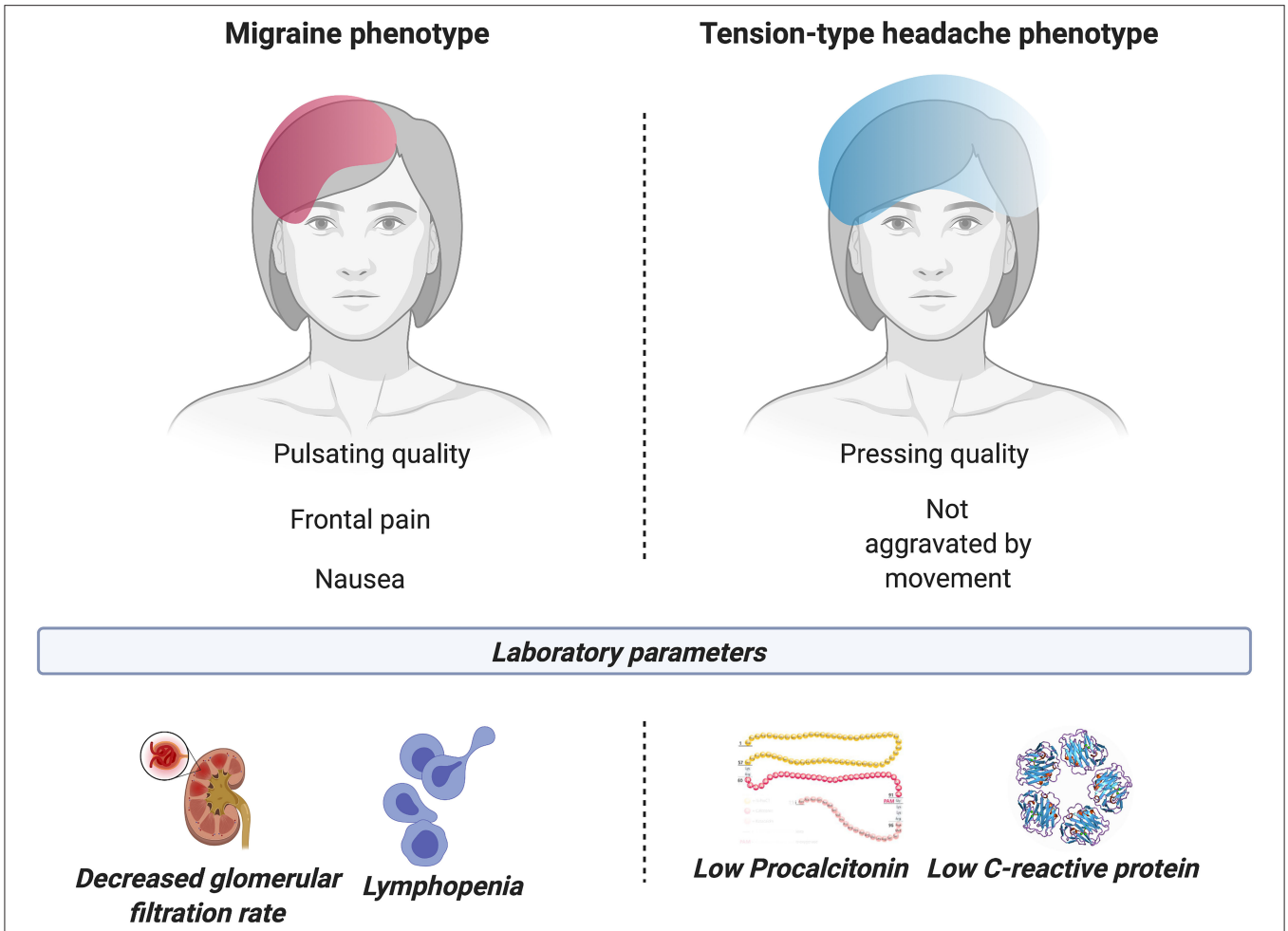


FIGURE 5 | Summary of the laboratory tests (worst levels and values on admission) in association with headache phenotypes. Symptoms of migraine and TTH were linked to laboratory biomarkers of COVID-19 status.

With reference to the lymphopenia in the phenotype with migraine features, a lower lymphocyte count value has been found in patients with severe COVID-19 (21). Furthermore, we found that abnormal (higher) ferritin levels were associated with criterion D for migraine from the ICHD-3. Higher serum ferritin levels have been found in patients with severe COVID-19 (21). These results may imply a relationship between COVID-19 state, laboratory biomarkers and headache, with a phenotype with migraine characteristics related possibly to severe COVID-19.

In accordance with the relationship between lymphocyte and ferritin values, compared to the phenotype with migraine characteristics, lower CRP and PCT values (on admission and worst levels) were found in patients with a phenotype with TTH features. Considering that TTH features used in this study oppose migraine characteristics (e.g., headache not aggravated by physical activity in TTH, and aggravated by activity in migraine), these results are in line with previous COVID-19 and migraine studies. Severe COVID-19 has been found in patients with high CRP and PCT levels (21), and high CRP levels have been identified in patients with migraine with relative high frequency (seven or more days with headache per month) and chronic migraine (28), and migraine with aura (28, 29). High CRP levels have been identified to be correlated with a cytokine storm, showing high CRP levels in patients with severe COVID-19 (30). Increased circulating pro-inflammatory cytokines have been suggested to be related to headache attributed to COVID-19, triggering perivascular trigeminal nerve endings (4). Additionally, we measured D-dimer levels, with high levels found previously in patients with COVID-19 (21), but we identified no clear pattern related to D-dimer.

In this study, frequent symptoms of headache were associated with biomarkers of endothelium damage, such as high PCT and CRP levels. PCT and CRP have been proposed as agents that impair endothelial cell function (31, 32), and the endothelium may be a key target in COVID-19 (33). Considering that biomarkers of endothelial damage have been found in patients with migraine (34), the possible damage of endothelium related to COVID-19 may suggest a possible relationship between severity of COVID-19 and headache, specific of COVID-19 or related to migraine symptomatology. Interestingly, a significant

positive association was found between patients with prior history of diabetes and migraine symptoms, i.e., prior history diabetes was related to higher odds of presenting headache with migraine features. Considering the diverse mechanisms of endothelial dysfunction in diabetes (35), the endothelium damage in COVID-19 and migraine may explain that patients with diabetes suffered with higher odds a headache with migraine characteristics. This endothelial damage would cause headache, but perhaps it would not generate further complication related to an extremely high severe COVID-19 state.

Higher odds of presenting headache with migraine features were also associated with progressive pain. This result may imply that the phenotype with migraine characteristics would not appear at the beginning of the COVID-19 course, but in a later stage, related possibly to a worse COVID-19 state. Other factors associated with a headache with migraine characteristics were persistent and treatment resistant headache. These previous characteristics, together with frequent features observed in this sample such as intense and frontally localized pain, have been reported in drug-induced aseptic meningitis, which also presents migraine symptoms occasionally (36). Viral meningitis has been proposed as a neuropathological mechanism of COVID-19 (37). Hence, the frequent symptoms found in this sample suggest that headache related to COVID-19 may be linked to meningeal irritation, in line with the previously commented IL-6 pathophysiological mechanisms related to calcitonin gene-related peptide release.

The presence of the most common headache symptoms in this sample (frontal or bilateral diffuse pain, intense pain, pressing pain, and hypersensitivity to stimuli) was related to the laboratory biomarkers of severe COVID-19 state, i.e., lymphopenia and high values of CRP and PCT. These features combine characteristics from both migraine and TTH, which may explain that some subjects simultaneously fulfilled criteria C for migraine and TTH from the ICHD-3. Furthermore, these features may define a third phenotype which could be "COVID-19 specific," which would be more intense than a headache with TTH characteristics, but not than a phenotype with migraine characteristics. The existence of diverse phenotypes is in line with heterogeneity and several patterns of headache during COVID-19 infection reported in healthcare workers (38). A possible factor related to the commented "COVID-19 specific" phenotype may be anosmia, one of the most characteristic symptoms of COVID-19 (39). Talavera et al. (40) found that COVID-19 patients with anosmia, compared to those without anosmia, presented a higher prevalence of headache and lower severity and mortality rate, and also higher values of lymphocyte count, increased glomerular filtration rate, and lower CRP levels. These values would be in line with our results, which showed higher glomerular filtration rate and lymphopenia in patients with migraine features, associated with a more severe course in this study, and lower CRP levels, linked to the phenotype with TTH features. Thus, anosmia may be related to a headache phenotype characteristic of COVID-19, possibly with no association with a severe course of the disease. The possible intermediate headache intensity and disability between migraine and TTH of the suggested "COVID-19 specific" phenotype may explain the lack of statistically significant results of anosmia in this study. Future studies should analyze with more detail the relationship between anosmia and headache during COVID-19.

Some limitations are worth mentioning in this study. Only hospitalized patients were included in the study because they were recruited at the beginning of the COVID-19 crisis, which implied that RT-PCR diagnostic test were used mainly in patients who needed hospital admission. No patients with extremely severe condition, including death and patients who were not able to take part in the interview, were included in the sample, which limits the results related to COVID-19 severity. Sample size was another important limitation. Although sample size was not excessively small, some adjustments were necessary to avoid extreme overfitting effects in the multivariate GLM. Also, more sophisticated clustering methods than PCA, such as k-means, were not possible because of this. The phenotype with TTH features that we associated with lower intense headache was obtained in patients that had a relative high pain intensity and needed admission, and we were not able to elucidate whether mild state (or mild headache intensity) patients with COVID-19 presented the same phenotype or a different one. The cross-sectional nature of the study was another factor that made it impossible to assess whether a single patient could present different headache phenotypes depending on the course of the disease. In relation with the longitudinal course of headache during COVID-19, there was no headache diary available for each patient and the analysis was limited to the inpatient stay, with no chance to assess the evolution of the symptoms. Further studies should try to avoid these limitations using a validated structured interview and a headache diary for a better evaluation of the course of headache.

In conclusion, headache attributed to COVID-19 can be manifested in diverse phenotypes associated with migraine and TTH characteristics. The phenotype associated with migraine symptoms was related to a worse clinical course of COVID-19, including a relationship with hematologic and inflammatory markers of the disease, and it was also linked to higher intensity and disability caused by headache. Headache should be considered as an important symptom in the clinical course of COVID-19, especially when manifested with migraine characteristics, taking into account that it is a common and disabling symptom of COVID-19. Future studies should assess the longitudinal evolution of headache in patients with COVID-19 to characterize accurately the different headache phenotypes and their relationship with the clinical course of the disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Valladolid East Ethics review board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ÁP-G, ÁLG, and DG-A designed and conceptualized the study. JT and DG-A collected the data. ÁP-G and DG-A analyzed and interpreted the data and drafted the manuscript. RdL-G, ÁLG, and JP-E revised the manuscript for intellectual content. All authors agreed and approved the manuscript.

FUNDING

This work was supported by the Institute of Health Carlos III (ISCIII), with the following reference: Convocatoria de expresiones de interés para la financiación de proyectos de investigación sobre el SARS-CoV-2 y la enfermedad COVID-19 con cargo al FONDO-COVID19 en el marco del Real Decreto-ley 8/2020, de 17 de marzo, de medidas urgentes extraordinarias para hacer frente al impacto económico y social del COVID-19 (Reference Number 07.04.467804.74011.0).

ACKNOWLEDGMENTS

We thank the patients for their collaboration and all the people who faced COVID-19. ÁP-G was supported by Junta de Castilla y León (Spain) and the European Social Fund (ID: 376062, Base de Datos Nacional de Subvenciones).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.583870/full#supplementary-material

REFERENCES

1. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
2. Berger JR. COVID-19 and the nervous system. *J Neurovirol*. (2020) 26:143–8. doi: 10.1007/s13365-020-00840-5
3. Belvis R. Headaches during COVID-19: my clinical case and review of the literature. *Headache J Head Face Pain*. (2020) 60:1422–1426. doi: 10.1111/head.13841
4. Bolay H, Gül A, Baykan B. COVID-19 is a real headache! *Headache J Head Face Pain*. (2020) 60:1415–1421. doi: 10.1111/head.13856
5. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect*. (2020) 80:607–13. doi: 10.1016/j.jinf.2020.03.037
6. Bourgonje AR, Abdulle AE, Timens W, Hillebrands J-L, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol*. (2020) 251:228–48. doi: 10.1002/path.5471
7. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med*. (2020) 58:1131–4. doi: 10.1515/cclm-2020-0198
8. García-Azorín D, Trigo J, Talavera B, Martínez-Pías E, Sierra Á, Porta-Etessam J, et al. Sensitivity and type of red flags in patients with Covid-19 and headache: a series of 104 patients. *Headache J Head Face Pain*. (2020) 60:1664–1672. doi: 10.1111/head.13927
9. World Health Organization. *Coronavirus Disease (COVID-19) Technical Guidance: Laboratory Testing for 2019-nCoV in Humans* (2020). Available online at: www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance (accessed May 31, 2020).
10. Ministry of Health (Spain). *Technical Documents. Hospital Management of COVID-19*. (2020). Available from: www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Protocolo_manejo_clinico_ah_COVID-19.pdf (accessed May 31, 2020).
11. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition. *Cephalalgia*. (2018) 38:1–211. doi: 10.1177/0333102417738202
12. García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, Talavera B, et al. Neurological comorbidity is a predictor of death in Covid-19 disease: a cohort study on 576 patients. *Front Neurol*. (2020) 11:781. doi: 10.3389/fneur.2020.00781
13. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B*. (1995) 57:289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x
14. Schankin CJ, Straube A. Secondary headaches: secondary or still primary? *J Headache Pain*. (2012) 13:263–70. doi: 10.1007/s10194-012-0443-8
15. De Marinis M, Welch KM. Headache associated with non-cephalic infections: classification and mechanisms. *Cephalalgia*. (1992) 12:197–201. doi: 10.1046/j.1468-2982.1992.1204197.x
16. Carvalho GF, Vianna-Bell FH, Florencio LL, Pinheiro CF, Dach F, Bigal ME, et al. Presence of vestibular symptoms and related disability in migraine with and without aura and chronic migraine. *Cephalalgia*. (2019) 39:29–37. doi: 10.1177/0333102418769948
17. Damasio H. Migraine, thrombocytopenia, and serotonin metabolism. *Lancet*. (1977) 2:512–3. doi: 10.1016/S0140-6736(77)91644-0
18. Damasio H, Beck D. Migraine thrombocytopenia, and serotonin metabolism. *Lancet*. (1978) 1:240–2. doi: 10.1016/S0140-6736(78)90484-1
19. Danese E, Montagnana M, Lippi G. Platelets and migraine. *Thromb Res*. (2014) 134:17–22. doi: 10.1016/j.thromres.2014.03.055
20. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. (2020) 506:145–8. doi: 10.1016/j.cca.2020.03.022
21. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. (2020) 58:1021–8. doi: 10.1515/cclm-2020-0369
22. Zeller JA, Frahm K, Baron R, Stingele R, Deuschl G. Platelet-leukocyte interaction and platelet activation in migraine: a link to ischemic stroke? *J Neurol Neurosurg Psychiatry*. (2004) 75:984–7. doi: 10.1136/jnnp.2003.019638
23. Koçer A, Koçer E, Memişogullari R, Domaç FM, Yüksel H. Interleukin-6 levels in tension headache patients. *Clin J Pain*. (2010) 26:690–3. doi: 10.1097/AJP.0b013e3181e8d9b6
24. Yan J, Melemedjian OK, Price TJ, Dussor G. Sensitization of dural afferents underlies migraine-related behavior following meningeal application of interleukin-6 (IL-6). *Mol Pain*. (2012) 8:6. doi: 10.1186/1744-8069-8-6
25. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. *Ecancermedicalscience*. (2020) 14:1022. doi: 10.3332/ecancer.2020.1022
26. Edvinsson L. Role of CGRP in migraine. *Handb Exp Pharmacol*. (2019) 255:121–30. doi: 10.1007/164_2018_201
27. Oprée A, Kress M. Involvement of the proinflammatory cytokines tumor necrosis factor-alpha, IL-1 beta, and IL-6 but not IL-8 in the

development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin. *J Neurosci*. (2000) 20:6289–93. doi: 10.1523/JNEUROSCI.20-16-06289.2000
28. Hagen K, Stovner LJ, Nilsen KB, Kristoffersen ES, Winsvold BS. The impact of C-reactive protein levels on headache frequency in the HUNT study 2006-2008. *BMC Neurol*. (2019) 19:229. doi: 10.1186/s12883-019-1462-8
29. Tietjen GE, Khubchandani J, Herial N, Palm-Meinders IH, Koppen H, Terwindt GM, et al. Migraine and vascular disease biomarkers: a population-based case-control study. *Cephalalgia*. (2018) 38:511–8. doi: 10.1177/0333102417698936
30. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients. *Aging Clin Exp Res*. (2020) 32:2141–58. doi: 10.1007/s40520-020-01677-y
31. Wagner N-M, Van Aken C, Butschkau A, Bierhansl L, Kellner P, Schleusener V, et al. Procalcitonin impairs endothelial cell function and viability. *Anesth Analg*. (2017) 124:836–45. doi: 10.1213/ANE.0000000000001574
32. Hein TW, Singh U, Vasquez-Vivar J, Devaraj S, Kuo L, Jialal I. Human C-reactive protein induces endothelial dysfunction and uncoupling of eNOS *in vivo*. *Atherosclerosis*. (2009) 206:61–8. doi: 10.1016/j.atherosclerosis.2009.02.002
33. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. *J Clin Med*. (2020) 9:1417. doi: 10.3390/jcm9051417
34. Gryglas A, Smigiel R. Migraine and stroke: what's the link? What to do? *Curr Neurol Neurosci Rep*. (2017) 17:22. doi: 10.1007/s11910-017-0729-y
35. Avogaro A, Albiero M, Menegazzo L, de Kreutzenberg S, Fadini GP. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. *Diabetes Care*. (2011) 34(Suppl. 2):S285–90. doi: 10.2337/dc11-s239
36. Holle D, Obermann M. Headache in drug-induced aseptic meningitis. *Curr Pain Headache Rep*. (2015) 19:29. doi: 10.1007/s11916-015-0505-0
37. Koralnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. *Ann Neurol*. (2020) 88:1–11. doi: 10.1002/ana.25807
38. Porta-Etessam J, Matías-Guiu JA, González-García N, Gómez Iglesias P, Santos-Bueso E, Arriola-Villalobos P, et al. Spectrum of headaches associated with SARS-CoV-2 infection: study of healthcare professionals. *Headache J Head Face Pain*. (2020) 60:1697–1704. doi: 10.1111/head.13902
39. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. (2020) 277:2251–61. doi: 10.1007/s00405-020-05965-1
40. Talavera B, García-Azorín D, Martínez-Pías E, Trigo J, Hernández-Pérez I, Valle-Peñacoba G, et al. Anosmia is associated with lower in-hospital mortality in COVID-19. *J Neurol Sci*. (2020) 419:117163. doi: 10.1016/j.jns.2020.117163

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 18 December 2020
doi: 10.3389/fneur.2020.613719

The Impact of the COVID-19 Pandemic on People With Epilepsy. An Italian Survey and a Global Perspective

Barbara Mostacci[1†], Laura Licchetta[1,2†], Carlotta Cacciavillani[2], Lidia Di Vito[1], Lorenzo Ferri[2], Veronica Menghi[2], Carlotta Stipa[1], Patrizia Avoni[1,2], Federica Provini[1,2], Lorenzo Muccioli[2], Luca Vignatelli[1], Stefania Mazzoni[1], Paolo Tinuper[1,2] and Francesca Bisulli[1,2]*

[1] IRCCS Istituto delle Scienze Neurologiche di Bologna, Full Member of the ERN EpiCare, Bologna, Italy, [2] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

OPEN ACCESS

Edited by:
Giovanni Assenza,
Campus Bio-Medico University, Italy

Reviewed by:
Jacopo Lanzone,
Policlinico Universitario Campus Bio-Medico, Italy
Tommaso Tufo,
Catholic University of the Sacred Heart, Rome, Italy

***Correspondence:**
Laura Licchetta
laura.licchetta2@unibo.it;
licchetta@gmail.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 03 October 2020
Accepted: 24 November 2020
Published: 18 December 2020

Citation:
Mostacci B, Licchetta L, Cacciavillani C, Di Vito L, Ferri L, Menghi V, Stipa C, Avoni P, Provini F, Muccioli L, Vignatelli L, Mazzoni S, Tinuper P and Bisulli F (2020) The Impact of the COVID-19 Pandemic on People With Epilepsy. An Italian Survey and a Global Perspective. Front. Neurol. 11:613719. doi: 10.3389/fneur.2020.613719

Objectives: We explored the impact of the coronavirus disease-19 (COVID-19) emergency on the health of people with epilepsy (PwE). We also investigated their attitude toward telemedicine.

Methods: The PubMed database up to September 10, 2020 was searched for questionnaire-based studies conducted in PwE during the COVID-19 emergency, and the literature retrieved was reviewed. In addition, all patients who had a telephone consultation with our center between May 7 and July 31, 2020 were invited to fill in a 57-item online questionnaire focusing on epilepsy and comorbidities, any changes in lifestyle or clinical conditions and any emergency-related problems arising during the COVID-19 emergency, and their views on telemedicine. Associations between variables were detected through X^2 test and Fisher's exact test. Univariate and multivariate logistic regression models were used to evaluate the effects of different factors on clinical conditions.

Results: Twelve studies met the literature search criteria. They showed that the rate of seizure worsening during the emergency ranged from 4 to 35% and was mainly correlated with epilepsy severity, sleep disturbances and COVID-19-related issues. Our questionnaire was filled in by 222 PwE or caregivers. One hundred (76.6%) reported unchanged clinical conditions, 25 (11.3%) an improvement, and 27 (12%) a deterioration. Reported clinical worsening was associated with a psychiatric condition and/or medication (OR = 12.59, $p < 0.001$), sleep disorders (OR = 8.41, $p = 0.001$), limited access to healthcare (OR = 4.71, $p = 0.016$), and experiencing seizures during the emergency (OR = 4.51, $p = 0.007$). Telemedicine was considered acceptable by 116 subjects (52.3%).

Conclusions: Most PwE did not experience a significant change in their clinical conditions during the COVID-19 emergency. However, severity of epilepsy, concomitant disability, comorbid psychiatric conditions, sleep disorders and limited access to healthcare may affect their health.

Keywords: COVID-19, emergency, epilepsy, survey, telemedicine

INTRODUCTION

The first half of 2020 saw a rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections worldwide. The outbreak of coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, quickly reached pandemic proportions, seriously impacting the health systems of many countries. Italy was the first country in the Western world to be hard hit by the disease. On February 21, 2020, the Italian government issued the first of a series of legislative decrees that introduced increasingly stringent measures, closing down non-essential activities and severely restricting travel. These measures were rapidly extended to the whole of Italy. By March 11, the country's entire population was required to comply with strict home confinement (lockdown) measures.

The emergency posed an unprecedented challenge to our healthcare system (HS). The rapid HS re-organization together with the lockdown measures produced a restriction of care provision to all non-urgent conditions, including chronic neurological diseases. It has been reported that seizures in people with epilepsy (PwE) might be triggered by stress (1), including major environmental stressors (2). Sleep and other lifestyle changes may also influence seizure occurrence. Stress linked to health concerns, restricted healthcare access, and lifestyle changes due to home confinement and remote working might all be factors influencing seizure occurrence and the overall well-being of PwE. We set out to explore the impact of the recent lockdown measures on the health of PwE. A further aim was to explore how PwE felt about telemedicine, as the present, unprecedented situation has given us (and others worldwide) our first experience of application of this modality in epilepsy care. In this paper, after reviewing the literature on the use of questionnaires in the fields of epilepsy and COVID-19, we present the original results of an online survey conducted in Italy.

METHODS

Review of the Literature

The PubMed database up to September 10, 2020 was searched for English-language questionnaire-based studies conducted in PwE during the COVID-19 emergency. The search was conducted using the terms: ("Epilepsy"[Mesh]) AND "COVID-19" [Supplementary Concept]) AND "Surveys and Questionnaires"[Mesh]; ("Epilepsy"[Mesh]) AND "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]; "Epilepsy"[Mesh]) AND "Coronavirus Infections"[Mesh].

Only studies based on questionnaires aimed at patients and/or caregivers were considered.

Questionnaire

Setting

In response to the COVID-19 emergency, our institute, like many other healthcare facilities, underwent a major reorganization: by March 14, the inpatient facilities had been converted into a COVID-19 hospital and the operating theaters into a COVID-19 intensive care unit. Therefore, inpatient admissions for epilepsy diagnosis, monitoring and surgery were suspended. The activity of the outpatient clinic was also reorganized, in compliance with orders from local authorities aimed at limiting interpersonal contact. With the exception of selected urgent cases, first visits were suspended, as were follow-up EEGs, while follow-up consultations were performed almost exclusively through telephone calls with the treating clinician. From June 3, the full lockdown measures in Italy were partially relaxed. Travel between different regions was possible once again and facilities gradually reopened. Our inpatient clinic reopened on June 1. First visits and face-to-face check-ups for patients with vagal nerve stimulation implants or those in need of a neurological examination (e.g., for alleged side effects) were restored; however, at the time writing, most follow-up appointments are still conducted by telephone, as the authorities recommend use of this modality whenever feasible.

Questionnaire Design

Drawing on our Epilepsy Center clinicians' experiences of remote contact with patients during the first 2 months of lockdown, we created, using Google Forms, a 57-item, Italian language, self-administered questionnaire aimed at PwE. The instrument was designed to collect the following information: compiler identity (patient/caregiver/guardian), date of compilation, personal information (8 closed-ended +1 open ended questions), living situation (4+2 questions), possible COVID-19 infection (3+2 questions), changes in clinical conditions during the COVID-19 emergency (2 closed-ended questions), clinical information (5+3 questions), changes in lifestyle, and any problems or concerns related to the home confinement and limited access to healthcare resources since the implementation of the first emergency legislative decree on 23 February (10+10 questions), Finally, the responder was asked to express an opinion on the replacement of face-to-face appointments with telephone consultations.

Patient Recruitment

All patients who had had a telephone consultation with our center in the period from May 7 to July 31 2020 were sent a link to the questionnaire and invited to participate in the survey. It was underlined that participation was voluntary and anonymous. Although the questionnaire was available on the internet, it was not promoted in any other way. In order to avoid duplicates, patients were required to register with an e-mail address instead of a password. At the start of the questionnaire, patients were required to consent to the use of their data, in aggregate form, for research and scientific publication purposes. Only those responding "I agree" were able to access further questions. Data were processed according to the European regulation n. 2016/679 (GDPR). Patient recruitment closed on 31 July, 2020.

Statistical Analysis

Data manipulation and statistical analysis were performed using STATA software (version 14.0). To facilitate interpretation of the data, some numeric variables (e.g., age) were recoded as categorical, while some categorical variables (e.g., change in clinical conditions) were re-coded into fewer categories.

Moreover, some variables were created specifically in order to consider additional aspects (i.e., time since last seizure, subsequently coded into categories). A "reported psychiatric condition and/or medication" variable was also generated by grouping patients who, in the open-ended questions, reported a current psychiatric diagnosis or took psychotropic drugs. Variables on therapy and sleep changes, derived from open-ended questions, were coded into categories. A further variable derived from the open-ended questions concerned the presence of sleep disorders. Descriptive statistics were run on all variables, except the uncoded open-ended questions. Subsequently, associations between qualitative variables were investigated through bivariate analyses using a X^2 test, or Fisher's exact test in the case of low expected frequencies. A multiple correspondence analysis was also applied to detect associations between a subset of variables through a multidimensional technique. Lastly, both univariate and multivariate logistic regression models, the latter with a backward elimination criterion, were implemented to evaluate the effect of different factors on variation of clinical conditions, in terms of worsening vs. not worsening.

RESULTS

Review of the Literature

We found 12 studies based on questionnaires aimed at PwE and/or their caregivers, conducted during the COVID-19 emergency. **Table 1** reports their main characteristics (methods and population).

Seizure Course During the Emergency

Nine questionnaires investigated seizure course during vs. prior to the emergency. The rate of seizure worsening ranged from 4 to 35% (3–11).

Worsening was significantly associated with several seizure and epilepsy factors: drug-resistant epilepsy (3, 7) number of anti-seizure medications (ASMs) (3, 9), and not being seizure free (9) or having more seizures at baseline (3, 7). In single studies, tonic-clonic seizures during the COVID-19 pandemic (9) and tumor-related etiology (3) were associated with worsening.

Seizure worsening was also associated with more disturbed sleep (3, 9) and with depression and anxiety factors: history of depression, anti-depressant use, more severe depression and anxiety symptoms (9). Fear of epilepsy was associated with worsening in two studies (3, 7).

Several authors reported an association with COVID-19 emergency-related issues (9), including reduced income (3) and difficulties obtaining ASMs (10).

Two studies reported a correlation with higher age (7, 10), however, since the first concerned a pediatric population, the data are not comparable. A Chinese study reported associations with Wuhan provenance and a history of exposure to COVID-19 (7).

Seizure improvement was also reported, albeit in a minority of studies, with rates ranging from 4 to 14.1% (6, 10, 11) and it was associated with improved sleep (6), less severe anxiety symptoms (6), and taking less than two ASMs (11).

Depression and Anxiety

Depression and anxiety were considered and measured, in different ways, in six studies. Alkhotani et al. reported "psychiatric disorders" in 40% of their subjects with epilepsy. In a survey of people with and without epilepsy (9), depression was reported in 19% of PwE vs. 17% of controls; in both groups, 8% were taking anti-depressant drugs although, overall, PwE had more severe depressive symptoms, as shown by higher Beck Depression Inventory (BDI-II) scores (9). In a study designed specifically to explore anxiety and depression, Hospital and Anxiety Depression Scale (HADS) scores indicative of anxiety were reported in 50.4% of the subjects, while 39.8 and 46.9%, respectively, had HADS and Patient Health Questionnaire (PHQ-9) scores indicative of depression. In this latter study, female gender and financial problems were significantly associated both with anxiety and with depression. Living in high-income countries decreased the odds for anxiety, while difficulties accessing ASMs increased the odds for depression (12).

One investigation looking specifically at lockdown-related symptoms showed depression in 8.6% and anxiety in 26.7% of subjects (3). In another, 59.4% of the responders reported increased stress (4). In a third survey, 9.6% of PwE and 6.8% of controls reported that since the start of the COVID-19 restrictions, they had begun taking new psychotropic drugs for insomnia (38.2%), depression (14.5%), and anxiety (47.4%) (9). In a subsequent work on the same questionnaire the authors reported on how PWE and PWoE coped with the pandemic restrictions, according to a Natural Language Processing (NLP), examining the single words with which they described how the lockdown changed their life. While words over-reported in the group of PwoE were related to anxiety in the context of a reactive stress response, PWE overexpressed words connected to sadness and worries with their disease. Moreover, PwE expressed positive relief feelings more frequently than PwoE (13).

A further survey evaluated several social and psychological items, asking participants to rate them, on a 10-point Likert scale, for two periods: before vs. after the pandemic emergency. This revealed differences, not large but statistically significant, in the strength of their social support networks, perceived isolation, and levels of anxiety (8).

Finally, behavioral deterioration was reported in 30.3% of a population of children with developmental and epileptic encephalopathies (DEE). Of note, in the same survey, new-onset symptoms of anxiety (68.6%) or depression (69.7%) were reported in caregivers. The main variables associated with behavioral deterioration were type of epilepsy, living in a home without a terrace or yard, and caregiver anxiety (10).

Sleep Changes

Sleep changes were reported in 8.2–71.2% (3, 4) and insomnia in 28.2% (3) of PwE. However, in a survey comparing PwE with controls without epilepsy, the quality of sleep did not differ significantly between the two groups: values out of range on the Pittsburgh Sleep Quality Index were reported in 46.9% of PwE and 42.4% of controls. The most affected aspects of sleep were, in decreasing order: subjective evaluation of sleep quality, sleep latency, and sleep duration (9).

TABLE 1 | Characteristics of the questionnaires.

First author	Country	Method of distribution/ administration	Period of recruitment	*N* of items	Single/ multicenter	Topics covered	*N*. of patients	Age in years*
Áledo-Serrano A.	Spain	Online questionnaire	7 April−11 April 2020	na	na (patients advocacy groups)	General data, seizure frequency, COVID-19, lockdown related problems	277 DEE 161 (58.1%) F 116 (41.9%) M	12.4 (mean)
Alkhotani A.	Saudi Arabia	Electronic self-administered questionnaire distributed by treating neurologist	April 2020	na	Multicenter	General data, seizure frequency, lockdown related problems	156 97 (62.2%) F 59 (37.8%) M	<20–>60
Fonseca E.	Spain	Telephone survey administered directly to patients (or caregiver) by the neurologist	16 March−17 April 2020	19	Single-center	General data, seizure frequency, COVID-19, lockdown related problems satisfaction with telemedicine	255 121 (47.5%) F 134 (52.5%) M	17–94
Asadi-Pooya Ali A.	Iran	By telephone	27 March−31 March 2020	semi-structured	Single-center study	General data, seizure frequency, COVID-19, problems obtaining drugs	100 47 (47.0%) F 53 (53.0%) M	11–75
Assenza G.	Italy	Online questionnaire	11 April−16 April 2020	48	na (online survey)	General data, seizure frequency, COVID-19, lockdown related problems	928 456 PwE 472 PwoE 691 (74.5%) F 237 (25.5%) M	18–89 (overall)
Cabona C.	Italy	Telephone questionnaire administered by the neurologist	9 March−30 April 2020	semi-structured	Multicenter	General data, seizure frequency, COVID-19, lockdown related problems	189 103 (54.5%) F 86 (45.5%) M	45 (median)
Hernando-Requejo V.	Spain	By telephone	20 March−13 April 2020	na	na	General data, seizure frequency, COVID-19	49 23 (46.9%) F 26 (53.1%) M	na
Huang S.	China	Online questionnaire	23 February−5 March 2020	88	Single-center	General data, seizure frequency, COVID-19, lockdown related problems	362 166 (45.9%) F 196 (54.1%) M	10–19–≥60
Miller W. R.	USA	Online questionnaire	27 March−30 March 2020	65	Single-center	General data, seizure frequency, COVID-19, lockdown related problems	94 47 (50.0%) F 47 (50.0%) M	19–88
van Hees S.	Multinational	Online questionnaire	10 April−18 May 2020	na	Multicenter	General data, seizure frequency, COVID-19, lockdown related problems	399 320 (80.2%) F 79 (19.8%) M	38.22 (mean)
von Wrede R.	Germany	Audit directly administered to patients (or their caregiver)	23 March−8 May 2020	na	Single-center	General data, seizure frequency, satisfaction with telemedicine	239 126 (52.7%) F 113 (47.3%) M	18–93
Hao X.	China	Online questionnaire (medical information was collected from electronic medical records)	1 February−29 February 2020	na	Single-center	General data, seizure frequency, COVID-19, lockdown related problems	252 Pwe 252 PwoE For both Pwe and PwoE: 126 (52.4%) F 120 (47.6%) M	29.3 (mean of PwE) 29.4 (mean of PwoE)

**range, unless otherwise specified, PwE = people with epilepsy, PwoE = people without epilepsy, DEE = patients with developmental and epileptic encephalopathies, na = not available/not applicable.*

Lockdown-Related Problems

Postponed neurological tests were reported by 14.5–61% of responders in three studies (3, 9, 12). Issues with drug supply were reported by 2.7–73% (3, 5, 6, 8, 9). Inability to contact their child's neurologist was reported in as many as 62.8% of cases in a Spanish survey aimed at caregivers of children with DEE. (10)

In a large multinational survey, 22.8% of PwE reported financial problems, including difficulty paying housing costs/bills, eating properly and paying for ASMs. These issues were significantly more common in people living in low- to middle-income countries (12).

People With Epilepsy's Fears and Worries During the COVID-19 Emergency

Two studies addressed specific fears of PwE during the pandemic. Fears regarding epilepsy in general were reported in 19.6–23.9% of respondents (3, 7). In one of the studies, PwE reported moderate-to-critical worries concerning seizures during the epidemic (24% of cases), lack of professional consultation (41.2%), and medication supply (48.62%) (7). Fear of infection was reported by 14.5% of PwE in the other study (3).

In a further study, participants reported heightened stress due to social reasons (28.2%), fear of SARS-CoV-2 infection (19.2%), and financial reasons (7%) (4).

In a Chinese study, PwE were significantly more concerned about the pandemic than healthy controls, and recorded significantly higher scores on the Kessler Psychological Distress Scale. Furthermore, a higher proportion of PwE had severe distress scores. Higher levels of distress were associated with drug-resistant epilepsy and time spent following the news about COVID-19 (14).

Satisfaction With Telemedicine

In two different studies, one settled in Spain (3) and one in Germany (15), 82–83.9% of PwE stated they were satisfied with telemedicine. However, there emerged no clinical predictors of a positive attitude toward it. In the German study, the patients underlined the following advantages of telemedicine: no need for transport (71%), greater convenience (64%), short waiting times (51%), and no travel expenses (41%), while lack of personal contact (44%), and of further diagnostics (45%) were identified as the main disadvantages.

Looking to the future, 38–74% patients saw the usefulness of telephone visits, although the patients in the German study also wanted further appointments onsite, and 36.5% of the Spanish series stated that they preferred face-to-face consultations. In the Spanish study telemedicine was more positively viewed by those most fearful of COVID-19 (3), whereas in the German study a better perception of telemedicine was associated with younger age, not being native German speaker, and a shorter history as a patient at the department. Conversely, longer duration of epilepsy, taking ASMs, and a longer history as a patient at the department were positive predictors of the desire for onsite consultations (15).

COVID-19 Confirmed Diagnosis

Several of the reviewed studies collected data on people with alleged symptoms of COVID-19. However, due to the lack of uniformity between these studies, we here focus solely on confirmed diagnoses. The rate of confirmed SARS-CoV-2 infections was 0.2–2.5% (3, 5, 7, 9, 12), which generally corresponded to the expected background for the given country in the same period. In the study by Assenza et al., the rate of infection in people with and without epilepsy was comparable (0.2 vs. 0.4%) (9). One study found no changes in seizure frequency (3), while another reported an increase in three of the nine cases (12).

Questionnaire

In total, 245 PwE responded to our questionnaire. However, 23 questionnaires were excluded: 12 because the respondent did not consent to data processing; 10 because they appeared to be duplicates (showing the same registration e-mail address and key variables as another response); finally, one questionnaire was excluded as the patient was a minor. In the case of duplicated questionnaires, we kept the most recent. The analyzed questionnaires therefore numbered 222. Responders were identified by consecutive numbers. Their mean age was 43.5 years (range 18–84). **Table 2** lists other general characteristics of the population. Most responders (*n*. 201, 90.5%) lived with other people. Thirty-four (15.3%) usually lived in a residential facility or attended a day center; of these, 20 (9%) reported they currently did so. At recruitment, half of the sample (*n*. 114, 51.3%) had been seizure free for 1 year or more. Ninety-nine patients (44.6%) were on ASM monotherapy, 109 (49.1%) on ASM polytherapy, 8 (3.6%) did not use drugs, and 6 (0.9%) did not answer.

Seventy-five patients (33.8%) suffered from additional diseases; 102 (46%) took other medications, besides ASMs. Thirty-one patients (14%) reported a psychiatric diagnosis or current psychiatric therapy; for the analysis, these patients were grouped under the variable "reported psychiatric condition and/or medication."

Seventy-three patients (32.9%) had at least one seizure after February 23.

One hundred patients (76.6%) reported that their clinical conditions had not changed since the start of the COVD-19 restrictions. Twenty-five patients (11.3%) reported an improvement: great in 11 (5%) and moderate in 14 (6.3%), and 27 (12.2%) a deterioration: moderate in 25 (11.3%) and severe in 2 (1%). However, among those who reported a clinical worsening, 14 (6.3%) had a worsening in seizures, while 13 were seizure free, therefore the worsening did not refer to epilepsy. Among these latter patients, nine had a reported psychiatric condition and/or medication and one had several diseases including cancer. Two patients reported the occurrence of a status epilepticus.

Fifty-three patients (23.9%) reported sleep changes. In particular, 19 (8.5%) reported various degrees or types of disturbed sleep, 25 (11.3%) a change of sleep pattern, and 4 (1.8%) an improvement in sleep.

Thirty persons (13.5%) reported problems with access to healthcare. Among them, seven had problems contacting

TABLE 2 | General characteristics of the population.

	Frequency	Percentage
Compiler		
Patient	157	70.72
Parent/caregiver/guardian	65	29.28
Total	222	100.00
Age (categories)		
18–29	53	23.87
30–39	41	18.47
40–49	46	20.72
50–59	48	21.62
60–84	34	15.32
Total	222	100.00
Sex		
M	94	42.34
F	128	57.66
Total	222	100.00
Marital status		
Married	91	40.99
De facto relationship	10	4.50
Divorced/separated	12	5.41
Single	104	46.85
Widowed	5	2.25
Total	222	100.00
Employment		
Unemployed	35	15.77
Employee	52	23.42
Self-employed	16	7.21
Retired	37	16.67
Student	18	8.11
Other	64	28.83
Total	222	100.00
Education		
No education/primary school	14	6.31
Secondary school	49	22.07
High school	106	47.75
University degree or higher	46	20.72
Missing	7	3.15
Total	222	100.00
Disability		
No	126	56.76
<100%	42	18.92
100%	52	23.42
Missing	2	0.90
Total	222	100.00
Driving license		
No	101	45.50
Yes	121	54.50
Total	222	100.00

their general practitioner, and four contacting their treating neurologist.

Eighteen persons (8.1%) reported drug supply problems. They included nine who reported difficulty obtaining Depakin 500 Chrono, which has been in short supply in Italy since the end of March[1]. Three persons had difficulty getting their therapeutic plans renewed (a legal requirement for some medications subject to prescription restrictions in Italy) and seven persons (3.1%) getting their driving license renewed. Forty-two persons (18.9%) stated that they had work/financial problems and 37 (32.7%) had concerns over possible problems linked to the pandemic and related restrictions.

We found statistically significant associations between reported worsening of clinical conditions and disability (20% of persons with disability reported a clinical worsening vs. 6% of those without disability, $X^2 = 9.22$, $p = 0.002$), reported psychiatric condition and/or medication (42 vs. 7%, Fisher's exact $p < 0.001$), sleep disorders (47 vs. 9%, Fisher's exact $p < 0.001$), changes in social and working life (16 vs. 3%, $X^2 = 6.65$, $p = 0.010$), and problems with limited access to healthcare (27 vs. 10%, Fisher's exact $p = 0.016$). The multiple correspondence analysis confirmed this pattern of associations, defining in particular a strong association between reported worsening of clinical conditions, a reported psychiatric condition and/or medication and the presence of sleep disorders. We also detected these relationships through univariate logistic regression models, showing a higher probability of reported clinical worsening among individuals with a disability (OR = 3.64, $p = 0.004$, 95% CI = [1.52;8.73]), a reported psychiatric condition and/or medication (OR = 9.13, $p < 0.001$, 95% CI = [3.72; 22.40]), sleep disorders (OR = 9.25, $p < 0.001$, 95% CI = [3.33; 25.71]), changes in their working and social life (OR = 5.69, $p = 0.021$, 95% CI = [1.31; 24.79]), and problems due to limited access to healthcare (OR = 3.31, $p = 0.012$, 95% CI = [1.30; 8.46]). In order to identify statistically significant covariates, controlling for all potential confounding factors, a multivariate logistic regression model was implemented, with a backward elimination criterion. The factors found to increase the probability of reported clinical worsening were: a reported psychiatric condition and/or medication (OR = 12.59, $p < 0.001$, 95% CI = [4.06; 38.99]), sleep disorders (OR = 8.41, $p = 0.001$, 95% CI = [2.31; 30.70]), problems with limited access healthcare (OR = 4.71, $p = 0.016$, 95% CI = [1.34; 16.56]), and experiencing at least one seizure after February 23, as compared with patients reporting seizure freedom lasting 1 year or more (OR = 4.51, $p = 0.007$, 95% CI = [1.51; 13.47]).

Eighty-five persons (38.3%) were opposed to the idea of replacing face-to-face appointments with telephone consultations, while 63 (28.4%) felt that the latter might be useful only occasionally and for minor problems; 53 (23.9%) would accept telephone consultations all or most of the time, while 21 (9.5%) "did not know." Patients with disability and those who were not seizure free were the least inclined to see telephone consultations or video calls replacing face-to-face contact. In this regard, statistically significant associations were found with disability ($X^2 = 12.79$, $p = 0.005$), time of last seizure ($X^2 = 21.18$, $p = 0.002$), and changes in social and working life ($X^2 = 12.67$, $p = 0.005$).

[1]Available online at: https://www.lice.it/LICE_ita/commissione_farmaco/commissione_farmaco.php (accessed September 30, 2020).

Two patients (0.9%) self-reported a SARS-CoV-2 infection; one was asymptomatic and the other severe, requiring hospitalization. The latter reported a worsening of epilepsy and in particular "tremor and slightly more frequent seizures."

DISCUSSION

The COVID-19 emergency has presented numerous challenges to our way of life, changing routines and generating unprecedented fears and worries. Moreover, it has seriously limited access to healthcare for people with chronic conditions, including epilepsy.

Several groups of researchers, in different parts of the world, have explored the impact of the current emergency on PwE, and our own survey adds to this body of knowledge. We investigated the issues faced by adult PwE during the COVID-19 emergency in Italy, studying a sample probably made up exclusively of patients of a tertiary center that, being based in a hospital temporarily transformed into a COVID-19 hospital, had to reorganize its activities during the pandemic emergency.

Our population mainly comprised patients with moderate to severe forms of epilepsy: almost half of them had experienced seizures during the previous year and almost half were on polytherapy. Moreover, it is a population with a high rate of comorbidities: half of the patients have a disability, 15.3% usually lived in a facility or attended a day center, one third reported additional diseases, and almost half took additional medications.

Our literature review showed that seizure worsening rates varied between populations; however, the majority of people surveyed reported unchanged conditions. In most populations seizures worsened in <10% of PwE (3, 4, 6, 7), a finding that may also reflect the natural fluctuations of epilepsy itself, given that no causal relationship could be established, particularly in studies performed after only 1 month of confinement. In our survey, which was conducted some months after the beginning of the emergency, and thus covered a longer observation period, 6.3% of patients reported seizure worsening, which was among the lowest reported rates. In general, the large majority of patients (76.6%) reported unchanged clinical conditions. The remaining patients were equally distributed between improvement and worsening of clinical conditions, where worsening did not necessarily refer to seizures. Indeed, reported worsening was also significantly associated with disability, reported psychiatric condition and/or medication and sleep disorders. These findings support the view that quality of life in people with epilepsy is multifactorial (16), and are also in line with the results of a survey in children with DEE, in whom behavioral worsening emerged as a major issue (10).

Moderate to high rates of comorbidity with mood disorders, as well as new onset of anxiety, depressive symptoms and heightened stress were reported in the literature (3, 4, 9), and in one study a considerable proportion of individuals started taking psychotropic drugs during lockdown (9). In our population, 14.3% of patients had a reported psychiatric condition and/or medication, which is a relatively low prevalence. However, our questionnaire did not directly address this aspect, nor we did administer any specific scale to assess it. Of note, however, in our population, as well as in others (3, 9), the presence of a reported psychiatric condition and/or medication was one of the main factors associated with reported clinical worsening.

Sleep changes during confinement, including a rise in sleep disturbances, were relatively common in our and other populations (3, 4, 9). However, this is not a specific feature of patients with epilepsy as demonstrated by a survey including controls (9) and by studies in general populations (17). Nevertheless, sleep changes and sleep disturbances were significantly associated with reported clinical worsening both in our and other surveys (3, 9).

The fact that specific emergency-related problems were the ones showing the largest variations between the different populations probably reflects differences in national health system organization, lockdown rules, average incomes and differences in the timing of data collection. In our population, a minority of patients (13.5%) reported problems with limited access to healthcare, the most common being difficulty contacting their general practitioner, which is not surprising given the overwhelming burden placed on GPs during the emergency, and the large number of them (in Italy) who contracted COVID-19. It should be highlighted, however, that problems accessing healthcare were associated with reported clinical worsening both in our population and in others (9, 10).

The low number of people experiencing problems obtaining prescription drugs or getting therapeutic plans and driving licenses renewed possibly reflects the efficiency of the action taken by the Italian government in this regard, namely to postpone legal deadlines until the end of the emergency. Among the 8.1% who reported drug supply problems, half referred to difficulty obtaining Depakin 500 Chrono, which has been in short supply in Italy since the end of March, due to production problems[1]. The observation that the system held up well, compared with other reported data (3, 5, 6, 8, 10), could be attributed at least in part to the fact that, in many Italian regions, ASMs are normally supplied directly by hospitals in large quantities at a time, thereby limiting the risk of shortages for patients.

The decision to resort to telemedicine was favorably viewed by just over half of our patients and around half of these also felt that in future it should be used only on certain occasions and to deal with minor problems. Similarly, despite a very high level of satisfaction with telephone consultations, more than one third of the patients in a Spanish study stated that they would prefer face-to-face appointments in the future (3), while the majority of the patients in a German study agreed to future telemedicine consultations, but only if combined with onsite visits (15). It should be mentioned that for the patients in our study, telemedicine took the form of telephone consultations as we were not equipped for videocalls, and this could have influenced their answers. Moreover, as elsewhere, telemedicine did not allow further diagnostic (15, 18, 19). According to an online survey endorsed by the main national neurophysiological scientific societies, the number of EEGs performed in neurophysiological centers all over Italy dropped by 76% during the 1st weeks of lockdown (18). The COVID emergency has accelerated the

implementation of telemedicine in Italy leading also to the issue of specific national recommendations on its use in the context of neurophysiology, including remote inter-hospital consultations (19), which could allow EEG recording while limiting people travels to reach a tertiary center, possibly impacting both on telemedicine effectiveness and on patients' satisfaction.

Neither our survey nor the other reported surveys were designed to provide information on SARS-CoV-2 infection in PwE, however their collective data seem to indicate prevalence rates reflecting those in the general population (9). A worsening of seizures has been signaled in some cases (12), including one of the two patients who reported the infection in our survey.

Our study has several limitations. First, since it concerned a web-based survey, precise information on type of epilepsy was unavailable, and other important clinical information, such as comorbid conditions, was self-reported, and, besides, we did not administer psychometric scales. Second, for the same reason, there was probably a selection bias toward a younger age group and a higher level of education. Third, due to its cross-sectional design, caution is needed when inferring causal relationships. Fourth, respondents were not asked to specify their region of residence, which might have been an important aspect, as different regions in Italy were differently hit by the pandemic. However, a previous Italian report did not find regional differences in any aspect investigated (9).

In conclusion, our survey, in line with others conducted elsewhere, showed that most PwE did not experience a significant change in their clinical conditions as a consequence of home confinement and healthcare reorganization during the COVID-19 emergency. However, severity of epilepsy, concomitant disability, comorbid depression and anxiety, new-onset sleep changes, and limited access to healthcare may affect seizure frequency and other health determinants. Follow-up studies are needed to confirm these observations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BM and LL conceptualized and designed the study, and drafted the questionnaire and manuscript. CC, LD, LF, VM, CS, PA, FP, and LM collected and interpreted the data. SM performed statistical analysis. FB, PT, and LV critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We thank Stefania Gamberini and Antonia Iurescia for helping in disseminating the questionnaire and Catherine Wrenn for editing the English text. We were grateful to all the people with epilepsy who participated in the survey.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.613719/full#supplementary-material

REFERENCES

1. Novakova B, Harris PR, Ponnusamy A, Reuber M. The role of stress as a trigger for epileptic seizures: a narrative review of evidence from human and animal studies. *Epilepsia*. (2013) 54:1866–76. doi: 10.1111/epi.12377
2. Neufeld MY, Sadeh M, Cohn DF, Korczyn AD. Stress and epilepsy: the Gulf war experience. *Seizure*. (1994) 3:135–9. doi: 10.1016/S1059-1311(05)80204-3
3. Fonseca E, Quintana M, Lallana S, Restrepo JL, Abraira L, Santamarina E, et al. Epilepsy in time of COVID-19: a survey-based study. *Acta Neurol Scand*. (2020). doi: 10.1111/ane.13335. [Epub ahead of print].
4. Alkhotani A, Siddiqui MI, Almuntashri F, Baothman R. The effect of COVID-19 pandemic on seizure control and self-reported stress on patient with epilepsy. *Epilepsy Behav*. (2020) 112:107323. doi: 10.1016/j.yebeh.2020.107323
5. Asadi-Pooya AA, Farazdaghi M, Bazrafshan M. Impacts of the COVID-19 pandemic on Iranian patients with epilepsy. *Acta Neurol Scand*. (2020). doi: 10.1111/ane.13310. [Epub ahead of print].
6. Cabona C, Deleo F, Marinelli L, Audenino D, Arnaldi D, Rossi F, et al. Epilepsy course during COVID-19 pandemic in three Italian epilepsy centers. *Epilepsy Behav*. (2020) 112:107375. doi: 10.1016/j.yebeh.2020.107375
7. Huang S, Wu C, Jia Y, Li G, Zhu Z, Lu K, et al. COVID-19 outbreak: the impact of stress on seizures in patients with epilepsy. *Epilepsia*. (2020). doi: 10.1111/epi.16635. [Epub ahead of print].
8. Miller WR, Von Gaudecker J, Tanner A, Buelow JM. Epilepsy self-management during a pandemic: experiences of people with epilepsy. *Epilepsy Behav*. (2020) 111:107238. doi: 10.1016/j.yebeh.2020.107238
9. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol*. (2020) 11:737. doi: 10.3389/fneur.2020.00737
10. Aledo-Serrano Á, Mingorance A, Jiménez-Huete A, Toledano R, García-Morales I, Anciones C, et al. Genetic epilepsies and COVID-19 pandemic: lessons from the caregiver perspective. *Epilepsia*. (2020) 61:1312–4. doi: 10.1111/epi.16537
11. Hernando-Requejo V, Huertas-González N, Lapeña-Motilva J, Ogando-Durán G. The epilepsy unit during the COVID-19 epidemic: The role of telemedicine and the effects of confinement on patients with epilepsy. Consulta de epilepsia durante la pandemia de COVID-19: papel de la telemedicina y efectos del confinamiento en pacientes epilépticos. *Neurologia*. (2020) 35:274–6. doi: 10.1016/j.nrl.2020.04.014
12. Van Hees S, Siewe Fodjo JN, Wijtvliet V, Van den Bergh R, de Moura Villela EF, da Silva CF, et al. Access to healthcare and prevalence of anxiety and depression in persons with epilepsy during the COVID-19 pandemic: a multicountry online survey. *Epilepsy Behav*. (2020) 112:107350. doi: 10.1016/j.yebeh.2020.107350

13. Lanzone J, Cenci C, Tombini M, Ricci L, Tufo T, Piccioli M, et al. Glimpsing the impact of COVID19 lock-down on people with epilepsy: a text mining approach. *Front Neurol*. (2020) 11:870. doi: 10.3389/fneur.2020.00870
14. Hao X, Zhou D, Li Z, Zeng G, Hao N, Li E, et al. Severe psychological distress among patients with epilepsy during the COVID-19 outbreak in southwest China. *Epilepsia*. (2020) 61:1166–73. doi: 10.1111/epi.16544
15. Von Wrede R, Moskau-Hartmann S, Baumgartner T, Helmstaedter C, Surges R. Counseling of people with epilepsy via telemedicine: experiences at a German tertiary epilepsy center during the COVID-19 pandemic. *Epilepsy Behav*. (2020) 112:107298. doi: 10.1016/j.yebeh.2020.107298
16. Luoni C, Bisulli F, Canevini MP, De Sarro G, Fattore C, Galimberti CA, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. *Epilepsia*. (2011) 52:2181–91. doi: 10.1111/j.1528-1167.2011.03325.x
17. Gualano MR, Lo Moro G, Voglino G, Bert F, Siliquini R. Effects of Covid-19 lockdown on mental health and sleep disturbances in Italy. *Int J Environ Res Public Health*. (2020) 17:4779. doi: 10.3390/ijerph17134779
18. Assenza G, Lanzone J, Ricci L, Boscarino M, Tombini M, Galimberti CA, et al. Electroencephalography at the time of Covid-19 pandemic in Italy. *Neurol Sci*. (2020) 41:1999–2004. doi: 10.1007/s10072-020-04546-8
19. Stipa G, Gabbrielli F, Rabbito C, Di Lazzaro V, Amantini A, Grippo A. et al. The Italian technical/administrative recommendations for telemedicine in clinical neurophysiology. *Neurol Sci*. (2020) 24:1–9. doi: 10.1007/s10072-020-04732-8

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 22 December 2020
doi: 10.3389/fneur.2020.610648

Case Report: Acute Spinal Cord Myelopathy in Patients With COVID-19

Eman M. Khedr[1], Ahmed A. Karim[2] and Radwa K. Soliman[3]*

[1] Department of Neuropsychiatry, Assiut University Hospitals, Assiut, Egypt, [2] Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany, [3] Department of Radiology, Assiut University Hospitals, Assiut, Egypt

COVID-19 is typically associated with fever and severe respiratory symptoms including dry cough and dyspnea. However, COVID-19 may also affect both central and peripheral nervous systems. To date, the incidence rate of spinal cord involvement in COVID-19 is not known and the pathogenesis is still not fully understood. We report here two female patients admitted to Assiut University Hospitals/Egypt during the period from first of July to August 10, 2020. Both presented with a positive SARS-CoV-2 polymerase chain reaction (PCR) nasopharyngeal swab, elevated serum d-dimer and ferritin levels, and bilateral ground glass appearance in a CT chest scan. The first was a 60-year-old female with acute onset of flaccid paraplegia 10 days after flu-like symptoms, in whom MRI revealed transverse myelitis. The second was a 21-year-old female with symptoms of acute quadriplegia, fever, headache, and anosmia in whom an MRI scan revealed long cervico-thoracic myelopathy. Anterior spinal artery occlusion and possibly transverse myelitis were considered as differential diagnosis of long segment myelopathy.

Keywords: case report, COVID-19, spinal cord myelopathy, anterior spinal artery occlusion, transverse myelitis, anterior spinal artery infarct, magnetic resonance image (MRI), SARC V2

OPEN ACCESS

Edited by:
Sheng-Feng Sung,
Ditmanson Medical Foundation
Chia-Yi Christian Hospital, Taiwan

Reviewed by:
Chih-Hao Chen,
National Taiwan University
Hospital, Taiwan
David García-Azorín,
Hospital Clínico Universitario de
Valladolid, Spain

****Correspondence:***
Eman M. Khedr
emankhedr99@yahoo.com;
emankhedr99@aun.edu.eg

Specialty section:
This article was submitted to
Neuroinfectious Diseases,
a section of the journal
Frontiers in Neurology

Received: *26 September 2020*
Accepted: *16 November 2020*
Published: *22 December 2020*

Citation:
Khedr EM, Karim AA and Soliman RK (2020) Case Report: Acute Spinal Cord Myelopathy in Patients With COVID-19. Front. Neurol. 11:610648. doi: 10.3389/fneur.2020.610648

INTRODUCTION

The pandemic of the coronavirus disease 2019 (COVID-19) is spreading rapidly across the world. COVID-19 is typically associated with fever and severe respiratory symptoms including dry cough and dyspnea. Interestingly, there have been several reports of cases with neurological symptoms (1) affecting both central and peripheral nervous systems. The most common serious central nervous system (CNS) complications are cerebrovascular diseases (1). However, spinal cord involvement seems to be rare in COVID-19. To our knowledge, only a few case reports have been published (2–5).

Here, we discuss two case reports of spinal cord myelopathy following acute COVID-19 pneumonia: the first with acute flaccid paraplegia caused by transverse myelitis (post-infection), and the second with acute quadriplegia and cervicothoracic myelopathy secondary to anterior spinal artery occlusion or possibly transverse myelitis.

CASE PRESENTATION 1

A 60-year-old female came to the hospital with a 3-day history of high-grade fever and dry cough followed by weakness and numbness of both lower limbs (walking only with support) with girdle-like pain at the mid-thoracic level. Two days later, the weakness had progressed to complete lower limb paralysis with loss of sensation below the T4 level, retention of urine and fecal incontinence. The patient's previous medical history was innocuous apart from hypothyroidism. She is presently treated with Levothroxine (Eltroxine 100 mg once daily on an empty stomach). There was no personal or family history of previous neurological disorder. She had received no vaccinations in previous months.

On examination: Mental state was normal and speech and cranial nerves were unaffected. There was complete paralysis of both lower limbs, with hypotonia and hyporeflexia and a positive Babinski sign bilaterally. Sensation to light touch was diminished below T4 with loss of pricking pain, temperature sensation and vibration (tested by a tuning fork).

Laboratory tests: SARS-CoV-2 polymerase chain reaction (PCR) was positive in a nasopharyngeal swab, with elevated serum D-dimer (8 mg/L) and ferritin (350 ng/mL) (reference values: D-dimer up to 0.55 mg/L and ferritin 10–291 ng/mL). C-reactive protein (CRP) and erythrocytic sedimentation rate (ESR) 1st and 2nd hour were also elevated (120 mg/dL, 90 and 160 for the 1st and 2nd hour, respectively) (reference value; CRP up to 1 mg/dL, ESR; 1st and 2nd hour 5–10 mm/H). WBCs $7.9 \times 10^9/\mu L$, RBC $4.18 \times 10^6/\mu L$, hemoglobin 10.70 g/dL, platelet $188 \times 10^3/\mu L$, neutrophils 80.9% (high), lymphocytes 15% (low), eosinophil 0.70 (low), basophil 0% and monocyte 2% (reference values: WBCs $4–10 \times 10^3/\mu L$, hemoglobin 12–15 g/dL, platelets $140–450 \times 10^3/\mu L$, relative neutrophil 40–75%, relative lymphocytes 20–45%, relative monocytes 2–10%), eosinophils (2–6%), and basophils (0–1%). All electrolytes were normal (Na^+, K^+, Mg^{2+}, and Ca^{2+}). Liver and renal functions were normal.

There was a bilateral ground glass appearance on chest CT. A sagittal T2-weighted MRI image of the cervical and dorsal spine (**Figures 1a,b**) revealed a poorly delineated long segment of hyperintense signal extending from T4 to T8 involving the central region and occupying more than two-thirds of the cross-sectional area of the cord, consistent with transverse myelitis. An axial T2-weighted image shows the central hyperintense signal involving the cord.

The patient was treated with methylprednisolone 1 g IV for 5 days followed by slow oral prednisone tapering for 2 weeks, which resulted in no improvement. Randomized trials have validated the use of plasma exchange in severe cases that are unresponsive to pulsed corticosteroid administration (6, 7); the patient received five sessions of plasma-pharesis (one session every 2 days), but with no improvement. After the fourth session of plasma-pharesis, she developed right ilio-femoral deep venous thrombosis (DVT). She received low molecular heparin 0.6 IU subcutaneously every 6 h for 5 days with improvement of DVT but the lower limb paralysis was not improved. A few days later, she had an attack of severe dyspnea and cyanosis with pulmonary embolism as confirmed by CT scan of the chest. She was ventilated but died a few hours later.

CASE PRESENTATION 2

A 21-year-old otherwise healthy female came to our clinic with a 10-day history of high-grade fever, dry cough, and anosmia followed by acute onset (taking few hours) flaccid paralysis and numbness of both lower limbs with difficulty in voiding. One day later, she developed weakness and numbness of both upper

FIGURE 1 | Magnetic resonance imaging (MRI) of spine. **(a)** Sagittal T2-weighted image of the cervical and dorsal spine reveals poorly delineated long segment of hyperintense signal, clearly evident from T4 to T8. **(b)** Axial T2-weighted image showing the hyperintense signal involving more than two thirds of the cross-sectional area of the cord.

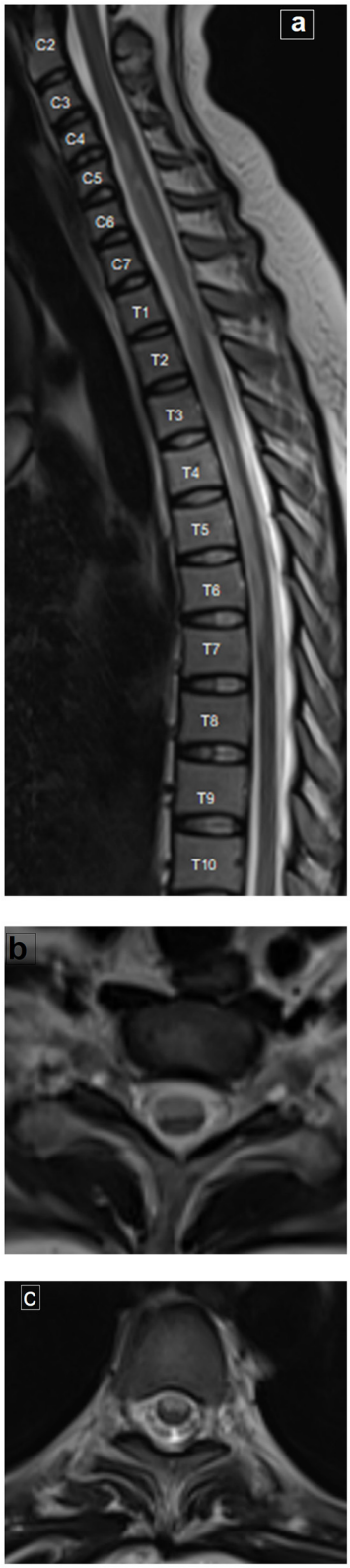


FIGURE 2 | MRI of the spine. **(a)** Sagittal T2-weighted image of the whole spine shows extensive long hyperintense signal extending from C5 to T7,

(Continued)

FIGURE 2 | associated with mild cord swelling. **(b, c)** Axial T2-weighted images at the cervical and dorsal levels, respectively, showing the hyperintense signal occupying the anterior two thirds of the cord, bilaterally (with involvement of both the gray and white matter).

limbs with retention of urine and fecal incontinence. Autonomic symptoms included fluctuations of heart rate with frequent attacks of palpitation, and dizziness and fainting upon sitting from recumbent position. She had received no vaccinations in previous months, and there was no history of a previous similar attack. On general examination, heart was free with normal blood pressure and symmetry of both arms. On neurological examination, she had quadriplegia with greater involvement of the lower limbs, areflexia, and a bilateral Babinski sign. Pain and temperature sensation was absent up to the C4 level with preserved touch, vibration, and joint position sense.

Laboratory tests: SARS-CoV-2 PCR was positive in a nasopharyngeal swab, and serum D-dimer (4.6 mg/L) and ferritin (502 ng/mL) were elevated. Blood counts were as follows: neutrophils 85.7% (high), lymphocytes 17% (low), eosinophil 0.50 (low), basophil 0% and monocyte 3%, WBCs $6.7 \times 10^3/\mu L$, RBC $4.9 \times 10^6/\mu L$, hemoglobin 10.8 g/dL, platelet $333 \times 10^3/\mu L$. Electrolytes were normal (Na^+, K^+, Mg^{2+}, Ca^{2+}, and PO_4). Elevated ESR 1st hour 100 and 150 for 2nd hour, CRP (111 mg/dL), and lactic dehydrogenase (LDH) (356 U/L) were also recorded (reference value; LDH 100–190 U/L). Coagulation profile was normal (prothrombin time 12.8 s, concentration 96%, and INR 1.03) (normal value of coagulation profile prothrombin time was 11–14 s, prothrombin concentrate was 70–130%, PTT was 26–40 s, and INR was 0.5–1.07).

Visual and brain stem auditory evoked potentials were normal. Chest CT showed a bilateral ground glass appearance with no evidence of aortic dissection. Electrocardiography was normal.

MRI examination of the spine revealed an extensive hyperintense signal on T2-weighted imaging, extending from C5 to T7, and occupying the anterior two thirds of the cord with involvement of both gray and white matter. This was associated with mild swelling of the cord (**Figures 2a–c**). The possibility of anterior spinal artery occlusion was considered given the clinical presentation, laboratory, and MRI findings. A CT of the chest showed no evidence of aortic dissection with normal heart and symmetrical blood pressure in both arms. Thus, we think it unlikely that the lesion was the result of aortic dissection-related occlusion of multiple supplying arteries. Given her age, multiple sclerosis was considered as a possible diagnosis. However, the long segment of cord involvement, together with the normal evoked potentials and no positive MRI findings in the brain, excluded multiple sclerosis. The possibility of transverse myelitis was also considered as a differential diagnosis of long segment myelopathy; however, the complete preservation of deep sensation on clinical examination could support the diagnosis of anterior spinal artery occlusion.

The patient was treated with methylprednisolone 1 g IV for 5 days but no improvement. Corticosteroid was, therefore, stopped

gradually over the next 10 days and the patient was treated with Rivaroxaban (20 mg/day) for 30 days with short wave therapy and passive exercise without improvement. Finally, she received intravenous immunoglobulin (IVIG) 0.4 g/kg/day for 5 consecutive days and was followed up for another month. There was mild improvement in upper limb strength while the lower limbs were still flaccid.

DISCUSSION

Human coronaviruses can be neuroinvasive and neurotropic (7, 8). In particular, SARS-CoV appears to cause a variety of both CNS and PNS disorders such as cerebrovascular stroke, encephalitis, Guillain–Barre Syndrome, and isolated cranial nerve palsy. Although the pathophysiological mechanisms are unclear, there are two likely possibilities: hematogenous dissemination (9) and neuronal retrograde dissemination (10). The first requires the presence of virus in the blood, where it can infect the endothelium. In contrast, neuronal retrograde dissemination occurs when the virus infects sensory or motor nerve endings and is transported retrogradely or anterogradely into the CNS (11, 12). Transverse myelitis is a rare complication of COVID-19 and it is still unsettled whether the myelitis is a direct result of viral infection or an autoimmune sequelae.

Our first case involved dorsal transverse myelitis occurring shortly after COVID-19 infection. In transverse myelitis, the lesion usually involves the central part of the cord, occupying more than two thirds of its cross section and extends longitudinally over more than one segment (13). Since no other causes of myelitis could be identified and since inflammatory markers (D-dimer, ferritin level, CRP, and ESR) were very high, we postulated that this was due to a post-infectious secondary immunogenic overreaction. Others have previously shown that human coronaviruses like SARS can directly infect the central nervous system (14), and it has been suggested that this could provoke systemic cytokine production, which might contribute to the pathophysiology of COVID-19 (15).

To date, four reports of similar cases have been published in the literature, all of which link COVID-19 to acute myelitis as a neurological complication. The first was in Wuhan, China, where Zhao et al. (16) described a 66-year-old patient who developed acute flaccid paraplegia and urinary incontinence. They postulated focal myelitis but without MRI imaging or serological confirmation. The second case was in Boston where a 28-year-old female with a history of hypothyroidism and treatment with levothyroxine developed symptoms of productive cough and low-grade temperature followed by acute myelitis 7 days later (4). In the third case, Munz et al. (3) reported a 60-year-old patient with acute onset moderate spastic paraparesis with retention of urine. An MRI of the spine revealed a T2 signal hyperintensity at Th 9 level suggestive of acute transverse myelitis. AlKetbi et al. (2) reported the fourth case of acute myelitis in a 32-year-old male COVID-19-positive patient. Two days after presenting with flu-like symptoms, he experienced a sudden-onset paraplegia with urinary retention. A spinal MRI revealed a large volume of hyperintense signal involving predominantly the gray matter in the cervical, dorsal, and lumbar regions.

Our second case is the first report of a young female, initially diagnosed as transverse myelitis. Yet, as she presented clinically with characteristic features of acute paralysis of four limbs with loss of pain and temperature together with preserved dorsal column function and MRI findings of bilateral involvement of the anterior 2/3 of spinal cord, we considered the possibility of anterior spinal artery occlusion. Diffusion MRI would be helpful to confirm such diagnosis at early onset. Unfortunately, an MRI scan was only available at a later stage for this patient. Although the extensive longitudinal involvement along the cord (as shown in our case) is most frequently associated with large vessel dissection, other causes of thromboembolism and coagulopathy also have been shown to be associated with long segment involvement (17).

As our patient is young with no vascular risk factors, and no evidence of aortic or vertebral dissection but had high levels of inflammatory markers (such as CRP, ESR, and ferritin) and markers of coagulation such as D-dimer, we consider that her condition was most probably related to vasculopathy as well as hypercoagulopathy. In line with this suggestion, Beyrouti and co-workers reported six severely affected patients who had large cerebral infarcts and elevated D-dimer levels ($\geq$1,000 μg/L) consistent with a coagulopathy (18).

The fact that young people with COVID-19 have an unexpectedly high frequency of ischemic stroke but few risk factors may mean that other causes peculiar to COVID-19 are at play. One possibility is that viral invasion of the vascular endothelium (endotheliitis) contributes to vascular ischemia of the spinal cord.

The diagnosis of MS clinically isolated syndrome can be suspected at this age; however, the absence of clinical and MRI finding of dissemination in space and the involvement of multiple segments with the long hyperintense signal as appeared on MRI spine negate this possibility.

Limitations

The absence of diffusion imaging in the second case is a major limitation since this would help to confirm the diagnosis of spinal artery infarction. However, MRI was only available at a later stage.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Faculty of Medicine, Medical Ethics Committee. Assiut University IBR no 17300470. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

EK performed neurological examination and wrote the first draft of the article and is responsible for the overall content. RS has evaluated the radiological images and contributed mainly to the discussion of the cases. AK and the two authors contributed significantly to the discussion of the patient and revision of the first draft. All authors approved the final article and assured all the questions regarding the accuracy of the article.

REFERENCES

1. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol.* (2020) 19:767–83. doi: 10.1016/s1474-4422(20)30221-0
2. AlKetbi R, AlNuaimi D, AlMulla M, AlTalai N, Samir M, Kumar N, et al. Acute myelitis as a neurological complication of COVID-19: a case report and MRI findings. *Radiol Case Rep.* (2020) 15:1591–5. doi: 10.1016/j.radcr.2020.06.001
3. Munz M, Wessendorf S, Koretsis G, Tewald F, Baegi R, Krämer S, et al. Acute transverse myelitis after COVID-19 pneumonia. *J Neurol.* (2020) 267:2196–7. doi: 10.1007/s00415-020-09934-w
4. Sarma D, Bilello LA. A case report of acute transverse myelitis following novel coronavirus infection. *Clin Pract Cases Emerg Med.* (2020) 4:321–3. doi: 10.5811/cpcem.2020.5.47937
5. Sotoca J, Rodríguez-Álvarez Y. COVID-19-associated acute necrotizing myelitis. *Neurol Neuroimmunol Neuroinflamm.* (2020) 7:e803. doi: 10.1212/nxi.0000000000000803
6. Awad A, Stüve O. Idiopathic transverse myelitis and neuromyelitis optica: clinical profiles, pathophysiology and therapeutic choices. *Curr Neuropharmacol.* (2011) 9:417–28. doi: 10.2174/157015911796557948
7. Greenberg BM, Thomas KP, Krishnan C, Kaplin AI, Calabresi PA, Kerr DA. Idiopathic transverse myelitis: corticosteroids, plasma exchange, or cyclophosphamide. *Neurology.* (2007) 68:1614–7. doi: 10.1212/01.wnl.0000260970.63493.c8
8. Desforges M, Le Coupanec A, Brison E, Meessen-Pinard M, Talbot PJ. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. *Adv Exp Med Biol.* (2014) 807:75–96. doi: 10.1007/978-81-322-1777-0_6
9. Desforges M, Le Coupanec A, Dubeau P. Human coronaviruses and other respiratory viruses: underestimated opportunistic pathogens of the central nervous system? *Viruses*. (2019) 12:14. doi: 10.3390/v12010014
10. Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. *Eur J Neurol.* (2020) 27:1764–73. doi: 10.1111/ene.14277
11. Berth SH, Leopold PL, Morfini GN. Virus-induced neuronal dysfunction and degeneration. *Front Biosci (Landmark Ed).* (2009) 14:5239–59. doi: 10.2741/3595
12. Swanson PA, 2nd, McGavern DB. Viral diseases of the central nervous system. *Curr Opin Virol.* (2015) 11:44–54. doi: 10.1016/j.coviro.2014.12.009
13. Goh C, Desmond PM, Phal PM. MRI in transverse myelitis. *J Magn Reson Imaging.* (2014) 40:1267–79. doi: 10.1002/jmri.24563
14. Li YC, Bai WZ, Hashikawa T. Response to commentary on "The neuroinvasive potential of SARS-CoV-2 may play a role in the respiratory failure of COVID-19 patients". *J Med Virol.* (2020) 92:707–9. doi: 10.1002/jmv.25824
15. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science (New York, NY).* (2020) 368:473-4. doi: 10.1126/science.abb8925
16. Zhao K, Huang J, Dai D, Feng Y, Liu L, Nie S. Acute myelitis after SARS-CoV-2 infection: a case report. *MedRxiv*. (2020). doi: 10.1101/2020.03.16.20035105
17. Hsu JL, Cheng MY, Liao MF, Hsu HC, Weng YC, Chang KH, et al. The etiologies and prognosis associated with spinal cord infarction. *Ann Clin Transl Neurol.* (2019) 6:1456–64. doi: 10.1002/acn3.50840
18. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 06 January 2021
doi: 10.3389/fneur.2020.607193

Stroke Admissions, Stroke Severity, and Treatment Rates in Urban and Rural Areas During the COVID-19 Pandemic

Hebun Erdur[1,2†], Bob Siegerink[2†], Christoph Leithner[1,2], Christiana Franke[1], Irina Lorenz-Meyer[1,2], Sarah Theen[1], Anselm Angermaier[3], Stephan Kinze[4], Joachim E. Weber[1,2,5], Jessica L. Rohmann[2,6], Jan F. Scheitz[1,2], Christian H. Nolte[1,2,5,7,8], Matthias Endres[1,2,5,7,8] and Heinrich J. Audebert[1,2]*

[1] Klinik und Hochschulambulanz für Neurologie, Charité - Universitätsmedizin Berlin, Berlin, Germany, [2] Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany, [3] Department of Neurology, University Medicine Greifswald, Greifswald, Germany, [4] Klinik für Neurologie, Unfallkrankenhaus Berlin, Berlin, Germany, [5] Berlin Institute of Health (BIH), Berlin, Germany, [6] Institute of Public Health, Charité – Universitätsmedizin Berlin, Berlin, Germany, [7] DZHK (German Center for Cardiovascular Research), partner site Berlin, Berlin, Germany, [8] DZNE (German Center for Neurodegenerative Diseases), partner site Berlin, Berlin, Germany

OPEN ACCESS

Edited by:
Tomohisa Nezu,
Hiroshima University, Japan

Reviewed by:
Naoto Kinoshita,
Hiroshima Prefectural Hospital, Japan
Xabier Urra,
Hospital Clínic de Barcelona, Spain

***Correspondence:**
Hebun Erdur
hebun.erdur@charite.de

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 16 September 2020
Accepted: 09 December 2020
Published: 06 January 2021

Citation:
Erdur H, Siegerink B, Leithner C, Franke C, Lorenz-Meyer I, Theen S, Angermaier A, Kinze S, Weber JE, Rohmann JL, Scheitz JF, Nolte CH, Endres M and Audebert HJ (2021) Stroke Admissions, Stroke Severity, and Treatment Rates in Urban and Rural Areas During the COVID-19 Pandemic. Front. Neurol. 11:607193. doi: 10.3389/fneur.2020.607193

Background: Many regions worldwide reported a decline of stroke admissions during the early phase of the coronavirus disease 2019 (COVID-19) pandemic. It remains unclear whether urban and rural regions experienced similar declines and whether deviations from historical admission numbers were more pronounced among specific age, stroke severity or treatment groups.

Methods: We used registry datasets from (a) nine acute stroke hospitals in Berlin, and (b) nine hospitals from a rural TeleNeurology network in Northeastern Germany for primary analysis of 3-week-rolling average of stroke/TIA admissions before and during the COVID-19 pandemic. We compared course of stroke admission numbers with regional cumulative severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) infections. In secondary analyses, we used emergency department logs of the Berlin Charité University hospital to investigate changes in age, stroke severity, and thrombolysis/thrombectomy frequencies during the early regional Sars-CoV-2 spread (March and April 2020) and compared them with preceding years.

Results: Compared to past years, stroke admissions decreased by 20% in urban and 20-25% in rural hospitals. Deviations from historical averages were observable starting in early March and peaked when numbers of regional Sars-CoV-2 infections were still low. At the same time, average admission stroke severity and proportions of moderate/severe strokes (NIHSS >5) were 20 and 20–40% higher, respectively. There were no relevant deviations observed in proportions of younger patients (<65 years), proportions of patients with thrombolysis, or number of thrombectomy procedures. Stroke admissions at Charité subsequently rebounded and reached near-normal levels after 4 weeks when the number of new Sars-CoV-2 infections started to decrease.

Conclusions: During the early pandemic, deviations of stroke-related admissions from historical averages were observed in both urban and rural regions of Northeastern Germany and appear to have been mainly driven by avoidance of admissions of mildly affected stroke patients.

Keywords: stroke, COVID19, SARS-CoV-2, epidemiology, public health

INTRODUCTION

Authorities and governments worldwide have released public health recommendations and restrictions in order to contain the outbreak of Sars-CoV-2. Avoidance of physical contact whenever possible has been one of the most important recommendations in the early phase of the COVID-19 pandemic in Europe. Large regional outbreaks overwhelming local health systems and increasing nosocomial Sars-CoV-2 infections have alarmed the public, prompting the German government among others to issue a strict physical distancing decree on March 22, 2020 (1). Parallel to implementing lockdown rules, hospitals reported decreased admissions of patients with acute cardio- and cerebrovascular diseases in emergency departments (2). As a reaction, health providers advised the public not to avoid necessary medical attendance for chest pain or neurological deficits but patients may have chosen to stay at home because of fear of infection with Sars-CoV-2 (3).

In this descriptive study, we aimed to quantify acute stroke hospitalizations in metropolitan and rural hospitals in Northeastern Germany before and during the early local phase of the COVID-19 pandemic. We hypothesized that fewer patients with stroke and TIA presented to hospitals and that this decrease was predominantly driven by patients with mild stroke severity. In addition to stroke severity, we investigated age groups, proportions of patients who received thrombolysis, and numbers of thrombectomies.

METHODS

Data Availability Statement

Data and analysis code will be made available upon reasonable request to the corresponding author.

Study Design and Population

In our primary analysis, we investigated hospital admissions for ischemic stroke, hemorrhagic stroke, and TIA in both an urban and a rural setting in Berlin and Northeastern Germany, respectively. For this, we used data obtained from two data sources: (a) from nine Berlin hospitals with stroke units participating in a metropolitan stroke registry (B-SPATIAL, ClinicalTrials.gov Identifier: NCT03027453) and (b), from inpatient case data of nine hospitals participating in an acute TeleNeurology network in the rural areas of the states of Brandenburg and Mecklenburg-Western Pomerania in Northeastern Germany (ANNOTeM, German Clinical Trials Register Identifier: DRKS00013067). A complete list of participating hospitals and a map of both registries is presented in the **Supplementary Material**. For this study, we included all patients with a main ICD-10 diagnosis code of hemorrhagic or ischemic stroke (I60–I63) or transient ischemic attack (TIA, G45) without restriction in onset to admission times from January 1, 2018 to March 31, 2020 on an individual patient level.

For our secondary analyses, we obtained data from the emergency department logs of our tertiary care center Charité – Universitätsmedizin Berlin (Campus Benjamin Franklin and Campus Virchow Klinikum). These logs include information of all patients who were diagnosed with hemorrhagic or ischemic stroke or TIA (I60–63 and G45) by a neurologist in the emergency department. These data include routinely recorded information on age, stroke severity as assessed by National Institutes of Health Stroke Scale (NIHSS), intravenous thrombolysis, and thrombectomy. Because the weekly numbers of patients with thrombectomy were small, we provide these numbers on a per month basis. We included all stroke-related events documented in the emergency department logs from January 1, 2016 to May 13, 2020 for the current analysis.

Statistical Analyses

Stroke data were plotted for the hospital stroke admission analyses from Jan 1, 2018 to March 31, 2020 and for the Charité emergency department stroke logs from Jan 1, 2016 to and including May 12, 2020. Calendar dates were transformed to number of days from January 1st of each year, with full weeks (1–52) defined as 7-day stretches, to facilitate comparability between years. Only full weeks were included. In the primary analysis, the data from prior years (before January 1, 2020) was used to obtain a historical reference value, which was computed as the weekly average number of admissions. In secondary analyses, we depict historical weekly averages and deviations in proportions of stroke patients <65 years, NIHSS on admission, proportion of more severe stroke (NIHSS >5), and number and proportion of patients who received intravenous thrombolysis and/or thrombectomy. Setting the weekly averages over the past years to 100%, we plotted the relative deviations for each week for 2020 as well as past years. We show the data with a rolling average with a 3 week window to reduce the noise in the data; all graphs with weekly number accompanied with the corresponding confidence interval that quantify the precision of the data are shown in the **Supplementary Material**.

Weekly numbers of officially confirmed Sars-CoV-2 infections and registered COVID-19 deaths in the city of Berlin and Northeastern Germany (obtained from https://www.berlin.de/corona/fallstatistik/ and https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Fallzahlen.html) were overlaid on these plots for contextualization of the unfolding COVID-19

pandemic in our setting. All descriptive analyses and plots were performed in STATA 14.

Ethics

ANNOTeM was approved by the Charité Ethics Committee (ANNOTeM: EA4/188/17). The B-SPATIAL and Charité emergency department stroke data contain prospectively collected data records for the purpose of quality improvement measures as regulated by German Social Code, Book V, §135a. The Berlin legislation for hospitals (§25 Berliner Krankenhausgesetz) allows the use of B-SPATIAL and Charité routine care and quality monitoring data for scientific evaluations and is exempt from approval by a local review board. Before using the data from B-SPATIAL, ANNOTeM, and Charité, all individual datasets were anonymized.

RESULTS

Metropolitan Area of Berlin

From January 1, 2018 to March 31, 2020, a total of 19,435 patients were diagnosed and recorded with ischemic stroke, hemorrhagic stroke, or TIA in nine Berlin acute stroke hospitals participating in the B-SPATIAL registry with a weekly average of 172 (SD ±21) patients. **Figure 1A** shows the 3-week rolling averages of stroke and TIA cases in 2020 with a sharp deviation of 20% fewer patients compared to the past years' average recorded in week 13 (covering the period from March 18 to April 7, 2020).

Rural Area of Northeastern Germany

A total of 3,855 patients diagnosed with ischemic stroke, hemorrhagic stroke, or TIA were admitted to one of nine ANNOTeM hospitals in Northeastern Germany from January 1, 2018 to March 31, 2020 with a weekly mean of 33 (SD ±4) cases. **Figure 1B** shows a negative deviation of stroke and TIA cases 20–25% compared to the weekly historical average during weeks 12 and 13.

Charité Hospital

From January 1, 2016 to May 12, 2020 two emergency departments of the Charité logged 8,779 ischemic stroke, hemorrhagic stroke, and TIA patients with a weekly mean number of 39 (SD ±6). The number of cases was 25–35% lower compared to the historical average from weeks 11 to 14 (**Figure 2**). The number of stroke patients increased again since week 15 but remained slightly below the historical average.

The average of the weekly mean NIHSS on admission had been 5.5 (SD ±1.2) in the pre-pandemic period. During the pandemic period, the mean NIHSS of stroke patients was about 20% higher compared to the historical average throughout weeks 10–18 (**Figure 3A**). In 2020, weekly mean NIHSS in weeks 1–8 was 5.5 (SD ±0.8), in weeks 9–12 6.4 (SD ±0.6), in weeks 12–16 6.8 (SD ±1.1), and in weeks 17–19 5.8 (SD 1.2). Similarly, the proportion of patients with moderate to severe stroke (NIHSS >5) was about 20-40% higher compared to the historical average from weeks 9 to 15 but returned to the average thereafter (**Figure 3B**).

The proportion of younger patients (<65 years) was similar to the historical average (**Figure 4A**). In 2020, weekly mean number of patients who received thrombolysis in weeks 1–8 was 7.5 (SD ±1.7), in weeks 9–12 3.0 (SD ±1.9), and in weeks 12–16 6.7 (SD ±2.0). The proportion of patients who received thrombolysis was similar to the historical average (**Figure 4B**). We did not observe a substantial deviation in the number of stroke patients treated with thrombectomy (average of 24 per month in 2019, 29 in March 2020, and 19 in April 2020).

DISCUSSION

In three different datasets from the metropolitan area of Berlin and the rural region of Northeastern Germany, the weekly number of stroke and TIA patients presenting to hospitals declined sharply in the early phase of the COVID-19 pandemic. Patients admitted during this period had more severe strokes compared with preceding years. While the weekly mean average of patients who received thrombolysis declined during the early pandemic, the proportion of patients treated with thrombolysis and numbers of performed thrombectomies were similar to the historical averages. The decline in stroke admissions occurred parallel to media reports of increasing numbers of Sars-CoV-2 infections in other European countries and reached its maximum shortly after nationwide decrees restricting physical contacts were issued. Notably, this decline occurred before a relevant increase of Sars-CoV-2 infections and COVID-19 deaths was seen in Berlin and Northeastern Germany. Admission numbers in the emergency department of the Charité in Berlin increased again to near-normal levels after a low plateau of 4 weeks while restrictions were still in place.

In our primary analysis, we assessed admissions of stroke and TIA patients to 18 hospitals in an urban and a rural region in Northeastern Germany. Our data sources are derived from local registries and included only confirmed stroke and TIA diagnoses with a high degree of data completeness. In addition, our emergency department data sources providing information on age, stroke severity, and thrombolysis allowed us to characterize the population of affected stroke patients in more detail in the secondary analyses.

Declines in hospital admissions for stroke and TIA during the COVID-19 pandemic have also been reported from China (4) (≈40% fewer admissions) and Spain (5, 6) (≈23–25% fewer admissions). Our results add new information and indicate that patients with no or only mild deficits were less often admitted during the early local COVID-19 pandemic period, suggesting that these patients tended to avoid hospitalization. It is tempting to speculate that fear of infection with Sars-CoV-2 was the major reason. In contrast to patients with TIA and minor stroke, patients with moderate or severe stroke may feel a much higher need to seek appropriate medical care and therefore may have still presented to hospitals despite fear of infection with Sars-CoV-2. Decreased social support hampering the detection of stroke may also have contributed to the decline in stroke cases.

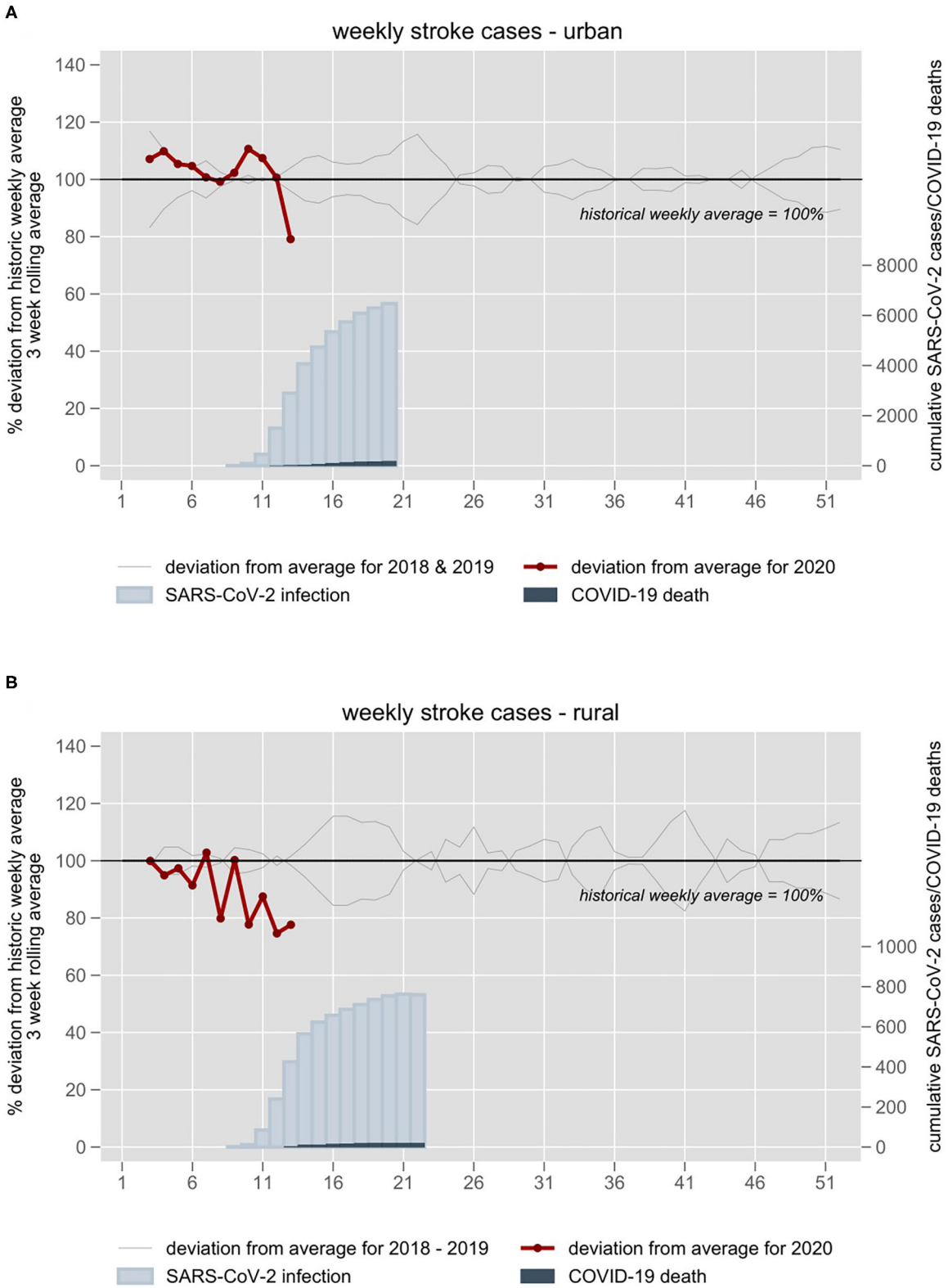


FIGURE 1 | Stroke and TIA admission numbers of **(A)** nine stroke units in the metropolitan area of Berlin and **(B)** nine hospitals of a TeleNeurology Network in Northeastern Germany 2018–2020. Admission numbers are plotted against week numbers. All individual years are plotted in gray. The 3-week rolling average of 2018–2019 is set at 100%. The year 2020 is plotted in red. Blue inlays depict cumulative confirmed Sars-CoV-2 infections and COVID-19 deaths in the respective weeks.

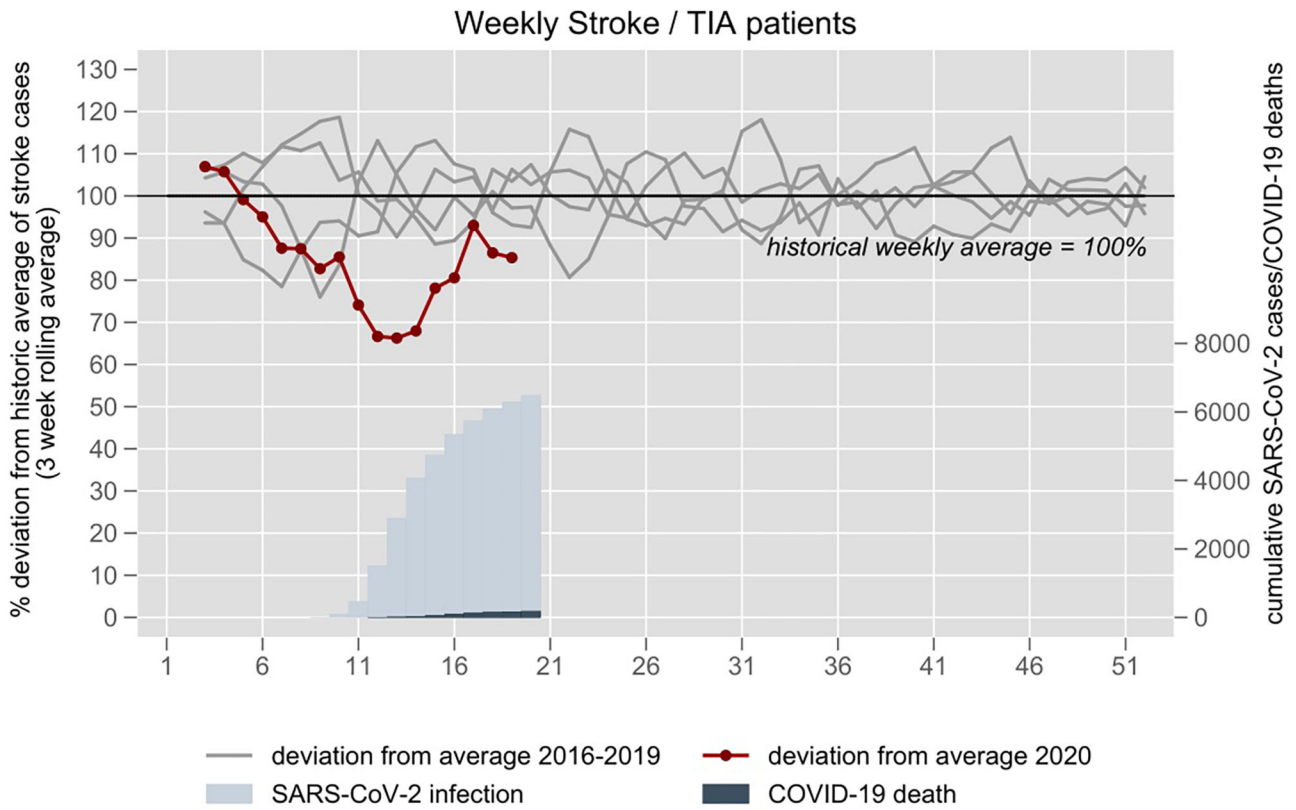


FIGURE 2 | Stroke and TIA related emergency department visits at the University hospital Charité in Berlin 2016–2020. The 3-week rolling average of 2016–2019 is set at 100%. The year 2020 is plotted in red. Blue inlay depicts cumulative confirmed Sars-CoV-2 infections and COVID-19 deaths in the respective weeks.

Our findings do not indicate a relevant deviation of hospital attendance according to age compared with previous years' weekly averages. Also, in contrast to studies from China (4) and France (7), and suggested by data on decreasing use of an imaging software to support thrombectomy decisions (8), we did not observe a relevant deviation of numbers of patients receiving thrombectomy compared with historical averages. While the number of patients treated with thrombolysis declined during the early pandemic, the proportion of patients with thrombolysis did not show a relevant deviation compared to historical averages in our study, which is probably attributable to the overall lower number of admissions in the same period.

The metropolitan area of Berlin and the region of Northeastern Germany were affected by relatively low numbers of Sars-CoV-2 infections compared to other European regions (in particular Northern Italy, Madrid and Catalonia in Spain, Paris and Grand-Est in France) and the United States (State of New York). The comparatively low numbers of local Sars-CoV-2 infections in Northeastern Germany (total of 12,115 confirmed infections as of June 23, 2020 in the three German states of Berlin, Brandenburg, and Mecklenburg-Western Pomerania with 6.8 million inhabitants) have not overwhelmed the regional health systems so far. In Northeastern Germany, the need for ICU beds has not exceeded the ICU capacity; measures to rapidly increase the capacity were executed in the early pandemic phase. Even during the time of highest COVID-19 related ICU occupancy at the Charité on April 26, 2020, there were 24% fewer hospitalized patients in the Charité compared to the year before (internal statistics). Although the German government ordered hospitals to suspend all elective hospital admissions on March 18 in order to reserve hospital beds for expected COVID-19 patients, TIA and stroke patients have always been regarded as medical emergencies in emergency departments with no policy for outpatient workup. Therefore, while public health measures were successful in containing the spread of Sars-CoV-2 infections, they may have led to collateral damage on medical care for a subgroup of stroke patients with TIA and minor stroke who may have stayed at home rather than to seek medical help.

Interestingly, our emergency department data indicate that this decline in admissions may be transient as the number of stroke patients returned to near normal levels after 4 weeks although restrictions were still in place and the numbers of hospitalized COVID-19 patients increased. Our descriptive analyses suggest the need for public communication strategies to ensure that patients with stroke or TIA (and supposedly other critical disease) symptoms present to hospitals and receive adequate diagnostic evaluation and treatment despite an ongoing health emergency. After noticing a drop in stroke and heart attack cases, the Charité hospital informed the public on March 29, 2020, that patients with stroke or heart attack symptoms

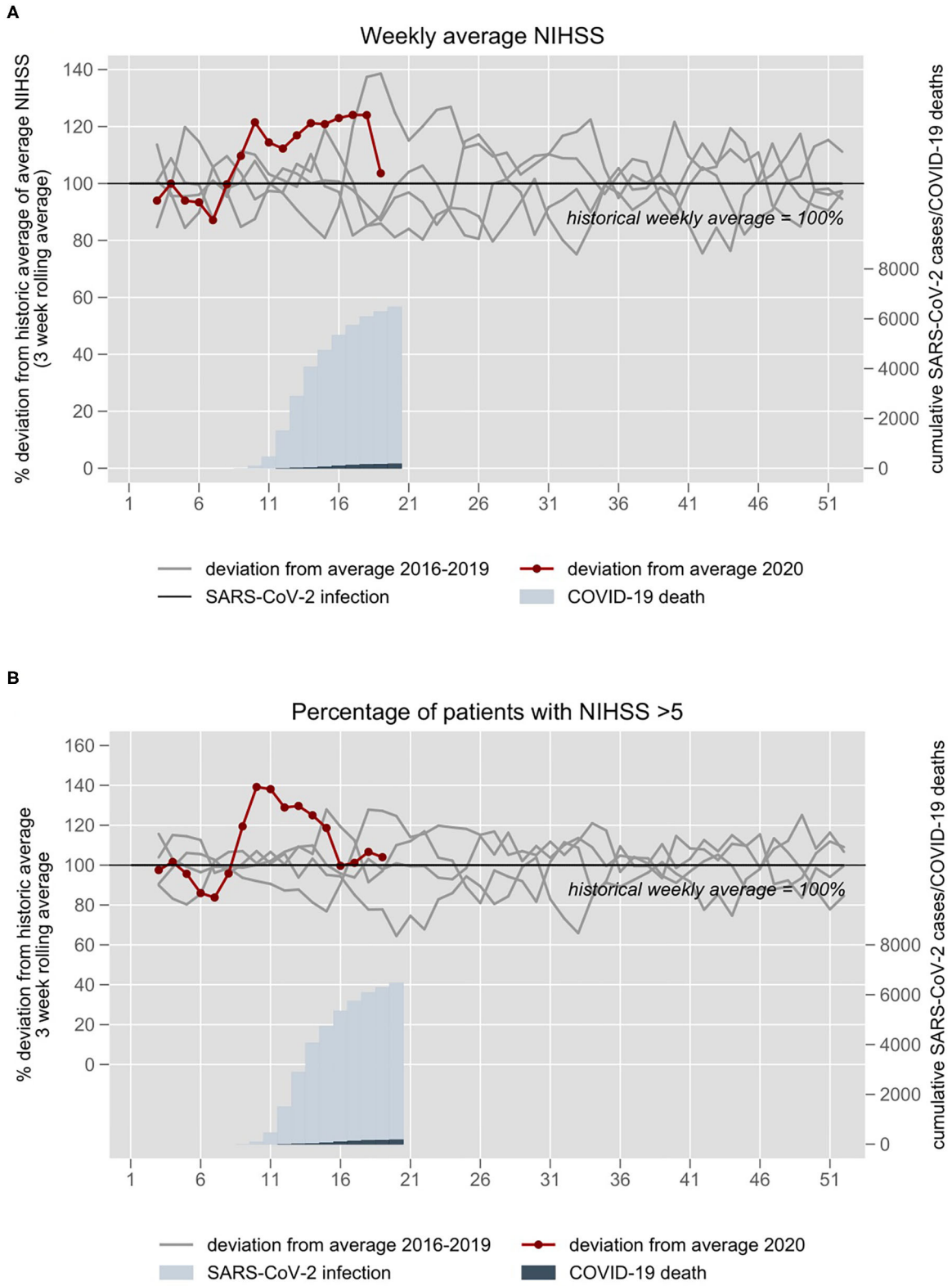


FIGURE 3 | (A) NIHSS on admission and **(B)** proportion of patients with moderate to severe stroke (NIHSS >5) at the University hospital Charité in Berlin 2016–2020. The 3-week rolling average of 2016–2019 is set at 100%. The year 2020 is plotted in red. Blue inlays depict cumulative confirmed Sars-CoV-2 infections and COVID-19 deaths in the respective weeks.

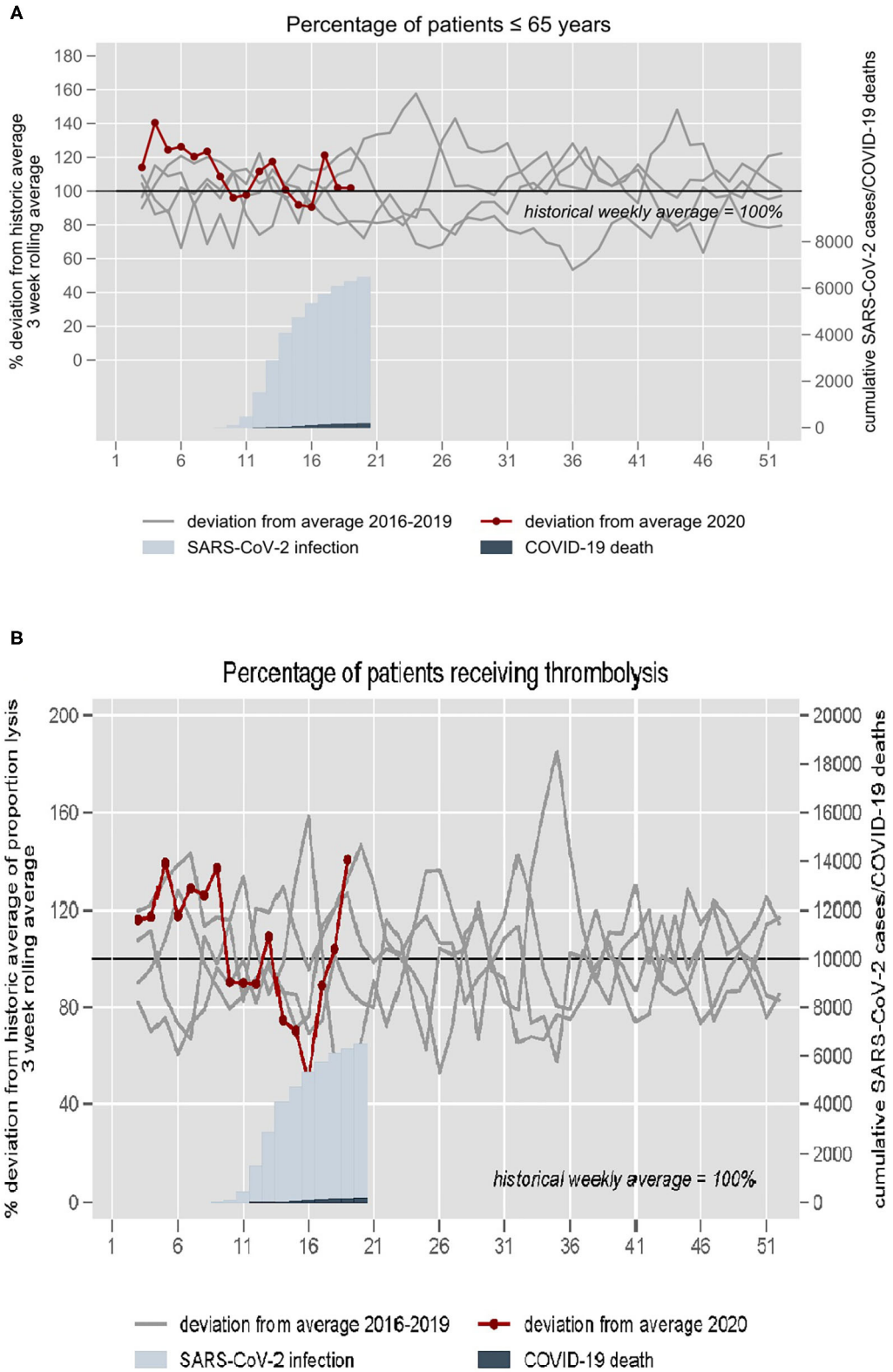


FIGURE 4 | (A) Proportion of patients ≤65 years and **(B)** proportion of patients treated with thrombolysis at the University hospital Charité in Berlin 2016–2020. The 3-week rolling average of 2016–2019 is set at 100%. The year 2020 is plotted in red. Blue inlays depict cumulative confirmed Sars-CoV-2 infections and COVID-19 deaths in the respective weeks.

should immediately contact the emergency services (9). This may have contributed to the observed increase of stroke admissions afterwards. Measures need to be taken to ensure safe transfer and evaluation of stroke patients and to inform the public about the risk of missed and untreated TIA and stroke.

There are several limitations of our study. First, we did not include all hospitals in Berlin and in Northeastern Germany; nevertheless, our data covers 9 of 15 stroke units in Berlin and a large area in rural Northeastern Germany, indicating that our data is representative for the regional situation of stroke admissions. Second, because of different regional spreads of Sars-CoV-2 and differences in health system capacities, our results may not be generalizable to other settings. Third, registry data regarding hospital admissions used in the primary analyses was only available until to the end of March 2020. This lag is caused due to the nature of these lists as they are based on hospital main diagnosis code at discharge. The data used in the secondary analyses from the emergency department stroke logs are updated in real time, and therefore, were available through May 12, 2020, affording us more detailed insights as the pandemic situation unfolded. Specifically, after the initial decline in the early phase, we observed increasing numbers of stroke cases in the second half of April. Further research should investigate the evolution of stroke numbers beyond the early phase of the COVID-19 pandemic. It is unclear whether fewer hospital admissions for TIA and minor stroke will result in a higher frequency of more severe strokes in the weeks or months afterwards attributable to delayed secondary prevention. Finally, our study does not provide data on reasons why patients may have avoided hospitals.

In summary, we observed a relevant deviation of the weekly numbers of stroke and TIA patients presenting to hospitals in the early local phase of the COVID-19 pandemic in Berlin and Northeastern Germany compared with historical averages. Our results may inform health officials and authorities that containment measures should be paralleled by measures to ensure adequate awareness, diagnostic workup and treatment for serious diseases that may present with minor symptoms, such as stroke, which can have major consequences if not addressed early.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HE, BS, CL, CF, JR, JS, CN, ME, and HA: conception and design of the work. All authors: acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content, and final approval of the version to be published.

FUNDING

We acknowledge support from the German Research Foundation (DFG) and the Open Access Publication Fund of Charité – Universitätsmedizin Berlin. ANNOTeM is funded by the German Innovation Funds (01NVF16028).

ACKNOWLEDGMENTS

We thank the Berliner Schlaganfall-Allianz e.v. and Center for Stroke Research Berlin (Dr. Andreas Meisel and Daniel Heppe) for providing their map of Stroke Units in Berlin.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.607193/full#supplementary-material

REFERENCES

1. *German Government: Extension of the Decree on the Limitation of Social Contacts.* Available online at: https://www.bundesregierung.de/breg-de/themen/coronavirus/besprechung-der-bundeskanzlerin-mit-den-regierungschefinnen-und-regierungschefs-der-laender-1733248 (accessed September 16, 2020).
2. Bernstein L, Stead Sellers F. Patients with heart attacks, strokes and even appendicitis vanish from hospitals. *The Washington Post* (2020, April 19). Available online at: https://www.washingtonpost.com/health/patients-with-heart-attacks-strokes-and-even-appendicitis-vanish-from-hospitals/2020/04/19/9ca3ef24-7eb4-11ea-9040-68981f488eed_story.html (accessed September 16, 2020).
3. Is it safe to go to the hospital during COVID-19 pandemic? Doctors say yes. *American Heart Association News* (2020, May 4). Available online at: https://www.heart.org/en/news/2020/05/04/is-it-safe-to-go-to-the-hospital-during-covid-19-pandemic-doctors-say-yes (accessed September 16, 2020).
4. Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke*. (2020) 51:1996–2001. doi: 10.1161/STROKEAHA.120.030225
5. Rudilosso S, Laredo C, Vera V, Vargas M, Renú A, Llul L, et al. Acute stroke care is at risk in the era of COVID-19: experience at a Comprehensive Stroke Center in Barcelona. *Stroke*. (2020) 51:1991–5. doi: 10.1161/STROKEAHA.120.030329
6. Montaner J, Barragán-Prieto A, Pérez-Sánchez S, Escudero-Martínez I, Moniche F, Sánchez-Miura JA, et al. Break in the stroke chain of survival due to COVID-19. *Stroke*. (2020) 51:2307–14. doi: 10.1161/STROKEAHA.120.030106
7. Kerleroux B, Fabacher T, Bricout N, Moïse M, Testud B, Vingadassalom S, et al. Mechanical thrombectomy for acute ischemic stroke amid the COVID-19 outbreak: decreased activity, and increased care delays. *Stroke*. (2020) 51:2012–7. doi: 10.2139/ssrn.3571545
8. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral effect of Covid-19 on stroke evaluation in the United States. *N Engl J Med*. (2020) 383:400–1. doi: 10.1056/NEJMc2014816

9. Charité–Universitätsmedizin Berlin. *Stroke and Heart Attack: Charité Appeal to the Citizens of Berlin to Urgently Seek Medical Help if They Experience Symptoms*. Available online at: https://www.charite.de/en/research/research_news/research_news/artikel/detail/stroke_and_heart_attack_charite_appeal_to_the_citizens_of_berlin_to_urgently_seek_medical_help_if_t/ (accessed September 16, 2020).

Conflict of Interest: JR's position is funded by a grant from the Else-Kröner-Fresenius Foundation (www.ekfs.de, GSO/EKFS-17). She also reports financial support from Novartis Pharma for a self-initiated research project on migraine remission in aging on a population level unrelated to this work. CN reports lecture fees paid from Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer Pharma, Abbott and Gore. ME received funding from DFG under Germany's Excellence Strategy – EXC-2049 – 390688087, BMBF, DZNE, DZHK, EU, Corona Foundation, and Fondation Leducq. He also reports grants from Bayer and fees paid to the Charité from Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Amgen, GSK, Sanofi, Covidien, Novartis, Pfizer, all outside the submitted work. HA reports being the principal investigator of the ANNOTeM network, funded by the German Innovation Funds and having acquired funding for the B-SPATIAL Registry by the German Research Foundation (DFG). He also reports having received speaker and consultancy honoraria by Bayer Healthcare, BMS, Boehringer Ingelheim, Novo-Nordisk, Pfizer and Takeda.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 06 January 2021
doi: 10.3389/fneur.2020.609227

Triage and Allocation of Neurocritical Care Resources During the COVID 19 Pandemic - A National Survey

Florian Gessler[1†], Felix Lehmann[2†], Julian Bösel[3], Hannah Fuhrer[4], Hermann Neugebauer[5], Katja E. Wartenberg[6], Stefan Wolf[7], Joshua D. Bernstock[8,9], Wolf-Dirk Niesen[4†] and Patrick Schuss[10†] on behalf of the IGNITE-study group[‡]*

[1] Department of Neurosurgery, University Hospital Frankfurt, Frankfurt, Germany, [2] Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany, [3] Department of Neurology, Kassel General Hospital, Kassel, Germany, [4] Department of Neurology, University Hospital Freiburg, Freiburg, Germany, [5] Department of Neurology, University Hospital Würzburg, Würzburg, Germany, [6] Department of Neurology, University Hospital Leipzig, Leipzig, Germany, [7] Department of Neurosurgery, Charité University Hospital Berlin, Berlin, Germany, [8] Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, United States, [9] Harvard Medical School, Harvard University, Boston, MA, United States, [10] Department of Neurosurgery, University Hospital Bonn, Bonn, Germany

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Malte Ottenhausen,
Johannes Gutenberg University Mainz, Germany
Tai-Heng Chen,
Kaohsiung Medical University, Taiwan

***Correspondence:**
Florian Gessler
f.gessler@med.uni-frankfurt.de

[†] These authors have contributed equally to this work

[‡] A list of collaborators is provided in the Supplementary Appendix

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care, a section of the journal Frontiers in Neurology

Received: 22 September 2020
Accepted: 08 December 2020
Published: 06 January 2021

Citation:
Gessler F, Lehmann F, Bösel J, Fuhrer H, Neugebauer H, Wartenberg KE, Wolf S, Bernstock JD, Niesen W-D and Schuss P (2021) Triage and Allocation of Neurocritical Care Resources During the COVID 19 Pandemic - A National Survey. Front. Neurol. 11:609227. doi: 10.3389/fneur.2020.609227

Objective: In light of the ongoing COVID-19 pandemic and the associated hospitalization of an overwhelming number of ventilator-dependent patients, medical and/or ethical patient triage paradigms have become essential. While guidelines on the allocation of scarce resources do exist, such work within the subdisciplines of intensive care (e.g., neurocritical care) remains limited.

Methods: A 16-item questionnaire was developed that sought to explore/quantify the expert opinions of German neurointensivists with regard to triage decisions. The anonymous survey was conducted via a web-based platform and in total, 96 members of the Initiative of German Neurointensive Trial Engagement (IGNITE)-study group were contacted via e-mail. The IGNITE consortium consists of an interdisciplinary panel of specialists with expertise in neuro-critical care (i.e., anesthetists, neurologists and neurosurgeons).

Results: Fifty members of the IGNITE consortium responded to the questionnaire; in total the respondents were in charge of more than 500 Neuro ICU beds throughout Germany. Common determinants reported which affected triage decisions included known patient wishes (98%), the state of health before admission (96%), SOFA-score (85%) and patient age (69%). Interestingly, other principles of allocation, such as a treatment of "youngest first" (61%) and members of the healthcare sector (50%) were also noted. While these were the most accepted parameters affecting the triage of patients, a "first-come, first-served" principle appeared to be more accepted than a lottery for the allocation of ICU beds which contradicts much of what has been reported within the literature. The respondents also felt that at least one neurointensivist should serve on any interdisciplinary triage team.

Conclusions: The data gathered in the context of this survey reveal the estimation/perception of triage algorithms among neurointensive care specialists facing

COVID-19. Further, it is apparent that German neurointensivists strongly feel that they should be involved in any triage decisions at an institutional level given the unique resources needed to treat patients within the Neuro ICU.

Keywords: COVID-19, SARS-CoV, pandemic, patient triage, neurocritical care

INTRODUCTION

Faced with a potential second wave of the coronavirus disease-19 (COVID-19) Europe is again bracing for a potential resurgence of the virus driven in part by the liberalization of social distancing regulations (1). Unfortunately, intensive care unit (ICU) beds, ventilators, dialysis machines and personal protective equipment (PPE) have been and may continue to be scarce resources in regions with a high incidence of COVID-19.

As such, neurointensivists and their patients may face the prospect of rationing allocating valuable resources and in so doing be forced to triage patients when faced with overwhelming numbers COVID-19 patients in need of critical care (2). It is prudent to note that managing scarce medical resources/medically triaging patients is a foreign concept for most physicians throughout the Western world.

In order to determine triage criteria and possible algorithms for the allocation of limited ICU resources among neurointensivists, a survey was sent to members of the Initiative of German Neurointensive Trial Engagement (IGNITE)-study group in the early stages of the COVID-19 pandemic.

MATERIALS AND METHODS

Our COVID-19 triage survey was created in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines. The survey was sent to members of the Initiative of German Neurointensive Trial Engagement (IGNITE) consortium which consists of an interdisciplinary panel of specialists with expertise in neuro-critical care (i.e., anesthetists, neurologists and neurosurgeons) in March of 2020 prior to the initial wave of infections in Germany. Ninety-six neurointensivists were contacted via email. No incentives for participation in the survey were offered and those who refused to participate and/or did not complete the survey (i.e., more than three questions missing) were considered non-responders. The survey was available for a total duration of 3 weeks.

Briefly, the survey was developed by a multidisciplinary team whose members were from the Departments of Neurology, Neurosurgery and Anesthesiology & Intensive Care Medicine at the University Hospitals of Bonn, Frankfurt am Main and Freiburg. It was subsequently reviewed and revised based on feedback from other clinicians in terms of clarity, readability and content. Adaptive questioning was employed to reduce the complexity of the questions posed. In its final form, there were 1 to 2 questions per page and 12 pages in total. The anonymous survey was conducted via a web-based platform (SurveyMonkey Inc.; San Mateo, California, USA; www.surveymonkey.com). Unique visitors were identified based on IP addresses and were used to prevent multiple entries from the same individual. In cases of duplicate entries, the first entry was kept for analyses.

RESULTS

Respondent Demographics

A total of 50 neurocritical care experts throughout Germany took part in the survey; yielding a response rate of ∼ 55%. Seventy percentage of the respondents were employed at a University hospital, 26% at a hospital providing maximum academic care (>700 hospital beds), whereas 4% of respondents were employed at a hospital providing secondary care (500–700 hospital beds). Of the 50 neurointensivists who participated in the survey 84% specialized in neurology, 12% in neurosurgery and 4% in anesthesiology/critical care. Together, the respondents were responsible for a total of 519 Neuro ICU beds throughout Germany (**Figure 1**).

Triage of Critical Care Resources

In the event that ICU beds were exhausted only 46% of the respondents recommended that decisions regarding the triage of resources for neuro-critical care patients be made by neurointensivists alone. However, the survey respondents also felt that at least one specialist in neuro-critical care should be an integral part of any central interdisciplinary triage team. Furthermore, the neurointensivists surveyed favored the involvement of local ethics committees should patient triage/diversion of resources be necessary.

Sixty-nine percentage of respondents felt that neurocritical resources should be made available to other critically ill patients thereby allowing for the admission and/or treatment of COVID-19 patients should the need arise. While the vast majority of polled neurointensivists appeared willing to share resources to help impacted areas (71%), many also felt that the needs of the local community the hospital was intended to serve should not be ignored (27%). In the case of limited but available ICU resources, 54% of respondents stated they would support the transfer of interstate and/or international patients for treatment, while 27% would recommend transferring critical patients from the vicinity of the hospital with higher priority.

When faced with hypothetical occupancy rate of 80% for ICU beds, the vast majority of respondents (78%) felt that the responsibility for the triage of patients should fall to an interdisciplinary team within the Emergency Department. With regard to patients already admitted to a Neuro ICU, 59% of the respondents felt that the triage of those patients should be managed a triage team guided by neurointensivists.

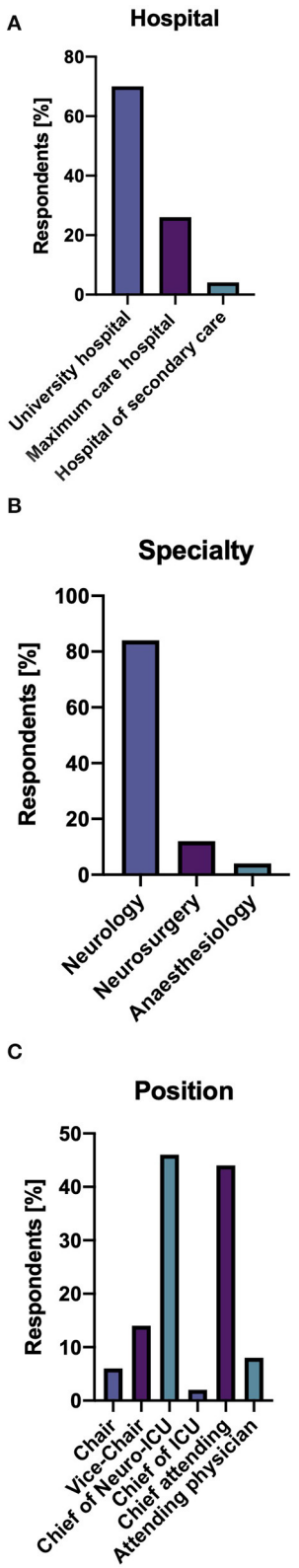


FIGURE 1 | Characteristics of respondents. Bar charts of **(A)** type of institution, **(B)** respondent specialty, and **(C)** respondent position.

Evaluation of Prioritization Principles

In the event that all ICU resources have been exhausted, patients within the ICU and/or scheduled for admission to the ICU may have to be triaged. The most important determinants affecting triage in this situation as per our survey were as follows: "known patient wishes" (98%), followed by "known state of health before acute deterioration" (96%), "SOFA score" (85%), and "patient age" (69%) (**Figure 2A**).

In addition, the majority of respondents also felt the following principles were important with regard to the triaging of ICU resources and should be weighed heavily: "youngest first" (61%), "patient is a health care worker" (50%), "first-come, first-serve" (20%), and "iatrogenic complications leading to ICU necessity" (16%). Unsurprisingly, respondents also felt that "worst short-time prognosis" and "results of daily visits by the ethics committee" were important factors to consider when making individual triage decisions (**Figure 2B**).

DISCUSSION

The work presented herein offers a valuable overview of patient triage from experts in a highly subspecialized field of intensive care medicine (3). Such work may have an immediate impact as Europe braces for a second wave of COVID-19 (1).

With a surge in infected patients suffering from COVID-19, patient triage with regard to ICU resources became necessary in various countries throughout Europe. Accordingly, a high degree of transparency is needed with regard to the principles, values, and criteria employed to facilitate such triage decisions is needed. While algorithms/tools have been proposed to facilitate the triage of critical ill patients, such an approaches have a myriad of shortcomings (4, 5). It is also prudent to note that while the information/values by which triage teams base their decisions are often abstract/imprecise they may have practical utility in that they serve to alleviate the moral distress/legal questions individual clinicians may face when triaging limited resources (6).

Critically the neurointensivists queried did not feel comfortable handing over responsibility for the patients they were taking care of, with the vast majority (78%) feeling that patient triage should be performed immediately upon presentation by an interdisciplinary team. Further when triaging for special-care ICU admission (i.e., neuro/neonatal), they felt that subspecialists should be an integral part of any interdisciplinary triage team. Such thoughts do not necessarily align with the work of Kirkpatrick et al. who have noted that to ensure an equitable distribution of resources, triage teams must be sheltered from the influence of factors that appear to be relevant only to the care of individuals (6). In line with such thinking the concept of allocation mandates that when medical resources are scarce, they must be used as efficiently as possible to achieve the greatest possible overall benefit (7). While recommendations on triage for viral pandemics and/or cases of (bio)terrorist attacks have been published, scarce data is available regarding the acceptance of such principles (8). Amongst such

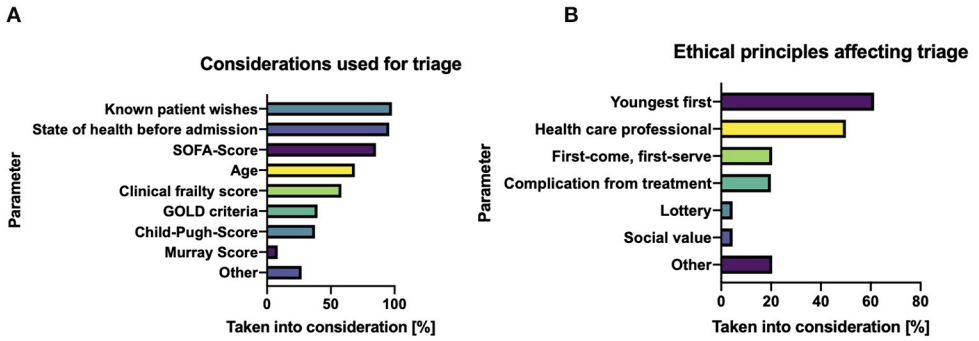


FIGURE 2 | Tools for guiding triage decisions. **(A)** Determinants influencing triage at a stage of absolute intensive care scarcity. **(B)** Ethical principles of allocation during patient triage.

previously published principles of allocation, decisions took into account age (i.e., the "youngest first") and exposure (i.e., "members of the health care sector") seemed to be the most accepted parameters amongst the neurointensivists that were surveyed (6, 7).

It goes without saying that withdrawing healthcare resources (e.g., mechanical ventilation) from one party to give to another poses unparalleled stress on everyone that is involved in the process (i.e., triage teams, patients, physicians, relatives etc.) (7, 9). Of note, published guidelines do support the withdrawal of mechanical ventilation during certain public health crises, yet little work has described how such decisions would be practically implemented (9, 10). The results of our survey clearly illustrate that a variety of different tools, scores and/or metrics should be used to ensure that any resultant assessment is valid. Interestingly, a "first-come, first-serve" principle was accepted considerably more often (20%) than a "lottery system" (5%) with regard to patient triage. This opinion is notably discordant with the recent recommendations, which argue that the principle of "first-come, first-served" should not be employed (11). The thoughts of the neurointensivists surveyed appeared more aligned with the rule of absolute equality, as lottery system might lead to the discontinuation of treatment for a patient who may have a better chance of a meaningful outcome, even in the context of a "prognosis-matched lottery" (11). Further, the loss of physician input and decisional autonomy that would result from a lottery system may be untenable for many, including those within health care and society at large.

The COVID-19 pandemic has stretched many health systems to their very limits and beyond, and ultimately threatens to do so again if the pandemic reignites (1, 3). While decisions regarding the allocation of ICU resources will remain challenging it is the authors' hope/contention that our survey which quired individuals with regard to their thoughts/practice may ultimately relieve some of the individual burden shouldered by individual physicians throughout the world during such unprecedented times.

Limitations

It is prudent to note that our study has several limitations. First and foremost, the present study was conducted via an online survey and was limited to members of the IGNITE consortium whose views may not necessarily be consistent with neurointensivists outside of Germany. Further, the survey sought only the neurointensivists which may differ dramatically from other critical care providers. In addition, this survey was based on – at that time - hypothetical circumstances in intensive care units. This might cause a different interpretation of the question resulting in divergent answers and thus, under certain circumstances, an erroneous interpretation. Accordingly, future studies that sample broader populations/subdisciplines of physicians/surgeons may ultimately be warranted. Despite such shortcomings, this survey does in fact represent the first assessment of triage behavior by neurointensivists in the face of the COVID-19 pandemic.

CONCLUSIONS

The data presented within this survey highlight core tenants of patient triage paradigm as viewed by neurointensivists. Such work has made clear that neurointensivists feel that they should be involved in multidisciplinary triage team should ICU resources be exhausted in the face of a pandemic related patient surge.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

FG, FL, W-DN, and PS: conception of the work/study, supervision, and drafting of the manuscript. JBö, HF, HN, KW, and SW: acquisition of data. FG, JBe, and PS: analysis/interpretation of the work and critical revision of the manuscript. All authors critically revised the work and gave final approval to the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.609227/full#supplementary-material

REFERENCES

1. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science*. (2020) 368:860–8. doi: 10.1126/science.abb5793
2. Hulsbergen AFC, Eijkholt MM, Balak N, Brennum J, Bolger C, Bohrer AM, et al. Ethical triage during the COVID-19 pandemic: a toolkit for neurosurgical resource allocation. *Acta Neurochir*. (2020) 162:1485–90. doi: 10.1007/s00701-020-04375-w
3. Truog RD, Mitchell C, Daley GQ. The toughest triage - allocating ventilators in a pandemic. *N Engl J Med*. (2020) 382:1973–5. doi: 10.1056/NEJMp2005689
4. Zivot J. Coronavirus disease 2019 triage teams: death by numbers. *Crit Care Med*. (2020) 48:1241–2. doi: 10.1097/CCM.0000000000004435
5. Sprung CL, Joynt GM, Christian MD, Truog RD, Rello J, Nates JL. Adult ICU triage during the coronavirus disease 2019 pandemic: who will live and who will die? recommendations to improve survival. *Crit Care Med*. (2020) 48:1196–202. doi: 10.1097/CCM.0000000000004410
6. Kirkpatrick JN, Hull SC, Fedson S, Mullen B, Goodlin SJ. Scarce-resource allocation and patient triage during the COVID-19 Pandemic: JACC review topic of the week. *J Am Coll Cardiol*. (2020) 76:85–92. doi: 10.1016/j.jacc.2020.05.006
7. White DB, Lo B. A framework for rationing ventilators and critical care beds during the COVID-19 pandemic. *JAMA*. (2020) 323:1773–4. doi: 10.1001/jama.2020.5046
8. Rubinson L, Nuzzo JB, Talmor DS, O'Toole T, Kramer BR, Inglesby TV. Augmentation of hospital critical care capacity after bioterrorist attacks or epidemics: recommendations of the working group on emergency mass critical care. *Crit Care Med*. (2005) 33:2393–403. doi: 10.1097/01.CCM.0000173411.06574.D5
9. Cohen IG, Crespo AM, White DB. Potential legal liability for withdrawing or withholding ventilators during COVID-19: assessing the risks and identifying needed reforms. *JAMA*. (2020) 323:1901–2. doi: 10.1001/jama.2020.5442
10. Piscitello GM, Kapania EM, Miller WD, Rojas JC, Siegler M, Parker WF. Variation in ventilator allocation guidelines by US state during the coronavirus disease 2019 pandemic: a systematic review. *JAMA Netw Open*. (2020) 3:e2012606. doi: 10.1001/jamanetworkopen.2020.12606
11. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, et al. Fair allocation of scarce medical resources in the time of covid-19. *N Engl J Med*. (2020) 382:2049–55. doi: 10.1056/NEJMsb2005114

Disclaimer: This manuscript is solely based on data obtained via our COVID-19 survey and does not necessarily reflect the official opinion(s)/sentiment(s) of the German Society for Neurocritical Care.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

OPINION
published: 08 January 2021
doi: 10.3389/fneur.2020.605315

Process Changes for Stroke Care and Electroencephalography on a Neurology Service in a Hospital at the Epicenter of the COVID-19 Pandemic

Helen Valsamis[1], Noa Sheikin[1], Susan Law[1] and Samah Abdul Baki[2]*

[1] Kings County Hospital Center, SUNY Downstate Medical Center, Brooklyn, NY, United States, [2] Bio Signal Group, Brooklyn, NY, United States

Keywords: change in process, EEG, critical care, stroke, COVID-19

SUMMARY

The United States, with over 11 million cases and ∼250,000 deaths (1), has become the epicenter of the COVID-19 worldwide pandemic since the first case was identified in Washington State on January 19, 2020.

In New York City the first case of community acquired COVID-19 was identified on March 1, 2020 and the number of known cases increased rapidly making the city the epicenter of COVID-19 in the United States. Public hospitals became deluged with patients as the communities they serve, urban poor and minority, were disproportionately affected by the disease. COVID-19 often affects the nervous system with both central and peripheral sequalae, neurology services had to adapt to a new landscape (2–6).

This paper will report on the process changes for the neurology service, in particular for stroke and electroencephalography (EEG) services, at King County Hospital Center (KCHC), a 637 bed, public, university-affiliated, teaching hospital in central Brooklyn, New York, which serves a predominantly African American community. Implementing those changes resulted in maintaining our pre-COVID structure and quality of care despite the workflow, economic, and technical challenges induced by the virus.

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Lina Palaiodimou,
University General Hospital Attikon, Greece

****Correspondence:***
Helen Valsamis
helen.valsamis@nychhc.org

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *24 October 2020*
Accepted: *07 December 2020*
Published: *08 January 2021*

Citation:
Valsamis H, Sheikin N, Law S and Abdul Baki S (2021) Process Changes for Stroke Care and Electroencephalography on a Neurology Service in a Hospital at the Epicenter of the COVID-19 Pandemic. Front. Neurol. 11:605315. doi: 10.3389/fneur.2020.605315

KCHC AS COVID SURGES IN NEW YORK CITY

The first known COVID-19 patient was admitted to KCHC on March 13, 2020, almost 2 weeks after the first known case of COVID-19 was identified in New York City. The number of cases rapidly increased first in Manhattan and then in Brooklyn before in Queens and then in the Bronx. In March and April as case numbers surged at KCHC, strategies to protect patients and staff were developed and implemented rapidly as we learned first-hand about the disease.

NEUROLOGY PPE POLICY WITHIN THE HOSPITAL-WIDE RESPONSE

Initially, COVID-19 was thought to be a respiratory disease. However, in the first few days of the surge of patients, multiple Neurology and Emergency Medicine personnel were exposed to COVID-19 patients who presented with strokes but without respiratory complaints. The Neurology Service responded by promptly instituting a policy that full personal protective equipment (PPE)

including N95 masks and face shields be used for performing stroke codes, adapting procedures for performing neurologic examinations, and changing the workflow for EEG. We also reorganized our services and participated in many facets of the hospital-wide COVID-19 response

STAFFING AND SERVICE RESTRUCTURING

As was the case in many other hospitals when COVID-19 arrived, our Neurology Department made staffing changes to support the COVID-19 effort. We disbanded our Neuro Critical Care Service and sent the attendings into the Intensive Care Unit (ICU) attending pool as the hospital expanded its ICU bed capacity from 40 to 200 ICU beds. The Neurology Consultation Service provided neurology guidance on critically ill patients with neurologic conditions. Our Neuro Critical Care attendings graciously answered our questions on difficult to manage patients. Our current stroke fellow is also an Emergency Medicine attending and he put his fellowship on hold and went full time to the Emergency Department (ED) during the peak of the crisis.

The inpatient Neurology Service expanded to become a combined Neurology-COVID service caring for patients with neurological conditions, COVID-19, or both. We received training on the evolving management of COVID-19 from Infectious Disease and ICU attendings. We also held a journal club on the neurologic manifestations of COVID-19 and regularly emailed pertinent articles to the entire Neurology faculty and all trainees. The Pulmonary Service consulted regularly on our patients on mechanical ventilation and BIPAP. The infectious disease attendings came by on a daily basis to advise us on both the management of COVID-19 and multiple other medical issues. Our Adult Neurology residents and attendings also rotated onto the Medicine services which were almost all COVID-19 wards. Of the two approaches, expanding the scope of the Neurology-COVID-Medicine service worked better. We maintained our pre-COVID structure and were better able to maintain the morale of our teams.

On the outpatient side, we rapidly transitioned from in-person visits to telephone visits (televisits) and eventually our Stroke Clinic instituted video visits. Electromyography and outpatient EEG studies were suspended until the surge passed. Our Pediatric Neurology fellows performed nasopharyngeal swabs for outpatient and employee testing. Our Adult and Pediatric Neurology attendings helped out Employee Health with the phone calls to quarantined staff. Our Pediatric Neurology fellows also rounded with the ICU teams and served as the liaison with the families who were not allowed to visit their loved ones.

Our Stroke Nurse Practitioner became the PPE trainer for stroke codes but also for trauma codes. She quickly trained all of the staff on both Trauma and Neurology in proper PPE donning, use, and doffing. In addition, she developed Stroke code kits comprised of N-95 masks, face shields, gowns, bonnets, and gloves, so the responder had a pre-assembled set of PPE and could rapidly prepare to safely answer a stroke code.

STROKE CODES, NEUROLOGICAL EXAM, APHASIA TESTING, AND PUPIL EXAMINATIONS

We also analyzed and adapted the workflow of the stroke code and neuro exam. Prior to the pandemic, we used laminated pocket cards for aphasia testing. During the pandemic we blew up the pocket cards used for aphasia testing onto 8.5 × 11 sheets of paper that were discarded after each use. Pen lights were encased in sealed plastic bags to facilitate repeated cleanings with gel before and after each patient encounter. Fundoscopic examinations were halted due to the prolonged close interaction. Pupil examinations and cranial nerve examinations are also performed in close proximity to the patient's face, so we required N-95 mask and face shield use for all patient encounters in order to perform these procedures safely.

HOT AND COLD ZONES AT KCHC

Throughout the hospital patients were cohorted into "hot zones" for COVID-19 positive patients and "cold zones" for COVID-19 negative ones. As much as possible hot and cold zones were separate wards. Patients under investigation for COVID-19 (PUIs) were housed in single rooms in hot zones until their status could be determined for an appropriate ward allocation. However, due to the specialized nature of our Stroke Unit, the Neurology unit became a "mixed zone" unit for much of the surge. Attending rounds started with the COVID-19 negative patients, then PUIs, and finished with COVID-positive patients. Rounds were asynchronous with only the attending and the resident caring for the patient entering the patient's room.

STROKE SERVICE AND A SURPRISING INCREASE IN ADMISSIONS DURING COVID-19

The Stroke Service developed a stroke cart with interactive video that could be monitored remotely so that when the attending and resident went into the patient's room to examine the patient, the rest of the team could view the interaction and observe social distancing. In particular, this enabled the on-call residents to remotely view the patient's neurologic examination and maintain the quality of care. Unlike other centers, KCHC has seen an increase in both ischemic and hemorrhagic stroke volumes during the month of March of the pandemic in comparison to the same period in 2019 (**Figure 1**). In the earliest phase of the surge of COVID-19 cases, all the stroke patients were COVID-19 positive. As the pandemic progressed the number of stroke cases decreased and then returned to pre-COVID levels as the patients became COVID negative.

Aside from the new PPE requirements and shortened more distant neurological examinations, stroke codes were minimally affected by COVID-19. We had the same indications for tPA administration and used the same algorithms for thrombectomies. At the surge's peak, when ICU beds were tight and we were able to provide a step-down level of care

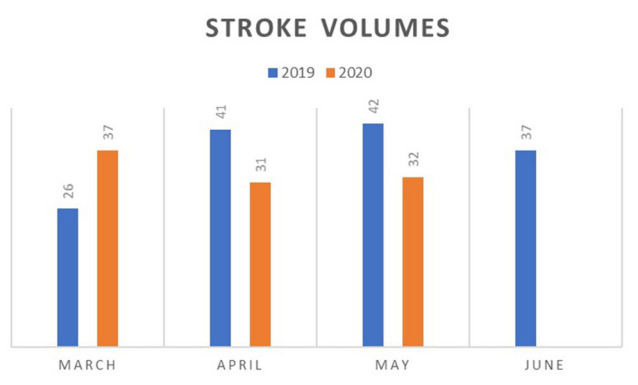


FIGURE 1 | March through June Stroke Volumes (2019 vs 2020).

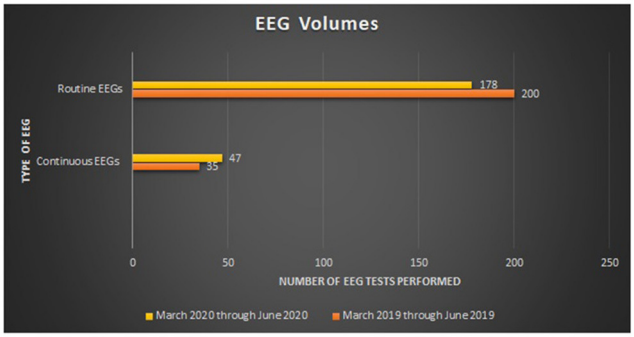


FIGURE 2 | March through June EEG Volumes (2019 vs 2020).

on our Neurology unit, we modified our tPA administration pathway using the Safety Trial of Low-Intensity Monitoring After Thrombolysis (OPTIMIST) trial as a basis (7). The streamlined OPTIMIST protocol was chosen given that it limits the frequency of patient interactions, while still maintaining patient safety. We administered tPA in the ED and performed the initial 2 h of neuro checks every 15 min as usual. At that point, the patient was transferred to the Neurology unit where neuro checks were performed every hour for 8 h. A non-contrast computerized tomography of the head was performed and, if no hemorrhage was demonstrated, the patient then received neuro checks every 4 h to complete 24 h of post-tPA monitoring. We did not see an increase in complications using this modified tPA administration pathway.

POINT OF CARE EEG OVERCOMING THE CHALLENGES DURING COVID-19

After stroke codes, performing EEG was the next highest risk procedure due to the prolonged interaction time and close proximity to the patient's head. The American Clinical Neurophyisology Society recommendations for minimizing equipment contamination and the amount of time the EEG tech needs to stay in the room were followed (8). They stated that efforts should be made to limit technician exposure to potentially infectious patients; to consider rapid application EEG with disposable, single use caps/ templates; use of antiseptic wipes to clean all surfaces of the equipment that has entered any COVID+/PUI patient room; consider using one use plastic covers to shield EEG equipment in COVID+/PUI rooms; consider keeping the machine outside the patient's room (via long wiring).

Our EEG technicians wore the same PPE as used for stroke codes and we modified the EEG procedures to minimize patient interactions in several ways. We used the novel Bio-Signal group system of disposable electrode strips. We chose this system because it allows for good electrode coverage of most of the brain with 16 electrodes (as opposed to 21 with the traditional 10–20 system) and is rapidly applied (9). The average traditional electrode setup time is 27 min. In addition to deployment time, the tech would normally have to reenter the patient's room to check signal quality at least 3 times for a 24-h study. After training, our EEG technicians were able to apply the novel, rapidly deployable system in 3 min. In addition, we configured the EEG acquisition system to allow the EEG to display on a laptop located outside the patient's room so that the EEG technician could leave the patient's room and still monitor the EEG quality. The studies were uploaded to a server via a sender application on the laptop allowing the neurologists to interpret the studies remotely.

From March 1, 2019 through June 5, 2019, 235 inpatient EEG studies were performed of which 200 were routine and 35 were continuous and for the same time period in 2020, a total of 225 EEG studies were performed (4% decrease), of which 178 were routine (11% decrease) and 47 were continuous (34% increase) (**Figure 2**). This increase in continuous EEG volumes is in contrast to other institutions which witnessed a dramatic decrease (10).

CONCLUSION

The COVID-19 pandemic hit Brooklyn and Kings County Hospital Center hard as it did elsewhere and is continuing to do so today. As a public hospital we made do with limited financial resources and leveraged technology and the resourcefulness of our staff. The Neurology Service attending physicians, residents and technicians altered their daily processes to adapt to the overwhelming nature of this virus. Adhering to strict Infection Control protocols, receiving a crash course in medical management of the COVID-19 patient, modifying our stroke code and examination protocols, and employing advanced technology for the performance of EEG allowed the service to perform its tasks safely and efficiently and to maintain quality of care.

AUTHOR CONTRIBUTIONS

HV and SA contributed to the study design, data analysis, and editing. NS and SL provided editorial and have reviewed and approved the final work. All authors contributed to the article and approved the submitted version.

REFERENCES

1. *Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering at Johns Hopkins University*. (2020). Available online at: https://coronavirus.jhu.edu/map.html (accessed November 19, 2020).
2. Mao L, Jin H, Wang M, Wang M, Hu Y, Chen S, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
3. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. *Neurology*. (2020) 95:e1060–e1070. doi: 10.1212/WNL.0000000000009937
4. Tsvigoulis G, Palaiodimou, L, Katsanos AH, Caso V, Köhrmann M, Molina C, et al. Neurological manifestations and implications of COVID-19 pandemic. *Ther Adv Neurol Disord*. (2020) 13:1–14. doi: 10.1177/1756286420932036
5. Frontera J, Savadia S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, et al. A prospective study of neurologic disorders in hospitalized COVID-19 patients in New York City. *Neurology* [Preprint]. (2020) 10. doi: 10.1212/WNL.0000000000010979
6. Divani AA, Andalib S, Biller J, Di Napoli M, Moghimi N, Rubinos CA, et al. Central nervous system manifestations associated with COVID-19. *Current Neurol Neurosci Rep*. (2020) 20:60. doi: 10.1007/s11910-020-01079-7
7. Faigle R, Butler J, Carhuapoma HR, Johnson B, Zink EK, Shakes T, et al. Safety trial of low-intensity monitoring after thrombolysis: optimal post Tpa-Iv monitoring in ischemic stroke (OPTIMIST). *Neurohospitalist*. (2020) 10:11–15. doi: 10.1177/1941874419845229
8. *American Clinical Neurophysiology Society (ACNS) Recommendations Technologist Safety and Staffing*. (2020). Available online at: https://www.acns.org/UserFiles/file/ACNSCOVID-19Recs_TechSafetyStaffing_v1.pdf (accessed March 22, 2020).
9. Zehtabchi S, Abdel Baki SG, Omurtag A, Sinert R, Chari G, Roodsari GS, et al. Effect of micro-electroencephalogram on clinical management and outcomes of emergency department patients with altered mental status: a randomized controlled trial. *Acad Emerg Med*. (2014) 21:283–91. doi: 10.1111/acem.12324
10. Sethi NK. EEG during the COVID-19 pandemic: what remains the same and what is different. *Clin Neurophysiol*. (2020) 131:1462. doi: 10.1016/j.clinph.2020.04.007

Conflict of Interest: SA reports support from Bio Signal Group. In addition, SA has a U.S. patent 13/284,886.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 12 January 2021
doi: 10.3389/fneur.2020.625272

Case Report: The Coronavirus Disease 2019 (COVID-19) Pneumonia With Multiple Thromboembolism

*Tingting Cao[1], Guqin Zhang[2], Huabing Xie[1], Emily Pellegrini[3], Jin Li[4], Xiaoxing Chen[5] and Huaqin Pan[6,7]**

[1] Department of Gastroenterology, Zhongnan Hospital of Wuhan University, Wuhan, China, [2] Department of Respiratory and Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China, [3] Dascena Inc., San Francisco, CA, United States, [4] Department of Gastroenterology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, [5] Department of Geriatrics, Renmin Hospital of Wuhan University, Wuhan University, Wuhan, China, [6] Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China, [7] Clinical Research Center for Critical Care Medicine of Hubei Province, Wuhan, China

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in Wuhan, China, in late December 2019 and has since spread rapidly around the world. Severe coronavirus disease 2019 (COVID-19) pneumonia patients have abnormal blood coagulation function, but their thromboembolism prevalence is still unknown. We reported a case of a 49-year-old man infected with COVID-19, presenting with fever, chest pain, limb weakness, myalgia, and dyspnea. The patient was diagnosed with severe COVID-19 pneumonia, pulmonary thromboembolism (PTE), deep vein thrombosis (DVT), and cerebral infarction. He received supportive and empirical treatment including anticoagulant treatment, anti-inflammatory treatment, oxygen supply, and inhalation therapy. The patient's symptoms, CT images, and laboratory results improved after treatment, and a throat swab was reported to be negative for SARS-CoV-2 virus by polymerase chain reaction (PCR) test. However, on day 51 of illness onset, CT reexamination demonstrated hemorrhagic infarction. Anticoagulant therapy was discontinued temporarily. After the patient tested negative for SARS-CoV-2 virus by PCR test six more times, he was discharged and remained in home quarantine. This case highlights the importance of clinician attentiveness to the appearance of multiple thromboembolism, especially in patients with severe pulmonary damage. It also emphasizes the diagnostic value of early CT imaging and the need for effective treatment once thrombotic events occur.

Keywords: COVID-19, SARS-CoV-2 virus, pneumonia, multiple thromboembolism, anticoagulant treatment

OPEN ACCESS

Edited by:
Giovanni Assenza, Campus Bio-Medico University, Italy

Reviewed by:
Francesco Motolese, Campus Bio-Medico University, Italy
Alessandro Iadanza, University of Siena, Italy

***Correspondence:**
Huaqin Pan
phq2012@whu.edu.cn

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *02 November 2020*
Accepted: *26 November 2020*
Published: *12 January 2021*

Citation:
Cao T, Zhang G, Xie H, Pellegrini E, Li J, Chen X and Pan H (2021) Case Report: The Coronavirus Disease 2019 (COVID-19) Pneumonia With Multiple Thromboembolism. Front. Neurol. 11:625272. doi: 10.3389/fneur.2020.625272

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pneumonia is a neo-type respiratory infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV). SARS-CoV-2 broke out in Wuhan, Hubei, China, in late December 2019 and was subsequently identified as a public health emergency of international concern by the World Health Organization (1). Although respiratory

compromise with dominant symptoms of fever and cough is the cardinal feature of the disease, previous studies have reported that ∼20% of COVID-19 patients have had severe coagulation abnormalities. These abnormalities predispose patients to thrombotic events such as deep vein thrombosis (DVT), venous thromboembolism (VTE), and potential pulmonary thromboembolism (PTE) and are associated with patient mortality (1–5). In this study, we report a case of a COVID-19 pneumonia patient who developed multiple thromboembolism including DVT, PTE, and cerebral infarction, which may provide further evidence for the suggestive management for such patients.

CASE

A 49-year-old man in Wuhan sought care for a half-month history of fever up to 38°C, cough, myalgia, and dyspnea, without chills, diarrhea, nausea, vomiting, or hemoptysis. Results of a pharyngeal swab specimen analysis by the SARS-CoV-2 real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) test confirmed the patient to be positive for COVID-19 (**Figure 1**).

On day 15 of illness onset, he was admitted to the general isolation ward (GIW) in Leishenshan Hospital and was diagnosed with severe COVID-19. Physical examination revealed a body temperature of 38.3°C, a blood pressure of 121/85 mmHg, a pulse of 102 beats per minute, and a respiratory rate of 23 breaths per minute. Laboratory results were summarized as follows:

- Lymphocyte count and percentage dramatically decreased.
- Levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were noticeably elevated.
- Prothrombin time prolongated, and levels of D-dimer and fibrinogen were in the normal range.
- Myocardial enzyme was in the normal range (**Table 1**).
- The chest computed tomography (CT) scan showed bilateral peripheral ground glass opacification (GGO) (**Figure 2**).

The patient was supplied immediately with persistent low flow oxygen therapy, abidol hydrochloride (200 mg three times daily, po.), and Chinese medicine as antiviral therapy, and moxifloxacin (400 mg once daily, i.v.) as antibacterial therapy and symptomatic and supportive treatment. However, the patient's state became progressively aggravated despite active treatments. Five days after admission, he suddenly developed dyspnea with a lower temperature of 36.0°C, as well as a tachycardia and a decreased oxygen saturation value of 52%. He immediately received non-invasive mechanical ventilation (NIMV) because of respiratory failure. A low dose of methylprednisolone and low molecular weight heparin (LWMH) were given concurrently for prophylactic anticoagulation and anti-inflammatory based on the clinical experience. On day 7 of hospitalization, the patient's clinical condition improved and he received high-flow mask oxygen inhalation therapy (**Figure 1**).

Abbreviations: COVID-19, Coronavirus disease 2019; SARS-COV-2, Severe acute respiratory syndrome coronavirus 2; CT, computed tomography; ICU, intensive care unit; PTE, pulmonary thromboembolism; VTE, venous thrombus embolism; LMWH, low molecular weight heparin.

On day 8 of hospitalization, the patient experienced weakness in his left upper limb and speech dysfunction. Physical examination indicated Grade 0 muscle strength in the left upper limb while other limbs were normal, the mouth was deviated, and pathological reflection of Babinski's sign was not induced; bilateral pupils were equally in diameter and sensitive to direct or indirect light reflex. Laboratory examination indicated that sensitive troponin I was 0.323 ng/ml (reference 0–0.04 ng/ml). The patient's coagulation function, CK, and CK-MB were normal. These results indicated onset of cerebral infarction. The patient was transferred to the intensive care unit (ICU).

On February 24th, the patient subsequently developed severe precordial pain. Urgent electrocardiogram indicated sinus tachycardia rather than cardiac ischemia. After treatment with nitroglycerin, atorvastatin, clopidogrel, and aspirin, the patient still had a chest pain. It was speculated that PTE was occurring. Vascular ultrasound of lower limbs showed deep vein thrombosis of the right lower extremity. Computer tomography pulmonary angiography indicated a filling defect in the trunk and branches of the right inferior pulmonary artery. Cerebral CT showed slightly low-density shadows in the right parietal lobe and the left temporal lobe (**Figure 2**). Laboratory reexamination indicated increases in lymphocyte count and percentage, mild decreases in AST and ALT, prolonged PT and APTT times, high platelet count, and high levels of D-dimer and fibrinogen. The patient was supplied immediately with persistent low flow oxygen therapy, low molecular heparin calcium (0.4 ml, every 12 h, im.), piperacillin and tazobactam (4.5 g, every 8 h, iv.), omeprazole (40 mg, once daily, iv.), Lipitor (20 mg, once daily, po.), aspirin (0.1 g, once daily, po), clopidogrel (75 mg, once daily, po), magnesium isoglycyrrhizinate (200 mg once daily, iv.), and a low dose of methylprednisolone (60 mg once daily, iv.).

After treatments, the patient's symptoms continued to alleviate. Laboratory reexamination indicated that the lymphocyte count and percentage increased reposefully and AST; ALT was mildly decreased while coagulation function was still not improved. Levels of D-dimer and fibrinogen remained high. The patient felt severe chest pain again on March 6. Electrocardiogram indicated sinus tachycardia. Results of a bedside chest radiograph displayed progress of bilateral interstitial infiltrating shadows. To relieve pain, the patient was given diclofenac sodium suppositories and low molecular heparin calcium continuously until day 33 of hospitalization. Amounts of methylprednisolone were gradually decreased to 20 mg on day 32 of hospitalization.

On March 11, the patient was transferred to the GIW for intensive consolidation therapy. All symptoms had resolved except for intermittent chest pain and disorder of limb activity. He received ongoing treatment in the GIW, including anticoagulant therapy with LMWH, hepatic functional protection therapy, anti-inflammatory treatment, and Chinese medicinal therapy. A CT of the lungs indicated pulmonary cavitation in the right lower lobe. Meropenem and linezolid were empirically administered as anti-infective treatments for multidrug resistance bacterial infection particularly gram-positive coccus infection. On March 17, cerebral CT indicated hemorrhagic infarction and the anticoagulant therapy was

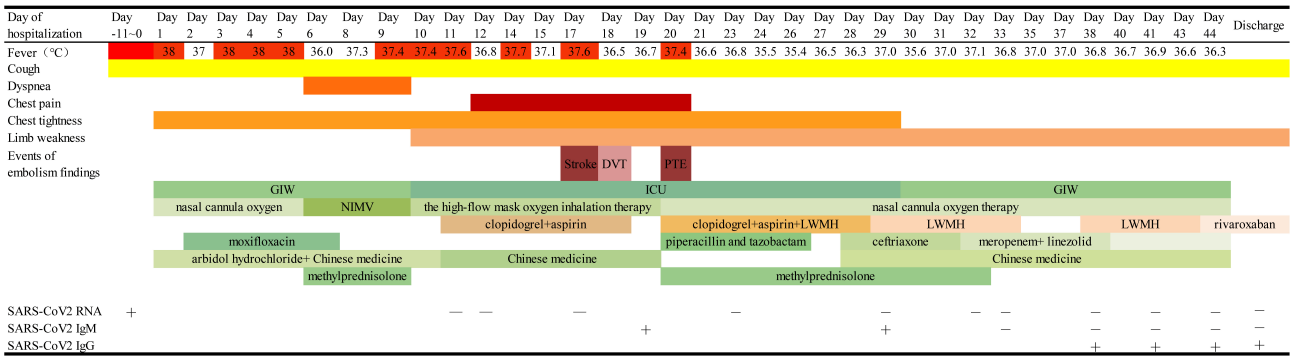


FIGURE 1 | Timeline of disease course according to days from admission, and days of follow-up from February 13 to March 27, 2020. ICU, intensive care unit; GIW, general isolation ward; NIMV, non-invasive mechanical ventilation; LMWH, low-molecular-weight heparin; DVT, deep venous thrombosis; PTE: pulmonary thromboembolism.

TABLE 1 | Clinical laboratory results.

Measure	Normal range	02/18 Day 6	02/21 Day 9	02/23 Day 11	02/24 Day 12	02/28 Day 16	03/02 Day 19	03/03 Day 20	03/03 Day 20	03/06 Day 23	03/09 Day 26	03/12 Day 29	03/14 Day 31	03/16 Day 33	03/21 Day 38	03/24 Day 41	03/27 Day 44
WBC	3.5–9.5	7.18	8.7	11.39	9.47	7.41	6.53	6.59	6.98	5.41	7.05	3.89	4.74	3.35	3.38	2.98	3.4
PLT	125–350	99	96	84	99	298	355	366	395	439	475	378	285	242	179	155	137
NEUT#	1.8–6.3	6.91	7.95	10.37	8.35	6.14	5.45	5.16	5.88	4.16	5.29	2.37	3.42	1.98	2.24	1.7	1.61
LYMPH#	1.1–3.2	0.14	0.45	0.61	0.55	0.46	0.46	0.43	0.29	0.56	0.74	0.76	0.65	0.87	0.75	0.84	1.32
PT (S)	9.4–12.5	12.1	12	11.4	12	11.4	12.1	12.5	14.2	12.7	12.2	11.9		11.2	10.9	11.2	
APTT (S)	25.1–36.5	20.1	18.6	19.2	24.3	28.4	28.2	28.5	35.5	31.6	30.8	26.2		22.9	23.2	25.6	
DD2 (ng/mL)	0–500	28.16	30.91	21.22	12.77	6.86	5.28	4.48	3795	3973	4027	737		242	196	157	
ALT (U/L)	9–50	80	144	187	213	113	154	149	216	267	197	111		91	49	42	45
AST (U/L)	15–40	93	118	118	101	39	99	73	164	138	60	48		55	24	19	27
CREA (μmol/L)	64–104	56.9	61.5	56.3	58	46.2		56.8	45.3	50.7	57.3	67.2		61	57.1	53	61.2
CK-MB (ng/ml)	0–6.36		4.22	4.43	1.98	3.66	1.89	1.26				1.47		1.20	1.17	1.34	
HS-TNI (ng/ml)	0–0.04		0.258	0.323	0.108	0.03	0.012	0.010				0.010		0.010	0.010	0.010	
CRP (mg/L)	0–10.0				31.39	107.29	10	10	127.5	27.1		0.89		0.5	0.5	0.5	0.5
PCT (ng/ml)	<0.05	0.81	0.27	0.09	0.05	0.09	0.079		<0.05	0.05	<0.05				0.02	0.03	
IL6 (pg/mL)	0–7						88.37		87.31	9.98	12.08	147.1	215.5		120.1	81.43	
PIC (μg/mL)	<0.8								2.765	2.853	1.538	0.684		1.106	0.552		
t-PAI-C (μg/mL)	<17.0								15.6	8.8	9.3	5.9		10.0	8.6		
TM (TU/mL)	3.8–13.3								7	7.5	8.5	9.5		10.4	8.700		
TAT (ng/ml)	<4								5.2	5.3	4.1	3.3		3.4	2.9		

WBC, white blood cell; Hgb, hemoglobin; NEUT, neutrophil; LYM, lymphocyte; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CREA, serum creatinine; CRP C-reactive protein; PCT, procalcitonin; IL-6 interleukin- 6; APTT activated partial thromboplastin time; PT prothrombin time; DD D—dimer; PIC plasmin-α2-antiplasmin complex; TAT thrombin–antithrombin complex; t-PAI-C plasminogen activator inhibitor-1; TM thrombomodulin.

discontinued until March 20. The patient reported less pain and fatigue in his chest in the following days. He was treated with rivaroxaban (10 mg once daily, po.) when low molecular heparin calcium was discontinued. Physical examination revealed that muscle strength in the left upper limb was Grade 4; task-related dystonia was coming to normal, without numbness of the limbs, inarticulate speech, blurred vision, paresthesia, ataxia, and dystonia. Biochemistry and laboratory examination indicators gradually returned to normal levels. When the patient tested negative for SARS-CoV-2 virus by

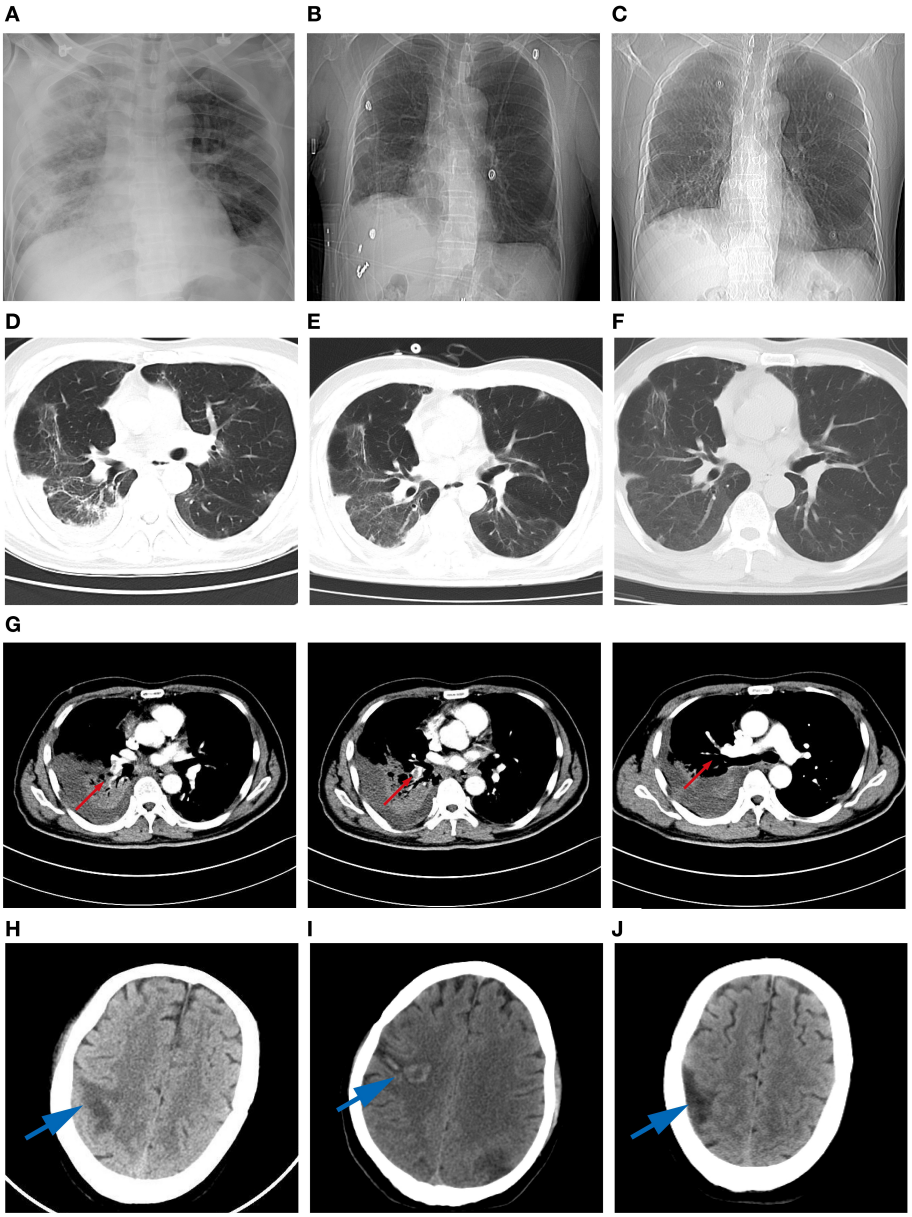


FIGURE 2 | High-resolution computed tomography images during the disease course. **(A)** chest X-ray image revealing ground-glass opacities (GGO) in the both lobes on day 13 of hospitalization. **(B)** GGO in the both lobes on day 36. **(C)** Thickened lung markings in the right lobe on day 44. **(D)** Multiple-ground-glass opacification in the basal segment of lobes on day 17. **(E)** GGO in both lower lobes on day 27. **(F)** GGO in the middle lobe of the right lung on day 44. **(G)** Filling defect in the trunk and branches of the right inferior pulmonary artery (red arrow). **(H)** Slightly low-density shadows in the right parietal lobe and the left temporal lobe on day 17 of hospitalization (blue arrow). **(I)** Hemorrhagic infarction in the right parietal lobe on day 27 (blue arrow). **(J)** Low-density shadows in the right parietal lobe on day 44 (blue arrow).

PCR test six more times, he was discharged and remained in home quarantine.

DISCUSSION

Coagulopathy is regarded as a common complication in patients with severe COVID-19, the clinical syndrome caused by SARS-CoV-2. The overlap in symptoms between COVID-19 and thromboembolism present a challenge for clinical diagnosis, especially for those patients without any high-risk factors. The patient we reported on in this case study was categorized as being at low-risk for venous thromboembolism according to the Padua prediction scale.

Previous studies have shown that patients with severe acute respiratory distress syndrome (SARS) have slightly decreased platelet counts and prolonged coagulation profiles and are prone to thromboembolic complications (6–9). SARS-CoV-2 shares over 88% homology with SARS coronavirus; indeed, recent

studies have demonstrated that COVID-19 patients are at high risk for venous and arterial thromboembolic disease and that these diseases may be associated with increased COVID-19 severity and poor prognosis (2, 3, 10–12). Several researches described that the incidence of thrombotic complications is up to 30% of patients with COVID-19 in ICU and 2–6% of patients hospitalized with COVID-19 developed stroke (13–16). COVID-19-associated cerebrovascular manifestations seem to be mainly ischemic stroke (16–18). Most patients were generally older and with comorbidities such as hypertension, diabetes, and hyperlipoidemia, which were risk factors for ischemia stroke (18–20). Therefore, it remains ambiguous whether these strokes were caused by SARS-CoV-2 or these high-risk populations suffered strokes and also were infected at the same time. Younger patients with stroke have also been reported (9, 21). There is a study reported that widespread microthrombi and patches of infarction were observed in an autopsy series from COVID-19 patients (21). That SARS-CoV-2 infection does play some roles in causing stroke and increases stroke risk. A cross-sectional survey of 143 patients with confirmed COVID-19 pneumonia showed a 46.1% DVT incidence rate (22). The prevalence of DVT was associated with adverse outcomes, including an increased proportion of deaths, a decreased proportion of hospital discharges, and lower actuarial survival rates (22). A separate report from Cui et al. also reported that ∼25% (20/81) of patients admitted to the ICU may have concurrent thromboembolic phenomena and 8 patients with VTE events died (23). While still in need of further evidence, it has been speculated that severe hypoxemia and a significant inflammatory response can lead to systemic coagulation activation (24–26). Hyperinflammation seen with "cytokines storm" and hypoxia-associated metabolic derangements are potential mechanisms of a SARS-CoV-2-related hypercoagulable state; in addition, SARS-CoV-2 may directly cause endothelial apoptosis by binding to ACE2 on endothelial cells and promote coagulation activation and thrombin generation (21, 27). This body of work suggests that adequate thromboprophylaxis and discovery in the early stages of thrombotic complications are of vital importance for the prognosis of hospitalized patients with COVID-19.

In the present case, the patient was immediately given low-molecular-weight heparin anticoagulant therapy as soon as the embolization event occurred. However, the therapeutic effect of anticoagulation on the patient was not as remarkable as was to be expected during the course of early treatment. We did not detect a decrease in fibrinogen levels and an improvement in coagulation function until heparin treatment on day 7 of hospitalization, which was slightly different from the curative effect of heparin in pulmonary embolism patients without COVID-19. Notably, the patient presented with hemorrhagic infarction during the subsequent therapy so much that it was necessary for anticoagulant therapy to be discontinued. For COVID-19 patients at high risk of bleeding and severe illness, it is therefore important that appropriate anticoagulation measures be taken to ensure effective treatment of thromboembolism. Zhai et al. recommended pharmacological prevention with low-molecular-weight heparin as a first-line treatment in patients at low or moderate risk of bleeding, as well as a curative anticoagulant with LMWH as a first-line treatment in patients suspected for VTE (28). Trigonis et al. observed that different pharmacologic prophylaxis regimens make almost no difference in the incidence of deep venous thrombosis (29). Since there is limited experience with COVID-19-associated thromboembolism, there has been no scientific consensus about the prevention and treatment for thromboembolism in COVID-19 patients.

In summary, this is a first report of a COVID-19 pneumonia patient with PTE, DVT, and cerebral infarction in Wuhan. Following an active treatment regimen consisting of anticoagulant therapy and anti-inflammatory treatment, the patient recovered well. However, due to the limited nature of this case, further research on predisposing factors and protocols for the treatment of COVID-19 pneumonia patients with multiple thromboembolisms is warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study is approved by the Medical Ethics Committees, Zhongnan Hospital of Wuhan University (No. 2020099K), and the patient provided consent to participate. Written informed consent for publication of the clinical details and/or clinical images was obtained from the patient.

AUTHOR CONTRIBUTIONS

HP and TC contributed to the conceptions and design. GZ, HX, XC, and JL collected clinical data. TC wrote the raw draft. HP and EP MEng contributed to the language editing. All authors have read and approved the manuscript.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus

pneumonia in Wuhan, China: a descriptive study. *Lancet*. (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72314 cases from the chinese center for disease control and prevention. *JAMA*. (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
5. Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol*. (2020) 127:104364. doi: 10.1016/j.jcv.2020.104364
6. Peiris JS, Yuen KY, Osterhaus AD, Stöhr K. The severe acute respiratory syndrome. *N Engl J Med*. (2003) 349:2431–41. doi: 10.1056/NEJMra032498
7. Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. (2003) 348:1986–94. doi: 10.1056/NEJMoa030685
8. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med*. (2004) 10 (12 Suppl):S88–97. doi: 10.1038/nm1143
9. Lew TW, Kwek TK, Tai D, Earnest A, Loo S, Singh K, et al. Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA*. (2003) 290:374–80. doi: 10.1001/jama.290.3.374
10. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. (2020) 382:e60. doi: 10.1056/NEJMc2009787
11. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. (2020) 18:1743–6. doi: 10.1111/jth.14869
12. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. (2020) 323:1488–94. doi: 10.1001/jama.2020.3204
13. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol*. (2020) 19:767–83. doi: 10.1016/S1474-4422(20)30221-0
14. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. (2020) 26:1017–32. doi: 10.1038/s41591-020-0968-3
15. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. (2020) 191:145–7. doi: 10.1016/j.thromres.2020.04.013
16. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in covid-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. (2020) 191:9–14. doi: 10.1016/j.thromres.2020.04.024
17. Morassi M, Bagatto D, Cobelli M, D'Agostini S, Gigli GL, Bnà C, et al. Stroke in patients with SARS-CoV-2 infection: case series. *J Neurol*. (2020) 267:2185–92. doi: 10.1007/s00415-020-09885-2
18. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. (2020) 5:279–84. doi: 10.1136/svn-2020-000431
19. Hess DC, Eldahshan W, Rutkowski E. COVID-19-related stroke. *Transl Stroke Res*. (2020) 11:322–5. doi: 10.1007/s12975-020-00818-9
20. González-Pinto T, Luna-Rodríguez A, Moreno-Estébanez A, Agirre-Beitia G, Rodríguez-Antigüedad A, Ruiz-Lopez M. Emergency room neurology in times of COVID-19: malignant ischaemic stroke and SARS-CoV-2 infection. *Eur J Neurol*. (2020) 27:e35–6. doi: 10.1111/ene.14286
21. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. (2020) 383:120–8. doi: 10.1056/NEJMoa2015432
22. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: prevalence, risk factors, and outcome. *Circulation*. (2020) 142:114–28. doi: 10.1161/CIR.0000000000000887
23. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost*. (2020) 18:1421–4. doi: 10.1111/jth.14830
24. Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet*. (2020) 395:1517–20. doi: 10.1016/S0140-6736(20)30920-X
25. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. *J Clin Virol*. (2020) 127:104362. doi: 10.1016/j.jcv.2020.104362
26. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol*. (2020) 75:2950–73. doi: 10.1016/j.jacc.2020.04.031
27. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. (2020) 18:844–7. doi: 10.1111/jth.14768
28. Zhai Z, Li C, Chen Y, Gerotziafas G, Zhang Z, Wan J, et al. Prevention and treatment of venous thromboembolism associated with coronavirus disease 2019 infection: a consensus statement before guidelines. *Thromb Haemost*. (2020) 120:937–48. doi: 10.1055/s-0040-1710019
29. Trigonis RA, Holt DB, Yuan R, Siddiqui AA, Craft MK, Khan BA, et al. Incidence of venous thromboembolism in critically ill coronavirus disease 2019 patients receiving prophylactic anticoagulation. *Crit Care Med*. (2020) 48:e805–8. doi: 10.1097/CCM.0000000000004472

Conflict of Interest: EP was employed by the company Dascena, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 14 January 2021
doi: 10.3389/fneur.2020.623933

Cognitive Telerehabilitation for Older Adults With Neurodegenerative Diseases in the COVID-19 Era: A Perspective Study

Sara Bernini[1], Fabrizio Stasolla[2], Silvia Panzarasa[3], Silvana Quaglini[3], Elena Sinforiani[1], Giorgio Sandrini[1,4], Tomaso Vecchi[1,4], Cristina Tassorelli[1,4] and Sara Bottiroli[1,2]*

[1] Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) Mondino Foundation, Pavia, Italy, [2] Faculty of Law, Giustino Fortunato University, Benevento, Italy, [3] Department of Electrical, Computer, and Biomedical Engineering, University of Pavia, Pavia, Italy, [4] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

The COVID-19 pandemic is a global health problem that is radically transforming public and private healthcare organizations around the world, negatively affecting the rehabilitative treatments of non-COVID pathologies as well. In this situation, it becomes crucial to be able to guarantee the continuity of care also to all those patients with neurodegenerative diseases unable to reach healthcare services. Remote communication technologies are gaining momentum as potentially effective options to support health care interventions—including cognitive rehabilitation—while patients can stay safely at home. In this context, we are implementing HomeCoRe (i.e., Home Cognitive Rehabilitation software) in order to offer an innovative approach and a valid support for home-based cognitive rehabilitation in neurodegenerative diseases, such as mild cognitive impairment and early dementia. HomeCoRe has been developed within a research project between engineers and clinicians in order to obtain a usable and safe cognitive rehabilitation tool. This software has multiple advantages for patients and therapists over traditional approaches, as shown in its use in hospital settings. HomeCoRe could then represent an opportunity for accessing cognitive rehabilitation in all those situations where patients and therapists are not in the same location due to particular restrictions, such as COVID-19 pandemic.

Keywords: telerehabilitation, telemedicine, information and communication technologies, COVID-19 pandemic, cognitive impairment, cognitive rehabilitation, cognitive training, neurodegenerative diseases

OPEN ACCESS

Edited by:
Giovanni Assenza, Campus Bio-Medico University, Italy

Reviewed by:
Jacopo Lanzone, Policlinico Universitario Campus Bio-Medico, Italy
Alessandro de Sire, University of Eastern Piedmont, Italy

****Correspondence:***
Sara Bernini
sara.bernini@mondino.it

Specialty section:
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

Received: *30 October 2020*
Accepted: *03 December 2020*
Published: *14 January 2021*

Citation:
Bernini S, Stasolla F, Panzarasa S, Quaglini S, Sinforiani E, Sandrini G, Vecchi T, Tassorelli C and Bottiroli S (2021) Cognitive Telerehabilitation for Older Adults With Neurodegenerative Diseases in the COVID-19 Era: A Perspective Study. Front. Neurol. 11:623933. doi: 10.3389/fneur.2020.623933

INTRODUCTION

With the rise in life expectancy during the last decades, we are witnessing a steady increase in the number of older adults in the total population with a high risk of developing neurodegenerative diseases (1). In particular, among these, dementia represents one of the major health problems in older adults, with progressive deterioration of cognition, daily functioning, and behavior that together lead to disability. This is further exacerbated by the existing link among cognitive decline, hospitalization, and mortality, resulting in a considerable challenge to patients, caregivers, and the health system in term of resources allocation (2). The transitional phase between normal and pathological cognitive aging is a clinical condition called Mild Cognitive Impairment (MCI), which represents a risk factor for the development of dementia (3). Although not all MCI patients

progress to dementia, interventions at this pre-dementia stage may be able to reduce/slow down the deterioration along the continuum of MCI and dementia (4).

Because of the limited effectiveness of pharmacological therapies, attempts have been made to provide identification of other factors in patients' care that may delay the onset and slow progression of cognitive decline in MCI. In particular, non-pharmacological interventions have received increasing attention in recent years (5). Particularly, there is evidence that cognitive training is an effective intervention strategy in improving or at least maintaining cognitive level in MCI patients, thus slowing the progression to dementia (6, 7). Cognitive training and enhancement activities can indeed activate brain compensation mechanisms to tackle the physiological and pathological neuro-degeneration processes (8). Traditional cognitive training includes paper-and-pencil exercises usually administered in hospital settings and, less frequently, at patients' homes (9). Since this kind of intervention has some limitations—e.g., time, costs, and patients' accessibility, to name a few—their provision outside the clinical setting is often reduced (10, 11). In recent years, the development of Information and Communication Technologies (ICT) has kindled interest in alternative rehabilitative approaches. In particular, computer-based cognitive training allows one to overcome the limits of traditional paper-and-pencil techniques providing patient-tailored interventions that can be easily delivered not only in-person but also remotely at patients' homes (12). It means that they could simplify the therapist's work in terms of the planning, design, and management of the cognitive intervention also outside from the clinical setting.

To date, unprecedented new challenges to patients' care have been determined by the COVID-19 pandemic, including difficulties accessing routine treatments, such as cognitive rehabilitation, for individuals with neurodegenerative diseases. Hence, in parallel to the increase in the number of studies that claim for ICTs implementation in patient management, their effective integration in the routine clinical practice is still limited (13). The aim of this perspective article is to explore current evidence-based recommendations on the efficacy of ICT-based cognitive rehabilitation to achieve/continue adequate cognitive stimulation in the current pandemic. In this context, it is also offered a perspective about an innovative approach and a valid support for home-based cognitive rehabilitation in neurodegenerative diseases, which is HomeCoRe (i.e., Home Cognitive Rehabilitation software).

TELEMEDICINE AND TELEREHABILITATION

Telemedicine is defined as an interface in a virtual patient-clinician relationship to provide primary and secondary care by ICT (14). It is not intended to replace the healthcare model based on face-to-face interaction, but rather it is its declination varying according to patients' needs and characteristics (15). Telemedicine could be useful in the management of chronic diseases having high social impact and issues related to continuous long-term care, including diseases related to aging, such as dementia and other neurodegenerative disorders (14).

In particular, telerehabilitation (TR) is a young telemedicine subfield that could be defined as the set of instruments and protocols aimed at providing rehabilitation at a distance (16). Allowing remote delivery of different rehabilitation services in different medical conditions, TR provides benefits for the healthcare system and patients in terms of cost-effectiveness and feasibility for large-scale implementations. TR can use different types of technologies, such as sensor-based technology, tele/video-conference, specific *ad hoc* development software, or virtual reality (17).

Narrowing down the field to neurology, the main pathology treated by TR is stroke followed by traumatic brain injury, multiple sclerosis, and Parkinson's disease (18). For instance, some evidence suggests that physical and speech therapy delivered by TR to post-stroke patients is no worse than conventional in-person interventions in terms of reliability and effectiveness (19, 20). Even if motor and speech/voice impairments have been the main targets of TR (18), the interest for the treatment of other disabilities, such as the cognitive deficit following acquired neurological or neurodegenerative diseases, is growing steadily (21). In this field, the cognitive TR literature is more recent and mostly focuses on treating cognitive impairment in patients with stroke (22), multiple sclerosis (23), and brain tumors (24, 25).

COGNITIVE TELEREHABILITATION IN NEURODEGENERATIVE DISEASES

So far, few studies have been conducted to assess feasibility and efficacy of cognitive TR in older people with neurodegenerative diseases, such as MCI, Alzheimer's disease, and frontotemporal dementia. With the growing interest in this field, many study protocols have recently proliferated in the literature [e.g., (26)]. Only two systematic reviews (27, 28) are available on this topic. Cognitive TR has comparable effects in terms of efficacy, validity, and reliability to conventional in-person rehabilitation. However, as reported by Maresca and colleagues (28), most studies are characterized by small samples and lack of standardized procedures, aims, and targets. Accordingly, further randomized controlled trials (RCT) are strongly needed to improve our knowledge of how to use home-based cognitive TR effectively to delay the progression of cognitive impairment in people with MCI and dementia.

This necessity is further supported by the fact that some concerns have slowed the integration of cognitive TR into clinical practice (29, 30), but the existing literature gives some recommendations to overcome them.

First, the loss of human contact with the clinician and the limited flexibility in the adoption of devices most appropriate for patients' differing needs could hinder adherence to TR (17). Similarly, people with advanced age or cognitive deficit might have poor computer skills and difficulties managing technological devices on their own (31). Furthermore, patients' characteristics, such as hearing and vision impairments and the level and

type of cognitive impairment may influence the number of post-rehabilitation benefits. All these factors could in fact be an important cause of distraction, especially for older people who may have little or no experience or confidence using technology (32). Hence, platforms should be developed in order to be accessible and user-friendly; duration and frequency of rehabilitation activities should be tailored according to patients' characteristics (33); therapists should monitor adherence and performance of each session remotely during the whole period of treatment (34). In any case, there is evidence that cognitive TR is a valuable and well-accepted methodology, and comparable effects have been found between TR and in-hospital treatment in terms of global cognitive performance in patients with early phases of cognitive deterioration (35).

Second, even if caregivers are supportive and facilitate adherence to TR in daily routines (36), it is important to avoid their excessive involvement to limit the burden of the approach and to prevent thwarting the benefits of the treatment itself. Furthermore, patients without a compliant caregiver could be excluded by the use of TR, representing a selection bias for this kind of intervention (37). However, there is evidence also about the possibility of using telemedicine devices in MCI patients living alone. In particular, it seems that in this case patients' compliance depends on the level of monitoring he/she remotely receives (38). In addition, it is important to consider that easy-access TR tools can produce benefits (e.g., autonomy, mood, self-efficacy, quality of life, etc.) in patients, with consequent positive effects also for caregivers (39).

With these considerations in mind, TR constitutes a unique opportunity in the field of cognitive rehabilitation. It indeed represents a replacement for in-person treatment or its continuation, providing equitable access to care for patients with neurodegenerative diseases (40, 41). Such an opportunity could be useful not only for older patients with dementia or physical disabilities, but also for those presenting pre-dementia symptoms while of working age or geographically remote. More generally, TR could have a pivotal role in the clinical practice in all those situations where patients and therapists cannot be in the same location, due to patients' requirements or, as in the case of the COVID-19 pandemic, because of particular emergencies.

COGNITIVE TELEREHABILITATION DURING COVID-19 PANDEMIC

The COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, is a global health problem that has radically transformed public and private healthcare organizations around the world (42). This enduring health emergency, and the consequent adaptation of healthcare facilities, negatively influences the rehabilitative treatments of non-COVID pathologies, with an impact on the quality of life of patients (especially those with cognitive symptoms) and their families. In particular, social isolation, a long confinement period, and personal experiences combined with pre-existing diseases may play an important role in exacerbating cognitive decline and dementia (43). As an urgent response to provide continuity of care and social connectedness during the COVID-19 pandemic, new alternative options of cognitive rehabilitation are needed. To this end, remote communication technologies are increasingly considered as potentially effective options to support healthcare interventions, among which is cognitive rehabilitation, directly at the patient's home, reducing risks of possible infections (44–46). Aging *per se* is, in fact, associated with vulnerabilities of a physical, psychosocial, and environmental nature (47), determining more comorbidities and hospitalizations and, as a consequence, an increasing chance of being infected with COVID-19 (48). Such a susceptibility to morbidity and mortality from COVID-19 becomes more pronounced in those older adults with dementia (49). Hence, rehabilitation via remote communication technologies may represent a viable alternative tool to access care while reducing the risk of COVID-19 infection and avoiding unnecessary travel and discomfort to the patient and other family members (50).

Within this framework, cognitive TR may be viewed as a valid recovery tool (51) deriving from the reshape of cognitive rehabilitation with the use of technologies (52). Hence, based on these promising results and forced by the COVID-19 pandemic contingency, new studies and a larger diffusion of cognitive TR approaches are expected (53–55). To date, most efforts have been devoted to using telemedicine/telerehabilitation to address patients' recovery after COVID-19, which is very important in order to monitor and manage resulting deficits (56–61). For instance, Salawu and colleagues (60) have proposed a multidisciplinary TR program for patients with COVID-19 discharged from hospitals with residual rehabilitation needs. However, telemedicine and telerehabilitation should be implemented also in non-COVID patients in various settings of neurological care (36, 62, 63). From this perspective, Motolese and colleagues (36) explored the feasibility of a smartphone application for monitoring motor and cognitive performance of non-demented Parkinson's disease outpatients during the lockdown. Ramalho and colleagues (64) proposed a protocol of telemental healthcare to be applied to populations with different levels of needs, including older adults in need of constant home-based assistance. Again, in the field of pathological aging, other recommendations pertain to the management of behavioral and psychological symptoms of dementia or long-term care of older adults living in nursing homes via telemedicine (65). To the best of our knowledge, no experience has been published on the use of TR in older adults with cognitive impairment during COVID-19, even if strongly recommended (53–55).

A PERSPECTIVE FOR FUTURE COGNITIVE REHABILITATION: HomeCoRe

During the past years, we have implemented and used a computer-supported cognitive training program (Cognitive Rehabilitation—CoRe—software) for in-person sessions in the hospital setting (66, 67). CoRe has been developed within a research project between engineers and clinicians. We reported that CoRe was safe and effective with respect to cognition in

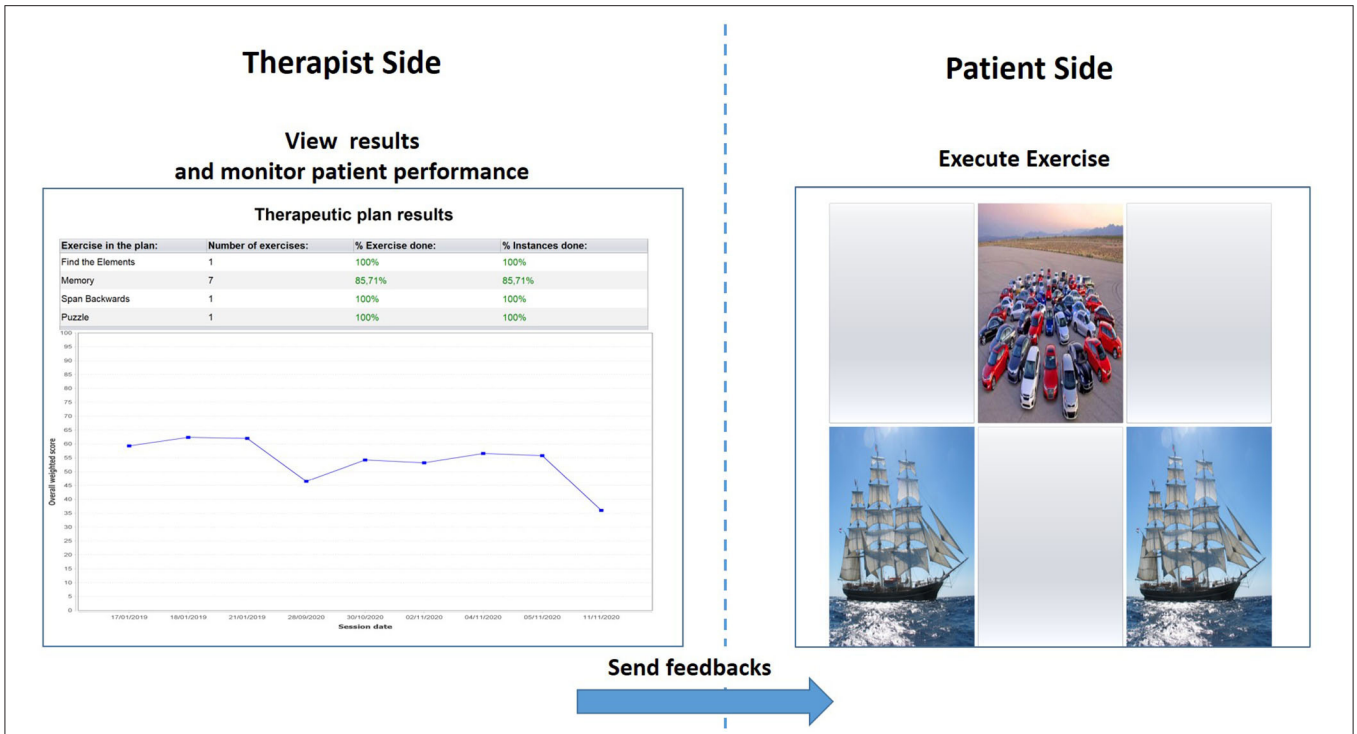


FIGURE 1 | Therapist interface for monitoring results and patient performance in terms of overall Weighted Score **(left)** and patient interface for the execution of the memory exercise **(right)**.

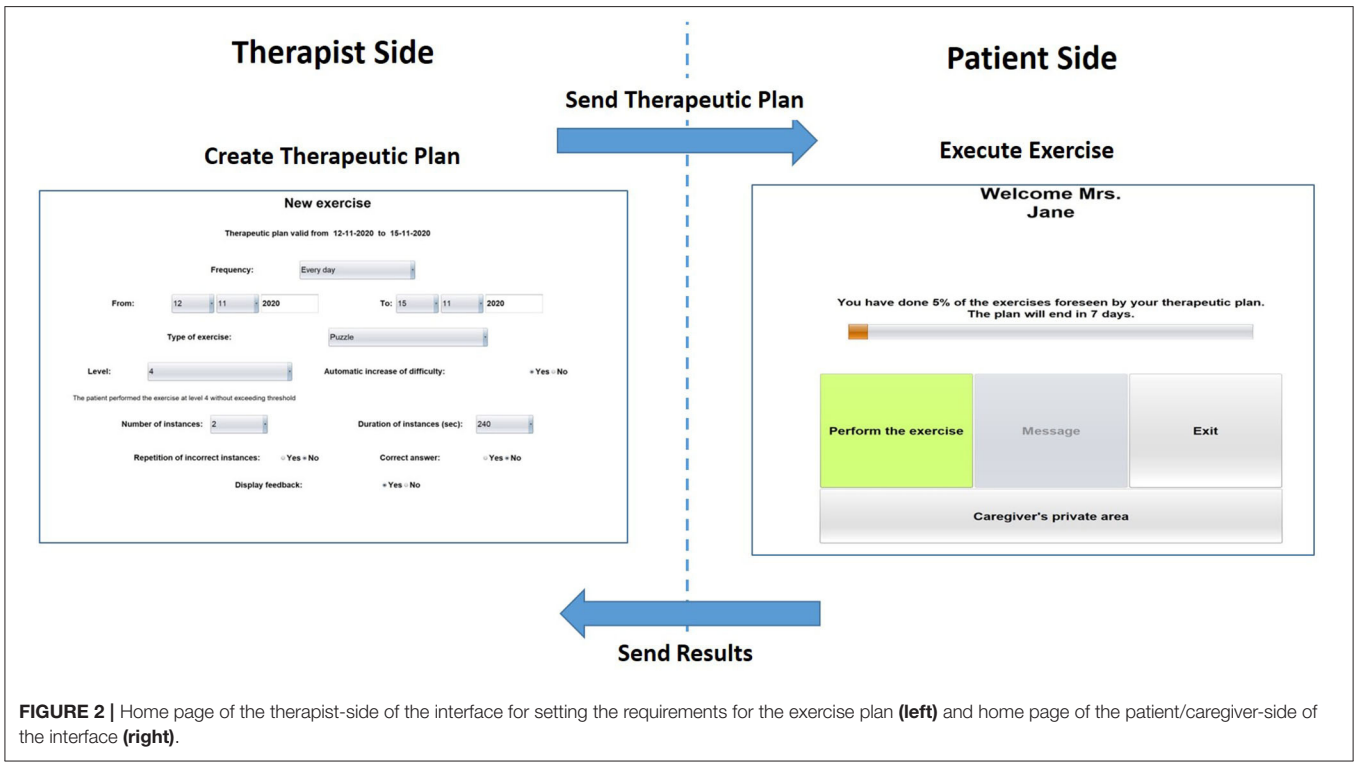


FIGURE 2 | Home page of the therapist-side of the interface for setting the requirements for the exercise plan **(left)** and home page of the patient/caregiver-side of the interface **(right)**.

inpatients with Parkinson Disease-Mild Cognitive Impairment (68, 69) and also in older adults with other forms of early cognitive impairment (70). Following these encouraging results observed in the hospital setting, we recently developed a TR version of CoRe that allows the provision of treatment at patients' homes: HomeCoRe (71).

HomeCoRe is a patient-tailored intervention aimed at stimulating several cognitive abilities (e.g., logical-executive functions, attention/processing speed, working memory, and episodic memory) through a series of sessions of 2D exercises planned remotely for multiple advantages for therapists and patients. It is timesaving, ready to use, and able to set exercises for each training session automatically. Exercises take place in an adaptive mode. In particular, during their dynamic generation, the individual patients' performance data (accuracy and number of aids required) are analyzed in order to set the appropriate difficulty level. Furthermore, for each exercise and each level, thresholds are defined so as to allow difficulty levels to be progressively increased. In addition, the system calculates an "overall weighted score (WS)," taking into account the correctness of the answers, the execution time, and the difficulty of the exercises. The WS informs the therapist about each patient's performance in a single value. Hence, WS represents a useful and advantageous index that can be used to assess and monitor both the overall outcome of a training session and the global trend of the rehabilitation (**Figure 1**).

The HomeCoRe architecture includes two main components, the therapist side and the patient/caregiver side, as well as the communication channels between them. The therapist side of the interface allows the remote setting and monitoring of all requirements of the treatment plan (e.g., frequency and duration of the plan, types of exercise, and difficulty level) (see **Figure 2**). The patients/caregiver side of the interface is very simple to use, and it allows for viewing and executing the exercises of the day and communicating with the therapist (see **Figure 2**).

In a recent work (71), we interviewed and surveyed inpatients to investigate their willingness to continue rehabilitation at home by using HomeCoRe after discharge. Caregivers were also interviewed, due to their role in both supporting and motivating patients. The survey results showed that most of both patient participants and caregivers appreciated HomeCoRe and intended to have a further home commitment. Subsequently, we tested the functionality and usability of HomeCoRe by using in-hospital workstations that simulated home sessions. Currently, we are carrying out a pilot study on a small sample of patients in the early stage of cognitive deterioration testing HomeCoRe directly at patients' homes. This will allow evaluating both patients' and caregivers' experience (e.g., compliance, benefits) and the cognitive effects of HomeCoRe rehabilitation. The output of this pilot study will inform a randomized clinical trial to explore the cost-effectiveness of cognitive telerehabilitation via HomeCoRe compared with in-person cognitive rehabilitation in patients with neurodegenerative diseases.

HomeCoRe promises to qualify as an innovative approach and a valid support for cognitive rehabilitation in neurodegenerative diseases. In addition, as a TR tool, HomeCoRe will allow extending the duration of the rehabilitation treatment of inpatients beyond the hospital discharge, which often coincides with treatment interruption, due to the scarcity of healthcare personnel for homecare. It also offers a unique opportunity to deliver cognitive rehabilitation to people who live in remote areas or who cannot reach healthcare services due to physical impairments or particular restrictions, such as the COVID-19 pandemic.

CONCLUSION

Due to the progressive aging of our population, the number of people with MCI or dementia is expected to grow consistently, with a social impact and economic burden on the healthcare system. Therefore, the World Health Organization (WHO) stresses taking global action against cognitive decline and dementia, encouraging governments worldwide to focus on prevention and to improve healthcare services. In addition, in line with the new health and social order that has been determined since the COVID-19 pandemic, it is crucial to offer a cognitive rehabilitation modality that can be used directly at home, in a condition of distance and safety for both family members and the patient her/himself. To this end, remote communication technologies are increasingly regarded as potentially effective options—with the appropriate recommendations (29, 30)—to support cognitive rehabilitation (53–55). In this framework, HomeCoRe is software for cognitive rehabilitation in neurodegenerative diseases that could be incorporated into clinical routine protocols as a complementary non-pharmacological therapy to support the continuum of care from the hospital to the patient's home.

In conclusion, the COVID-19 pandemic has determined new chances to embrace technology allowing people to maintain their connection with the outside world during isolation (72, 73). Such opportunities can also be extended to the delivery of care for neurodegenerative diseases, producing a technological evolution in the healthcare system (74–76) and dementia practice (53–55, 77), in the coming years.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by San Matteo Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SBe and SBo have conceived the work. All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

FUNDING

This project was funded by the Current Research Fund of the Italian Ministry of Health at the National Neurological Institute C. Mondino Foundation (Ricerca Corrente 2020).

REFERENCES

1. Stenberg K, Hanssen O, Edejer TT-T, Bertram M, Brindley C, Meshreky A, et al. Financing transformative health systems towards achievement of the health sustainable development goals: a model for projected resource needs in 67 low-income and middle-income countries. *Lancet Glob Heal.* (2017) 5:e875–87. doi: 10.1016/S2214-109X(17)30263-2
2. Olazarán J, Muñiz R, Reisberg B, Peña-Casanova J, del Ser T, Cruz-Jentoft AJ, et al. Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. *Neurology.* (2004) 63:2348–53. doi: 10.1212/01.wnl.0000147478.03911.28
3. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol.* (1999) 56:303–8. doi: 10.1001/archneur.56.3.303
4. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. *Clin Geriatr Med.* (2014) 30:421–42. doi: 10.1016/j.cger.2014.04.001
5. Karakaya T, Fußer F, Schröder J, Pantel J. Pharmacological treatment of mild cognitive impairment as a prodromal syndrome of Alzheimer's disease. *Curr Neuropharmacol.* (2013) 11:102–8. doi: 10.2174/157015913804999487
6. Faucounau V, Wu YH, Boulay M, De Rotrou J, Rigaud AS. Cognitive intervention programmes on patients affected by mild cognitive impairment: a promising intervention tool for MCI? *J Nutr Health Aging.* (2010) 14:31–5. doi: 10.1007/s12603-010-0006-0
7. Mowszowski L, Batchelor J, Naismith SL. Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique? *Int Psychogeriatrics.* (2010) 22:537–48. doi: 10.1017/S1041610209991748
8. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, et al. Harnessing neuroplasticity for clinical applications. *Brain.* (2011) 134:1591–609. doi: 10.1093/brain/awr039
9. Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev.* (2003) 4:CD003260. doi: 10.1002/14651858.CD003260
10. García-Casal JA, Loizeau A, Csipke E, Franco-Martín M, Perea-Bartolomé MV, Orrell M. Computer-based cognitive interventions for people living with dementia: a systematic literature review and meta-analysis. *Aging Ment Health.* (2017) 21:454–67. doi: 10.1080/13607863.2015.1132677
11. Zokaei N, MacKellar C, Cepukaityte G, Patai EZ, Nobre AC. Cognitive training in the elderly: bottlenecks and new avenues. *J Cogn Neurosci.* (2017) 29:1473–82. doi: 10.1162/jocn_a_01080
12. Irazoki E, Contreras-Somoza LM, Toribio-Guzmán JM, Jenaro-Río C, van der Roest H, Franco-Martín MA. Technologies for cognitive training and cognitive rehabilitation for people with mild cognitive impairment and dementia. A systematic review. *Front Psychol.* (2020) 11:648. doi: 10.3389/fpsyg.2020.00648
13. Sim I. Mobile devices and health. *N Engl J Med.* (2019) 381:956–68. doi: 10.1056/NEJMra1806949
14. Chirra M, Marsili L, Wattley L, Sokol LL, Keeling E, Maule S, et al. Telemedicine in neurological disorders: opportunities and challenges. *Telemed e-Health.* (2019) 25:541–50. doi: 10.1089/tmj.2018.0101
15. Nesbitt TS, Hilty DM, Kuenneth CA, Siefkin A. Development of a telemedicine program: a review of 1,000 videoconferencing consultations. *West J Med.* (2000) 173:169–74. doi: 10.1136/ewjm.173.3.169-a
16. Zampolini M, Todeschini E, Bernabeu Guitart M, Hermens H, Ilsbroukx S, Macellari V, et al. Tele-rehabilitation: present and future. *Ann Ist Super Sanita.* (2008) 44:125–34.
17. Peretti A, Amenta F, Tayebati SK, Nittari G, Mahdi SS. Telerehabilitation: review of the state-of-the-art and areas of application. *JMIR Rehabil Assist Technol.* (2017) 4:e7. doi: 10.2196/rehab.7511
18. Rogante M, Grigioni M, Cordella D, Giacomozzi C. Ten years of telerehabilitation: a literature overview of technologies and clinical applications. *NeuroRehabilitation.* (2010) 27:287–304. doi: 10.3233/NRE-2010-0612
19. Cherney LR, van Vuuren S. Telerehabilitation, virtual therapists, and acquired neurologic speech and language disorders. *Semin Speech Lang.* (2012) 33:243–57. doi: 10.1055/s-0032-1320044
20. Kairy D, Lehoux P, Vincent C, Visintin M. A systematic review of clinical outcomes, clinical process, healthcare utilization and costs associated with telerehabilitation. *Disabil Rehabil.* (2009) 31:427–47. doi: 10.1080/09638280802062553
21. Caltagirone C, Zannino GD. Telecommunications technology in cognitive rehabilitation. *Funct Neurol.* (2008) 23:195–9.
22. Laver KE, Adey-Wakeling Z, Crotty M, Lannin NA, George S, Sherrington C. Telerehabilitation services for stroke. *Cochrane Database Syst Rev.* (2020) 1:CD010255. doi: 10.1002/14651858.CD010255.pub3
23. Yeroushalmi S, Maloni H, Costello K, Wallin MT. Telemedicine and multiple sclerosis: a comprehensive literature review. *J Telemed Telecare.* (2020) 26:400–13. doi: 10.1177/1357633X19840097
24. Galiano-Castillo N, Arroyo-Morales M, Lozano-Lozano M, Fernández-Lao C, Martín-Martín L, Del-Moral-Ávila R, et al. Effect of an Internet-based telehealth system on functional capacity and cognition in breast cancer survivors: a secondary analysis of a randomized controlled trial. *Support Care Cancer.* (2017) 25:3551–9. doi: 10.1007/s00520-017-3782-9
25. van der Linden SD, Sitskoorn MM, Rutten G-JM, Gehring K. Feasibility of the evidence-based cognitive telerehabilitation program Remind for patients with primary brain tumors. *J Neurooncol.* (2018) 137:523–32. doi: 10.1007/s11060-017-2738-8
26. Fabbri L, Mosca IE, Gerli F, Martini L, Pancani S, Lucidi G, et al. The games for older adults active life (GOAL) project for people with mild cognitive impairment and vascular cognitive impairment: a study protocol for a randomized controlled trial. *Front Neurol.* (2019) 10:1–9. doi: 10.3389/fneur.2018.01040
27. Cotelli M, Manenti R, Brambilla M, Gobbi E, Ferrari C, Binetti G, et al. Cognitive telerehabilitation in mild cognitive impairment, Alzheimer's disease and frontotemporal dementia: a systematic review. *J Telemed Telecare.* (2019) 25:67–79. doi: 10.1177/1357633X17740390
28. Maresca G, Maggio MG, De Luca R, Manuli A, Tonin P, Pignolo L, et al. Tele-neuro-rehabilitation in Italy: state of the art and future perspectives. *Front Neurol.* (2020) 11:563375. doi: 10.3389/fneur.2020.563375
29. Gentry MT, Lapid MI, Rummans TA. Geriatric telepsychiatry: systematic review and policy considerations. *Am J Geriatr Psychiatry.* (2019) 27:109–27. doi: 10.1016/j.jagp.2018.10.009
30. Standing C, Standing S, McDermott M-L, Gururajan R, Kiani Mavi R. The paradoxes of telehealth: a review of the literature 2000-2015. *Syst Res Behav Sci.* (2018) 35:90–101. doi: 10.1002/sres.2442
31. Richardson M, Zorn TE, Weaver K. *Senior's Perspectives on the Barriers, Benefits and Negatives Consequences of Learning and Using Computers.* Hamilton: Department of Management Communication, University of Waikato (2002).
32. Peel NM, Russell TG, Gray LC. Feasibility of using an in-home video conferencing system in geriatric rehabilitation. *J Rehabil Med.* (2011) 43:364–6. doi: 10.2340/16501977-0675
33. Jeong IC, Liu J, Finkelstein J. Factors affecting adherence with telerehabilitation in patients with multiple sclerosis. *Stud Health Technol Inform.* (2019) 257:189–93. doi: 10.3233/978-1-61499-951-5-189
34. Gil-Pagés M, Solana J, Sánchez-Carrión R, Tormos JM, Enseñat-Cantallops A, García-Molina A. A customized home-based computerized cognitive rehabilitation platform for patients with chronic-stage stroke: study protocol for a randomized controlled trial. *Trials.* (2018) 19:191. doi: 10.1186/s13063-018-2577-8
35. Jelcic N, Agostini M, Meneghello F, Bussè C, Parise S, Galano A, et al. Feasibility and efficacy of cognitive telerehabilitation in early Alzheimer's disease: a pilot study. *Clin Interv Aging.* (2014) 9:1605–11. doi: 10.2147/CIA.S68145
36. Motolese F, Magliozzi A, Puttini F, Rossi M, Capone F, Karlinski K, et al. Parkinson's disease remote patient monitoring during the COVID-19 lockdown. *Front Neurol.* (2020) 11:567413. doi: 10.3389/fneur.2020.567413
37. Moo LR, Gately ME, Jafri Z, Shirk SD. Home-based video telemedicine for dementia management. *Clin Gerontol.* (2020) 43:193–203. doi: 10.1080/07317115.2019.1655510
38. Smith GE, Lunde AM, Hathaway JC, Vickers KS. Telehealth home monitoring of solitary persons with mild dementia. *Am J Alzheimer's Dis Other Dementias®.* (2007) 22:20–6. doi: 10.1177/1533317506295888

39. Nijland N, van Gemert-Pijnen J, Boer H, Steehouder MF, Seydel ER. Evaluation of internet-based technology for supporting self-care: problems encountered by patients and caregivers when using self-care applications. *J Med Internet Res.* (2008) 10:e13. doi: 10.2196/jmir.957
40. Choi J, Twamley EW. Cognitive rehabilitation therapies for Alzheimer's disease: a review of methods to improve treatment engagement and self-efficacy. *Neuropsychol Rev.* (2013) 23:48–62. doi: 10.1007/s11065-013-9227-4
41. Ramos-Ríos R, Mateos R, Lojo D, Conn DK, Patterson T. Telepsychogeriatrics: a new horizon in the care of mental health problems in the elderly. *Int Psychogeriatrics.* (2012) 24:1708–24. doi: 10.1017/S1041610212000981
42. WHO (2020). Available online at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed November 30, 2020).
43. Korczyn AD. Dementia in the COVID-19 Period. *J Alzheimers Dis.* (2020) 75:1071–2. doi: 10.3233/JAD-200609
44. Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med.* (2020) 382:1679–81. doi: 10.1056/NEJMp2003539
45. Tozzi AE, Gesualdo F, D'Ambrosio A, Pandolfi E, Agricola E, Lopalco P. Can digital tools be used for improving immunization programs? *Front public Heal.* (2016) 4:36. doi: 10.3389/fpubh.2016.00036
46. Woodall T, Ramage M, LaBruyere JT, McLean W, Tak CR. Telemedicine services during COVID-19: considerations for medically underserved populations. *J Rural Health.* (2020) doi: 10.1111/jrh.12466. [Epub ahead of print].
47. Banerjee D. "Age and ageism in COVID-19": elderly mental health-care vulnerabilities and needs. *Asian J Psychiatr.* (2020) 51:102154. doi: 10.1016/j.ajp.2020.102154
48. Banerjee D. The impact of Covid-19 pandemic on elderly mental health. *Int J Geriatr Psychiatry.* (2020) doi: 10.1002/gps.5320. [Epub ahead of print].
49. Bauer K, Schwarzkopf L, Graessel E, Holle R. A claims data-based comparison of comorbidity in individuals with and without dementia. *BMC Geriatr.* (2014) 14:10. doi: 10.1186/1471-2318-14-10
50. Maggio MG, De Luca R, Manuli A, Calabrò RS. The five 'W' of cognitive telerehabilitation in the Covid-19 era. *Expert Rev Med Devices.* (2020) 17:473–5. doi: 10.1080/17434440.2020.1776607
51. Gamito P, Oliveira J, Coelho C, Morais D, Lopes P, Pacheco J, et al. Cognitive training on stroke patients via virtual reality-based serious games. *Disabil Rehabil.* (2017) 39:385–8. doi: 10.3109/09638288.2014.934925
52. Bartolo M, Intiso D, Lentino C, Sandrini G, Paolucci S, Zampolini M, et al. Urgent measures for the containment of the coronavirus (Covid-19) epidemic in the neurorehabilitation/rehabilitation departments in the phase of maximum expansion of the epidemic. *Front Neurol.* (2020) 11:423. doi: 10.3389/fneur.2020.00423
53. Bloem BR, Dorsey ER, Okun MS. The coronavirus disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. *JAMA Neurol.* (2020) 77:927–8. doi: 10.1001/jamaneurol.2020.1452
54. Mantovani E, Zucchella C, Bottiroli S, Federico A, Giugno R, Sandrini G, et al. Telemedicine and virtual reality for cognitive rehabilitation: a roadmap for the COVID-19 pandemic. *Front Neurol.* (2020) 11:926. doi: 10.3389/fneur.2020.00926
55. Platz T, Sandrini G. Specialty grand challenge for neurorehabilitation research. *Front Neurol.* (2020) 11:349. doi: 10.3389/fneur.2020.00349
56. Negrini S, Kiekens C, Bernetti A, Capecci M, Ceravolo MG, Lavezzi S, et al. Telemedicine from research to practice during the pandemic "instant paper from the field" on rehabilitation answers to the COVID-19 emergency. *Eur J Phys Rehabil Med.* (2020) 56:327–30. doi: 10.23736/S1973-9087.20.06331-5
57. de Sire A, Andrenelli E, Negrini F, Negrini S, Ceravolo MG. Systematic rapid living review on rehabilitation needs due to COVID-19: update as of April 30th, 2020. *Eur J Phys Rehabil Med.* (2020) 56:354–60 doi: 10.23736/S1973-9087.20.06378-9
58. Curci C, Pisano F, Bonacci E, Camozzi DM, Ceravolo C, Bergonzi R, et al. Early rehabilitation in post-acute COVID-19 patients: data from an Italian COVID-19 Rehabilitation Unit and proposal of a treatment protocol. *Eur J Phys Rehabil Med.* (2020) 56:633–41. doi: 10.23736/S1973-9087.20.06339-X
59. Turolla A, Rossettini G, Viceconti A, Palese A, Geri T. Musculoskeletal physical therapy during the COVID-19 pandemic: is telerehabilitation the answer? *Phys Ther.* (2020) 100:1260–4. doi: 10.1093/ptj/pzaa093
60. Salawu A, Green A, Crooks MG, Brixey N, Ross DH, Sivan M. A proposal for multidisciplinary tele-rehabilitation in the assessment and rehabilitation of COVID-19 survivors. *Int J Environ Res Public Health.* (2020) 17:4890. doi: 10.3390/ijerph17134890
61. Sivan M, Halpin S, Hollingworth L, Snook N, Hickman K, Clifton I. Development of an integrated rehabilitation pathway for individuals recovering from COVID-19 in the community. *J Rehabil Med.* (2020) 52:jrm00089. doi: 10.2340/16501977-2727
62. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol.* (2020) 11:737. doi: 10.3389/fneur.2020.00737
63. Stipa G, Gabbrielli F, Rabbito C, Di Lazzaro V, Amantini A, Grippo A, et al. The Italian technical/administrative recommendations for telemedicine in clinical neurophysiology. *Neurol Sci.* (2020). doi: 10.1007/s10072-020-04732-8. [Epub ahead of print].
64. Ramalho R, Adiukwu F, Gashi Bytyçi D, El Hayek S, Gonzalez-Diaz JM, Larnaout A, et al. Telepsychiatry during the COVID-19 pandemic: development of a protocol for telemental health care. *Front Psychiatry.* (2020) 11:552450. doi: 10.3389/fpsyt.2020.552450
65. Soares WB, Silvestre IT, Lima AM de O, de Almondes KM. The Influence of telemedicine care on the management of behavioral and psychological symptoms in dementia (BPSD) risk factors induced or exacerbated during the COVID-19 pandemic. *Front psychiatry.* (2020) 11:577629. doi: 10.3389/fpsyt.2020.577629
66. Alloni A, Sinforiani E, Zucchella C, Sandrini G, Bernini S, Cattani B, et al. Computer-based cognitive rehabilitation: the CoRe system. *Disabil Rehabil.* (2017) 39:407–17. doi: 10.3109/09638288.2015.1096969
67. Alloni A, Quaglini S, Panzarasa S, Sinforiani E, Bernini S. Evaluation of an ontology-based system for computerized cognitive rehabilitation. *Int J Med Inform.* (2018) 115:64–72. doi: 10.1016/j.ijmedinf.2018.04.005
68. Bernini S, Alloni A, Panzarasa S, Picascia M, Quaglini S, Tassorelli C, et al. A computer-based cognitive training in mild cognitive impairment in Parkinson's disease. *NeuroRehabilitation.* (2019) 44:555–67. doi: 10.3233/NRE-192714
69. Bernini S, Panzarasa S, Barbieri M, Sinforiani E, Quaglini S, Tassorelli C, et at. A double-blind randomized controlled trial of the efficacy of cognitive training delivered using two different methods in mild cognitive impairment in Parkinson's disease: preliminary report of benefits associated with the use of a computerized tool. *Aging Clin Exp Res.* (2020) doi: 10.1007/s40520-020-01665-2. [Epub ahead of print].
70. Rodella C, Bernini S, Panzarasa S, Sinforiani E, Picascia M, Quaglini S, et al. *A Double-Blind Randomized Controlled Trial Combining Cognitive Training (CoRe) and Neurostimulation (tDCS) in the Early Stages of Cognitive Impairment, Unpublished Paper*. (2020)
71. Quaglini S, Panzarasa S, Alloni A, Sacchi M, Sinforiani E, Bottiroli S, et al. HomeCore: bringing cognitive rehabilitation at home. *Stud Health Technol Inform.* (2019) 264:1755–6. doi: 10.3233/SHTI190632
72. Shao YK, Mang J, Li PL, Wang J, Deng T, Xu ZX. Computer-based cognitive programs for improvement of memory, processing speed and executive function during age-related cognitive decline: a meta-analysis. *PLoS ONE.* (2015) 10:e0130831. doi: 10.1371/journal.pone.0130831
73. Ting DSW, Carin L, Dzau V, Wong TY. Digital technology and COVID-19. *Nat Med.* (2020) 26:459–61. doi: 10.1038/s41591-020-0824-5
74. Bashshur R, Doarn CR, Frenk JM, Kvedar JC, Woolliscroft JO. Telemedicine and the COVID-19 pandemic, lessons for the future. *Telemed J E Health.* (2020) 26:571–3. doi: 10.1089/tmj.2020.29040.rb
75. Ohannessian R, Duong TA, Odone A. Global telemedicine implementation and integration within health systems to fight the COVID-19 pandemic: a call to action. *JMIR Public Heal Surveill.* (2020) 6:e18810. doi: 10.2196/18810
76. Smith AC, Thomas E, Snoswell CL, Haydon H, Mehrotra A, Clemensen J, et al. Telehealth for global emergencies: implications for coronavirus disease 2019 (COVID-19). *J Telemed Telecare.* (2020) 26:309–13. doi: 10.1177/1357633X20916567

77. Scuteri D, Matamala-Gomez M, Bottiroli S, Corasaniti MT, De Icco R, Bagetta G, et al. Pain assessment and treatment in dementia at the time of coronavirus disease COVID-19. *Front Neurol.* (2020) 11:890. doi: 10.3389/fneur.2020.00890

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 15 January 2021
doi: 10.3389/fneur.2020.615061

The National Institutes of Health COVID-19 NeuroDatabank and NeuroBiobank: A National Resource for Learning, Discovery, and Progress

Andrea B. Troxel[1]*, *Jennifer A. Frontera*[2] *and Carolina Mendoza-Puccini*[3]

[1] Department of Population Health, New York University Grossman School of Medicine, New York, NY, United States, [2] Department of Neurology, New York University Grossman School of Medicine, New York, NY, United States, [3] Division of Clinical Research, National Institute of Neurological Disorders and Stroke, Bethesda, MD, United States

Patients suffering from COVID-19 experience a wide range of symptoms and sequelae, including increasingly recognized neurological problems. A concerted effort is necessary to identify and characterize these issues, whether newly appearing as a result of COVID-19 disease or exacerbations of underlying conditions. A national resource to collect information and/or biospecimens regarding neurological complications of COVID-19 offers an opportunity for broad representation, harmonization, and rapid learning, all while ensuring robust protection of confidential information through the use of global unique identifiers to protect patient privacy.

Keywords: COVID-19, registry, neurology, epidemiology, patient privacy, rare conditions

OPEN ACCESS

Edited by:
Giovanni Assenza,
Campus Bio-Medico University, Italy

Reviewed by:
Maura Pugliatti,
University of Ferrara, Italy
Ettore Beghi,
Mario Negri Pharmacological Research Institute (IRCCS), Italy

****Correspondence:***
Andrea B. Troxel
andrea.troxel@nyulangone.org

Specialty section:
This article was submitted to Neuroepidemiology, a section of the journal Frontiers in Neurology

Received: *08 October 2020*
Accepted: *14 December 2020*
Published: *15 January 2021*

Citation:
Troxel AB, Frontera JA and Mendoza-Puccini C (2021) The National Institutes of Health COVID-19 NeuroDatabank and NeuroBiobank: A National Resource for Learning, Discovery, and Progress. Front. Neurol. 11:615061. doi: 10.3389/fneur.2020.615061

INTRODUCTION

There is accumulating evidence of neurological complications of COVID-19, but their prevalence, etiology, and long-term cognitive and functional sequelae remain unknown. The current neurologic COVID-19 literature consists primarily of retrospective studies that often conflate non-specific symptoms (e.g., agitation, executive dysfunction, myalgias, dizziness, and headache) with neurologic diagnoses (e.g., stroke, seizures, and Guillain-Barre syndrome), leading to wide variability in neurologic event prevalence estimates (4–84% across studies) (1–3). While initial reports speculated on the neuro-invasiveness of SARS-CoV-2, no convincing pathologic data exist to support neurotropism (4). Conversely, case reports of Guillain-Barre syndrome and acute disseminated encephalitis suggested post-infectious, autoimmune-mediated neurological injury. Furthermore, an emerging literature describing a post-viral syndrome characterized by fatigue, cognitive problems, and neuropsychiatric disorders points to a potential second wave of subacute COVID-19-related neurological conditions (5). It remains unclear whether neurologic disorders in the context of COVID-19 represent a causal relationship, secondary effects of severe systemic illness, or mere coincidence.

Local medical and research institutions across the world have generated datasets with information on COVID-19 patients and have collected biosamples of, for example, blood, plasma, cerebrospinal fluid, and placenta and brain tissue. However, most such resources were established hurriedly with little to no funding or staff and often missed the peak of the pandemic in their regions. Furthermore, data on symptoms, tests, treatments, and outcomes of patients with COVID-19 exist in the idiosyncratic electronic health records (EHRs) of individual hospitals and clinics. Collectively, this information has the potential to accelerate research, enable learning about the

prevalence and consequences of COVID-19 complications, and facilitate the development of prevention and treatment strategies. But its current fragmentary state hampers scientific progress. An urgent challenge is to assemble, harmonize, and curate these diverse resources and make them widely available to researchers.

The practical challenges of establishing harmonized data collection and biobanking are formidable, and include ownership as well as data security, privacy, harmonization, and standards. Here we discuss ways to overcome these challenges in the context of neurological complications of COVID-19, although our experience can be applied in other domains.

The NIH COVID-19 NeuroDatabank and NeuroBiobank (NIH-NeuroCOVID), funded in July 2020 by the National Institute of Neurological Diseases and Stroke (NINDS), was developed as a resource for investigators interested in pooled COVID-19 neurological event data. The main goals of the program are to identify neurologic phenotypes, risk factors, regional effects, socio-economic factors, and therapeutic responses among patients with new or complicated neurological disorders and concomitant COVID-19. Numerous features of the NIH-NeuroCOVID initiative enhance its promise as a basis for rapid accumulation of knowledge, sharing of harmonized data and curated information, and leveraging of geographically and socially diverse populations to accelerate real-time learning.

METHODOLOGY

Inclusion/Exclusion Criteria

The databank will include both hospitalized patients and outpatients across the age spectrum including maternal/neonate (birth to 30 days of life) dyads, children, pregnant women, and the general adult population. Inclusion criteria are laboratory confirmed SARS-CoV-2 infection (either by RT-PCR molecular testing, antigen, or antibody testing) and at least one new or worsened symptom related to the nervous system.

Data Curation

A key feature supporting the power of the program as an engine of inquiry is the standardization of data elements that may arise from a variety of sources into a set of defined common data elements (CDEs). The NeuroCOVID data management system will include robust quality control measures, with a limited set of critical required elements and a much wider set of optional elements; this will ensure that the most important information is captured uniformly while enabling ancillary studies of a broader range of topics.

Data collection will follow a standardized format and systematic coding, to maximize our ability to represent information in a consistent manner. Building upon standardized NIH/NINDS common data elements (CDEs), we created additional variables to capture COVID-19-specific medical complications as well as new or worsened neurological disorders. The harmonization of variable definitions, capturing aspects of infection, disease course, treatment, outcomes, and complications, will enable analyses that define the scope of the problem, indicate associations that may be important for treatment and management, and present further avenues for examination. To assess causality, we adapted previously published association criteria developed for COVID-19 related meningitis, encephalitis, central nervous system vasculitis, and myelitis (3). We included additional variables to establish the timing from COVID-19 diagnosis or initial symptom onset. For ease of use and generalizability, we will use the World Health Organization Clinical (WHO) Progression Score to determine COVID-19-related severity of illness and the modified Rankin Score (in adults) and the Pediatric Functional Status Scale (in neonates and children) to assess neurological function at the time of hospital discharge or outpatient presentation. Other hospital metrics include the NIH stroke score, Glasgow Coma score, sequential organ failure assessment (SOFA), Pediatric Logistic Organ Dysfunction Score (PELOD-2), Confusion Assessment Method (CAM or CAM-ICU), length of stay, intensive care unit requirement, ventilator days, and discharge disposition. All of these instruments are among the most commonly documented scoring systems utilized by health systems across the U.S.

Data Security

To enable widespread sharing of the resources created by NeuroCOVID, we have established robust processes for de-identification of both data and biospecimens, with protection of patient privacy as a guiding principle. All data and samples will be stripped of personal identifiers and linked only to a Global Unique Identifier (GUID); this process enforces retention of personal protected health information only at the originating site (one-way encryption), and enables linking of patient data from multiple sources, and between pregnant mothers and their newborn infants. Dates and other potentially identifying elements are converted into a series of hash-codes using a specialized algorithm to ensure non-identifiability and the inability to link back to individuals following submission of data. This robust process of de-identification will ensure the creation of fully anonymized datasets that can then be widely, and securely, shared with researchers, in full accordance with NIH data sharing policies and goals.

Governance

We have created a web-based portal to accept applications to use NeuroCOVID resources (https://med.nyu.edu/departments-institutes/population-health/divisions-sections-centers/biostatistics/research/nih-neurodatabank-neurobiobank). Research proposals to use data and/or biospecimens will be uploaded via a streamlined interface. Our Steering Committee, comprising international experts in neurology, infectious disease, and biostatistics and epidemiology, will assess these proposals with respect to scientific rigor, adequate design and statistical power, suitability of analytic methods, and appropriate plans for dissemination. Proposals of sufficient quality and scientific merit will be approved and investigators will be provided with the requested materials. We have developed publication policies to appropriately credit contributors. We will provide researchers who use NeuroCOVID data with support to encourage application of appropriately robust methods for the analysis of observational data (e.g., estimation of propensity scores followed by matching to render groups more comparable)

to address the problems with selection bias and other forms of confounding that are inherent in observational data sources (6).

DISCUSSION

The NIH COVID-19 NeuroDatabank will harness the power of pooling information, so critical in a rapidly evolving pandemic (7). This has multiple advantages. Foremost is the ability to incorporate data from a truly diverse population of patients, including underrepresented, vulnerable populations, whether they be defined by race/ethnicity, socioeconomic status, or social and/or physical marginalization (e.g., rural, homeless, or justice-system-involved populations). While we cannot guarantee the representativeness of the data collected, a strong effort will be made to enroll a diverse patient population and encourage participation by a variety of institutions and practitioners. A second advantage is the ability, by casting a wide net across the nation and potentially the globe, to uncover and document rare effects that are impossible to detect with less far-ranging or more focused sampling. This effort in data collection will enable a rich characterization of the emerging neurological effects of COVID-19, and just as importantly, of the impact of the infection on existing or latent neurologic illnesses.

An additional unique feature of NIH-NeuroCOVID is the pairing of the comprehensive national NeuroDatabank with the NeuroBiobank, a resource that will accept, catalog, store, and track biospecimens from COVID-19 patients with neurological symptoms. The samples stored and tracked will constitute a rich resource, available to researchers following a simple application process, for the study of mechanistic questions, epidemiological associations, and potential therapies. The ability to link the granular demographic, clinical, and social data collected in the NeuroDatabank with the biospecimen material housed in the NeuroBiobank provides an important opportunity for learning and discovery.

NIH-NeuroCOVID will not replace efforts to identify effective treatments via well-designed and conducted RCTs. There is no substitute for gold-standard RCT evidence (8). But NIH-NeuroCOVID offers an important adjunct, which may be more agile and able to quickly provide critical pieces of information.

CONCLUSION

The NIH COVID-19 NeuroDatabank and NeuroBiobank constitute an important national resource with robust infrastructure, quality control measures, and assurance of patient privacy and confidentiality. They address the mandate for comprehensive inclusion of diverse populations; indeed, widespread participation and uptake are crucial to their success. The resources provide a critical foundation for the generation of hypotheses and ideas for management and treatment of COVID-19 and its neurological complications, and the evaluation of those hypotheses with harmonized and representative data. The initiative offers a model for responding to public health crises that will undoubtedly arise in the future to test our national capacity and capability as stewards of public health and wellness.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AT, JF, and CM-P contributed equally to conception and writing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grant 3U24NS113844-01S1 from the National Institutes of Health.

REFERENCES

1. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in severe SARS-CoV-2 infection. *N Engl J Med.* (2020) 382:2268–70. doi: 10.1056/NEJMc2008597
2. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology.* (2020) 95:e1060–70. doi: 10.1212/WNL.0000000000009937
3. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol.* (2020) 19:767–83. doi: 10.1016/S1474-4422(20)30221-0
4. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological Features of Covid-19. *N Engl J Med.* (2020) 383:989–92. doi: 10.1056/NEJMc2019373
5. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun.* (2020) 87:34–9. doi: 10.1016/j.bbi.2020.04.027
6. Hernán MA, Robins JM. *Causal Inference: What If.* Boca Raton, FL: Chapman & Hall/CRC (2020).
7. Petkova E, Antman EM, Troxel AB. Pooling data from individual clinical trials in the COVID-19 era. *J Am Med Assoc.* (2020) 324:543–5. doi: 10.1001/jama.2020.13042
8. Califf RM, Hernandez AF, Landray M. Weighing the benefits and risks of proliferating observational treatment assessments: observational cacophony, randomized harmony. *JAMA.* (2020) 324:625–6. doi: 10.1001/jama.2020.13319

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 18 January 2021
doi: 10.3389/fneur.2020.615172

Unmet Needs of People With Parkinson's Disease and Their Caregivers During COVID-19-Related Confinement: An Explorative Secondary Data Analysis

Anne-Marie Hanff[1], Claire Pauly[2,3], Laure Pauly[2,3], Valerie E. Schröder[2,3], Maxime Hansen[1,2], Guilherme Ramos Meyers[2,3], Anne Kaysen[3], Linda Hansen[2], Femke Wauters[2] and Rejko Krüger[1,2,3] on behalf of NCER-PD*

[1] Transversal Translational Medicine, Luxembourg Institute of Health, Strassen, Luxembourg, [2] Parkinson Research Clinic, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg, [3] Translational Neuroscience, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-Belval, Luxembourg

OPEN ACCESS

Edited by:
Sheng-Feng Sung,
Ditmanson Medical Foundation
Chia-Yi Christian Hospital, Taiwan

Reviewed by:
Martin Klietz,
Hannover Medical School, Germany
Li-Chen Chang,
Chia-Yi Christian Hospital, Taiwan

***Correspondence:**
Anne-Marie Hanff
anne-marie.hanff@lih.lu

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 08 October 2020
Accepted: 21 December 2020
Published: 18 January 2021

Citation:
Hanff A-M, Pauly C, Pauly L, Schröder VE, Hansen M, Meyers GR, Kaysen A, Hansen L, Wauters F and Krüger R (2021) Unmet Needs of People With Parkinson's Disease and Their Caregivers During COVID-19-Related Confinement: An Explorative Secondary Data Analysis. Front. Neurol. 11:615172. doi: 10.3389/fneur.2020.615172

Self-perceived unmet needs in people with typical and atypical parkinsonism (PwP) and their caregivers, support network, personalized ways to address self-perceived unmet needs during confinement, as well as the prevalence of self-reported COVID-19 related symptoms, confirmed SARS-CoV-2 infection, and self-reported COVID-19 related hospitalization in Luxembourg and the Greater Region were assessed. From 18th March to 10th April 2020, 679 PwP were contacted by phone. Data was collected in the form of a semi-structured interview. The thematic synthesis identified 25 themes where PwP need to be supported in order to cope with consequences of the pandemic, and to adapt their daily and health-related activities. The present work highlights that in the context of personalized medicine, depending on the individual needs of support of the patient the identified self-perceived unmet needs were addressed in various ways ranging from one-directed information over interaction up to proactive counseling and monitoring. Family and health professionals, but also other support systems were taking care of the unmet needs of PwP (e.g., shopping, picking-up medication, etc.) during the pandemic. 7/606 PwP (1.15%) reported COVID-19 related symptoms, 4/606 (0.66%) underwent a rRT-PCR-based diagnostic test and 2/606 (0.33%) were confirmed as SARS-CoV-2 positive. None of these PwP reported being hospitalized due to COVID-19. Our results will allow health professionals to expand their services in a meaningful way i.e., personalize their support in the identified themes and thus improve the healthcare of PwP in times of crisis.

Keywords: COVID, needs assessment, health services needs and demand, Parkinson disease, pandemic, qualitative research

INTRODUCTION

The outbreak of COVID-19 was declared a global pandemic by the WHO in March 2020. As a result, many countries, including Luxembourg and the Greater Region, introduced restrictions and recommendations to prevent the spread of the virus emphasizing the urgency to adhere to social isolation and social distancing. These factors have profoundly changed people's daily routines over a short period of time and especially for people with an underlying chronic illness such as Parkinson's Disease (PD) (1).

Previous work by Prasad, Holla (2) focused on the perceptions and implications of COVID-19 in PwP and their caregivers. New problems attributed to the pandemic were reported and associated with loss of access to healthcare and medication. Additionally, worsening of extrapyramidal symptoms or appearance of new symptoms was reported by patients and healthcare professionals. Schirinzi et al. (3) analyzed 162 E-mails, phone texts and phone vocal messages spontaneously sent from PwP or caregivers to the PD Clinic. Queries and communications were classified in four groups depending on the content: relationship between COVID-19 and PD; acute changes in neurological symptoms; occurrence of intercurrent medical/surgical conditions and clinical services. As a limitation, the authors report that their work is not a systematic collection of information about self-perceived unmet needs in a PD population. Furthermore, the applied methodology of classification wasn't specified limiting the interpretation and the reproduction of the results.

Based on the nation-wide cohort of PwP recruited within the Luxembourg Parkinson's study (4) we were in a unique position to address the important issue of self-perceived unmet needs and the situation of PwP and their caregivers in Luxembourg and the Greater Region during COVID-19-related confinement.

Our study aimed at exploring the diversity of unmet needs of PwP and their caregivers during COVID-19-related confinement. Moreover, we investigated the reported support networks during confinement and personalized addressing of self-perceived unmet needs. Additionally, we assessed the frequency of self-reported COVID-19 related symptoms (i.e., fever, cough and/or respiratory distress), confirmed SARS-CoV-2 positive cases, and self-reported COVID-19 related hospitalization.

METHOD

Methods and findings are reported according to the reporting guideline COREQ (5).

In the frame of the Luxembourg Parkinson's study (4), participants of a cohort approved by the National Ethics Board (CNER Ref: 201407/13) were contacted by phone from 18th March to 10th April 2020, starting 2 days after implementation of confinement in Luxembourg. Overall, 679 PwP were eligible for being contacted by phone (resident in Luxembourg and the Greater Region, capable to participate). Consequently, the collection of diverse perspectives was allowed. Five hundred seventy-four of 679 (84.5%) were diagnosed with typical PD. PwP that were not reached after three contact attempts per phone and a contact attempt via email were classified as "not reachable."

The initial aim of the phone calls was to evaluate and ensure the provision of care for PwP during COVID-19-related confinement. To assess the presence of unmet needs, PwP and their family members were asked, whether they experienced a lack of care and who takes care of them during the confinement. Unmet needs were defined as the absence of diagnostic or therapeutic alternatives (6). COVID-19 related information was collected by asking the following questions: Do you suffer from COVID-19 related symptoms (i.e., fever, cough and/or respiratory distress)? If yes, did you get a COVID-19 test? If yes, did you get a positive COVID-19 result? If yes, were you hospitalized because of the COVID-19 infection? Data was collected by an interdisciplinary team of secretaries, project managers, nurses, medical doctors, and neuropsychologists in the form of a semi-structured interview. Nine interviewers were female and two were male. Most interviewers had experience in the conduction of phone calls and were already in contact with the PwP/their caregivers in the frame of the telephone questionnaires of the Luxembourg Parkinson Study and the annual follow-up visits. No further characteristics about the interviewer (bias, assumptions, reasons and interest in the

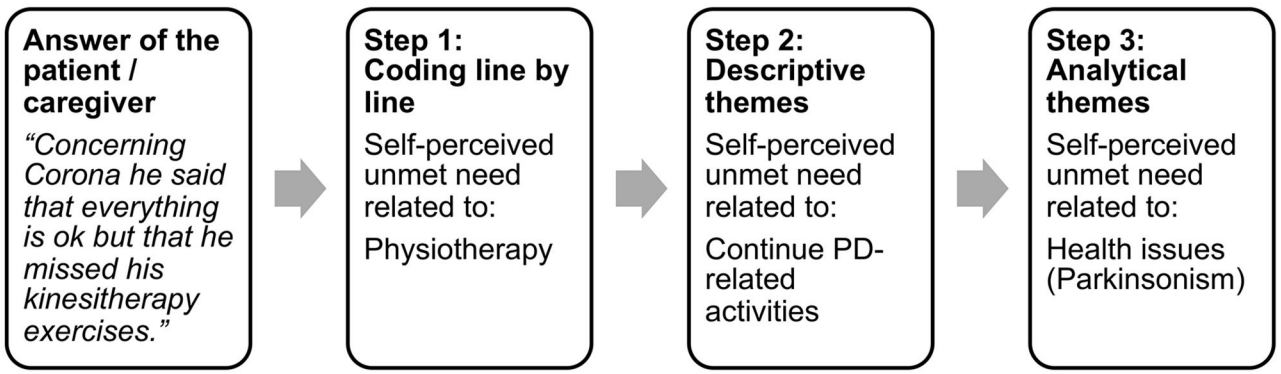


FIGURE 1 | Exemplar process from "coding line by line" to "analytical themes".

research topic) were documented.

The semi-structured interviews were neither recorded, nor transcripted. The authors expected interview notes to allow the descriptive exploration. The interview notes provided no information about the duration or the repetition of the interviews. No quantitative hypothesis was tested. The project was considered as explorative secondary data analysis (7).

Secondary data e.g., interview notes of PwP' and/or their caregivers' anonymous answers were analyzed by "thematic synthesis" (8). The method of "thematic synthesis" was chosen to systematically organize data into a structured format. Following questions were guiding the analysis: What unmet needs did PwP or their caregivers report? What support network did they mention? What interventions were offered by the clinical team to what kind of patients? **Figure 1** illustrates the method of the "thematic synthesis" i.e., the process from "coding line by line" to "analytical themes." In the first step, four team members independently coded the answers of the patients i.e., defined line by line the keywords describing the meaning and content of the semi-structured interviews. In the second step, the team members looked for similarities and differences between the defined keywords. Similar self-perceived unmet needs were grouped, named by a descriptive theme and this process resulted in a hierarchical tree structure with four layers (emotional distress, alternative ways to continue daily activities, COVID-19, parkinsonism) to organize a total of 25 descriptive themes illustrated in **Table 1**. In a third step, the "analytical themes" (Consequences of the pandemic situation and health issues) were generated. These represented a stage of interpretation whereby the clinical team "went beyond" the primary notes and generated new conceptions via group discussions. The 25 descriptive themes and the four layers were examined again in light of these constructs and changes were made accordingly. This cyclic process was repeated until the two analytical themes were able to describe each of the initially reported self-perceived unmet needs. A figure illustrating the coding tree is provided as **Supplementary Material 1**. The same method was applied for the identification of the different ways to address unmet needs and support network during confinement. After analyzing the interview notes, no relevant knowledge was obtained from new participants and data saturation was reached.

Descriptive statistics were performed on data covering COVID-19 related symptoms, patient-reported Real-time Reverse-Transcriptase-Polymerase Chain Reaction (rRT-PCR)-confirmed SARS-CoV-2-positive cases, related hospitalizations, and self-perceived unmet needs. SPSS Statistics version 25 was used, all tests were two-sided and p-values of ≤ 0.05 were considered statistically significant.

TABLE 1 | Self-perceived unmet needs of people with parkinsonism and their caregivers during COVID-19 related confinement were related to the following themes.

Consequences of the pandemic situation	
Emotional distress	**Alternative ways to continue daily activities**
Risk of infection with COVID-19 Physical distancing Restricted communication with family and friends Non-adherence to hygiene recommendations by health care professionals Administrative issues (finances, insurance,…) Illness and/ or death of a family member	Rescheduling private appointments (doctors, therapists, vacation,…) Transformed health system Communication with family and friends Shopping (food, hygiene articles,…) Hobbies (meeting with the music group,…)
Health Issues	
COVID-19	**Parkinsonism**
General recommendations Protection of vulnerable persons (living in the same household) Procedure in case of contact with COVID-19 positive person Survey of COVID-19 symptoms In the case of COVID-19 symptoms: Referral to a health professional	Vulnerability of PwP Interaction of PD-therapy with COVID-19 Reduced effectiveness of PD-medication due to reduced physical activity Availability of PD medication **Continue PD-related activities:** Parkinson Association Physiotherapy Prescription of PD medication **Unmet needs not related to COVID-19:** PD-related complications Treatment-related complications

RESULTS

We successfully contacted 89.25% (606/679) of the eligible PwP participating in the Luxembourg Parkinson's study (4). Descriptive statistics showed the mean age was 67.22 years (SD = 10.32), mean accomplished years of education was 12.91 years (SD = 1.13) and one third (205/606, 33.83%) of the respondents were female. To check for a potential bias due to PwP "not reachable via phone" (7, 9) a subgroup analysis was conducted comparing both groups' characteristics of PwP that were successfully contacted ($n = 606$) with those that were not reached ($n = 73$). The independent-sample t-test showed no significant differences in the demographic variables current age, years of education, and gender ($p > 0.05$).

In total 25 unmet needs were explored. Self-perceived unmet needs detailed in **Table 1** were either related to the consequences of the pandemic situation (emotional distress and alternative ways to continue daily activities) or to health issues (COVID-19 and parkinsonism). Of note, self-perceived unmet needs unrelated to COVID-19 e.g., typical PD symptoms or side-effects of PD medication remained important.

The **Supplementary Materials 2, 3** describes the analytical themes more in detail, and provides examples of interview notes.

As illustrated (**Figure 2**), the thematic synthesis highlighted that in the context of personalized medicine, depending on the individual needs of patient's support, the identified self-perceived

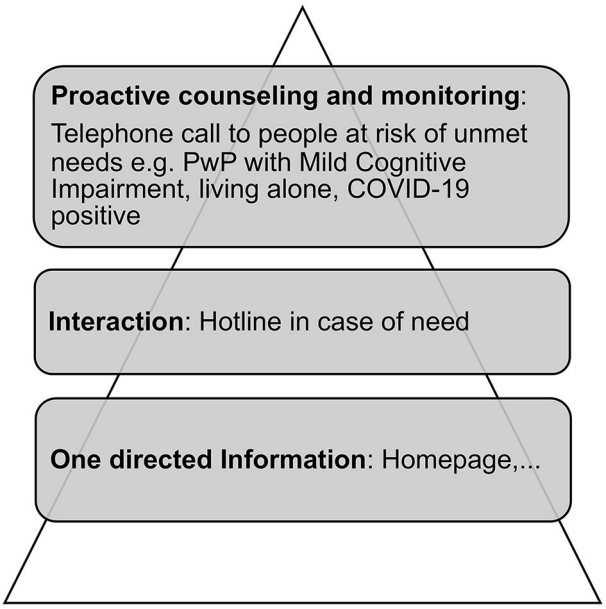


FIGURE 2 | Personalized addressing of self-perceived unmet needs.

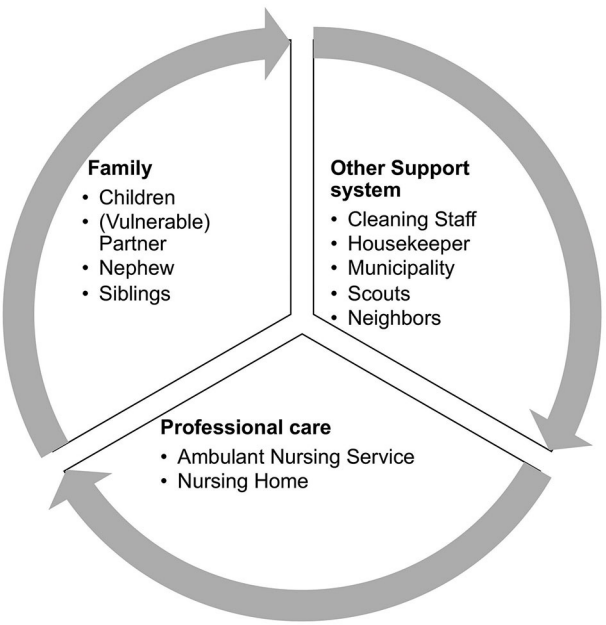


FIGURE 3 | Reported support network during confinement.

unmet needs were addressed in various ways ranging from one-directed information over interaction up to proactive counseling and monitoring.

The thematic synthesis revealed that the family and health professionals, but also other support systems were taking care of the unmet needs of PwP (e.g., shopping, pick-up of medication, etc.) during the pandemic (**Figure 3**).

Overall 7/606 PwP (1.15%) reported COVID-19 related symptoms, 4/606 (0.66%) underwent an rRT-PCR-based diagnostic test and 2/606 (0.33%) were confirmed as SARS-CoV-2 positive. None of these PwP reported a needed hospitalization due to COVID-19.

DISCUSSION

Our study assessed the self-perceived unmet needs of PwP and their caregivers during COVID-19-related confinement on a national level. Our observations indicate that, an increased support in the identified themes is necessary to cope with the consequences of the pandemic, i.e., the emotional distress, and to adapt their daily and health-related activities.

Unmet needs related to the consequences of the pandemic situation were explored and described for the first time. Whereas, Schirinzi et al. (3) analyzed incoming calls, the present work was based on proactively calling eligible participants of the Luxembourg Parkinson's Study. In contrast to this previous work on unmet needs in PwP, which classified queries and communications without specifying the applied methodology limiting the interpretation and the reproduction of the results, the applied thematic synthesis allowed us to "go beyond" the primary information and to transparently generate new conceptions (consequences of the pandemic situation and health issues). Our work confirms the results of Schirinzi et al. (3) having identified unmet needs related to health issues (e.g., relationship between COVID-19 and PD; acute changes in neurological symptoms; occurrence of intercurrent medical/surgical conditions; clinical services).

Participants of the present study reported the necessity to reschedule appointments with their neurologist, although PwP are in need of regular visits because of symptoms' progression and adjustment of their medication (2). E-Health solutions as described by Miele and colleagues (10) should be considered to ensure patient needs and continuity of care even in times such as the COVID-19 pandemic.

Another very important aspect of the pandemic is the increased reduction of physical activity. With the restrictions in place, people find themselves stuck at home without any possibility to go outside or to follow sessions with their physiotherapist (11). Recent findings (12, 13) have shown that physical exercise may attenuate clinical symptom progression in PD and a loss of exercise results in a worsening of the motor symptoms in PD. Additionally, a lack of physical activity can increase non-motor symptoms such as insomnia, constipation and could lead to psychological stress which, in return, also aggravates symptoms of PD (14). Our findings confirm previous results as participants reported unmet needs related to the inability to continue physiotherapy along with the consequences of reduced physical activity.

During confinement, the number of hours of caregiving increases dramatically, and as expected, our study identified family members as part of the reported support network. Consequently, caregiver burden presumably increases during confinement. Mosley, Moodie (15) summarized symptoms of PwP (e.g., motor and neuropsychiatric symptoms) associated with caregiver burden. Caregivers of PwP reporting such

symptoms during confinement should get proactive counseling and monitoring to reduce the risk of caregiver burnout, and prevent premature institutionalization of PwP.

The described personalized addressing of self-perceived unmet needs points out the importance of an individual approach in patient information, interaction, proactive counseling, and monitoring. The intensity of interactions increases with patient complexity. Peek and Baird (16) defined patient complexity as interference with standard care and decision-making by symptom severity or impairments, diagnostic uncertainty, difficulty engaging care, lack of social safety or participation, disorganization of care, and difficult patient-clinician relationships. In the present work, PwP with mild cognitive impairment, living alone or being COVID-19 positive could be considered as complex patients. This group of PwP at risk of unmet needs were contacted proactively to prevent complications resulting from the confinement. These findings help to develop personalized interventions for PwP during confinement.

The numbers of PwP reporting a SARS-CoV-2 infection corresponds to the prevalence in the general Luxembourgish population (17). However, these numbers must be interpreted with caution, as this study was conducted at the very beginning of the confinement. For this reason, the data does not allow conclusions to be drawn about the vulnerability of PwP.

In this explorative design, the qualitative method of data analysis was a valuable alternative to traditional quantitative methods as data was available in the form of a semi-structured interview. Implicit information i.e., unquantifiable patterns had to be observed first and only then, generalizations based on the observations could be made. To our knowledge, implicit information couldn't have been extracted by the traditional quantitative methods (9). The large number of participants as well combination of the quantitative and qualitative approaches helped to explore the diverse experience of PwP and their caregivers. Despite the limitations of secondary data analysis, our data flag important unmet needs of PwP to be targeted in situations of confinement as similar lockdowns may reoccur during the current and future pandemics.

Our results will allow health professionals to expand their services in a meaningful way i.e., personalize their support in the identified themes and thus improve the health care of PwP in times of crisis. Future validation of the results seems reasonable to quantify and prioritize the identified self-perceived unmet needs. We recommend future research about unmet needs during confinement to assess caregiver burden, hospitalization and institutionalization in order to be able to understand the consequences of the unmet needs during pandemic.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access the datasets should be directed to request.ncer-pd@uni.lu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Ethics Board (CNER Ref: 201407/13). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

A-MH: conception and design of the work, acquisition, analysis and interpretation of data, drafting, and final approval of the work. CP, LP, VS, and MH: acquisition, analysis and interpretation of data, drafting, critical revision, and final approval of the work. AK: acquisition of data, drafting, critical revision, and final approval of the work. GM, LH, and FW: acquisition of data, critical revision, and final approval of the work. RK: conception and design, critical revision, and final approval of the work. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

This work was supported by grants from the Luxembourg National Research Fund (FNR) within the National Centre of Excellence in Research on Parkinson's disease [NCERPD(FNR/NCER13/BM/11264123)]. RK has received research grants from Fonds National de Recherche de Luxembourg (FNR) as Coordinator of the National Centre for Excellence in Research on Parkinson's disease (NCER-PD) and within the PEARL Excellence Programme (FNR/P13/6682797/Krüger), and the following projects MiRisk (C17/BM/11676395), MotaSYN (12719684), MAMaSyn. Work of RK was supported by the German Research Council (DFG; KR2119/8-1), the Michael J. Fox Foundation (ID: 1480), the European Union's Horizon 2020 research and innovation program (WIDESPREAD; CENTRE-PD; grant agreement no. 692320), and the European Union's EIT Health grant for MoveIT (ID: 18034).

ACKNOWLEDGMENTS

First of all we would like to thank all participants of the Luxmebourg Parkinson's study for their important support to our research. Furthermore, we acknowledge the joint effort of the NCER-PD consortium members generally contributing to the Luxembourg Parkinson's Study as listed below: Aguayo, Gloria; Allen, Dominic; Ammerlann, Wim; Aurich, Maike; Balling, Rudi; Banda, Peter; Beaumont, Katy; Becker, Regina; Berg, Daniela; Binck, Sylvia; Bisdorff, Alexandre; Bobbili, Dheeraj; Brockmann, Kathrin; Calmes, Jessica; Castillo, Lorieza; Diederich, Nico; Dondelinger, Rene; Esteves, Daniela; Ferrand, Jean-Yves; Fleming, Ronan; Gantenbein, Manon; Gasser, Thomas; Gawron, Piotr; Geffers, Lars; Giarmana, Virginie; Glaab, Enrico; Gomes, Clarissa P.C.; Goncharenko, Nikolai; Graas, Jérôme; Graziano, Mariela; Groues, Valentin; Grünewald,

Anne; Gu, Wei; Hammot, Gaël; Hanff, Anne-Marie; Hansen, Linda; Hansen, Maxime; Haraldsdöttir, Hulda; Heirendt, Laurent; Herbrink, Sylvia; Herzinger, Sascha; Heymann, Michael; Hiller, Karsten; Hipp, Geraldine; Hu, Michele; Huiart, Laetitia; Hundt, Alexander; Jacoby, Nadine; Jarosław, Jacek; Jaroz, Yohan; Kolber, Pierre; Kutzera, Joachim; Landoulsi, Zied; Larue, Catherine; Lentz, Roseline; Liepelt, Inga; Liszka, Robert; Longhino, Laura; Lorentz, Victoria; Mackay, Clare; Maetzler, Walter; Marcus, Katrin; Marques, Guilherme; Martens, Jan; Mathay, Conny; Matyjaszczyk, Piotr; May, Patrick; Meisch, Francoise; Menster, Myriam; Minelli, Maura, Mittelbronn, Michel; Mollenhauer, Brit; Mommaerts, Kathleen; Moreno, Carlos; Mühlschlegel, Friedrich; Nati, Romain; Nehrbass, Ulf; Nickels, Sarah; Nicolai, Beatrice; Nicolay, Jean-Paul; Noronha, Alberto; Oertel, Wolfgang; Ostaszewski, Marek; Pachchek, Sinthuja; Pauly, Claire; Perquin, Magali; Reiter, Dorothea; Rosety, Isabel; Rump, Kirsten; Satagopam, Venkata; Schlesser, Marc; Schmitz, Sabine; Schmitz, Susanne; Schneider, Reinhard; Schwamborn, Jens; Schweicher, Alexandra; Simons, Janine; Stute, Lara; Trefois, Christophe; Trezzi, Jean-Pierre; Vaillant, Michel; Vasco, Daniel; Vyas, Maharshi; Wade-Martins, Richard; and Wilmes, Paul.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.615172/full#supplementary-material

REFERENCES

1. Helmich RC, Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *J Parkinsons Dis.* (2020) 10:351–4. doi: 10.3233/JPD-202038
2. Prasad S, Holla VV, Neeraja K, Surisetti BK, Kamble N, Yadav R, et al. Parkinson's disease and COVID-19: perceptions and implications in patients and caregivers. *Mov Disord.* (2020) 35:912–4. doi: 10.1002/mds.28088
3. Schirinzi T, Cerroni R, Di Lazzaro G, Liguori C, Scalise S, Bovenzi R, et al. Self-reported needs of patients with Parkinson's disease during COVID-19 emergency in Italy. *Neurol Sci.* (2020) 41:1373–5. doi: 10.1007/s10072-020-04442-1
4. Hipp G, Vaillant M, Diederich NJ, Roomp K, Satagopam VP, Banda P, et al. The Luxembourg Parkinson's study: a comprehensive approach for stratification and early diagnosis. *Front Aging Neurosci.* (2018) 10:326. doi: 10.3389/fnagi.2018.00326
5. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care.* (2007) 19:349–57. doi: 10.1093/intqhc/mzm042
6. Vreman RA, Heikkinen I, Schuurman A, Sapede C, Garcia JL, Hedberg N, et al. Unmet medical need: an introduction to definitions and stakeholder perceptions. *Value Health.* (2019) 22:1275–82. doi: 10.1016/j.jval.2019.07.007
7. Deutsche Gesellschaft für Epidemiologie (DGEpi). *Leitlinien und Empfehlungen zur Sicherung von Guter Epidemiologischer Praxis (GEP).* Ulm: Deutsche Gesellschaft für Epidemiologie (DGEpi) (2018).
8. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Med Res Methodol.* (2008) 8:45. doi: 10.1186/1471-2288-8-45
9. Polit DF, Beck Tatano C. *Nursing Research. Generating and Assessing Evidence for Nursing Practice*. Philadelphia: Wolters Kluwers (2017).
10. Miele G, Straccia G, Moccia M, Leocani L, Tedeschi G, Bonavita S, et al. Telemedicine in Parkinson's disease: how to ensure patient needs and continuity of care at the time of COVID-19 pandemic. *Telemed J E Health.* (2020) 26:1533–6. doi: 10.1089/tmj.2020.0184
11. Papa SM, Brundin P, Fung VSC, Kang UJ, Burn DJ, Colosimo C, et al. Impact of the COVID-19 pandemic on Parkinson's disease and movement disorders. *Mov Disord.* (2020) 35:711–5. doi: 10.1002/mds.28067
12. Schenkman M, Moore CG, Kohrt WM, Hall DA, Delitto A, Comella CL, et al. Effect of high-intensity treadmill exercise on motor symptoms in patients with *de novo* Parkinson disease: a phase 2 randomized clinical trial. *JAMA Neurol.* (2018) 75:219–26. doi: 10.1001/jamaneurol.2017.3517
13. van der Kolk NM, de Vries NM, Kessels RPC, Joosten H, Zwinderman AH, Post B, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol.* (2019) 18:998–1008. doi: 10.1016/S1474-4422(19)30285-6
14. Radder DLM, Sturkenboom IH, van Nimwegen M, Keus SH, Bloem BR, de Vries NM. Physical therapy and occupational therapy in Parkinson's disease. *Int J Neurosci.* (2017) 127:930–43. doi: 10.1080/00207454.2016.1275617
15. Mosley PE, Moodie R, Dissanayaka N. Caregiver burden in Parkinson disease: a critical review of recent literature. *J Geriatr Psychiatry Neurol.* (2017) 30:235–52. doi: 10.1177/0891988717720302
16. Peek CJ, Baird MA, Coleman E. Primary care for patient complexity, not only disease. *Fam Syst Health.* (2009) 27:287–302. doi: 10.1037/a0018048
17. Snoeck CJ, Vaillant M, Abdelrahman T, Satagopam VP, Turner JD, Beaumont K, et al. Prevalence of SARS-CoV-2 infection in the Luxembourgish population: the CON-VINCE study. *medRxiv [Preprint].* (2020). doi: 10.1101/2020.05.11.20092916

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 18 January 2021
doi: 10.3389/fneur.2020.611504

Acute Stroke Care in the With-COVID-19 Era: Experience at a Comprehensive Stroke Center in Japan

Junpei Koge, Masayuki Shiozawa and Kazunori Toyoda*

Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

Introduction: The pandemic of coronavirus disease 2019 (COVID-19) has had a significant impact on stroke healthcare, including the prehospital care system and in-hospital workflow. Japan experienced the outbreak of COVID-19, and the State of Emergency was declared during April 2020 and May 2020. The aim of the present study was to clarify the effect of the COVID-19 pandemic on a comprehensive stroke center in Japan.

Methods: We retrospectively reviewed consecutive patients with acute ischemic stroke admitted in our institute between December 2019 and July 2020. The patients who underwent reperfusion therapy (intravenous thrombolysis and/or mechanical thrombectomy) were divided into the pre-COVID-19 period (December 2019 to March 2020) and the With-COVID-19 period (April 2020 to July 2020). Study outcomes were the number of stroke admissions in our institute, workflow time metrics, the frequency of modified Rankin Scale score 0–2 at discharge, and brain imaging modalities before reperfusion therapy in patients who underwent reperfusion therapy.

Results: In our institute, the number of stroke admissions decreased during the State of Emergency and then increased after the lifting of the State of Emergency. Among patients who underwent reperfusion therapy (median age, 77 years; female 27%; median baseline National Institutes of Health Stroke Scale score, 10), times from hospital arrival to imaging [25 (21–33) min vs. 30 (25–38) min, $P = 0.03$] and to thrombolysis [38 (31–52) min vs. 51 (37–64) min, $P = 0.03$] were prolonged compared with the pre-COVID-19 period. There was no significant difference in the frequency of modified Rankin Scale score 0–2 at discharge between the two periods (32 vs. 45%, $P = 0.21$). The proportion of computed tomography vs. magnetic resonance imaging as an emergency brain imaging tool before reperfusion therapy changed, with computed tomography having become predominant in the With-COVID-19 period.

Conclusions: In our institute, the number of stroke admissions, workflow time metrics, and imaging modalities for reperfusion therapy were affected by the COVID-19 pandemic.

Keywords: acute ischemic stroke, COVID-19, neuroimaging, thrombolysis, mechanical thrombectomy

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Jiunn-Tay Lee,
Tri-Service General Hospital, Taiwan
Mengqi Zhang,
Central South University, China
Cheng-Yu Wei,
Chang Bing Show Chwan Memorial Hospital, Taiwan

****Correspondence:***
Junpei Koge
koge.jumpei@ncvc.go.jp

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *29 September 2020*
Accepted: *14 December 2020*
Published: *18 January 2021*

Citation:
Koge J, Shiozawa M and Toyoda K (2021) Acute Stroke Care in the With-COVID-19 Era: Experience at a Comprehensive Stroke Center in Japan. Front. Neurol. 11:611504. doi: 10.3389/fneur.2020.611504

INTRODUCTION

The emergence of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in Wuhan in December 2019 evolved into a pandemic that was declared on March 11, 2020 (1). As of September 9, 2020, a total of 27,477,869 patients had been reported, with 896,173 deaths worldwide (2). Although the most common presentation of patients with coronavirus disease 2019 (COVID-19) is symptoms due to respiratory disease, the clinical presentation of patients with COVID-19 varies considerably, ranging from asymptomatic infection to multiple organ failure. Recently, reports regarding the neurological manifestations of COVID-19 have been increasing: 8.0% of patients treated for COVID-19 presented with a preexisting neurologic illness (3), and it is estimated that 4.9% of COVID-19 patients have acute stroke (4). Healthcare providers engaged in neurological emergency care are inevitably at risk of COVID-19 exposure. Consequently, the COVID-19 global pandemic has a great impact on every aspect of emergency stroke healthcare, including the prehospital care system and the in-hospital workflow (5–7). In light of the in-hospital workflow, modified in-hospital stroke protocols designed to protect against COVID-19 transmission have been proposed (Protected Code Stroke) (8). Stroke team members are faced with the novel and significant challenge of providing high-quality emergency treatment while continuing their utmost effort to minimize infectious exposure. From the perspective of the prehospital care system, significant delays in stroke onset to hospital arrival time (9) and reduction of stroke admissions have been reported (10, 11).

Japan recorded its first COVID-19 patient on January 16, 2020, and experienced rapid spread of infection, mainly in urban areas. The State of Emergency was declared on April 7, 2020, for urban areas, and the declaration was extended to the rest of the country on April 16, 2020. After the declaration, the curve of infection spread flattened slowly. The State of Emergency was lifted on May 25, 2020. The number of COVID-19-positive cases increased again rapidly after the lifting of the declaration. As of September 9, 2020, the numbers of domestic infections and deaths reached 71,873 and 1,376, respectively (12). The mortality rate has remained relatively low, at 1.9%. The new COVID-19 cases and the cumulative number of COVID-19 deaths in Japan are shown in **Figure 1**.

On April 28, 2020, the Japan Stroke Society, an academic organization, published the Japan Stroke Society-Protected Code Stroke (13). The Japan Stroke Society-Protected Code Stroke was designated with priority on protecting stroke team members from COVID-19 infection exposure based on Protected Code Stroke (8). The Japan Stroke Society-Protected Code Stroke proposed the following main points: [1] to regard all stroke patients presenting to the emergency department as possibly infectious; [2] the appropriate use of personal protective equipment (PPE) and placement of a surgical mask on non-intubated patients; [3] preferential use of computed tomography (CT) as a neuroimaging modality with a chest CT scan to screen for findings suggestive of COVID-19 infection; and [4] to keep to a minimum medical staff involved in acute stroke care at the emergency department. Magnetic resonance imaging (MRI) was frequently used as the major diagnostic tool for acute stroke in Japan most recently (14), but the proportion of CT vs. MRI as an emergency brain imaging tool for acute stroke might change in many institutions, since CT has now become predominant.

As of the time of writing (September 2020), the outbreak in Japan has lasted about 6 months, including the second upward-sloping curve of spreading COVID-19 infection. In this paper, we aimed to investigate the impact of the COVID-19 pandemic on the healthcare system of acute stroke in a comprehensive stroke center in Japan. This paper focuses on current experience and highlighting the problems in providing optimized stroke healthcare for acute stroke patients in the With-COVID-19 era.

METHODS

Study Population

This was a single-center, observational cohort study performed at a comprehensive stroke center in Japan. We retrospectively reviewed consecutive patients with acute ischemic stroke admitted in our institute between December 2019 and July 2020. The patients who underwent reperfusion therapy (intravenous thrombolysis and/or mechanical thrombectomy) were stratified into the pre-COVID-19 period (December 2019 to March 2020) and the With-COVID-19 period (April 2020 to July 2020). An ethics committee approved a series of clinical studies including this study using the National Cerebral and Cardiovascular Center (NCVC) Stroke Registry (M23-073-7).

Acute Stroke Care in Suita City and the National Cerebral Cardiovascular Center

In Suita city (the north suburban city of metropolitan Osaka, total population of 375,000 people), acute stroke care is provided through a network of four acute hospitals. The emergency medical service (EMS) provides the urgent patient transport system with priority given to patients with suspected acute stroke brought to the nearest hospital with the appropriate diagnostic and therapeutic capacity. The NCVC is an urban comprehensive stroke center with 550 beds in Suita. The stroke service at the NCVC has a Stroke Care Unit with 18 beds managed by a multidisciplinary team of vascular neurologists, neurosurgeons, and neurointerventionalists. More than 1,000 patients with acute stroke/transient ischemic attack are hospitalized in our center every year, and roughly 150 acute reperfusion treatments including 70 mechanical thrombectomies are performed. The number of hospitalized patients in 2019 was 690 for ischemic stroke, 204 for intracranial hemorrhage, 55 for subarachnoid hemorrhage, and 70 for transient ischemic attack.

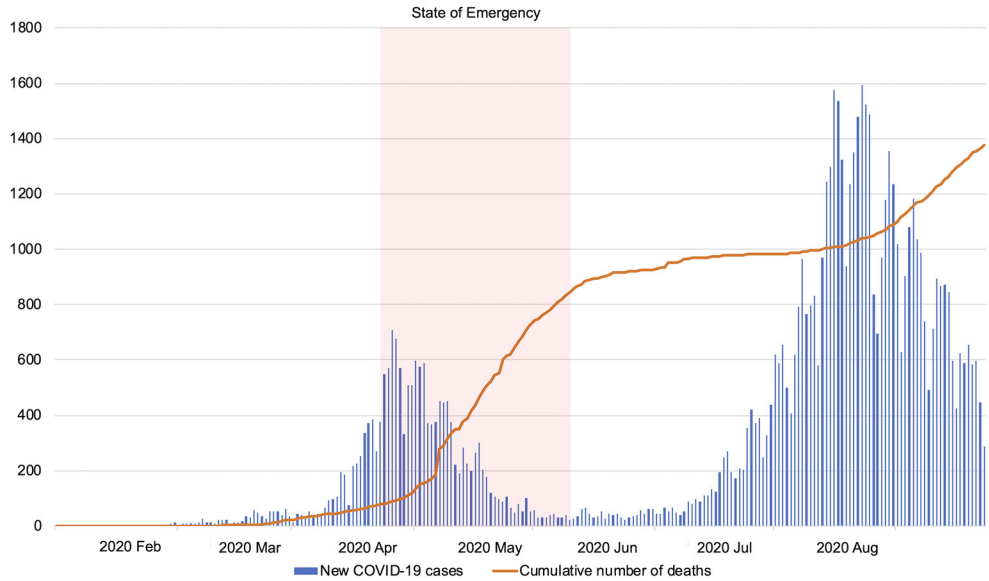


FIGURE 1 | The number of new COVID-19 cases and cumulative number of deaths in Japan (January 6, 2020–September 7, 2020). The State of Emergency was declared on April 7, 2020, and lifted on May 25, 2020. Edited based on the openly available data from the Ministry of Health, Labor and Welfare, Japan (https://www.mhlw.go.jp/stf/covid-19/open-data.html, in Japanese). COVID-19, coronavirus disease 2019.

Workflow in the National Cerebral Cardiovascular Center During the COVID-19 Pandemic

At the NCVC, all stroke inpatients have undergone polymerase chain reaction (PCR) testing for COVID-19 on the morning after admission since May 1, 2020. Patients before confirmation of a negative COVID-19 PCR have been admitted to an isolated bed in the Stroke Care Unit and transferred to the clean Stroke Care Unit after confirmation of a negative COVID-19 PCR. At the time of writing (September 2020), no stroke patient with COVID-19 has been admitted to the NCVC. The 24/7 multimodal brain imaging, including MRI and CT angiography, and mechanical thrombectomy (MT) are available. The novel institutional stroke protocol for the COVID-19 pandemic was developed and implemented in April 2020. Patients with fever above 37.5°C or respiratory symptoms and suspected of COVID-19 infection by physicians were deemed as suspected COVID-19 cases. When patients were admitted in the emergency department, all stroke team members wore PPE including an N-95 mask, face shield, gown, and gloves and placed a surgical mask on non-intubated patients regardless of suspicion of COVID-19 infection. All patients underwent portable chest X-ray in the emergency department before brain imaging. Head CT and CT angiography have been prioritized for initial brain imaging over MRI. If any abnormal findings were recognized on portable chest X-ray, head CT was selected for a neuroimaging modality and concurrent chest CT was performed for further screening of COVID-19 infection. When performing MRI for patients who are not confirmed negative for COVID-19 or suspected COVID-19 cases, cleaning and ventilation for 15 min or 2 h after the scan for complete disinfection have been performed, respectively. When performing brain imaging, the roles of the physician in charge of transportation and the physician who interprets images in the control room are separated to prevent infection exposure in the control room. Patients who are not confirmed negative for COVID-19 wear surgical masks during transportation and neuroimaging. Limiting other traffic through the healthcare facility during transportation of positive/suspected COVID-19 cases is recommended. MT for patients who are not confirmed negative for COVID-19 by PCR has been performed by the minimum number (≈5) of staff wearing full PPE (N-95 mask, surgical mask, face shield, cap, gown, gloves) to limit provider exposure and the amount of protective gear used. Cleaning and ventilation of the angiography suite for 2 h after procedures for COVID-19-positive or suspected COVID-19 cases have been performed. Swallowing assessment in patients before confirmation of negative COVID-19 PCR has mainly been performed by a repetitive saliva swallowing test under the standard PPE (surgical mask, face shield, gloves). The performance of carotid ultrasound and transesophageal echocardiography before confirmation of negative COVID-19 PCR has been limited.

Study Outcomes

The primary outcomes of the present study were [1] the number of stroke admissions and [2] reperfusion therapies in the NCVC. Other outcome measures were [1] workflow time metrics, such as from stroke onset to hospital arrival, hospital arrival to brain imaging, intravenous thrombolysis, or groin puncture, and stroke onset to intravenous thrombolysis or groin puncture; [2] modified Rankin Scale score 0–2 at discharge; and [3] brain imaging modalities before reperfusion therapy.

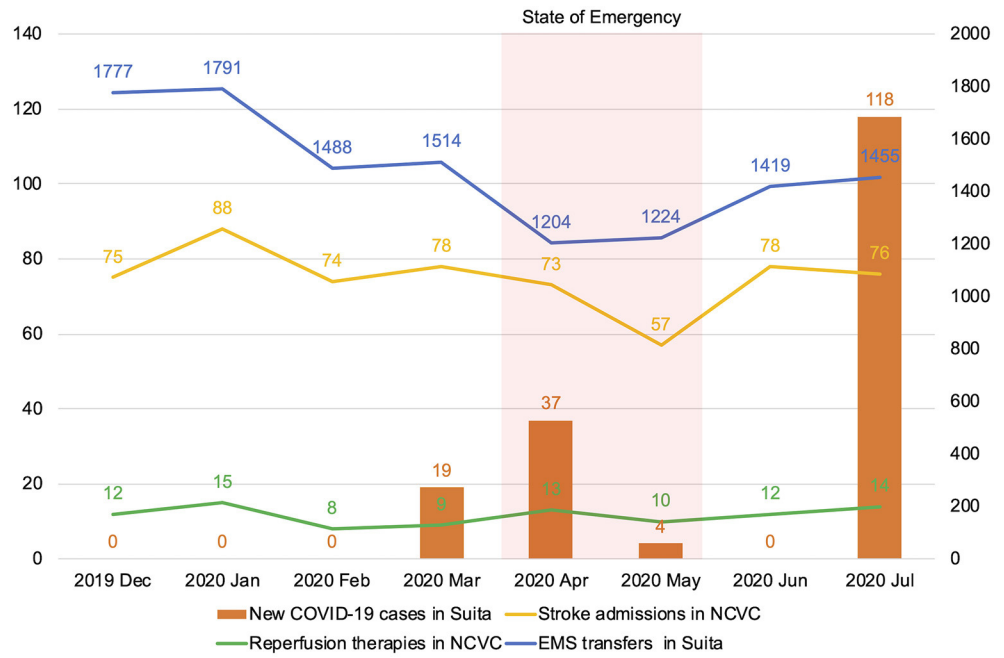


FIGURE 2 | Monthly volume of emergency medical service transfers and new coronavirus 2019 (COVID-19) cases in Suita city and stroke admissions and the number of reperfusion therapy cases in the National Cerebral and Cardiovascular Center. COVID-19, coronavirus disease 2019; NCVC, National Cerebral and Cardiovascular Center; EMS, emergency medical service.

Statistical Analyses

Categorical variables were presented as frequencies and percentages and compared with the Fisher's exact test. Continuous variables were presented as median and interquartile range and were compared with the Wilcoxon rank-sum test. All reported *P*-values are for a two-sided test, and $P < 0.05$ was considered significant. Statistical analyses were performed using JMP 14.2.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Emergency Medical Service Transfers in Suita City, Stroke Admissions, and Reperfusion Therapies in the National Cerebral Cardiovascular Center

In Osaka prefecture with a population of 8,822,000 residents, the total numbers of COVID-19 infections and deaths were 9,169 and 168, respectively, as of September 9, 2020 (15). The number of EMS transfers and new COVID-19 patients in Suita city decreased gradually after the declaration of the State of Emergency. The number of stroke admissions in the NCVC also decreased during the State of Emergency. The number of patients receiving reperfusion therapies in our institute remained unchanged. After the lifting of the State of Emergency, EMS transfers in Suita city and stroke admissions in the NCVC increased. The number of COVID-19 infections has increased 1 month after the lifting of the State of Emergency (the second wave of COVID-19). However, EMS transfers in Suita city, stroke admissions, and the number of patients who underwent reperfusion therapy in the NCVC did not decrease (**Figure 2**).

Workflow Time Metrics and Outcomes in Stroke Patients Who Underwent Reperfusion Therapies

The clinical characteristics and time metrics of acute stroke patients who underwent reperfusion therapy are shown in **Table 1**. There were no significant differences in the baseline characteristics, stroke subtypes, and treatment between the pre-COVID-19 and With-COVID-19 periods. The median time from stroke onset to hospital arrival was ≈30 min longer in the With-COVID-19 period compared with pre-COVID-19 period, though the differences were not significant. The median times from hospital arrival to brain imaging and from hospital arrival to thrombolysis were significantly longer than in the pre-COVID-19 period. There were insignificant increases of ≈10 min in median hospital arrival to groin puncture time in the With-COVID-19 period. There was no significant difference in the frequency of modified Rankin Scale score 0–2 at discharge between the two periods.

Brain Imaging Modalities Before Reperfusion Therapies

Before the COVID-19 pandemic, brain MRI was mainly used to evaluate the indication for reperfusion therapy according to the institutional policy. During the State of Emergency in the With-COVID-19 period, the proportion of patients undergoing CT

TABLE 1 | In-hospital workflow metrics in the periods before and during the With-COVID-19 pandemic in the National Cerebral and Cardiovascular Center.

	Pre-COVID-19 period	With-COVID-19 period	*P*-value
	December 2019 to March 2020 (*N* = 44)	April 2020 to July 2020 (*N* = 49)	
Age, year; median (IQR)	79 (65–86)	75 (65–86)	0.20
Female, n (%)	15 (34)	10 (20)	0.16
Premorbid mRS score, median (IQR)	0 (0–1)	0 (0–1)	0.55
Baseline NIHSS score, median (IQR)	11 (6–20)	10 (5–19)	0.56
Large artery atherosclerosis, n (%)	9 (20)	7 (14)	0.58
Cardioembolism, n (%)	23 (52)	26 (53)	1.00
Small vessel disease, (%)	1 (2)	0 (0)	0.47
Other cause, n (%)	9 (20)	11 (22)	1.00
Undetermined cause, n (%)	2 (5)	5 (10)	0.44
IVT only, n (%)	22 (50)	30 (61)	0.30
Bridging IVT with MT, n (%)	12 (27)	11 (22)	0.64
MT only, n (%)	10 (23)	8 (16)	0.60
Stroke onset to hospital arrival time, min, median (IQR)	71 (52–182)	109 (49–182)	0.54
Hospital arrival to brain imaging time, min, median (IQR)	25 (21–33)	30 (25–38)	0.03
Hospital arrival to thrombolysis time*, min, median (IQR)	38 (31–52)	51 (37–64)	0.03
Stroke onset to thrombolysis time*, min, median (IQR)	117 (89–175)	150 (106–210)	0.11
Hospital arrival to groin puncture time†, min, median (IQR)	70 (53–90)	82 (67–101)	0.16
Stroke onset to groin puncture time†, min, median (IQR)	186 (109–450)	210 (153–291)	0.79
mRS score 0–2 at discharge, n (%)	14 (32)	22 (45)	0.21

Numbers are n (%) or median (IQR) values as appropriate. Intergroup comparisons were performed using the Wilcoxon rank-sum test.
**Only patients who received intravenous thrombolysis are included.*
†Only patients who received mechanical thrombectomy are included.
IQR, interquartile range; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale.

increased due to the change of the institutional protocol. After the lifting of the State of Emergency in the With-COVID-19 period, the proportion of patients undergoing MRI increased especially in patients who only received intravenous thrombolysis. CT perfusion was frequently used for patients who received MT (**Figure 3**).

A Representative Acute Stroke Case With Suspected COVID-19 Infection

A patient in his mid-80's presented as an emergency to our institute with acute onset of left hemiparesis. He had had a fever and cough 2 weeks before admission. He was transferred to our hospital 59 min after symptom onset. His temperature was 37.5°C. Neurologically, he had a disturbance of consciousness, conjugate gaze preference toward the right side, and left hemiparesis, with a baseline National Institutes of Health Stroke Scale (NIHSS) score of 21. Oxygen saturation was 88% on room air. He was treated as a suspected COVID-19 case due to his presentation. All stroke team members wore PPE including an N-95 mask, face shield, gown, and gloves and performed an examination. A portable chest X-ray showed extensive consolidation in the left lung (**Figure 4A**). According to the institutional protocol, he underwent CT perfusion to determine eligibility for reperfusion therapy and chest CT was performed simultaneously. The time from hospital arrival to brain imaging was 22 min. Non-contrast CT showed no early ischemic changes. CT angiography showed an occlusion of the distal segment of the horizontal portion of the right middle cerebral artery (**Figure 4B**). CT perfusion showed the target mismatch in the area of the right middle cerebral artery. On chest CT, there was extensive consolidation in the left lung and pleural effusion in the left side (**Figure 4C**). He underwent thrombolysis and MT under local anesthesia. The times from hospital arrival to thrombolysis and to puncture were 34 and 83 min, respectively. While the patient was transported from the emergency department to the angiography suite, use of the flow line by other staff and patients was prohibited. Entry to the angiography suite was restricted to a minimum number of staff equipped with PPE. One pass with combined use of the stent retriever and aspiration catheter for the right middle cerebral artery occlusion retrieved white thrombi and achieved complete reperfusion. The groin puncture to reperfusion time was 25 min. On postoperative day 1, his neurological symptoms improved remarkably, and the NIHSS score was 2. Although his PCR testing for COVID-19 was negative, the consolidation on chest CT deteriorated. On postoperative day 5, he was transferred to another hospital for treatment of respiratory disease suspected to be organizing pneumonia.

DISCUSSION

The major findings of the present study were: [1] the number of stroke admissions in our institute decreased during the State of Emergency and increased after the lifting of the State of Emergency. The number of patients receiving reperfusion therapy remained stable; [2] times from hospital arrival to brain imaging and to thrombolysis were prolonged in the With-COVID-19 period compared with those in the pre-COVID-19 period, though clinical outcomes remained similar; [3] CT as an emergency brain imaging tool before reperfusion therapy became predominant in the With-COVID-19 period.

Acute stroke has been reported to occur in 2.8% of COVID-19-positive patients in Wuhan (16), and young-onset stroke with COVID-19 infection was reported to be marked from a hospital in New York City in early spring, 2020 (17). As a possible reason, infection has been thought to be associated with subsequent ischemic stroke (18). However, stroke admissions decreased in more recent reports during the COVID-19 pandemic in real-world settings (10, 11). A decrease was also observed in coronary

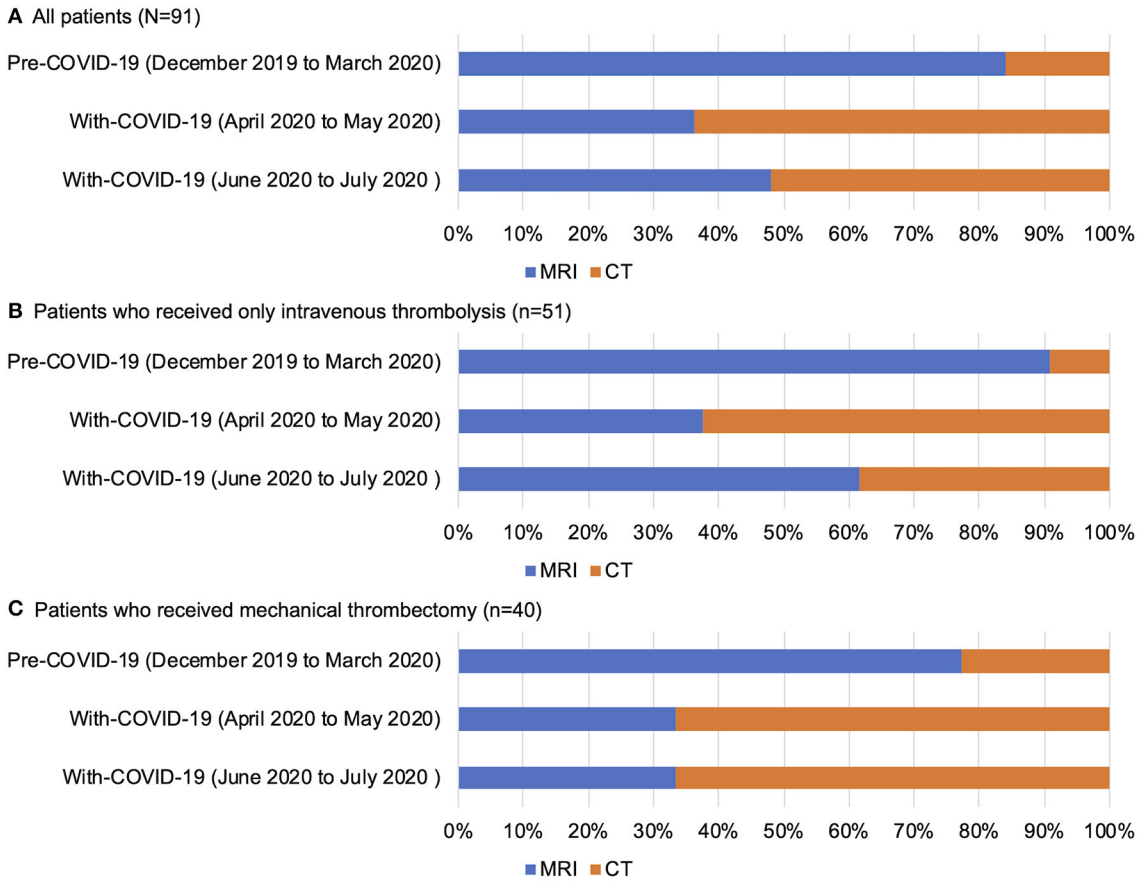


FIGURE 3 | Selection of brain imaging modalities before reperfusion therapy in all patients **(A)**, patients who received only intravenous thrombolysis **(B)**, and patients who received mechanical thrombectomy **(C)** in the National Cerebral and Cardiovascular Center. COVID, coronavirus disease.

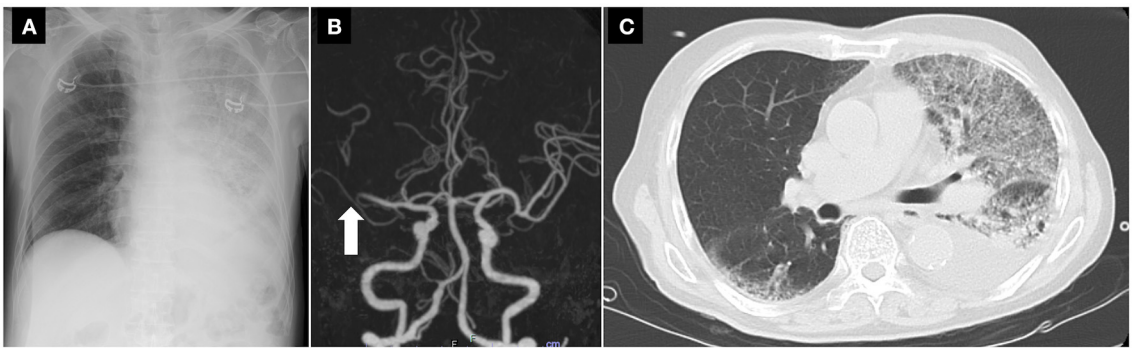


FIGURE 4 | A portable X-ray, CT angiography, and chest CT findings of the stroke patient with suspected COVID-19. **(A)** A portable chest X-ray showing extensive consolidation in the left lung. **(B)** CT angiography showing an occlusion of the distal portion of the right middle cerebral artery (*arrow*). **(C)** Chest CT showing extensive consolidation in the left lung and pleural effusion in the left side. CT, computed tomography.

artery disease admissions during the COVID-19 pandemic (19). The number of stroke admissions also decreased in our institute. Despite the decrease in the number of EMS transfers in our region, the number receiving reperfusion therapy in our institute did not decrease. A reason for this paradoxical finding might be that only patients with mild symptoms would hesitate to call EMS due to fear of COVID-19 contamination, but moderate to severely ill patients would not.

Increases in EMS transfers and stroke admissions after the lifting of the State of Emergency declaration implicate that

social restrictions rather than the COVID-19 pandemic may be associated with the decreased number of stroke admissions. Medication non-adherence due to refraining from attending clinics might lead to the increased number of stroke admissions after lifting the State of Emergency. Poor management of risk factors due to lack of exercise during the State of Emergency might also contribute to the increased risk of stroke.

Head CT as emergency brain imaging modality may have advantages during the COVID-19 pandemic, including short imaging time and screening for COVID-19 infection using concurrent chest CT scan. MRI has disadvantages, including the difficulty of ventilation and disinfection of equipment, uncertainty of body search for magnetic materials of staff with heavy PPE, and long study time. The American College of Radiology recommends to minimize the use of MRI except where absolutely necessary (20). Use of MRI for patients before confirmation of negative COVID-19 PCR had been limited during the first stage of the COVID-19 pandemic in our institute. However, in recent months, the number of cases undergoing MRI has been increasing. Although MRI-based patient selection has the drawback of time-consuming disinfection procedures after the scan, it has the advantage of the identification of diffusion-weighted imaging fluid-attenuated inversion recovery mismatch, early-onset lesions, and small lesions. Recently, we have selected the brain imaging modality according to the risk of COVID-19 infection (fever, exposures to anyone with known or suspected COVID-19 within the past 14 days, respiratory symptoms, abnormal findings on chest X-ray), stroke onset to hospital arrival time, and the severity of stroke. CT perfusion has been prioritized to judge the patient's eligibility for MT because its capability for selecting patients for MT is equal to that of MRI (21).

In our institute, the times from hospital arrival to brain imaging and to thrombolysis were longer in the With-COVID-19 period. Delays from hospital arrival to brain imaging might be explained by COVID-19 screening with chest X-ray in the emergency department before transport to imaging, infection prevention precautions in the emergency department, and changes to an unfamiliar stroke protocol. The delay in the hospital arrival to groin puncture time was small, but it was due to time saving by the preferred use of CT for imaging. Although the workflow that emphasizes infection control has been proposed (22), it is unclear whether the strategy can achieve the same time metrics before the COVID-19 pandemic. A multicenter, observational study in the COVID-19 era has reported a significant increase in the mean stroke onset-to-groin puncture time (23). However, recent studies from a tertiary level center have reported no clear delays in in-hospital time metrics, including door to imaging time or thrombolysis time (5, 9, 10). These studies have shown that tertiary level centers with abundant resources including multidisciplinary teams may be able to maintain in-hospital workflow metrics during the pandemic. Since the organized in-hospital strategy that balances infection control and time saving may require a multidisciplinary team approach, the strategy may be better suited for tertiary level centers. The imaging protocol including chest CT in addition to head CT may provide rapid screening for COVID-19 in the time-sensitive setting (24). In the With-COVID-19 era, a new in-hospital workflow that can reduce treatment times, while continuing all possible infection control measures, is warranted.

CONCLUSION

The stroke health care system in our region in Japan has been significantly affected by the COVID-19 pandemic despite the relatively low incidence of COVID-19. The State of Emergency seemed to be associated with a decreased number of EMS transfers and stroke admissions. In our institute, the institutional protocol for acute stroke patients was significantly modified, and some in-hospital time metrics after the COVID-19 pandemic were prolonged compared with those before the COVID-19 pandemic. The optimal in-hospital workflow considering the need to mitigate in-hospital COVID-19 transmission and a reduction in workflow time metrics has been sought in the With-COVID-19 era.

AUTHOR CONTRIBUTIONS

JK analyzed the data and wrote the manuscript. MS collected the data. KT supervised the manuscript. All authors contributed to the article and approved the final version of the manuscript.

FUNDING

This work was partly supported by the Japan Agency for Medical Research and Development (AMED) (20lk0201094h0002 and 20lk0201109h0001).

ACKNOWLEDGMENTS

The authors would like to thank Dr. Takeshi Yoshimoto (National Cerebral and Cardiovascular Center, NCVC) for data collection in the NCVC and Drs. Masatoshi Koga and Masafumi Ihara (NCVC) for editing the manuscript.

REFERENCES

1. Mahase E. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. *BMJ*. (2020) 368:m1036. doi: 10.1136/bmj.m1036
2. COVID-19 information and resources for JHU (2018). Available online at: https://hub.jhu.edu/novel-coronavirus-information (accessed September 9, 2020).
3. Herman C, Mayer K, Sarwal A. Scoping review of prevalence of neurologic cormorbidities in patients hospitalized for COVID-19. *Neurology*. (2020) 95:77–84. doi: 10.1212/WNL.0000000000009673
4. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. (2020) 3:279–84. doi: 10.1136/svn-2020-000431
5. Rudilosso S, Laredo C, Vera V, Vargas M, Renú A, Llull L, et al. Acute stroke care is at risk in the era of COVID-19: experience at

a comprehensive stroke center in Barcelona. *Stroke.* (2020) 51:1991–5. doi: 10.1161/STROKEAHA.120.030329
6. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmunzner B, Barlinn K, et al. Acute stroke in times of the COVID-19 pandemic: a multicenter study. *Stroke.* (2020) 51:2224–7. doi: 10.1161/STROKEAHA.120.030395
7. Hsiao J, Sayles E, Antzoulatos E, Stanton RJ, Sucharew H, Broderick JP, et al. Effect of COVID-19 on emergent stroke care: a regional experience. *Stroke.* (2020) 51:e2111–4. doi: 10.1161/STROKEAHA.120.030499
8. Khosravain H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected code stroke: hyperacute stroke management during the coronavirus disease 2019 (COVID-19) pandemic. *Stroke.* (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.029838
9. Teo KC, Leung WC, Wong YK, Liu RK, Chan AH, Choi OM, et al. Delays in stroke onset to hospital arrival time during COVID-19. *Stroke.* (2020) 51:2228–31. doi: 10.1161/STROKEAHA.120.030105
10. Uchino K, Kolikonda MK, Brown D, Kovi S, Colins D, Khawaja Z, et al. Decline in stroke presentations during COVID-19 surge. *Stroke.* (2020) 51:2544–7. doi: 10.1161/STROKEAHA.120.030331
11. Diegoli H, Magalhães PS, Martins SC, Moro CH, Franca PH, Safaneli J, et al. Decrease in hospital admissions for transient ischemic attack, mild and moderate stroke during the COVID-19 era. *Stroke.* (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
12. Minister of Health, Labour and Welfare. Available online at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000164708_00001.html (accessed September 9, 2020).
13. Japanese Stroke Society PCS Working Group. Protocol for stroke management during COVID-19 pandemic: protected code stroke, Japan Stroke Society edition (JSS-PCS). *Jpn J Stroke.* (2020). 42:315–43. doi: 10.3995/jstroke.10828
14. Okada T, Inoue M, Yamagami H, Tanaka K, Shiozawa M, Sonoda K, et al. Nationwide questionnaire survey on neuroimaging strategy for acute ischemic stroke in Japan. *Jpn J Stroke.* (2020) 42:502–8. doi: 10.3995/jstroke.10781
15. Osaka Prefectural Government. Available online at: https://covid19-osaka.info (accessed September 9, 2020).
16. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
17. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Eng J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787
18. Sebastian S, Stein LK, Dhamoon MS. Infection as a stroke trigger. *Stroke.* (2019) 50:2216–8. doi: 10.1161/STROKEAHA.119.025872
19. Filippo OD, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced rate of hospital admissions for ACS during COVID-19 outbreak in northern Italy. *N Engl J Med.* (2020) 383:88–9. doi: 10.1056/NEJMc2009166
20. ACR Guidance on COVID-19 and MR Use. Available online at: https://www.acr.org/Clinical-Resources/Radiology-Safety/MR-Safety/COVID-19-and-MR-Use (accessed September 9, 2020).
21. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Guierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
22. Qureshi AI, Abd-Allah F, Al-senani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. *Int J Stroke.* (2020) 15:540–54. doi: 10.1177/1747493020923234
23. Hajdu SD, Pittet V, Puccinelli F, Hassen WB, Maacha MB, Blanc R, et al. Acute stroke management during the COVID-19 pandemic: does confinement impact eligibility for endovascular therapy? *Stroke.* (2020) 51:2593–6. doi: 10.1161/STROKEAHA.120.032096
24. Dhillon PS, Pointon K, Lenthall R, Nair S, Subramanian G, McConachie N, et al. Regional mechanical thrombectomy imaging protocol in patients presenting with acute ischemic stroke during the COVID-19. *AJNR Am J Neuroradiol.* (2020) 41:184955 doi: 10.3174/ajnr.A6754

Conflict of Interest: KT received lecture honoraria from Nippon Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Bristol-Myers Squibb, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be directly construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 20 January 2021
doi: 10.3389/fneur.2020.613552

The Biosafety and Risk Management in Preparation and Processing of Cerebrospinal Fluid and Other Neurological Specimens With Potential Coronavirus Infection

Chien-Chin Chen[1,2*†], *Pei-Chun Chiang*[3†] *and Tsung-Hsien Chen*[3]

[1] Department of Pathology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan, [2] Department of Cosmetic Science, Chia Nan University of Pharmacy and Science, Tainan, Taiwan, [3] Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Junpei Koge,
National Cerebral and Cardiovascular Center, Japan
Enkhee Ochirjav,
National Center for Pathology, Mongolia
Indranil Chakrabarti,
North Bengal Medical College and Hospital, India

***Correspondence:**
Chien-Chin Chen
hlmarkc@gmail.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Neuroinfectious Diseases, a section of the journal Frontiers in Neurology

Received: 05 October 2020
Accepted: 24 December 2020
Published: 20 January 2021

Citation:
Chen C-C, Chiang P-C and Chen T-H (2021) The Biosafety and Risk Management in Preparation and Processing of Cerebrospinal Fluid and Other Neurological Specimens With Potential Coronavirus Infection. Front. Neurol. 11:613552. doi: 10.3389/fneur.2020.613552

The recent outbreak of coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2, has become a global threat. Due to neurological manifestations presented throughout the coronavirus disease process, the potential involvement of COVID-19 in central nervous system has attracted considerable attention. Notably, the neurologic system could be widely affected, with various complications such as acute cerebrovascular events, encephalitis, Guillain-Barré syndrome, and acute necrotizing hemorrhagic encephalopathy. However, the risk assessment of exposure to potential biohazards in the context of the COVID-19 pandemic has not been clearly clarified regarding the sampling, preparation, and processing neurological specimens. Further risk managements and implantations are seldom discussed either. This article aims to provide current recommendations and evidence-based reviews on biosafety issues of preparation and processing of cerebrospinal fluid and neurological specimens with potential coronavirus infection from the bedside to the laboratory.

Keywords: COVID-19, CSF, neurology, coronavirus, cytology, biosafety, myopathy, neuromuscular

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19) pandemic, an illness with the high transmissibility and a broad spectrum of clinical manifestation. As of December 15, 2020, the World Health Organization (WHO) reported more than 70 million cases and over 1.6 million deaths globally in the COVID-19 pandemic (1). COVID-19 is the third epidemic of human coronavirus diseases after the severe acute respiratory syndrome (SARS) in November 2002, and the Middle East respiratory syndrome (MERS) in September 2012 (2). In comparison with other epidemic coronaviruses, SARS-CoV-2 is less lethal but far more transmissible than MERS coronavirus (MERS-CoV) and SARS coronavirus (SAR-CoV) (3, 4). It is believed that SARS–CoV-2 can spread by respiratory droplets, unprotected direct contact with patients, and touching contaminated objects (5, 6). Since symptoms of COVID-19 can be in a wide variety of severity, medical professionals are in particular at risk of exposure to SARS-CoV-2 through close contact via respiratory droplets and contaminated surface and direct handling of contagious materials from patients with COVID-19 (7). With regard to the safe

collecting and handling clinical specimens in the pandemic, a few reports have emphasized the need for the worldwide standardization of biosafety protocols (5, 8, 9). Notably, the neurological manifestation and morbidities of COVID-19 have been widely reported (10–16). Mao et al. (15) reported that neurologic symptoms were present in 36.4% of all patients with COVID-19, especially more frequent in patients with severe illness. Moreover, in a patient with acute cerebellitis, the viral RNA of SARS-CoV-2 was detected in his oropharynx, nasopharynx, and cerebrospinal fluid (CSF) (17). However, the biosafety and risk assessment in preparation and processing of CSF and other neurological specimens were seldom discussed. This mini-review aims to provide an integrative, evidence-based review to guide the preparation and processing of neurological specimens with potential coronavirus infection and therefore to prevent nosocomial infection.

CORONAVIRUSES AND NEUROLOGIC DISEASES

Although COVID-19 primarily presents as a respiratory disease, SARS-CoV-2 affects multiple organs or systems, including the central nervous system (CNS), peripheral nervous system (PNS), and neuromuscular system (15, 18–20). In a large case cohort of COVID-19, 24.8% had CNS symptoms (e.g., dizziness, headache, and impaired consciousness), 8.9% had PNS symptoms, and 10.7% had skeletal muscle injury (15). In a nationwide surveillance of 125 patients with COVID-19 and neurological or psychiatric disease, 62% of them had a cerebrovascular event, while 31% of them presented with altered mental status (19). Similarly, the epidemic of SARS was reported with various neurological complications including encephalopathy, seizures, stroke, cranial nerve palsies, peripheral neuropathy, and myopathy (20–24). Also, patients with MERS were occasionally presented to have neurological symptoms and neuromuscular complications (24–27). The prevalence of CNS complications reached 0.04% for SARS and 0.20% for MERS, and besides the prevalence of PNS complications was 0.05% for SARS and 0.16% for MERS (14).

Although the mechanism of CNS involvement of COVID-19 remains unclear, there is a three-step model which refers to viral neuroinvasion, CNS clearance, and immune response (28). In the first stage, SARS-CoV-2 may enter the brain via the bloodstream and/or transcribriform route along the olfactory nerve, and the viral load in CSF should increase (28). The respiratory symptoms are minimal in the early stage. With the interaction between the spike protein S1 of SARS-CoV-2 and the host angiotensin-converting enzyme 2 receptor (ACE2), SARS-CoV-2 may enter both glial and neuronal cells (29). In some cases, the neuroinvasion may cause a direct neuronal damage and subsequently result in neurological symptoms. Moreover, the consumption and downregulation of ACE2 by SARS-CoV-2 virus may lead to imbalance of the renin angiotensin system resulting in endothelial dysfunction, vasoconstriction, and subsequently ischemic events (30). In the second stage, SARS-CoV-2 may infect the brainstem affecting the respiratory drive. The viral load in respiratory secretions would increase predominantly, but the viral load in CSF significantly decreases. The CSF clearance of SARS-CoV-2 may greatly contribute to a low virus detection rate in CSF samples from patients with COVID-19 and CNS involvement. In the third stage, an immuno-mediated CNS damage may form, since SARS-CoV-2 can trigger the production of antibodies against glial cells, as a para-infective or post-infective phenomenon (28). In consequence, the respiratory system would be severely affected and cause neurotoxic hypoxia with subsequent brain damage (28).

With regard to neuromuscular involvement of SARS-CoV-2, myositis, acute myelitis, Guillain Barre syndrome, Miller Fisher syndrome, polyneuritis cranialis, oculomotor paralysis and Bell's Palsy have been discussed to be associated with COVID-19 (18, 30–34). On electrodiagnostic testing, most of the abovementioned patients had demyelinating pattern, some had acute sensory motor axonal neuropathy, and few had acute motor axonal neuropathy (18). In a patient with COVID-19 and myositis, the muscle biopsy revealed inflammatory infiltration around vessels and endomysial extension, regeneration of muscular fibers, and elevated HLA Class ABC expression (33). The exact mechanism remains unknown, although a few hypothetic theories were proposed, including ACE2 mediated pathway, olfactory pathway, trans-synaptic pathway, and immune mediated pathway (18). Since the muscle cells express ACE2, the direct invasion by the SARS-CoV-2 entering the muscle cells via the ACE2 may be possible (30). In addition, cytokine storms in the advanced phase of COVID-19 could lead to immune-mediated muscle damages (30).

THE CLINICAL SAMPLING AND PREPARATION: LUMBAR PUNCTURE AND MUSCLE BIOPSY

Lumbar puncture (LP) is a medical procedure at the level of L2 to L5 vertebrae to collect CSF for examining infectious, inflammatory, and neoplastic diseases involving the CNS. In viral encephalitis, there is usually a mild to moderate CSF pleocytosis with predominant lymphocytes, normal glucose ratio, and slightly elevated protein (14, 35). The standard of diagnosing a CNS viral infection is to demonstrate the virus in the CNS, either from culture or polymerase chain reaction (PCR) of brain tissue or CSF.

Muscle biopsy (MB) is important for the evaluation and diagnosis of patients who are suspected of having an underlying neuromuscular disorder (36). With an open biopsy or needle biopsy technique under local anesthesia, bundles of skeletal muscles are taken for the required tests, including frozen sections for enzyme histochemistry, paraffin embedding for muscle fiber morphology and inflammatory patterns, electron microscopy for ultrastructural analysis, and biochemical testing for assessing storage and mitochondrial diseases (36).

In the pandemic, to perform a LP or a MB might be at risk to expose coronaviruses, since direct contact or respiratory droplets might be infectious. Since both LP and MB are time-consuming, the performer and all teammates would expose to

TABLE 1 | A summary of biosafety recommendations to prevent coronavirus (COVID-19) for lumbar puncture and muscle biopsy.

Before and after lumbar puncture or muscle biopsy	1. Ensure clinical triage and assess patients for early recognition of COVID-19 infection. 2. Conduct a site-specific and activity-specific risk assessment with appropriate risk control measures in place. 3. Have adequate PPE supplies in sufficient quantity. 4. Perform procedures in an adequately ventilated room with at least of 60 L/s/patient air flow. 5. Wear standard medical masks, eye protection (goggles) or facial protection (face shield), long-sleeved gowns, and gloves. 6. The process of contact with each patient, properly dispose of all PPEs and wastes and perform hand hygiene. 7. Clean and disinfect the surfaces that the patient was in contact with.
Precautions of transportation	1. Patient specimens from suspected or confirmed SARS-CoV-2 infection should be transported as UN3373, "Biological Substance Category B". 2. Deliver all specimens promptly by hand whenever possible. 3. Ensure that all personnel who transport specimens have received training in safe handling practices and spill decontamination procedures. 4. Timely notify the laboratory and correctly label the specimen with informative request forms.
Process samples	1. Diagnostic tests, such as cytology, biochemistry, and formalin-fixed paraffin sections, should be handled in a BSL-2 laboratory. 2. Wear and remove PPE properly, as determined by a detailed risk assessment, with hand hygiene. 3. Processing of all specimens before inactivation should take place in a validated biological safety cabinet or primary containment device. 4. All procedures should be performed in a manner that minimizes the generation of aerosols and droplets. 5. During processing, appropriate disinfectants with proven activity against coronaviruses should be used.

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; PPE, personal protective equipment; BSL-2, biosafety level 2.

patients' droplet aerosols in a poorly ventilated room. In closed rooms, the SARS-CoV-2 can be detectable in aerosols for 3 h and persists on surfaces (such as cardboard, stainless steel, and plastic surfaces) from 24 to 72 h (6). Thus, the sampling or collecting biological materials from patients should be careful and need to follow the recommendations or guidelines in the pandemic (5, 37–39). First, a site-specific and activity-specific risk assessment should be regularly performed to ensure the competency level of the healthcare workers, the equipment and facility, and the resources that are available. Meanwhile, clinical triage should be ensured by assessing all patients for early detection of COVID-19, and immediate isolation of patients with suspected COVID-19 in an area separate from others (37). Regarding the environment, LP and MB should be performed in an adequately ventilated room with at least of 60 liters/s/patient air flow (37). The environmental cleaning and disinfection procedures should be consistently and correctly performed. Notably, coronaviruses can be inactivated by surface disinfectants with 62–71% ethanol (C_2H_6O), 0.5% hydrogen peroxide (H_2O_2) or 0.1% sodium hypochlorite (NaClO) within 1 min (40).

Although LP and MB are not aerosol-generating procedures, the neurological professionals should wear a medical mask, eye protection (goggles) or facial protection (face shield), a clean long-sleeved gown, and gloves (37). After procedures, personal protective equipment and wastes should be properly disposed, and hand hygiene should be performed before and after contact with each patient. Lastly, it is important to clean and disinfect the surfaces that the patient was in contact with. With regard to the transportation, CSF or muscle for virus detection can be shipped at 2–8°C and delivered promptly to the laboratory (41). Notably, patient specimens from suspected or confirmed SARS-CoV-2 infection should be transported as UN3373, "Biological Substance Category B" (42, 43). All the biosafety recommendations are summarized in **Table 1**.

TO PROCESS CSF AND OTHER NEUROLOGICAL SPECIMENS

Since all specimens collected for laboratory investigations should be considered potentially infectious, all procedures must be performed according to risk assessment and strategies for biosafety (42, 43). Before inactivation of all specimens, the initial processing should be performed in a validated biological safety cabinet or primary containment device (42). In addition to detecting viruses by sequencing or PCR, all diagnostic laboratory works for neurological specimens, including biochemistry, cytology, and special stains should be performedat a facility using procedures equivalent to Biosafety Level 2 (BSL-2) (42, 43). In the light of inactivation of coronaviruses, fixatives with ethanol concentrations of 78%-95% for at least 30 s could inactivate SARS-CoV, and either 10% formalin or 4% paraformaldehyde for at least 30 min would efficiently inactivate MERS-CoV–infected cells (9). Alcohol fixed preparation also lyses red blood cells, reducing the risk of viremia. The abovementioned fixations are the reasons why specimens with Papanicolaou staining or formalin fixation can be taken as inactivated (9). Moreover, the external lysis buffer of common RNA extraction kits for viral detection is effective to inactivate SARS-CoV-2 without heat or other additional methods (42).

Currently, the identification of viral RNA through nucleic acid amplification technologies, such as reverse-transcription polymerase chain reaction (RT-PCR) in a patient's biological

TABLE 2 | The detection of SARS-CoV-2 in CSF from patients with COVID-19 and neurological symptoms.

References	Age/Gender	Neurological symptoms and/or diagnoses	No. of CSF positive/total patients	Note
Fadakar et al. (17)	47/Male	Progressive vertigo, headache, and ataxia. Acute cerebellitis.	1/1	SARS-CoV-2 RNA was detected in oropharyngeal, nasopharyngeal, and CSF specimens. The CSF analysis demonstrated mild pleocytosis (80% lymphocyte), normal glucose (60 mg/dL), elevated protein (58 mg/dL) and lactate dehydrogenase (134 u/L), and negative results in Gram stain, culture, and cytology.
Moriguchi et al. (47)	24/Male	Fever, unconsciousness, and neck stiffness. Meningitis/encephalitis.	1/1	SARS-CoV-2 RNA was not detected in the nasopharyngeal swab, but shown in CSF. The CSF cell count showed pleocytosis.
Cebrián et al. (48)	74/Female	Severe headache with photophobia, vomiting, and progressive confusion.	1/1	Both nasopharyngeal and CSF tests for SARS-CoV-2 RNA were positive. The CSF analysis yielded no specific finding (1 leukocyte/mm^3, 1 red blood cell/mm^3, protein: 30 mg/dL, glucose: 82 mg/dL, and opening pressure: 10 cmH_2O). Acid-fast bacilli and bacterial cultures and stains were negative.
Domingues et al. (49)	42/Female	Paresthesias of the left upper limb, left hemithorax, and hemiface. Demyelinating disease.	1/1	SARS-COV-2 RNA was positive in the first CSF sample, but negative in nasal and pharyngeal samples. The CSF analysis showed 1 leukocyte/mm^3, protein of 32 mg/dL, and glucose of 68 mg/dL.
El-Zein et al. (50)	40/Male	Visual hallucinations, forgetful, and confusion with orientation. Meningoencephalitis.	0/1	SARS-CoV-2 was positive in a nasopharyngeal swab, but negative in CSF. The CSF studies showed lymphocytic pleocytosis, elevated glucose (70 mg/dL), and decreased protein levels (19 mg/dL).
Lu et al. (51)	51/Male	Fever, pharyngalgia, excited, talkative, irritable, and energetic. COVID-19 with manic-like symptoms.	0/1	SARS-CoV-2 RNA was positive in sputum and stool, but negative in CSF. SARS-CoV-2 specific IgG antibody in CSF was positive. The CSF analysis demonstrated no pleocytosis and normal protein.
Vandervorst et al. (52)	29/Male	General weakness, dry cough, dyspnea, confusion, and disorientation. Encephalitis.	0/1	SARS-CoV-2 was positive in a nasopharyngeal swab, but negative in CSF. The CSF cell count, protein and glucose levels were within normal limits. Anti-SARS-CoV-2 IgM and IgG's were negative in CSF.
Sun and Guan (53)	N/A	N/A	1/1	CSF was tested positive for SARS-CoV-2 by gene sequencing.
Al Saiegh et al. (54)	31/Male and 62/Female	Male: severe headache and loss of consciousness with aneurysmal subarachnoid hemorrhage. Female: right hemiparesis and aphasia with a left middle cerebral artery occlusion.	0/2	Both patients' nasal swabs were positive for SARS-CoV-2 RNA, but both patients' CSF specimens were negative. No other data of CSF analysis were provided.
Bodro et al. (55)	25/Male and 49/Male	25-year-old: headache, left-sided paresthesias, and ipsilateral paresis. 49-year-old: fever, myalgia, temporospatial disorientation, confusion, and agitation.	0/2	SARS-CoV-2 RNA was positive in the nasopharyngeal swabs of both cases, but negative in CSF of both cases. In both patients, the CSF showed lymphocytic pleocytosis and increased proteins.
Benameur et al. (56)	31/Female, 34/Male, and 64/Male	31-year-old: respiratory failure, encephalitis and myelitis. 34-year-old: respiratory failure, encephalopathy with myoclonus. 64-year-old: respiratory failure and encephalopathy.	0/3	SARS-CoV-2 RNA was positive in the nasopharyngeal swabs of all 3 cases, but negative in CSF of all cases. The CSF data showed mild to markedly increased IgM for SARS-CoV-2 S1 protein in all 3 cases. And only one of three had neutrophilic pleocytosis with a high protein level.
Delorme et al. (57)	72/Male, 66/Female, 60/Female, and 69/Male	New-onset cognitive disturbances with central focal neurological signs or seizures.	0/4	SARS-CoV-2 RNA was positive in the nasopharyngeal swabs of all 4 cases, but negative in CSF of all cases. None of them had MRI features of encephalitis or significant CSF abnormalities.

(Continued)

TABLE 2 | Continued

References	Age/Gender	Neurological symptoms and/or diagnoses	No. of CSF positive/total patients	Note
Neumann et al. (58)	18 males and 12 females with a median age of 65.5 years	Altered mental state (33.3%), new paresis (30.0%), impaired consciousness (23.3%), hypo-/areflexia (30.0%), anosmia/hyposmia or ageusia/hypogeusia (20.0%), and seizures (16.7%).	0/30	In all 30 cases, RT-PCR tests for SARS-CoV-2 RNA from CSF were negative, although positive in all orophyryngeal swabs. Their CSF showed normal or slightly increased white blood cell count (≤8/μl) in 28 cases, while the CSF blood albumin ratio was normal in most cases.
Guilmot et al. (59)	12 males and 3 females with a median age of 62 years	Cranial neuropathy, coma, neuropsychiatric symptoms, delirium, and acute cerebrovascular disease.	0/13 (not perform in 2 patients with anticoagulation)	PCR for SARS-CoV-2 on the CSF was negative in all patients. The CSF lymphocytic pleocytosis was present only in two cases, one with anti-Caspr2-associated limbic encephalitis and the other with para-infectious polyradiculitis.
Uncini et al. (60)	27 males and 15 females with a median age of 57.5 years	Guillain- Barré syndrome, presenting hypoareflexia (80.9%) and limb weakness (76.2%).	0/25	In 42 cases with Guillain- Barré syndrome and SARS-CoV-2 infection, the SARS-CoV-2 RNA in CSF was negative in all 25 cases in whom was done. The CSF albuminocytological dissociation was found in 28/36 (77.8%).
Abu-Rumeileh et al. (61)	50 males and 23 females with a mean age of 55 years	Guillain- Barré syndrome with fever (73.6%), cough (72.2%), dyspnea (63.8%), hypo-/ageusia (22.2%), hypo-/anosmia (20.8%), and diarrhea (18.1%).	0/31	Only 31 cases were tested for SARS-CoV-2 RNA in CSF which was undetectable in all tested patients. The CSF albuminocytological dissociation was present in 71.2% of the cases (42/59). Mild pleocytosis, with a maximum cell count of 13/μl, was evident in 8.5% of cases (5/59).
Espíndola et al. (62)	N/A	Meningoencephalitis (1), encephalitis (1), facial palsy (2), delirium (2), intracranial hypertension (1), new daily persistent headache (1).	0/8	The CSF data revealed normal or mild elevated protein levels, while pleocytosis was particularly observed in the cases of meningoencephalitis.
Miller et al. (63)	21 males and 6 females with an average age of 37.5 years	Fever (48%), altered mental status (22%), headache (15%), dyspnea (7%), anosmia (6%), and psychosis (4%).	0/8	Only 8 cases were tested for SARS-CoV-2 RNA in CSF which was undetectable in all tested patients. The CSF analyses revealed elevated white blood cell counts (12/27) and protein (14/27).
Edén et al. (64)	5 males and 1 female with a median age of 60 years	Encephalopathies (4/6), suspected meningitis (1/6), and dysgeusia (1/6).	3/6	Three of six cases tested for SARS-CoV-2 RNA in CSF showed low levels of positivity in the first time (Ct values 39.0, 38.0, and 37.2). But the second test for SARS-CoV-2 RNA was undetectable in all these CSF samples. None of the patients had CSF pleocytosis. The albumin ratio and IgG-index in CSF were within the normal range in all cases.
Khodamoradi et al. (65)	49/Female	Fever, headache, malaise, nausea, and vomiting. Meningitis.	1/1	The RT-PCR for COVID-19 was positive in CSF, but negative in oropharyngeal/nasopharyngeal samples. The CSF analysis showed pleocytosis, elevated protein levels, and normal glucose levels.

CSF, cerebrospinal fluid; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; N/A, not available; MRI, magnetic resonance imaging; RT-PCR, reverse-transcriptase polymerase chain reaction.

samples, remains the gold standard for identifying infections with coronaviruses. Notably, SARS-CoV was detected in CSF by RT-PCR in two cases of encephalopathy (44, 45) and was cultured from brain tissues of an autopsy case (46). In the COVID-19 pandemic, although the neurological manifestations were not uncommon, SARS-CoV-2 RNA was rarely detected in CSF by RT-PCR (**Table 2**) (17, 47–65). And, to the best of our knowledge, there is no MB specimen demonstrating the evidence of SARS-CoV-2 infection via culture or RT-PCR. Based on the relative frequencies of detectable SARS-CoV-2 RNA in different samples from published reports, Chen and Chi (5) suggested to categorize the cytological and pathological

samples into the high risk, intermediate risk, and low risk groups. Accordingly, CSF and MB specimens can be categorized into the low risk group with limited evidence of SARS-CoV-2 RNA detection and should subsequently follow the principles of good microbiological practices and procedures to be handled (5). Although the presence of viral RNA is not equivalent to live infectious viruses, RT-PCR is an important method to identify infectious agents (66).

CONCLUSION

With the growing number of confirmed COVID-19 cases, it is essential that the neurological experts and clinical laboratories implement clinical triage, drastic measures, and appropriate procedures and facilities for ensuring the safety and interests of valuable healthcare workers in times of the pandemic. The lessons learned from SARS and MERS could give us more insights to conduct efficient preventive measures in healthcare settings. Although LP and MB are important diagnostic procedures for CNS and neuromuscular diseases, neurological practitioners must be well-prepared and avoid of non-emergent procedures to prevent potential exposures to COVID-19. The collection, transportation, and processing of neurological specimens should warrant the use of WHO guidelines, academic recommendations, and BSL-2 procedures. Herein, although the biological safety and security issues were rarely discussed in neurology, we hope that both neurologists and laboratory professionals can benefit from this integrative mini-review in dealing with the COVID-19 crisis.

AUTHOR CONTRIBUTIONS

C-CC: study concept and design, acquisition of data, manuscript writing, critical revision of the manuscript for important intellectual content, and study supervision. P-CC: acquisition of data, analysis and interpretation, manuscript writing, and critical revision of the manuscript for important intellectual content. T-HC: critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

REFERENCES

1. World Health Organization. *Weekly Epidemiological Update-15 December 2020*. (2020). Available online at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20201215_weekly_epi_update_18.pdf?sfvrsn=9c9aac11_5&download=true (accessed December 16, 2020).
2. Guarner J. Three emerging coronaviruses in two decades. *Am J Clin Pathol*. (2020) 153:420–1. doi: 10.1093/ajcp/aqaa029
3. Petersen E, Koopmans M, Go U, Hamer DH, Petrosillo N, Castelli F, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis*. (2020) 20:e238–44. doi: 10.1016/S1473-3099(20)30484-9
4. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect*. (2020) 26:729–34. doi: 10.1016/j.cmi.2020.03.026
5. Chen CC, Chi CY. Biosafety in the preparation and processing of cytology specimens with potential coronavirus (COVID-19) infection: perspectives from Taiwan. *Cancer Cytopathol*. (2020) 128:309–16. doi: 10.1002/cncy.22280
6. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. (2020) 382:1564–7. doi: 10.1056/NEJMc2004973
7. Zhou P, Huang Z, Xiao Y, Huang X, Fan XG. Protecting Chinese healthcare workers while combating the 2019 novel coronavirus. *Infect Control Hosp Epidemiol*. (2020) 41:745–6. doi: 10.1017/ice.2020.60
8. Wang YH, Bychkov A, Chakrabarti I, Jain D, Liu Z, He S, et al. Impact of the COVID-19 pandemic on cytology practice: an international survey in the Asia-Pacific region. *Cancer Cytopathol*. (2020). 128:895-904. doi: 10.1002/cncy.22354
9. Chen CC, Chi CY. Reply to Rapid on-site evaluation and the COVID-19 pandemic. *Cancer Cytopathol*. (2020) 128:910–2. doi: 10.1002/cncy.22296
10. Román GC, Spencer PS, Reis J, Buguet A, Faris MEA, Katrak SM, et al. The neurology of COVID-19 revisited: a proposal from the environmental neurology specialty group of the world federation of neurology to implement international neurological registries. *J Neurol Sci*. (2020) 414:116884. doi: 10.1016/j.jns.2020.116884
11. Zhou Y, Li W, Wang D, Mao L, Jin H, Li Y, et al. Clinical time course of COVID-19, its neurological manifestation and some thoughts on its management. *Stroke Vasc Neurol*. (2020) 5:177–9. doi: 10.1136/svn-2020-000398
12. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. *Nat Rev Neurol*. (2020) 24:1–9. doi: 10.1038/s41582-020-0398-3
13. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell*. (2020) 183:16–27.e1. doi: 10.1016/j.cell.2020.08.028
14. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol*. (2020) 19:767–83. doi: 10.1016/S1474-4422(20)30221-0
15. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. lan with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
16. Fan S, Xiao M, Han F, Xia P, Bai X, Chen H, et al. Neurological manifestations in critically ill patients with COVID-19: a retrospective study. *Front Neurol*. (2020) 11:806. doi: 10.3389/fneur.2020.00806
17. Fadakar N, Ghaemmaghami S, Masoompour SM, Shirazi Yeganeh B, Akbari A, Hooshmandi S, et al. A first case of acute cerebellitis associated with Coronavirus Disease (COVID-19): a case report and literature review. *Cerebellum*. (2020) 19:911–4. doi: 10.1007/s12311-020-01177-9
18. Katyal N, Narula N, Acharya S, Govindarajan R. Neuromuscular complications with SARS-COV-2 infection: a review. *Front Neurol*. (2020) 11:1052. doi: 10.3389/fneur.2020.01052
19. Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry*. (2020) 7:875–82. doi: 10.2139/ssrn.3601761
20. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain Behav Immun*. (2020) 87:18–22. doi: 10.1016/j.bbi.2020.03.031
21. Tsai LK, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. *Acta Neurol Taiwan*. (2005) 14:113–9. doi: 10.29819/ANT.200509.0002
22. Tsai LK, Hsieh ST, Chao CC, Chen YC, Lin YH, Chang SC, et al. Neuromuscular disorders in severe acute respiratory syndrome. *Arch Neurol*. (2004) 61:1669–73. doi: 10.1001/archneur.61.11.1669
23. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res*. (2014) 194:145–58. doi: 10.1016/j.virusres.2014.09.011
24. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. (2016) 14:523–34. doi: 10.1038/nrmicro.2016.81
25. Arabi YM, Harthi A, Hussein J, Bouchama A, Johani S, Hajeer AH, et al. Severe neurologic syndrome associated with Middle East

respiratory syndrome corona virus (MERS-CoV). *Infection*. (2015) 43:495–501. doi: 10.1007/s15010-015-0720-y
26. Algahtani H, Subahi A, Shirah B. Neurological complications of middle east respiratory syndrome coronavirus: a report of two cases and review of the literature. *Case Rep Neurol Med*. (2016) 2016:3502683. doi: 10.1155/2016/3502683
27. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological complications during treatment of Middle East respiratory syndrome. *J Clin Neurol*. (2017) 13:227–33. doi: 10.3988/jcn.2017.13.3.227
28. Panciani PP, Saraceno G, Zanin L, Renisi G, Signorini L, Battaglia L, et al. SARS-CoV-2: "Three-steps" infection model and CSF diagnostic implication. *Brain Behav Immun*. (2020) 87:128–9. doi: 10.1016/j.bbi.2020.05.002
29. Pennisi M, Lanza G, Falzone L, Fisicaro F, Ferri R, Bella R. SARS-CoV-2 and the nervous system: from clinical features to molecular mechanisms. *Int J Mol Sci*. (2020) 21:5475. doi: 10.3390/ijms21155475
30. Sharifian-Dorche M, Huot P, Osherov M, Wen D, Saveriano A, Giacomini PS, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci*. (2020) 417:117085. doi: 10.1016/j.jns.2020.117085
31. Chow CCN, Magnussen J, Ip J, Su Y. Acute transverse myelitis in COVID-19 infection. *BMJ Case Rep*. (2020) 13:e236720. doi: 10.1136/bcr-2020-236720
32. Munz M, Wessendorf S, Koretsis G, Tewald F, Baegi R, Krämer S, et al. Acute transverse myelitis after COVID-19 pneumonia. *J Neurol*. (2020) 267:2196–7. doi: 10.1007/s00415-020-09934-w
33. Zhang H, Charmchi Z, Seidman RJ, Anziska Y, Velayudhan V, Perk J. COVID-19-associated myositis with severe proximal and bulbar weakness. *Muscle Nerve*. (2020) 62:E57–60. doi: 10.1002/mus.27003
34. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. *Neurol Sci*. (2020) 41:3039–56. doi: 10.1007/s10072-020-04708-8
35. Solomon T, Hart IJ, Beeching NJ. Viral encephalitis: a clinician's guide. *Pract Neurol*. (2007) 7:288–305. doi: 10.1136/jnnp.2007.129098
36. Joyce NC, Oskarsson B, Jin LW. Muscle biopsy evaluation in neuromuscular disorders. *Phys Med Rehabil Clin N Am*. (2012) 23:609–31. doi: 10.1016/j.pmr.2012.06.006
37. World Health Organization. *Infection Prevention and Control During Health Care When Novel Coronavirus (nCoV) Infection Is Suspected. Interim Guidance, 19 March 2020*. (2020). Available online at: https://www.who.int/publications/i/item/10665-331495 (accessed September 27, 2020).
38. Ozoner B, Gungor A, Hasanov T, Toktas ZO, Kilic T. Neurosurgical practice during coronavirus disease 2019 (COVID-19) pandemic. *World Neurosurg*. (2020) 140:198–207. doi: 10.1016/j.wneu.2020.05.195
39. Fraser JF, Arthur AS, Chen M, Levitt M, Mocco J, Albuquerque FC, et al. Society of neurointerventional surgery recommendations for the care of emergent neurointerventional patients in the setting of COVID-19. *J Neurointerv Surg*. (2020) 12:539–41. doi: 10.1136/neurintsurg-2020-016098
40. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hosp Infect*. (2020) 104:246–51. doi: 10.1016/j.jhin.2020.01.022
41. World Health Organization. *Laboratory Testing for 2019 Novel Coronavirus (2019-nCoV) in Suspected Human Cases. Interim Guidance, 13 May 2020*. (2020). Available online at: https://www.who.int/publications/i/item/10665-331501 (accessed September 27, 2020).
42. World Health Organization. *Laboratory Biosafety Guidance Related to Coronavirus Disease (COVID-19). Interim Guidance, 13 May 2020*. (2020). Available online at: https://www.who.int/publications/i/item/laboratory-biosafety-guidance-related-to-coronavirus-disease-(covid-19) (accessed September 27, 2020).
43. Centers for Disease Control and Prevention. *Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with Coronavirus Disease 2019 (COVID-19)*. (2020). Available online at: https://www.cdc.gov/coronavirus/2019-ncov/lab/lab-biosafety-guidelines.html (accessed September 27, 2020).
44. Hung EC, Chim SS, Chan PK, Tong YK, Ng EK, Chiu RW, et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem*. (2003) 49:2108–09. doi: 10.1373/clinchem.2003.025437
45. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis*. (2004)10:342–44. doi: 10.3201/eid1002.030638
46. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Infect Dis*. (2005) 41:1089–96. doi: 10.1086/444461
47. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. (2020) 94:55–8. doi: 10.1016/j.ijid.2020.03.062
48. Cebrián J, Gonzalez-Martinez A, García-Blanco MJ, Celdrán-Vivancos D, Palacios EL, Reig-Roselló G, et al. Headache and impaired consciousness level associated with SARS-CoV-2 in CSF: a case report. *Neurology*. (2020) 95:266–8. doi: 10.1212/WNL.0000000000010213
49. Domingues RB., Mendes-Correa MC, de Moura Leite FBV, Sabino EC, Salarini DZ, Claro I, et al. First case of SARS-COV-2 sequencing in cerebrospinal fluid of a patient with suspected demyelinating disease. *J Neurol*. (2020) 20:1–3. doi: 10.21203/rs.3.rs-31801/v1
50. El-Zein RS, Cardinali S, Murphy C, Keeling T. COVID-19-associated meningoencephalitis treated with intravenous immunoglobulin. *BMJ Case Rep*. (2020) 13:e237364. doi: 10.1136/bcr-2020-237364
51. Lu S, Wei N, Jiang J, Wu L, Sheng J, Zhou J, et al. First report of manic-like symptoms in a COVID-19 patient with no previous history of a psychiatric disorder. *J Affect Disord*. (2020) 277:337–40. doi: 10.1016/j.jad.2020.08.031
52. Vandervorst F, Guldolf K, Peeters I, Vanderhasselt T, Michiels K, Berends KJ, et al. Encephalitis associated with the SARS-CoV-2 virus: a case report. *Interdiscip Neurosurg*. (2020) 22:100821. doi: 10.1016/j.inat.2020.100821
53. Sun T, Guan J. Novel coronavirus and the central nervous system. *Eur J Neurol*. (2020) 27:e52. doi: 10.1111/ene.14227
54. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T, et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *J Neurol Neurosurg Psychiatry*. (2020) 91:846–8. doi: 10.1136/jnnp-2020-323522
55. Bodro M, Compta Y., Llansó L, Esteller D, Doncel-Moriano A, Mesa A, et al. Increased CSF levels of IL-1β, IL-6, and ACE in SARS-CoV-2-associated encephalitis. *Neurol Neuroimmunol Neuroinflamm*. (2020) 7:e821. doi: 10.1212/NXI.0000000000000821
56. Benameur K, Agarwal A, Auld SC, Butters MP, Webster AS, Ozturk T, et al. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. *Emerg Infect Dis*. (2020) 26:2016–21. doi: 10.3201/eid2609.202122
57. Delorme C, Paccoud O, Kas A, Hesters A, Bombois S, Shambrook P, et al. Covid-19-related encephalopathy: a case series with brain FDG-PET/CT findings. *Eur J Neurol*. (2020) 27:2651–7. doi: 10.1111/ene.14478
58. Neumann B, Schmidbauer ML, Dimitriadis K, Otto S, Knier B, Niesen WD, et al. Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. *J Neurol Sci*. (2020) 418:117090. doi: 10.1016/j.jns.2020.117090
59. Guilmot A, Maldonado Slootjes S, Sellimi A, Bronchain M, Hanseeuw B, Belkhir L, et al. Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. *J Neurol*. (2020). doi: 10.1007/s00415-020-10108-x. [Epub ahead of print].
60. Uncini A, Vallat JM, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. *J Neurol Neurosurg Psychiatry*. (2020) 91:1105–10. doi: 10.1136/jnnp-2020-324491
61. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol*. (2020). doi: 10.1007/s00415-020-10124-x. [Epub ahead of print].
62. Espíndola OM, Siqueira M, Soares CN, Lima MASD, Leite ACCB, Araujo AQC, et al. Patients with COVID-19 and neurological manifestations show undetectable SARS-CoV-2 RNA levels in the cerebrospinal fluid. *Int J Infect Dis*. (2020) 96:567–9. doi: 10.1016/j.ijid.2020.05.123
63. Miller EH, Namale VS, Kim C, Dugue R, Waldrop G, Ciryam P, et al. Cerebrospinal analysis in patients with COVID-19. *Open Forum Infect Dis*. (2020) 7:ofaa501. doi: 10.1093/ofid/ofaa501

64. Edén A, Kanberg N, Gostner J, Fuchs D, Hagberg L, Andersson LM, et al. CSF biomarkers in patients with COVID-19 and neurological symptoms: a case series. *Neurology*. (2020). doi: 10.1212/WNL.0000000000010977. [Epub ahead of print].
65. Khodamoradi Z, Hosseini SA, Gholampoor Saadi MH, Mehrabi Z, Sasani MR, Yaghoubi S. COVID-19 meningitis without pulmonary involvement with positive cerebrospinal fluid PCR. *Eur J Neurol*. (2020) 27:2668–9. doi: 10.1111/ene.14536
66. Hepnar D, Adam P, Žáková H, Krušina M, Kalvach P, Kasík J, et al. Recommendations for cerebrospinal fluid analysis. *Folia Microbiol*. (2019) 64:443–52. doi: 10.1007/s12223-018-0663-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 25 January 2021
doi: 10.3389/fneur.2020.596871

A Sharp Decline in Burden of Stroke in Rural China During COVID-19 Pandemic

Jie Liu[1,2,3†], Qiaoxia Yang[4†], Xin Zhang[1†], Qiuxing Lin[1,2,3], Yuan Yang[1], Dandan Guo[1], Wenjing Mao[5], Jun Tu[1,2,3], Zeping Liu[6], Jidong Li[7], Xianjia Ning[1,2,3*] and Jinghua Wang[1,2,3*]*

[1] Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China, [2] Laboratory of Epidemiology, Tianjin Neurological Institute, Tianjin, China, [3] Key Laboratory of Post-neuroinjury Neuro-repair and Regeneration in Central Nervous System, Tianjin Neurological Institute, Ministry of Education and Tianjin City, Tianjin, China, [4] Department of Cardiology, Tianjin Medical University General Hospital, Tianjin, China, [5] Department of Neurology, North China University of Science and Technology Affiliated Hospital, Tangshan, China, [6] Department of Internal Medicine, Tianjin Jizhou People's Hospital, Tianjin, China, [7] Department of Neurosurgery, Tianjin Jizhou People's Hospital, Tianjin, China

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Helen L. Po,
MacKay Memorial Hospital, Taiwan
Huang-tz Ou,
National Cheng Kung University, Taiwan

***Correspondence:**
Jinghua Wang
jhw8799@yahoo.com;
jwang3@tmu.edu.cn
Xianjia Ning
xning@tmu.edu.cn
Jidong Li
jd_li_doctor@163.com

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 20 August 2020
Accepted: 28 December 2020
Published: 25 January 2021

Citation:
Liu J, Yang Q, Zhang X, Lin Q, Yang Y, Guo D, Mao W, Tu J, Liu Z, Li J, Ning X and Wang J (2021) A Sharp Decline in Burden of Stroke in Rural China During COVID-19 Pandemic. Front. Neurol. 11:596871. doi: 10.3389/fneur.2020.596871

This study aimed to explore trends in the burden from stroke associated with home quarantine during the COVID-19 pandemic. Patients with a first-ever stroke registered between January 1 and April 20 from 2010 to 2020 were included in this study. We compared the incidence and the rates of mortality, hospitalization, and diagnosis by neuroimaging for first-ever stroke among a low-income population in rural China during the study periods. Overall, 377 first-ever stroke patients were analyzed in this study period; men accounted for 59.2%. Compared with 2019, the incidence of first-ever stroke was 73.5% lower in 2020 ($P < 0.001$). The incidence of first-ever stroke was lower by 64.18% in 2020 than in the previous 5 years ($P = 0.002$) and by 65.42% in 2020 than in the previous 10 years ($P = 0.001$). Mortality from first-ever stroke in 2020 was not significantly different from that in 2019, but it was noticeably lower than that for the previous 5 and 10 years. However, rates of hospitalization and diagnosis by neuroimaging remained stable across the study period. These findings suggest that the home quarantine helped reduce outdoor activities at low temperatures, restrict gatherings, reduce alcoholism and high-fat diet, and lower pollution caused by factories. These changes were advantageous for helping high-risk groups to reduce the burden of stroke.

Keywords: stroke, epidemiology, incidence, burden, COVID-19

INTRODUCTION

The World Health Organization officially classified the novel COVID-19 outbreak as a global pandemic on March 11, 2020. As of April 22, 2020, the cumulative number of affected patients worldwide was more than 2.3 million. Not only has COVID-19 had a serious impact on health and the economy worldwide, but it has also brought about major changes in people's lives. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is extremely contagious. Over the last several months, governments across the world have issued self-isolation orders as a result of the COVID-19 outbreak. In China, the government issued a rule on January 23, 2020 to seal off the city of Wuhan, with a subsequent nationwide compulsory isolation order. These actions played an impressive role in blocking the spread of SARS-CoV-2.

Some studies have reported that patients with existing cardiovascular diseases may be at greater risk of developing severe COVID-19 (1, 2). An Italian study reported that cases of ischemic stroke decreased in the casualty department during the COVID-19 epidemic (3). However, the impact of isolation during the pandemic on chronic non-communicable diseases remains unknown, especially in low-income populations. Thus, we aimed to assess the effects of compulsory isolation during the COVID-19 pandemic on the burden of stroke in a low-income population in rural China.

METHODS

Participants and Study Design

The study population came from the Tianjin Brain Study (4, 5), which began in 1985 as an on-going population-based study conducted in Tianjin, China, a township of Jizhou District that contains 18 administrative villages. The total population of this township was 14,285 in 2010 and 14,534 as of April 20, 2020; 95% are low-income farmers whose annual per capita income was <100 USD in 1991 and <1,000 USD in 2010.

Since January 23, 2020, strict measures for controlling the COVID-19 epidemic have been enforced and strengthened after the lock-down strategy implemented in Wuhan, China (6). On January 24, 2020, a first-level public health emergency response was carried out in Tianjin and the counties under its jurisdiction (7). Tourist attractions, entertainment venues, libraries, and schools were ordered to shut down. It was recommended that healthy residents stay at home and avoid mass gatherings to reduce the spread of the virus. People returning home from other provinces and cities were required to be in a centralized quarantine facility and to undergo medical observation for more than 14 days. Symptomatic patients and those suspected to be infected were required to receive treatment in an isolation ward (8, 9).

Tianjin is one of four municipalities in China, which includes 15 administrative districts. Overall, 136 patients were diagnosed with SARS-CoV-2 infections from 13 administrative districts in Tianjin during the study period. However, Jizhou District is one of two districts with zero infection cases of SARS-CoV-2 in Tianjin.

The research protocol was approved by Tianjin Medical University General Hospital Ethics Committee, and all patients provided written informed consent.

Data Collection

Information on stroke patients was collected by the stroke surveillance network, which has been described previously (4). Briefly, in the Tianjin Brain Study, local licensed village physicians report stroke cases to physicians in community hospitals within 24 h of stroke onset. Physicians from the community hospital then visit the stroke patients' homes to confirm the stroke event and obtain information about the characteristics and clinical features. They then report confirmed and suspected stroke cases monthly to Tianjin Medical University General Hospital. Then, neurologists from Tianjin Medical University General Hospital use interviews to identify possible stroke events. The local licensed village physicians and the physicians from the community hospital are trained annually by a qualified neurologist.

Information was obtained by questionnaire about patients' age and education. Data regarding stroke subtypes, whether a diagnosis was made using computed tomography, and whether patients were hospitalized were collected within 24 h after patient admission was obtained by related medical records. In this study, patients were divided into three age groups: <45, 45–64, and ≥65 years. Education levels used years as the unit of measurement. Patients were divided into three education level groups: 0, 1–6, and ≥7 years.

Definition of Stroke Events

First-ever stroke was defined as the first occurrence (i.e., without a history of stroke) of a rapidly developed focal (or global) disorder of cerebral function of vascular origin that lasted more than 24 h (10).

Stroke was categorized into three subtypes: hemorrhagic stroke, ischemic stroke (IS), and uncategorized stroke. Hemorrhagic stroke was defined as an intracerebral hemorrhage (ICH) or subarachnoid hemorrhage. IS was defined as a thrombotic brain infarction due to temporary or permanent occlusion of a feeding artery or of venous thrombosis. Uncategorized stroke was defined when patients' strokes could not be categorized as hemorrhagic stroke or IS or when there was a lack of evidence of neuroimaging. Patients with transient ischemic attacks, subarachnoid hemorrhage, and silent stroke, a kind of stroke detected only by imaging, were excluded in this study. Stroke was diagnosed by a professional neurologist based on typical clinical symptoms combined with imaging findings. Patients without neuroimaging in this study were diagnosed as having full clinical strokes with significant clinical symptoms and signs. For this study, all-cause mortality of stroke patients was used for mortality data.

Statistical Analyses

Patients with a first-ever stroke who were registered between January 1 and April 20 for the years 2010 through 2020 were included in this study. Moreover, patients who died from stroke each year (i.e., 2010 through 2020) between January 1 and April 20 were also included in this study. Continuous variables, including age and education level, were analyzed with Student's *t*-tests and presented as means and standard deviations. Categorical variables are presented as frequencies and 95% confidence intervals (CIs); differences between groups were compared using chi-squared tests. All participants were categorized into three age groups (<45, 45–64, and ≥65 years) and three education groups based on the number of years of formal education (0, 1–6, and ≥7 years). The incidence of first-ever stroke events every year from 2010 to 2020 were calculated separately using the corresponding person-years. The age-standardized incidences were calculated with the direct method using the world standard population by 10 age groups: <35, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and ≥75 years (11).

TABLE 1 | Characteristics of the first-ever stroke from January 1st to April 20th during 2010 to 2020 in Tianjin Brain Study.

Category	Men	Women	Total
Total	223 (59.2)	154 (40.8)	377 (100)
Age, means (SD), years	65.21 (10.86)	66.42 (12.81)	65.70 (11.70)
Education, means (SD), years	4.92 (3.27)	3.44 (3.26)	4.32 (3.34)
Age group, *n* (%)			
<45 years	10 (4.5)	6 (3.9)	16 (4.2)
45–64 years	97 (43.5)	65 (42.2)	162 (43.0)
≥65 years	116 (52.0)	83 (53.9)	199 (52.8)
Education group, *n* (%)			
0 years	40 (17.9)	60 (39.0)	100 (26.5)
1∼6 years	123 (55.2)	71 (46.1)	194 (51.5)
>6 years	60 (26.9)	23 (14.9)	83 (22.0)
Stroke subtypes, *n* (%):			
IS	159 (71.3)	108 (70.8)	266 (71.1)
ICH	32 (14.3)	27 (17.5)	59 (15.6)
Uncategorized stroke	33 (14.3)	18 (11.7)	50 (13.3)
Hospitalized, *n* (%)			
Yes	90 (40.4)	72 (46.8)	162 (43.0)
No	133 (59.6)	82 (53.2)	215 (57.0)
Diagnosis by CT, *n* (%)			
Yes	190 (85.2)	136 (88.3)	326 (86.5)
No	33 (14.8)	18 (11.7)	51 (13.5)

IS, ischemic stroke; ICH, intracerebral hemorrhage.

Changes in rates were calculated as follows: (rate in 2020—rate in reference years)/rate of reference years, and results are expressed as percentages. Differences in the incidence and rates of mortality, hospitalization, and diagnosis by neuroimaging between 2010 and 2020 were analyzed using the chi-squared test. Statistical significance was defined as $P < 0.05$. SPSS version 19.0 for Windows (IBM Corp., Armonk, NY) was used for analyses.

RESULTS

Demographic and Clinical Characteristics of Patients With the First-Ever Stroke

Overall, there were 377 new cases between January 1 and April 20 for 2010 through 2020; men accounted for 59.2% ($n = 223$) of subjects. The average age was 65.7 years old overall (65.21 years for men and 66.42 years for women). The mean education level was 4.32 years (4.92 years for men and 3.44 years for women). There were 309 cases of IS (accounting for 82.0% of cases) and 62 cases of ICH (accounting for 16.4% of cases). Of these cases, 86.5% of patients were diagnosed by neuroimaging, but the rate of hospitalization was only 43% (**Table 1**).

Incidence of and Mortality From First-Ever Stroke for 2010 Through 2020

Table 2 shows that the incidence of first-ever stroke in 2020 was 61.92/100,000 person-years overall (77.73 for men and 44.02 for women). The highest incidence was among those people aged 65 years and older (344.12/100,000 person-years). The incidence of IS was 43.68/100,000 person-years and of ICH was 5.66/100,000 person-years. Simultaneously, mortality per 100,000 person-years in this period was 6.88 overall (12.96 for men, 68.82 for people aged 65 years and older). There was a noticeably lower incidence in 2020 than in any other time from 2010 through 2019 (**Figure 1**). Similar trends were observed for mortality.

Hospitalization and Diagnosis by Neuroimaging for 2010 to 2020

Table 3 shows that the hospitalization rate for first-ever stroke in 2020 was 77.78%; overall, 83.33% were men and 66.67% were women. The hospitalization rate was 100% in patients aged <45 years old. Moreover, the rate of diagnosis by neuroimaging in 2020 was 100% across sex, age, and stroke subtype groups.

Variation in Stroke Burden for 2020 vs. 2010–2019

Compared with the incidence of first-ever stroke in 2019, that in 2020 was 73.5% lower overall [$P < 0.001$; 69.93% for men [$P = 0.006$] and 78.57% for women [$P = 0.008$]]. There were similar trends in incidence for 2020 compared with that in the previous 5 years (2015–2019) and the previous 10 years (2010–2019), all $P < 0.05$. The overall incidence of first-ever stroke was significantly lower in 2020 than in the previous 5 years (64.18% lower; $P = 0.002$) and in the previous 10 years (65.42% lower; $P = 0.001$). These decreases were observed in both men (56.70 and 58.65% lower, respectively) and women (74.72 and 73.95% lower, respectively), but there was a greater difference observed for women. Moreover, the decreasing tendency was observed among those patients aged 45 years and over and with ischemic stroke across times. Of these, the greatest decrease was observed in patients aged 45–64 years, with a decrease of 81.24% from that in 2019 ($P = 0.003$). However, during the study period, the incidence of first-ever stroke remained stable for those patients aged <45 years and for those with ICH. There were no significant changes in mortality from first-ever stroke between 2019 and 2020, but mortality was noticeably lower than that for the previous 5 and 10 years across the sexes, age groups, and stroke types, except for patients aged <45 years and those with ICH.

The rates of hospitalization and diagnosis by neuroimaging remained stable across the study period (**Table 4**).

DISCUSSION

In this study, we assessed the effects of compulsory isolation during the COVID-19 pandemic on the burden of stroke in rural China in a low-income population. We compared the current incidence and rates of mortality, hospitalization, and diagnosis by neuroimaging for first-ever stroke during the COVID-19 pandemic in 2020 to those for previous years among a low-income population in rural China. We found that the incidence in 2020 was much lower than that in other time periods from 2010 through 2019 both in men and in women, in those aged 45 years and older, and for IS regardless of whether the reference was

TABLE 2 | The incidence and mortality of first-ever stroke from 1st January to 20th April during 2010 to 2020 (per 100 000 person-year).

Category	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
INCIDENCE											
Total	196.01	161.19	112.65	246.51	210.51	112.26	229.84	151.01	137.15	233.64	61.92
Gender:											
Man	239.81	146.33	93.76	304.07	197.89	118.66	249.08	155.22	116.08	258.50	77.73
Woman	147.51	177.73	133.59	180.89	224.85	104.98	208.02	146.24	161.05	205.43	44.02
Age group:											
<45 years	12.38	12.41	0.00	38.28	12.70	12.55	0.00	12.23	12.22	0.00	12.06
45–64 years	259.35	280.66	214.50	379.51	336.28	168.95	273.22	187.11	186.95	333.89	62.63
≥65 years	948.77	569.62	379.51	865.80	801.48	451.32	1271.46	757.10	630.91	1207.24	344.12
Stroke subtypes:											
IS	75.67	87.90	27.30	131.54	94.36	57.93	117.65	94.58	74.88	149.92	43.68
ICH	36.35	8.50	35.74	26.74	31.72	17.36	9.37	13.38	17.46	4.11	5.66
MORTALITY											
Total	105.01	112.13	197.14	154.95	161.39	98.22	69.65	123.55	82.29	20.62	6.88
Gender:											
Man	133.23	159.64	214.30	185.09	184.70	92.29	117.99	168.15	64.49	25.85	12.96
Woman	73.76	59.24	178.12	120.59	134.91	104.98	14.86	73.12	102.49	14.67	0.00
Age group:											
<45 years	0.00	12.41	12.56	25.52	25.41	37.66	0.00	12.23	12.22	0.00	0.00
45–64 years	129.67	64.77	193.05	168.67	126.10	42.24	63.05	187.11	83.09	41.74	0.00
≥65 years	569.26	759.49	1138.52	742.12	924.78	580.27	445.01	504.73	441.64	67.07	68.82
Stroke subtypes:											
IS	33.58	49.66	75.13	61.43	43.79	60.55	9.37	51.61	41.85	13.73	0.00
ICH	8.51	10.42	40.58	25.80	35.81	17.36	9.37	21.10	14.47	0.00	5.66

IS, ischemic stroke; ICH, intracerebral hemorrhage.

2019, 2015–2019, and 2010–2019. Similar results were observed in mortality for 2015–2019 and 2010–2019. However, the rates of hospitalization and diagnosis by neuroimaging remained stable across the study period.

As the main cause of death worldwide, epidemiological trends of stroke have been receiving much attention. With the development of treatment and nursing technology, the fatality rate of stroke will gradually decrease and the patient's prognosis will be improved. In addition, the popularization of medical insurance will increase the detection rate of mild strokes. From 2010 to 2020, China's economy and medical level indeed have achieved rapid development. However, our previous research in this population found that first-ever stroke incidence increased by an average of 10.7% per 1,000 USD increase in overall per capita gross domestic product adjusted for purchasing power parity and by 12.0% per 1,000 Yuan increase in per capita net income (12). Moreover, the incidence of first-ever stroke in this study population showed an increasing trend from 1992 to 2018 (13–15). However, the burden of stroke from January to April 2020 was contrary to previous research trends, and the present study showed that the incidence and mortality of stroke decreased dramatically during the COVID-19 pandemic.

It is well-known that drinking alcohol and consuming a high-fat diet are risk factors for stroke (16–18). However, a previous study showed that drinking alcohol had positive effects on stroke onset (16). Another study reported that the cardiovascular benefits of low-moderate alcohol consumption perhaps might have been overestimated and that alcohol consumption may have no positive health effects (19). In addition, an animal experiment confirmed that prolonged consumption of a high-fat diet aggravates the condition of stroke (20). An Iranian case-control study demonstrated that the risk of stroke increased as high-fat diet consumption increased (21).

The Spring Festival is the biggest festival in China and occurs on the first day in the lunar calendar. The longest vacations in China are during Spring Festival, which often continues for 7 days. During that time, whole families not only hold a dinner party every day, but they also visit relatives, neighbors, and friends to pay a New Year call. This visitation and reunion results in drinking alcohol, consuming a high-fat diet, and extra excitement and tension. Consequently, Spring Festival is the peak time of stroke onset every year. Thus, home quarantine to a large extent caused people to avoid other people, drinking alcohol, and consuming a high-fat diet, which has been shown to be a risk factor for stroke (16–18).

Moreover, outdoor temperature seems to be related to cerebrovascular events risk. A previous study reported that the mortality of stroke was related with temperature, and cold temperatures were the main cause of increased stroke burden (22). Another national study in China also reported that both

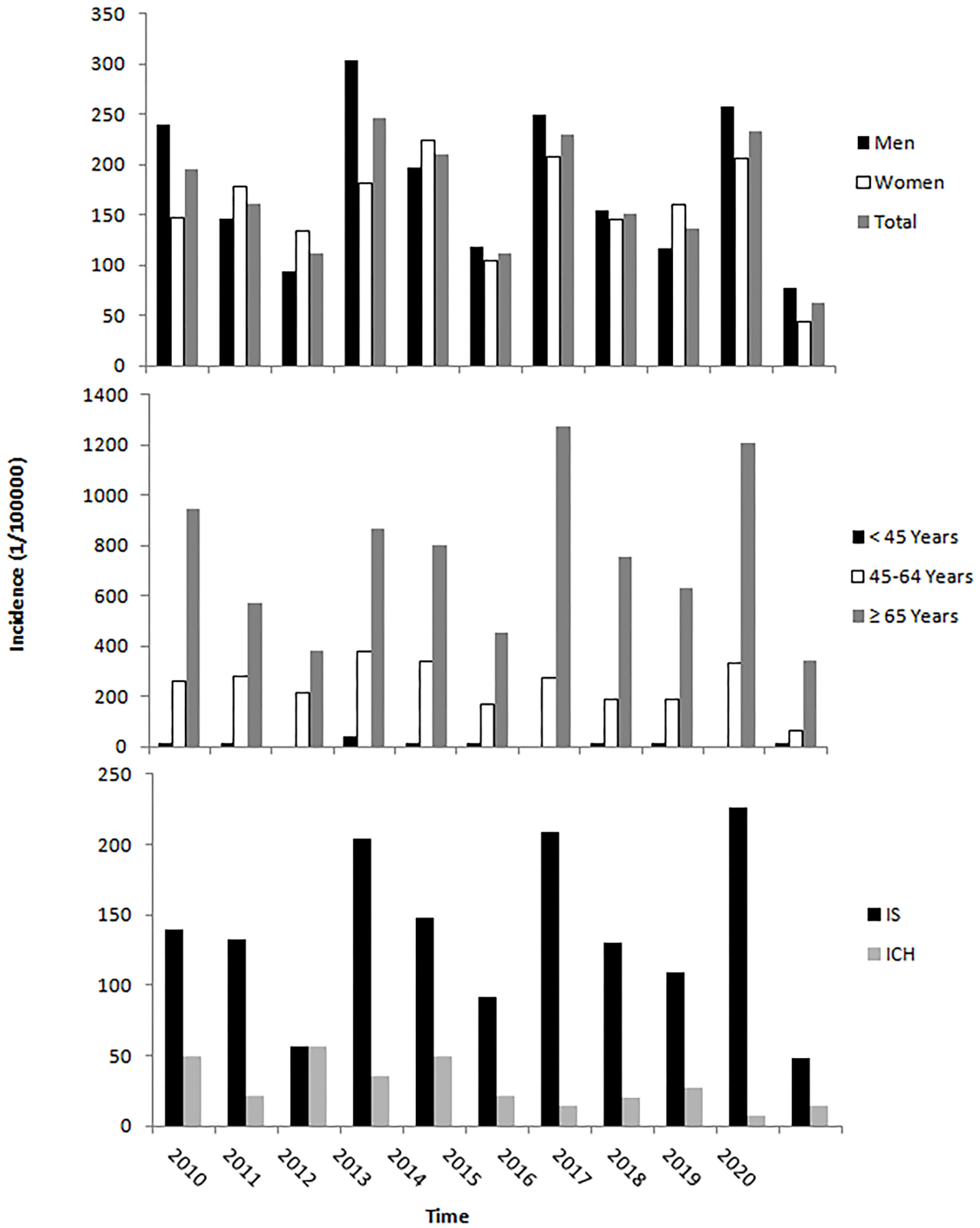


FIGURE 1 | The incidence of the first-ever stroke from January 1 to April 20 during 2010 to 2020. The incidence of the first-ever stroke from 1st January to 20th April in 2020 was lower than that in the same time in previous years across sex, age, and stroke types.

low and high temperature may increase the risk of stroke mortality, while the potential effect of cold temperature might last more than 2 weeks (23). Moreover, even a moderate decrease in temperature can increase the risk of ischemic stroke (24). The outdoor temperature in Tianjin from January to April is −3 to 4°C (25), which is the winter in Tianjin. Therefore, limiting outdoor activity and augmenting time spent indoors may contribute to the decreased incidence of first-ever stroke

TABLE 3 | Trends in the hospitalized rate and diagnosed by neuroimaging of first-ever stroke from 1st January to 20th April during 2010 to 2020 (%).

Category	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
HOSPITALIZED RATE											
Total	46.43	43.48	25.00	45.71	50.00	68.75	78.79	45.45	25.00	52.94	77.78
Gender:											
Man	38.89	36.36	28.57	39.13	53.33	77.78	73.68	41.67	33.33	55.00	83.33
Woman	60.00	50.00	22.22	58.33	46.67	57.14	85.71	50.00	18.18	50.00	66.67
Age group:											
<45 years	100.00	–	–	33.33	100.00	100.00	–	100.00	100.00	–	100.00
45–64 years	66.67	53.85	40.00	50.00	43.75	75.00	92.31	55.56	22.22	50.00	66.67
≥65 years	26.67	33.33	0.00	42.86	53.85	57.14	70.00	33.33	20.00	55.56	80.00
Stroke subtypes:											
IS	50.00	44.44	33.33	44.44	47.62	66.67	88	36.84	33.33	58.06	75.00
ICH	71.43	100.00	25.00	80.00	83.33	100.00	100.00	100.00	–	–	100.00
RATE OF DIAGNOSED BY NEUROIMAGING											
Total	82.14	86.96	87.50	91.43	90.00	93.75	81.82	100.00	95.00	94.12	100.00
Gender:											
Man	83.33	81.82	85.71	91.30	93.33	100.00	68.42	100.00	88.89	100.00	100.00
Woman	80.00	91.67	88.89	91.67	86.67	85.71	100.00	100.00	100.00	85.71	100.00
Age group:											
<45 years	100.00	100.00	–	100.00	100.00	100.00	–	100.00	100.00	–	100.00
45–64 years	100.00	92.31	100.00	100.00	100.00	87.50	100.00	100.00	100.00	100.00	100.00
≥65 years	66.67	77.78	66.67	78.57	76.92	100.00	70.00	100.00	90.00	88.89	100.00

IS, ischemic stroke; ICH, intracerebral hemorrhage.

TABLE 4 | Changes of the stroke burden from January 1st to April 20th in 2020 comparing to the same periods during 2010 to 2019 (%).

Time (Year)	Gender			Age group			Stroke subtypes	
	Total	Man	Woman	<45 years	45–64 years	≥65 years	IS	ICH
INCIDENCE								
2019	−73.50*	−69.93*	−78.57*	–	−81.24*	−71.50*	−74.16*	0.12
2015–2019	−64.18*	−56.70*	−74.72*	63.30	−72.77*	−60.02*	−58.42*	−75.92
2010–2019	−65.42*	−58.65*	−73.95*	7.77	−76.09*	−56.25	−60.98*	−61.73
MORTALITY								
2019	−66.63	−49.86	−100.00	–	−100.00	2.61	−100.00	–
2015–2019	−91.27*	−86.16*	−100.00*	−100.00	−100.00*	−83.26*	−100.00*	−71.79
2010–2019	−93.87*	−90.34*	−100.00*	−100.00	−100.00*	−88.93*	−100.00*	−58.54
HOSPITALIZED RATE								
2019	46.92	51.51	33.34	–	33.34	43.99	29.18	–
2015–2019	137.89	142.74	123.45	99.00	110.12	156.65	27.51	62.49
2010–2019	56.17	70.23	31.04	50.00	21.57	83.70	42.50	57.70
DIAGNOSED BY CT RATE								
2019	5.88	–	14.29	–	–	11.11	–	–
2015–2019	8.00	10.14	5.36	–	1.82	13.43	–	–
2010–2019	10.12	11.19	8.77	–	1.61	19.35	–	–

*IS, ischemic stroke; ICH, intracerebral hemorrhage. *P < 0.05.*

by inhibiting elevations in blood pressure. In addition, factories cut production or even shut down entirely during the COVID-19 pandemic, which indirectly reduced pollutant emissions. In the first half of 2020, the PM 2.5 concentration in Tianjin was 53 $\mu g/m^3$, a year-on-year decrease of 7.0% (26). The risk of stroke has been shown to increase among people with long-term exposure to particulate matter PM 2.5 (27). Short-term exposure to particulates in air pollution has been shown to be associated with increased mortality from ischemic heart disease (2). Therefore, shutting down factories and production so that

pollutant emissions are reduced may indirectly decrease stroke incidence and mortality.

Finally, a previous study has reported that viral infections can increase the risk of stroke and that the risk of stroke decreases by 24% after influenza vaccination (28, 29). A Spanish study demonstrated that hospitalization and mortality rates for stroke increased as influenza rates increased (30). Moreover, some studies have shown that the risks of morbidity and mortality were higher among older adults infected with viruses (31, 32), especially in January and February in North China. However, the spread of common influenza was effectively reduced due to compulsory isolation during the COVID-19 pandemic. In the present study, the incidence of first-ever stroke in 2020 was 81.24% lower in those aged 45–64 years and 71.5% lower in those aged 65 years and older compared with those for the preceding years.

During the period of the COVID-19 pandemic, the primary health care system in China played an important role in blocking transmission. Local rural physicians measured body temperature, handed out disinfection materials, and propagated the knowledge of prevention daily door-to-door. This practice was implemented to find new stroke patients early during this special period and thereby avoid delays in medical services due to isolation and allow patients to obtain timely medical treatment. In this study, it was observed that, compared with the same 4-months period in the past 10 years, the rates of hospitalization and diagnosis by neuroimaging in 2020 did not decrease during the COVID-19 pandemic. This result shows that home quarantine did not affect medical care-seeking behavior for stroke patients.

There are several limitations of this study. First, the study population was from 18 villages in Tianjin, which is not representative of the whole population in China. However, the large population study design and long study period may have reduced the impact of limited representation on the study results. Second, the observation period in 2020 only included the first 4 months. Thus, this result is not representative of the whole year. We would like to continue to follow to the end of the year and assess the whole impact of the pandemic on the burden of stroke in 2020. Finally, the data were analyzed using only descriptive statistics; we did not adjust for any potential confounders that could have affected the estimates of these changes. This statistical method could have partially affected results in this study.

CONCLUSIONS

This paper is the first report to demonstrate trends in the incidence and mortality of stroke associated with home quarantine during the COVID-19 pandemic in a low-income population in China. The incidence of first-ever stroke in 2020 was much lower than that from 2010 to 2019. A similar trend was observed for mortality when compared with that in 2015–2019 and 2010–2019. Moreover, the rates of hospitalization and diagnosis by neuroimaging in 2020 remained stable across the study period. Thus, home quarantine may play a beneficial role in preventing stroke in rural China. In addition, even though COVID-19 was a huge challenge for the health system, medical services have not been affected in China. These findings suggest that the home quarantine helped reduce outdoor activities at low temperatures, the restrict gatherings, reduction alcoholism and high-fat diet, and decrease pollution caused by factories, etc. These changes may have been advantageous for helping high-risk groups to reduce the burden of stroke. It is crucial to explore simple and valid approaches to reduce the burden of chronic non-communicable diseases.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Tianjin Medical University General Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XN, JLi, and JW were involved in conception and design and data interpretation for this article. JLiu, QY, XZ, QL, YY, DG, WM, JT, and ZL were involved in data collection, case diagnosis, and confirmation for this article. JLiu, QY, and XZ were involved in manuscript drafting. JW was involved in data analysis for this article. JW and XN were involved in the critical review in for this article. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We thank all participants of the Tianjin Brain Study and local medical care professionals for their valuable contributions. We pay the highest respect to all medical personnel fighting on the front line of fighting the COVID-19 epidemic.

REFERENCES

1. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected code stroke: hyperacute stroke Management during the coronavirus disease 2019 (COVID-19) pandemic. *Stroke*. (2020) 51:1891–5. doi: 10.1161/STROKEAHA.120.029838
2. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): a pooled analysis of published literature. *Int J Stroke*. (2020) 15:385–9. doi: 10.1177/1747493020921664
3. Morelli N, Rota E, Terracciano C, Immovilli P, Spallazzi M, Colombi D, et al. The baffling case of ischemic stroke disappearance from the

casualty department in the COVID-19 Era. *Eur Neurol*. (2020) 83:213–5. doi: 10.1159/000507666
4. Wang J, An Z, Li B, Yang L, Tu J, Gu H, et al. Increasing stroke incidence and prevalence of risk factors in a low-income Chinese population. *Neurology*. (2015) 84:374–81. doi: 10.1212/WNL.0000000000001175
5. Wang J, Ning X, Yang L, Tu J, Gu H, Zhan C, et al. Sex differences in trends of incidence and mortality of first-ever stroke in rural Tianjin, China, from 1992 to 2012. *Stroke*. (2014) 45:1626–31. doi: 10.1161/STROKEAHA.113.003899
6. *Wuhan COVID-19 Prevention and Control Headquarters Issued Circular No. 3*. Available online at: http://www.xinhuanet.com/politics/ (accessed April 23, 2020).
7. *Tianjin Initiates First-Level Public Health Emergency Response To COVID-19*. Available online at: http://www.chinanews.com/gn/ (accessed April 23, 2020).
8. *Firm Confidence to Win the War of Prevention and Control of Epidemic Situation—The Decision-Making and Deployment of the Politburo Standing Committee Meeting of the Cpc Central Committee Triggered a Strong Response from the Cadres and the Masses*. Available online at: http://www.locpg.gov.cn/jsdt/ (accessed April 23, 2020)
9. Tianjin Municipal Health Commission. *Notice on Issuing the Implementation Plan (Trial) of Community Prevention and Control of COVID-19 in Tianjin*. Available online at: http://wsjk.tj.gov.cn/art/2020/1/30/art_92_71078.html (accessed April 20, 2020).
10. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. (1980) 58: 113–30.
11. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. *Age Standardization of Rates: A New Who World Standard*. (GPE Discussion Paper Series, No 31). EIP/GPE/EBD, WHO, Geneva (2001).
12. Zhao P, Liu J, Hao Y, Lin Q, Gao Y, Tu J, et al. Macroeconomic Development and dramatic increase in stroke burden in rural China: a 25-year population-based study. *Front Neurol*. (2020) 11: 385. doi: 10.3389/fneur.2020.00385
13. Ning X, Sun J, Jiang R, Lu H, Bai L, Shi M, et al. Increased Stroke burdens among the low-income young and middle aged in rural China. *Stroke*. (2017) 48: 77–83. doi: 10.1161/STROKEAHA.116.014897
14. Lu H, Guo Z, Liu J, Zhang H, Zhao W, Wu Y, et al. Trends in stroke incidence among elderly low-income residents of rural China: a population-based study from 1992 to 2016. *Aging (Albany NY)*. (2018) 10:3438–49. doi: 10.18632/aging.101657
15. Wang J, Bai L, Shi M, Yang L, An Z, Li B, et al. Trends in Age of first-ever stroke following increased incidence and life expectancy in a low-income Chinese population. *Stroke*. (2016) 47:929–35. doi: 10.1161/STROKEAHA.115.012466
16. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet*. (2018) 391: 1513–23. doi: 10.1016/S0140-6736(18)30134-X
17. Liu G, Li Y, Hu Y, Zong G, Li S, Rimm EB, et al. Influence of Lifestyle on incident cardiovascular disease and mortality in patients with diabetes mellitus. *J Am Coll Cardiol*. (2018) 71:2867–76. doi: 10.1016/j.jacc.2018.04.027
18. Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, et al. 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. *Lancet Diabetes Endocrinol*. (2019) 7:673–83. doi: 10.1016/S2213-8587(19)30151-2
19. Chiva-Blanch G, Badimon L. Benefits and risks of moderate alcohol consumption on cardiovascular disease: current findings and controversies. *Nutrients*. (2019) 12:108. doi: 10.3390/nu12010108
20. Fifield KE, Rowe TM, Raman-Nair JB, Hirasawa M, Vanderluit JL. Prolonged high fat diet worsens the cellular response to a small, covert-like ischemic stroke. *Neuroscience*. (2019) 406:637–52. doi: 10.1016/j.neuroscience.2019.01.050
21. Boroujeni HK, Saadatnia M, Shakeri F, Keshteli AH, Saneei P, Esmaillzadeh A. Dairy consumption and risk of stroke: a case-control study. *Int J Prev Med*. (2016) 7:2. doi: 10.4103/2008-7802.173792
22. Yang J, Yin P, Zhou M, Ou C, Li M, Li J, et al. The burden of stroke mortality attributable to cold and hot ambient temperatures: epidemiological evidence from China. *Environ Int*. (2016) 92–93:232–8. doi: 10.1016/j.envint.2016.04.001
23. Chen R, Wang C, Meng X, Chen H, Thach TQ, Wong CM, et al. Both low and high temperature may increase the risk of stroke mortality. *Neurology*. (2013) 81:1064–70. doi: 10.1212/WNL.0b013e3182a4a43c
24. Hong YC, Rha JH, Lee JT, Ha EH, Kwon HJ, Kim H. Ischemic stroke associated with decrease in temperature. *Epidemiology*. (2003) 14:473–8. doi: 10.1097/01.ede.0000078420.82023.e3
25. Whether China. *Tianjin Weather for 12 Months*. Available online at: http://www.weather.com.cn/forecast/history.shtml?areaid=101030100&month=12
26. Tianjin Ecological Security Bureau. Available online at: http://sthj.tj.gov.cn/ (accessed November 21, 2020).
27. Qiu H, Sun S, Tsang H, Wong CM, Lee RS, Schooling CM, et al. Fine particulate matter exposure and incidence of stroke: a cohort study in Hong Kong. *Neurology*. (2017) 88:1709–17. doi: 10.1212/WNL.0000000000003903
28. Warren-Gash C, Blackburn R, Whitaker H, McMenamin J, Hayward AC. Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland. *Eur Respir J*. (2018) 51:1701794. doi: 10.1183/13993003.01794-2017
29. Siriwardena AN, Asghar Z, Coupland CC. Influenza and pneumococcal vaccination and risk of stroke or transient ischaemic attack-matched case control study. *Vaccine*. (2014) 32:1354–61. doi: 10.1016/j.vaccine.2014.01.029
30. López-Fernández L, López-Messa J, Andrés-de Llano J, Garmendia-Leiza JR, García-Cruces J, García-Crespo J. Relationship between seasonal influenza rates and hospitalization and mortality rates due to acute cardiovascular diseases in a Spanish region. *Med Clin (Barc)*. (2019) 153:133–40. doi: 10.1016/j.medcle.2019.06.008
31. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis*. (2012) 206:56–62. doi: 10.1093/infdis/jis309
32. van Asten L, van den Wijngaard C, van Pelt W, van de Kassteele J, Meijer A, van der Hoek W, et al. Mortality attributable to 9 common infections: significant effect of Influenza A, respiratory syncytial virus, influenza B, norovirus, and parainfluenza in elderly persons. *J Infect Dis*. (2012) 206:628–39. doi: 10.1093/infdis/jis415

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 29 January 2021
doi: 10.3389/fneur.2021.625144

Case Report: Myopathy in Critically Ill COVID-19 Patients: A Consequence of Hyperinflammation?

Viviana Versace[1], Luca Sebastianelli[1], Davide Ferrazzoli[1], Leopold Saltuari[1], Markus Kofler[2], Wolfgang Löscher[3] and Antonino Uncini[4]*

[1] Department of Neurorehabilitation, Hospital of Vipiteno (SABES-ASDAA), Vipiteno, Italy, [2] Department of Neurology, Hochzirl Hospital, Zirl, Austria, [3] Department of Neurology, Medical University Innsbruck, Innsbruck, Austria, [4] Department of Neuroscience, Imaging and Clinical Sciences, University "G. d'Annunzio", Chieti, Italy

Introduction: COVID-19-associated muscular complications may comprise myalgia, weakness, wasting, and rhabdomyolysis. Skeletal muscle damage in COVID-19 may be due to direct infection by the virus SARS-CoV-2 through interaction with the ACE2 receptor, systemic hyper-inflammatory state with cytokine release and homeostatic perturbation, an autoimmune process, or myotoxic drugs. Disclosing the cause of weakness in an individual patient is therefore difficult.

Case Description: We report two patients, who survived typical COVID-19 pneumonia requiring intensive care treatment and who developed early on myalgia and severe proximal weakness in all four limbs. Laboratory exams revealed elevated serum creatine kinase and markedly increased C-reactive protein and interleukin 6, concurring with a systemic inflammatory response. On admission in neurorehabilitation (4 and 7 weeks after COVID-19 onset, respectively), the patients presented with proximal flaccid tetraparesis and limb-girdle muscle atrophy. Motor nerve conduction studies showed decreased amplitude and prolonged duration of compound muscle action potentials (CMAPs) with normal distal motor latencies and normal conduction velocities in median and ulnar nerves. Needle electromyography in proximal muscles revealed spontaneous activity in one and myopathic changes in both patients.

Discussion: Clinical, laboratory, and electrodiagnostic findings in these patients were unequivocally consistent with myopathy. Interestingly, increased distal CMAP duration has been described in patients with critical illness myopathy (CIM) and reflects slow muscle fiber conduction velocity due to membrane hypo-excitability, possibly induced by inflammatory cytokines. By analogy with CIM, the pathogenesis of COVID-19-related myopathy might also depend on hyperinflammation and metabolic pathways that may affect muscles in a pathophysiological continuum from hypo-excitability to necrosis.

Keywords: COVID-19, SARS-CoV-2, critical illness myopathy, compound muscle action potential duration, interleukin 6

OPEN ACCESS

Edited by:
Jesús Porta-Etessam, Hospital Clínico San Carlos, Spain

Reviewed by:
Raghav Govindarajan, University of Missouri, United States
Marcus V. Pinto, Mayo Clinic, United States

****Correspondence:***
Viviana Versace
viviana.versace@sabes.it
orcid.org/0000-0003-4641-3532

Specialty section:
This article was submitted to Neuromuscular Diseases, a section of the journal Frontiers in Neurology

Received: *02 November 2020*
Accepted: *13 January 2021*
Published: *29 January 2021*

Citation:
Versace V, Sebastianelli L, Ferrazzoli D, Saltuari L, Kofler M, Löscher W and Uncini A (2021) Case Report: Myopathy in Critically Ill COVID-19 Patients: A Consequence of Hyperinflammation? Front. Neurol. 12:625144. doi: 10.3389/fneur.2021.625144

INTRODUCTION

Muscular complications in hospitalized coronavirus disease (COVID-19) patients may include myalgia, muscle weakness and wasting, elevated serum creatine kinase (CK), and rhabdomyolysis (1). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in skeletal muscle (2). However, SARS-CoV-2 particles, despite its broad organotropism beyond the respiratory tract, have not been demonstrated in muscle samples so far (3).

Besides the possibility of direct skeletal muscle injury by SARS-CoV-2, other conceivable causes of myopathies in COVID-19 may comprise an autoimmune process, such as in necrotizing autoimmune myositis, consequence of the systemic hyperinflammatory state, and myotoxicity by medication (e.g., hydroxychloroquine, anti-retroviral agents) (2, 4, 5). Moreover, severely affected COVID-19 patients with systemic inflammatory response, prolonged intensive care treatment with ventilation, and immobilization are prone to develop critical illness myopathy (CIM). Hence, explaining the exact cause of weakness in an individual patient may be difficult.

To date, CIM has been reported and at least electrodiagnostically confirmed in 20 patients with COVID-19 (6–9) (**Table 1**). Intensive care unit acquired muscle weakness was clinically diagnosed in 72% of COVID-19 patients at awakening (11). Compared to patients without muscle weakness, myopathic patients had longer ICU stays, prolonged duration of invasive mechanical ventilation, higher mean morning glycemia, higher exposure to corticosteroids, sedatives, analgesics, and neuromuscular blocking agents (11). Half of critically ill COVID-19 patients presented acute myopathy in a recent retrospective study (10).

CASE DESCRIPTION

Here, we report two patients who survived typical COVID-19 pneumonia, confirmed by RT-PCR test on nasopharyngeal swab and by chest computed tomography, which showed bilateral diffuse consolidations and ground-glass opacities. No personal or family medical history of rhabdomyolisis or myoglobinuria or any type of muscle pathology was known. Neither patient had ever received statin therapy or other potentially myotoxic agents. In general, the patients did not suffer from any previous relevant pathology.

Table 2 summarizes demographic, clinical, laboratory, and electrophysiological data.

Because of respiratory failure, both patients required intensive care treatment, including tracheostomy and ventilatory support for several weeks. Oral treatment with hydroxychloroquine 200 mg twice a day and lopinavir/ritonavir 400/100 mg twice a day was administered for 3 weeks. No antibiotics, corticosteroids or analgesics were administered. High serum levels of C-reactive protein (CRP) and interleukin 6 (IL-6) were documented during the acute phase (**Table 2**).

After weaning from sedation (intravenous sufentanil/propofol together with rocuronium bromide as muscle relaxant) and ventilation, the patients suffered mild dyspnea requiring oxygen support (2 l/min), complained of myalgia and fatigue, and showed on examination severe proximal muscles weakness in in both upper and lower limbs (Medical Research Council scale 2/5). Strength in distal muscle was normal. Deep tendon reflexes were hypoactive. No deep or superficial sensory disturbance was noted. Cranial nerve examination was unremarkable; in particular, no bulbar muscles weakness was found.

Laboratory examination revealed elevated creatine kinase (CK) (peak-levels 4,002 and 6,732 U/l, respectively) which progressively normalized in the following 3 weeks, but no myoglobinuria nor acute renal failure signs. Due to the Covid-19-related emergency situation in Italian Intensive Care Units, no further neuroradiological or histopathological muscle studies could be performed.

On admission in the neurorehabilitation unit (4 and 7 weeks after onset of COVID-19, respectively), both patients presented with flaccid proximal tetraparesis and limb-girdle muscle atrophy. A timeline of the clinical course is presented in **Figure 1**.

Motor nerve conduction studies showed normal distal latencies and normal conduction velocities. Distal compound muscle action potential (CMAP) amplitudes were decreased and CMAP durations were prolonged in median and ulnar nerves in both patients (**Table 2**, **Figure 2**). Sensory conduction velocities and sensory nerve action potential amplitudes were normal. Needle EMG showed spontaneous activity (fibrillation potentials) in patient 2 and a myopathic pattern with short duration motor unit action potentials, increased percentage of polyphasic potentials, and early recruitment at voluntary effort in proximal muscles in both patients. Distal muscles were unremarkable. Within 2 weeks from admission in neurorehabilitation, serum CK returned to normal values (23 and 201 U/l, respectively).

Clinical condition improved progressively in both patients, who were discharged home after 6–8 weeks of rehabilitation, with a muscle strength of 3/5 in proximal upper limb and 4/5 in proximal lower limb muscles, and normal walking capability. However, both complained of reduced endurance and increased fatigue during physical activity.

DISCUSSION

In the presented patients, clinical, laboratory and electrodiagnostic findings were consistent with a myopathy except for increased distal CMAP duration that is usually considered a hallmark of acquired demyelination. However, prolonged duration of distal CMAPs that did not change between distal and proximal stimulation (**Figure 2**), together with normal distal motor latencies and conduction velocities, indicates that in these patients, temporal dispersion of distal CMAP is due to slow muscle fibers conduction velocity. Indeed, prolonged distal CMAP duration, besides reduced CMAP amplitude, has previously been reported in patients with CIM, who presented, as compared to healthy controls, with reduced mean muscle fiber conduction velocity, which was inversely related to CMAP

TABLE 1 | Studies on COVID-19-patients with intensive care unit acquired myopathy.

	N of patients	Age mean (range) [years]	Sex	ICU stay mean (range) [days]	Medication	Clinical feature	NCS/EMG	Muscle biopsy	CK peak-level	IL-6 peak-level
(9)	7	NA	NA	NA	Antiretrovirals, neuromuscular blockers, corticosteroids, antibiotics	Generalized muscular weakness	Myopathy	Three patients (scattered necrotic and regenerative fibers, no inflammatory infiltrates)	181–3,228 μmol/l	N/A
(10)	5	N/A	N/A	N/A	Antirheumatics, antiretrovirals, corticosteroids, antibiotics	Generalized muscular weakness	Myopathy	ND	61–1,206 μg/l	NA
(8)	6	61 (51-72)	1 F	6-14 until NCS/EMG	Antirheumatics, antiretrovirals, corticosteroids, antibiotics, anticoagulants	Acute flaccid quadriplegia	Myopathy; reduced CMAP amplitude with markedly prolonged duration	ND	55–1,274 UI/L	18.4–5,402.2 ng/ml
(6)	1	68	M	65	Antibiotics	Severe symmetrical proximal and distal weakness and diffuse muscle wasting	Myopathy and bilateral peroneal compression neuropathy.	ND	NA	NA
(7)	1	62	F	30	Antirheumatics, antiretrovirals, antibiotics, neuromuscular blockers, antifungal drugs, corticosteroids.	Symmetrical muscle weakness predominant in lower limbs and proximal muscles.	Myopathy	ND	Normal	NA

ICU, intensive care unit; NCS/EMG, nerve conduction studies/electromyography; CK, creatine kinase; IL-6, interleukine 6; F, female; M, male; CMAP, compound muscle action potential; ND not done; NA not available.

duration (13, 14). Moreover, in an *in vitro* model, sera from patients with CIM applied to single muscle fibers induced depolarization of the resting membrane potential, reduced the action potential rise time, and increased inward sodium current peak amplitude (15). Evidence from human studies and animal models indicates that in CIM associated with sepsis (the so-called "SIM," sepsis-induced myopathy), systemic inflammatory response, and cytokine release induce a depolarizing shift of the muscle cell membrane potential, sodium channel inactivation, slowing of muscle fiber conduction velocity until total membrane inexcitability, increase of membrane permeability for Ca^{2+}, and eventually Ca^{2+}-dependent muscle necrosis by proteasome activation (16).

We hypothesize that in the reported patients, by analogy with SIM, myopathy was caused by the COVID-associated hyper-inflammatory state, as demonstrated by high initial serum levels of CRP and IL-6. Prolonged distal CMAP durations can be explained by muscle membrane hypo-excitability combined with slow muscle fiber conduction velocity in regenerating muscle fibers.

Interestingly also six reported COVID-10 patients with acute quadriplegic myopathy (8), showed markedly prolonged CMAP durations without evidence of acute myonecrosis (CK were slightly elevated in half patients and decreased in few days) and, with exception of one patient who died due to sepsis, showed rapid improvement of weakness (14–20 days). This can concur with the proposed mechanism of muscular impairment in COVID-19, ranging from membrane excitability dysfunction (which reflects in reduced amplitude and increased duration of CMAPs) with possible prompt recovery to myonecrosis, CK elevation, consequent muscle atrophy, and poorer outcome.

Serum IL-6 elevation is common in critically ill patients (16), but it also plays a central role in the COVID-19 inflammation cascade already at an early stage, preceding need for intensive care, and it correlates with disease severity (17).

TABLE 2 | Demographic, clinical, laboratory, and electrodiagnostic data.

Patient	Age	Sex	ICU stay	Clinical features	Laboratory findings (peak levels)						NCS/EMG: time since disease onset	Sensory NCS		Motor NCS				EMG
					CK	CRP	IL-6	D-dimer	WBC	Lymphocyte		SNAP amplitude	sNCV	CMAP amplitude	CMAP duration	DML	mNCV	Proximal muscles*
			[weeks]		[U/l]	[mg/l]	[pg/ml]	[mg/l]	[× 10^3/μl]	[× 10^3/μl]	[weeks]	[μV]	[m/s]	[mV]	[ms]	[ms]	[m/s]	
					40–220	*<0.8*	*<7.0*	*<0.5*	*3.6–10.5*	*1.1–4.5*								
1	77	M	6	Proximal weakness and muscle wasting in upper more than lower limbs; myalgia; fatigue	4,002	15.9	225.2	1.5	10.1	2.8	7	L median: 15.2	50	L median: 4.2	**9.3**	3.9	48	Myopathic
												R ulnar: 12.4	48	R ulnar: 5.7	**13.7**	2.9	55	
												R sural: 6.3	47	L peroneal: 2.1	7.3	3.1	40	
														R tibial: 2.4	4.2	4.0	41	
2	58	M	3	Predominantly proximal weakness in four limbs; hyporeflexia; myalgia	6,732	17.1	343.6	2.1	9.9	4.6	4	L median: 22.5	49	L median: 3.9	**9.0**	3.8	48	Myopathic
												R ulnar: 25.8	51	R ulnar: 4.8	**8.7**	2.5	50	
												R sural: 9.5	48	L peroneal: 1.2	6.5	4.0	39	
														R tibial: 2.2	6.7	4.1	40	

Laboratory data were obtained during intensive care. Clinical and electrodiagnostic data were obtained during neurorehabilitation.

M, male; F, female; ICU, intensive care unit; CK, creatine kinase; CRP, C-reactive protein; WBC, white blood cell count; IL, interleukin; NCS, nerve conduction study; EMG, electromyography; SNAP, sensory nerve action potential; sNCV, sensory nerve conduction velocity; CMAP, compound muscle action potential; DML, distal motor latency; mNCV, motor nerve conduction velocity; R, right; L, left.

The upper limits of normality (mean + 2 SD) for distal CMAP duration using a low frequency filter of 2 Hz are: median nerve = 7.3 ms, ulnar nerve = 7.5 ms, peroneal nerve = 7.3 ms, tibial nerve = 6.8 ms (12); abnormal values are marked in bold.

**Left deltoid, right triceps brachii, left iliopsoas, and right rectus femoris muscles.*

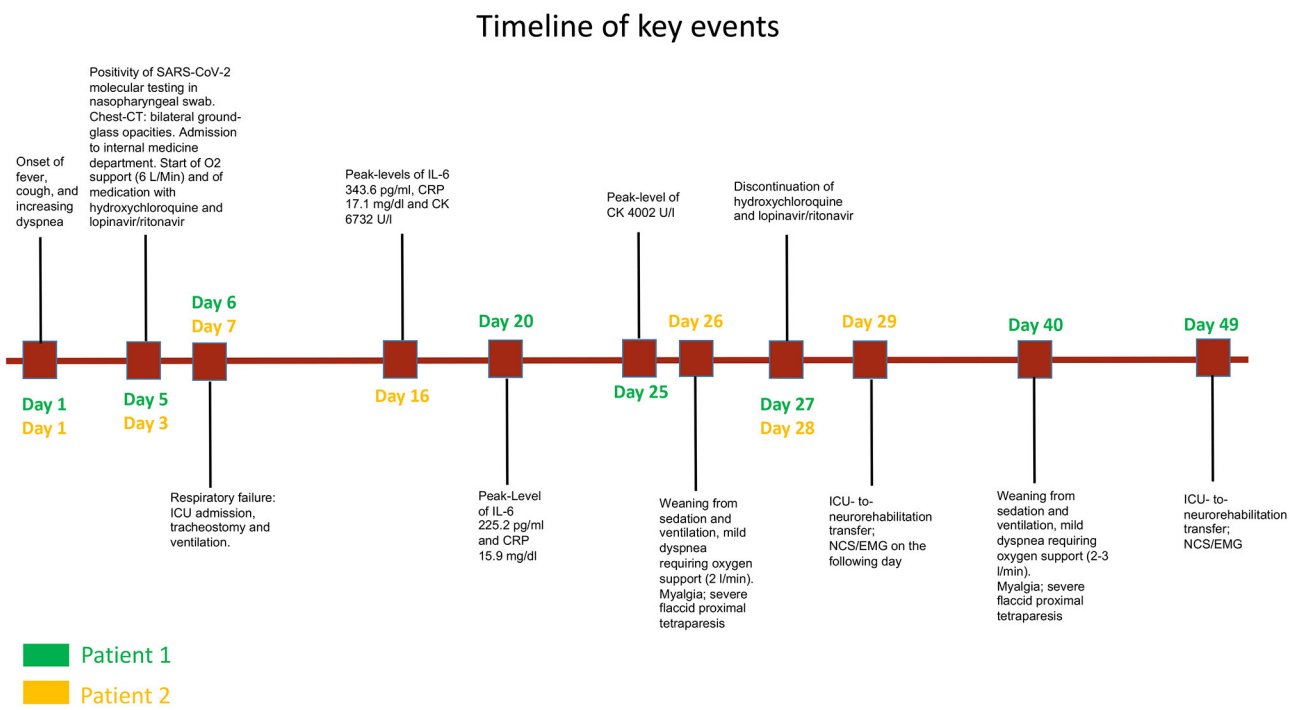


FIGURE 1 | Timeline of key events related to COVID-19 and myopathy in patient 1 (green labels) and patient 2 (yellow labels).

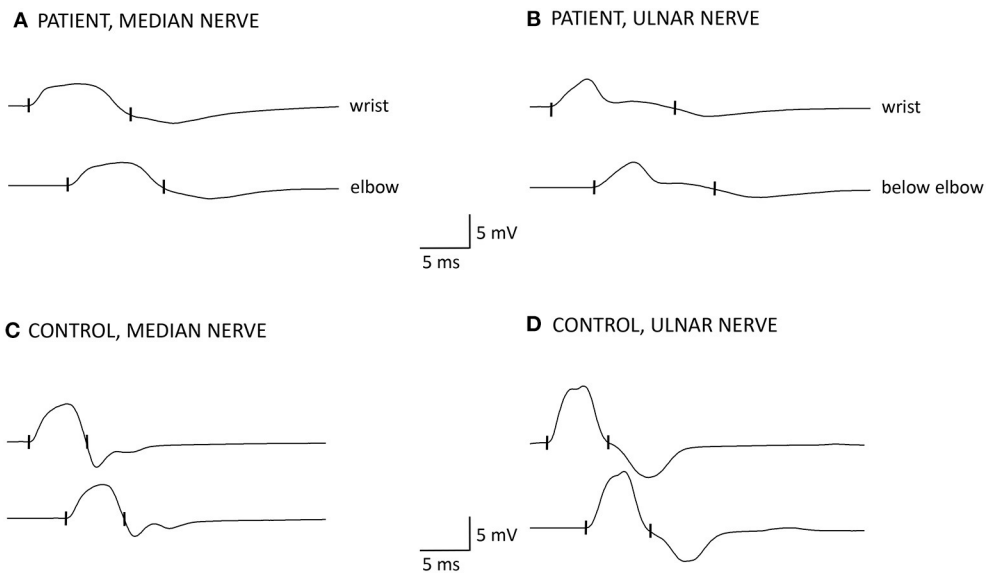


FIGURE 2 | Motor nerve conduction studies of patient 1 **(A,B)** compared to a healthy control subject **(C,D)**. Amplitude and duration of the negative phase of compound muscle action potentials (CMAPs) were measured at a sensitivity of 0.5 mV with a 2 Hz low frequency filter. The cut-off values for distal CMAP duration are according to reported normal values + 2 SD (12). **(A)** median nerve: distal CMAP amplitude is reduced (4.2 mV), distal motor latency (DML) is normal (3.9 ms), distal CMAP duration is increased (9.3 ms, 127% of upper limit of normal = 7.3 ms), conduction velocity (CV) is 48 m/s. CMAP amplitude and duration did not change between proximal and distal stimulation. Note the broadening and smooth contour of the negative phase of the distal CMAP and the reduction of the ensuing positive phase compared to panel **(C)** (CMAP duration = 5.7 ms); **(B)** ulnar nerve: distal CMAP amplitude is slightly reduced (5.7 mV), DML is normal (2.9 ms), distal CMAP duration is increased (13.7 ms, 183% upper limit of normal = 7.5 ms), CV is 55 m/s. CMAP amplitude and duration did not change with proximal stimulation. Note the very prolonged negative phase of the distal CMAP with a long tail and the absence of the ensuing positive phase compared to panel **(D)** (CMAP duration = 6.3 ms).

In conclusion, the same pathogenetic mechanism that causes interstitial pneumonia and damage to extrapulmonary tissues and organs in COVID-19, i.e., the inflammatory cytokine storm together with coagulopathy and macrophage activation, could contribute, in patients requiring prolonged critical care, to skeletal muscle damage (17).

Further studies are necessary to elucidate the pathogenesis of COVID-19-associated myopathy and to differentiate among direct infection, autoimmune process, and CIM due to hyperinflammation; in particular, muscle biopsy with specific investigations would be of crucial importance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the patients for the submission of their data and for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Material preparation, data collection, and analysis were performed by VV, LSe, and DF. The first draft of the manuscript was written by VV and MK. AU contributed substantially to the interpretation of the results, provided critical feedback, and revised the manuscript. All authors contributed in review and editing of the manuscript and approved its final version. All authors contributed to the study conception and design.

REFERENCES

1. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. *Neurol Sci.* (2020) 41:3039–56. doi: 10.1007/s10072-020-04708-8
2. Ferrandi PJ, Alway SE, Mohamed JS. The interaction between SARS-CoV-2 and ACE2 may have consequences for skeletal muscle viral susceptibility and myopathies. *J Appl Physiol (1985).* (2020) 129:864–7. doi: 10.1152/japplphysiol.00321.2020
3. Puelles VG, Lütgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med.* (2020) 383:590–2. doi: 10.1056/NEJMc2011400
4. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology.* (2020) 94:959–69. doi: 10.1212/WNL.0000000000009566
5. Dalakas MC. Guillain-Barré syndrome: The first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm.* (2020) 7:e781. doi: 10.1212/NXI.0000000000000781
6. Tankisi H, Tankisi A, Harbo T, Markvardsen LK, Andersen H, Pedersen TH. Critical illness myopathy as a consequence of Covid-19 infection. *Clin Neurophysiol.* (2020) 131:1931–2. doi: 10.1016/j.clinph.2020.06.003
7. Bagnato S, Boccagni C, Marino G, Prestandrea C, D'Agostino T, Rubino F. Critical illness myopathy after COVID-19. *Int J Infect Dis.* (2020) 99:276–8. doi: 10.1016/j.ijid.2020.07.072
8. Madia F, Merico B, Primiano G, Cutuli SL, De Pascale G, Servidei S. Acute myopathic quadriplegia in patients with COVID-19 in the intensive care unit. *Neurology.* (2020) 95:492–4. doi: 10.1212/WNL.0000000000010280
9. Cabañes-Martínez L, Villadóniga M, González-Rodríguez L, Araque L, Díaz-Cid A, Ruz-Caracuel I, et al. Neuromuscular involvement in COVID-19 critically ill patients. *Clin Neurophysiol.* (2020) 131:2809–16. doi: 10.1016/j.clinph.2020.09.017
10. Abenza-Abildúa MJ, Ramírez-Prieto MT, Moreno-Zabaleta R, Arenas-Valls N, Salvador-Maya MA, Algarra-Lucas C, et al. Neurological complications in critical patients with COVID-19. *Neurologia.* (2020) 35:621–7. doi: 10.1016/j.nrleng.2020.07.012
11. Van Aerde N, Van den Berghe G, Wilmer A, Gosselink R, Hermans G. Intensive care unit acquired muscle weakness in COVID-19 patients. *Intensive Care Med.* (2020) 46:2083–5. doi: 10.1007/s00134-020-06244-7
12. Mitsuma S, Van den Bergh P, Rajabally YA, Van Parijs V, Martin-Lamb D, Sonoo M, et al. Tokyo Metropolitan Neuromuscular Electrodiagnosis Study, Effects of low frequency filtering on distal compound muscle action potential duration for diagnosis of CIDP: a Japanese-European multicenter prospective study. *Clin Neurophysiol.* (2015) 126:1805–10. doi: 10.1016/j.clinph.2014.11.027
13. Kramer CL, Boon AJ, Harper CM, Goodman BP. Compound muscle action potential duration in critical illness neuromyopathy. *Muscle Nerve.* (2018) 57:395–400. doi: 10.1002/mus.25732
14. Allen DC, Arunachalam R, Mills KR. Critical illness myopathy: further evidence from muscle-fiber excitability studies of an acquired channelopathy. *Muscle Nerve.* (2008) 37:14–22. doi: 10.1002/mus.20884
15. Friedrich O, Hund E, Weber C, Hacke W, Fink RH. Critical illness myopathy serum fractions affect membrane excitability and intracellular calcium release in mammalian skeletal muscle. *J Neurol.* (2004) 251:53–65. doi: 10.1007/s00415-004-0272-z
16. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The sick and the weak: neuropathies/myopathies in the critically ill. *Physiol Rev.* (2015) 95:1025–9. doi: 10.1152/physrev.00028.2014
17. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev.* (2020) 19:102537. doi: 10.1016/j.autrev.2020.102537

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 11 February 2021
doi: 10.3389/fneur.2021.627493

Impact of National Lockdown on the Hyperacute Stroke Care and Rapid Transient Ischaemic Attack Outpatient Service in a Comprehensive Tertiary Stroke Centre During the COVID-19 Pandemic

Lucio D'Anna[1,2], Maddison Brown[1], Sikdar Oishi[1], Natalya Ellis[1], Zoe Brown[1], Paul Bentley[1,2], Brian Drumm[1], Omid Halse[1], Sohaa Jamil[1], Harri Jenkins[1], Abid Malik[1], Dheeraj Kalladka[1], Marius Venter[1], Joseph Kwan[1] and Soma Banerjee[1,2]*

[1] Department of Stroke and Neuroscience, Charing Cross Hospital, Imperial College London NHS Healthcare Trust, London, United Kingdom, [2] Department of Brain Sciences, Imperial College London, London, United Kingdom

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Andrea Zini,
IRCCS Institute of Neurological Sciences of Bologna (ISNB), Italy
Chih-Hao Chen,
National Taiwan University Hospital, Taiwan
Kazunori Toyoda,
National Cerebral and Cardiovascular Center, Japan
Georgios Tsivgoulis,
National and Kapodistrian University of Athens, Greece

***Correspondence:**
Lucio D'Anna
l.danna@imperial.ac.uk

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 09 November 2020
Accepted: 08 January 2021
Published: 11 February 2021

Citation:
D'Anna L, Brown M, Oishi S, Ellis N, Brown Z, Bentley P, Drumm B, Halse O, Jamil S, Jenkins H, Malik A, Kalladka D, Venter M, Kwan J and Banerjee S (2021) Impact of National Lockdown on the Hyperacute Stroke Care and Rapid Transient Ischaemic Attack Outpatient Service in a Comprehensive Tertiary Stroke Centre During the COVID-19 Pandemic. Front. Neurol. 12:627493. doi: 10.3389/fneur.2021.627493

Background: The COVID-19 pandemic is having major implications for stroke services worldwide. We aimed to study the impact of the national lockdown period during the COVID-19 outbreak on stroke and transient ischemic attack (TIA) care in London, UK.

Methods: We retrospectively analyzed data from a quality improvement registry of consecutive patients presenting with acute ischemic stroke and TIA to the Stroke Department, Imperial College Health Care Trust London during the national lockdown period (between March 23rd and 30th June 2020). As controls, we evaluated the clinical reports and stroke quality metrics of patients presenting with stroke or TIA in the same period of 2019.

Results: Between March 23rd and 30th June 2020, we documented a fall in the number of stroke admissions by 31.33% and of TIA outpatient referrals by 24.44% compared to the same period in 2019. During the lockdown, we observed a significant increase in symptom onset-to-door time in patients presenting with stroke (median = 240 vs. 160 min, $p = 0.020$) and TIA (median = 3 vs. 0 days, $p = 0.002$) and a significant reduction in the total number of patients thrombolysed [27 (11.49%) vs. 46 (16.25%, $p = 0.030$)]. Patients in the 2020 cohort presented with a lower median pre-stroke mRS ($p = 0.015$), but an increased NIHSS ($p = 0.002$). We registered a marked decrease in mimic diagnoses compared to the same period of 2019. Statistically significant differences were found between the COVID and pre-COVID cohorts in the time from onset to door (median 99 vs. 88 min, $p = 0.026$) and from onset to needle (median 148 vs. 126 min, $p = 0.036$) for thrombolysis whilst we did not observe any significant delay to reperfusion therapies (door-to-needle and door-to-groin puncture time).

Conclusions: National lockdown in the UK due to the COVID-19 pandemic was associated with a significant decrease in acute stroke admission and TIA evaluations at our stroke center. Moreover, a lower proportion of acute stroke patients in the pandemic cohort benefited from reperfusion therapy. Further research is needed to evaluate the long-term effects of the pandemic on stroke care.

Keywords: COVID-19, stroke, transient ischaemic attack, thrombolisis, stroke care, lock down

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) outbreak began in December 2019 in Wuhan, Hubei province, China and then spread to Europe in January 2020 (1). The index case entered the United Kingdom (UK) on January 23rd 2020 from Hubei province in China (2). Subsequently, unique measures such as large-scale application of social isolation, closing borders and nationwide lockdown were adopted in UK since March 23, throughout June 2020, to fight against COVID-19.

The COVID-19 outbreak has led to a huge reorganization of the health care systems worldwide and unprecedent strategies were rapidly implemented to face the increasing needs for COVID-19 patient such as resource allocation, mobilizing workforce, and optimizing bed availability (4). As a result several groups reported that stroke care suffered from a shortage of services and delays in time-dependent treatments and diagnostic work-up since the onset of the pandemic (3, 5–9). In addition, at the same time, observational studies showed a marked and unexplained reduction in the number of patients admitted in hospital with cardiovascular pathologies such as myocardial infarction and acute ischaemic stroke (3, 10–32). However, these preliminary global reports explored mainly the impact of the pandemic only on the overall volume of hospital admissions for acute stroke but with no report about the implications on the outpatient rapid Transient Ischaemic Attack (TIA) services.

In this study we sought to investigate the impact of the national lockdown measures during the COVID-19 pandemic on the rate of admission of stroke patients to the Hyper Acute Stroke Unit (HASU) and rate of patients evaluated in the rapid outpatient TIA service of a comprehensive tertiary stroke center in London (UK) compared to a pre-pandemic cohort. We also investigated clinical characteristics of the patients, stroke reperfusion therapies and treatment metrics.

METHODS

This was a an observational, retrospective, single-center study based on data of consecutive patients with acute stroke and transient ischaemic attack (TIA) admitted to the Hyper Acute Stroke Unit (HASU) or evaluated in the rapid outpatient TIA service of the Stroke Department, Charing Cross Hospital, Imperial College Health Care Trust London between March 23rd and 30th June 2019 and between March 23rd and 30th June 2020. The Stroke Department at Charing Cross Hospital is a comprehensive tertiary stroke center and is the North West London (UK) regional lead referral stroke center for mechanical thrombectomy for a population of over 6.4 million people. It cares for over 1,800 patients admitted to the HASU annually and over 900 patients assessed in the rapid outpatient TIA service annually. The 24/7 thrombectomy service treats stroke patients presenting within 6 h of symptom onset, as well as selected patients with wake-up stroke (unclear time of onset) or presenting between 6 to 24 h using computed tomography (CT) perfusion imaging protocols.

The Charing Cross Hospital as lead referral stroke center for mechanical thrombectomy accepts potential candidate for mechanical thrombectomy from the hyper acute stroke units of Luton and Dunstable University Hospital, Lister Hospital, Watford General Hospital, Northwick Park Hospital, Royal Berkshire Hospital, Wycombe Hospital, Royal London Hospital and University College London Hospital; but also from the acute stroke units at Chelsea and Westminster Hospital, Hillingdon Hospital and West Middlesex Hospital (**Figure 1**). Patients are accepted following a telephone consultation between the referring center and the on-call stroke consultant. The Charing Cross Hospital began performing diagnostic nasopharyngeal swabs for SARS-CoV-2 virus from March 3, 2020. Only between the 18th March and 30th April 2020, external stroke patients, proven to have COVID-19, were not transferred for thrombectomy at our hospital, but otherwise all external referral hospitals were instructed to continue referring patients for thrombectomy, including those with suspected COVID-19, via the same process as before the COVID-19 pandemic. The Thrombectomy management board released a new modified COVID stroke thrombectomy pathway with the aim to protect frontline health-care staff, reduce footprint across the hospital and maintain communication between team members (33). The primary outcome measure was to study the overall volume of patients admitted to our HASU and patients evaluated in our rapid outpatient TIA service between March 23rd and 30th June 2020 compared to the same period in 2019. The secondary clinical outcomes were to investigate patient demographics, clinical characteristics, proportion of acute recanalization therapy performed, stroke treatment metrics and final diagnosis between the two groups of patients (2020 vs. 2019).

Data Source and Data Collection Process

A database of admissions that is used for reporting to a central UK stroke data bank (Sentinel Stroke National Audit Programme) ensured the consecutive enrolment of eligible patients. Electronic medical records of eligible patients were obtained from the Imperial College Healthcare NHS Trust

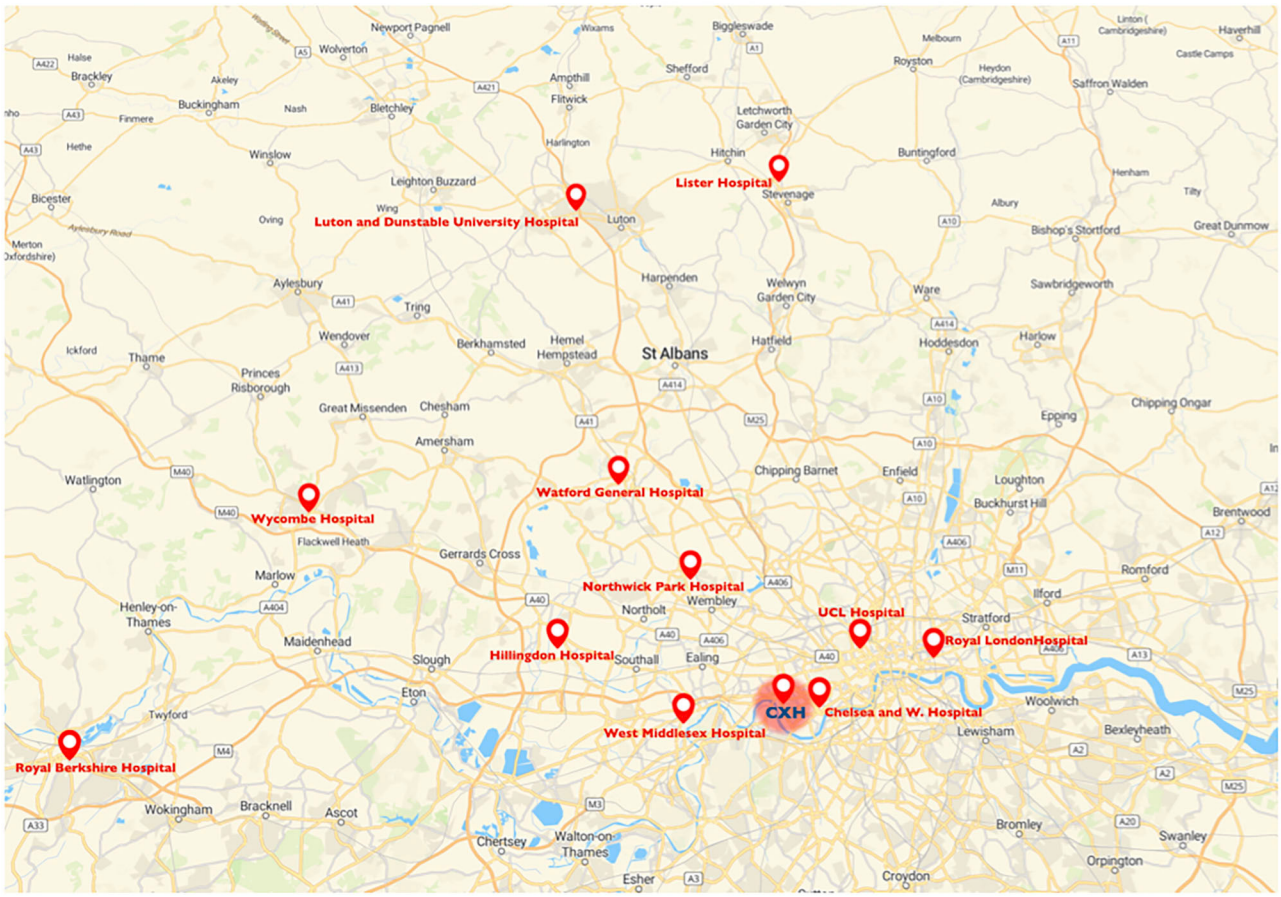


FIGURE 1 | Map of the catchment area for mechanical thrombectomy of the Charing Cross Hospital and referring centers. CXH, Charing Cross Hospital.

medical archive. Data of consecutive patients were extracted using a pre-specified case report file that included patient characteristics, including age, vascular risk factors and relevant medical history that were recorded during the admission. Events were captured by review of medical notes of all patients admitted to the HASU and referred to the rapid outpatient TIA service of the Imperial College Healthcare NHS Trust between March 23rd and 30th June 2020 and between March 23rd and 30th June 2019.

Definition of Study Variables

Ischaemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction (34). TIA was defined as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting <1 h, and without evidence of acute infarction (35). Intracerebral hemorrhage (ICH) refers to primary, spontaneous, non-traumatic bleeding occurring in the brain parenchyma (36). Cerebral venous thrombosis refers to thrombosis of the dural sinus and/or cerebral veins (CSVT) (37). Stroke mimics included migraine aura, seizures, syncope, peripheral vestibular disturbance, transient global amnesia, functional/anxiety disorder, amyloid spells, subarachnoid hemorrhage, structural brain lesion and paroxysmal symptoms due to demyelination (38). The severity of the index stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS) score on admission. The modified Rankin Scale (mRS) was used to assess patient's initial premorbid status pre-stroke and level of functional independence at 90 days of the patients who underwent mechanical thrombectomy. Data included point of first healthcare provider contact (999/F.A.S.T., emergency department or ED, local general practitioners or GP, etc). Data on known stroke risk factors were collected as follows: age, sex, current cigarette smoking, history of hypertension (blood pressure >140/90 mm Hg at least twice before acute stroke or already under treatment with antihypertensive drugs), history of diabetes mellitus (a random venous plasma glucose concentration >11.1 mmol/l or a fasting plasma glucose concentration >7.0 mmol/l or 2 h plasma glucose concentration >11.1 mmol/l 2 h after 75 g anhydrous glucose in an oral glucose tolerance test, or HbA1c >48 mmol/mol or under antidiabetic treatment), history of dementia, history of symptomatic ischemic heart disease (myocardial infarction, history of angina, or previous diagnosis of multiple lesions on thallium heart isotope scan or evidence of coronary disease on coronary angiography), history of symptomatic peripheral arterial disease (intermittent

claudication of presumed atherosclerotic origin; or ankle/arm systolic blood pressure ratio <0.85 in either leg at rest, or history of intermittent claudication with previous leg amputation, reconstructive surgery, or angioplasty), previous stroke/ TIA and previous ICH. Process time variables were collected prospectively, when applicable, and included door to needle time, door to computer tomography (CT) time, CT to decision time and onset to needle time for intravenous thrombolysis (IVT); and door to groin puncture time and onset to groin puncture time for endovascular thrombectomy (EVT).

Brief Description of the Workflow

Patients presenting with features of acute stroke were evaluated in the hyperacute setting with appropriate neuroimaging and vascular imaging when indicated: CT, computed tomography angiography (CTA), computed tomography perfusion (CTP) of the brain and magnetic resonance imaging (MRI). Patients who fulfilled the relevant indications and without exclusion criteria would undergo acute recanalization therapy. Eligible patients who presented up to 4.5 h of ischaemic stroke symptoms onset received IVT with recombinant-tissue plasminogen activator (r-TPA) (39). Stroke patients would be considered for endovascular thrombectomy (EVT) if they met the following criteria: pre-stroke mRS 0–2, NIHSS score 6 or more, Alberta Stroke Program Early CT score (ASPECTS) 5 or more and within 6 h of symptom onset, anterior circulation large vessel occlusion, basilar artery occlusion. Selected AIS patients within 6 to 24 h of last known normal may be included if they meet other DAWN or DEFUSE 3 eligibility criteria (39–41).

Local GPs in primary-care or Emergency Departments (ED) can refer any patient they suspect had a TIA, but whom they did not consider required immediate hospital admission, to our rapid outpatient TIA service. These patients or the caregiver at home (usually by telephone) are then contacted by our team to arrange a clinic appointment within 24 h of referral received. Our TIA clinic is organized to provide a standardized assessment to all our patients. On the same day, blood tests, ECG, brain imaging (usually CT), and carotid ultrasound imaging and a clinical assessment by a stroke physician are obtained. Patients are discharged home immediately after the assessment, unless the treating physician believes the patient requires urgent admission to our HASU.

Study Outcomes and Statistical Analysis

Continuous variables are presented as mean with standard deviation (sd) if values are normally distributed or as median with interquartile range (IQR) when they do not follow the normal distribution. We compared the distribution of continuous variables between groups with *t*-test or Wilcoxon rank-sum test as appropriate, whereas categorical values were compared with chi-square tests. Statistical significance was set at 0.05. All analyses were conducted with Stata 15.1 (StataCorp, College Station, TX).

TABLE 1 | Clinical characteristics of the two cohorts of patients admitted in HASU during the two study periods.

	23rd March to 30th June 2020 (*n* = 353)	23rd March to 30th June 2019 (*n* = 514)	*P*
Age, y (median, IQR)	70.5; 35–98	71.0; 24–96	0.863
Male, sex (%)	196 (56.97%)	250 (49.70%)	0.134
mRS pre-stroke (median, IQR)	0; 0–5	1; 0–4	0.015
NIHSS on arrival (median, IQR)	7; 0–30	4; 0–29	0.002
Symptom onset -to-door time, min (median, IQR)	240; 20–10,080	160; 27–23,040	0.020
Length of inpatient stay in HASU, days (median, IQR)	4; 1–60	2; 0–20	<0.001
First healthcare provider contacts used by stroke patients			
GP	69 (20.05%)	30 (5.96%)	
ED	172 (50%)	216 (42.94%)	
999/F.A.S.T. emergency call	103 (29.95%)	257 (51.1%)	
			<0.001
Final diagnosis			
Ischaemic stroke	235 (66.57%)	283 (55.06%)	
Intracranial hemorrhage	41(11.61%)	48 (9.34%)	
TIA	18 (5.1%)	49 (9.53%)	
CSVT	4 (1.13%)	2 (0.39%)	
Stroke mimic	55 (15.58%)	132 (25.68%)	
			<0.001

mRS, modified Rankin Scale; IQR, interquartile range; HASU, hyper acute stroke unit; GP, general practitioner; ED, emergency department; F.A.S.T., face, arm, speech, time; TIA, transient ischemic attack; CSVT, cerebral sinus venous thrombosis.

RESULTS

Hyperacute Stroke Care

Between the March 23rd and June 30th, 2019, we admitted 514 patients in our HASU while we documented 353 admissions between the March 23rd and June 30th, 2020. This represents a fall in admissions of 31.33%. In **Table 1** we showed the clinical characteristics of the two groups of patients admitted during the two study periods. There were no statistically significant differences with regards to age and gender distribution. However, patients admitted during the COVID-19 pandemic showed lower pre-stroke mRS scores ($p = 0.015$) and higher median NIHSS on arrival ($p = 0.002$) compared to the patients admitted in same period in 2019. Moreover, the median symptom onset-to-door time was significantly longer ($p = 0.020$) and the median length of inpatient stay in HASU was increased ($p < 0.001$) in the group of patients admitted between the 23rd March and 30th June 2020 compared to the same period in 2019.

We documented a statistically significant difference in terms of the first medical provider contact used by the stroke patients during the two study periods (**Table 1**) ($p < 0.001$). Between the 23rd March and 30th June 2020, 20.05% (vs. 5.96% in 2019) of the patients had their local GP as first medical provider contact while 29.95% (vs. 51.1% in 2019) of the patients used the emergency medical service 999/F.A.S.T.

Between the 23rd March and 30th June 2020, the final diagnosis was ischemic stroke in 235 (66.57%), intracranial

FIGURE 2 | Numbers of patients with diagnosis of intracranial hemorrhage, transient ischaemic attack, stroke mimic and ischaemic stroke between March 23rd and 30th June 2020 and between March 23 and 30 June 2019.

hemorrhage in 41(11.61%), TIA in 18 (5.1%), CSVT in 4 (1.13%) and stroke mimic in 55 (15.58%); in the same period in 2019 the final diagnosis was ischemic stroke in 283 (55.06%), intracranial hemorrhage in 48(9.34%), TIA in 49 (9.53%), CSVT in 2 (0.39%) and stroke mimic in 132 (25.68%) ($p < 0.001$) (**Table 1**) (**Figure 2**).

In **Table 2** we reported the clinical characteristics and type of acute treatments received by the two groups of patients with ischaemic stroke admitted in our HASU. Patients' clinical characteristics were similar in both groups but patients admitted in the 2020 cohort more frequently had diabetes ($p = 0.031$) and less frequently had a past history of dementia ($p = 0.042$), or intracranial hemorrhage ($p = 0.017$). Regarding the acute treatment received, patients admitted between 23rd March and 30th June 2020 less frequently underwent IVT alone ($p = 0.030$) while more frequently were treated with IVT combined with EVT ($p = 0.043$). There was no significant difference between the two cohorts of patients treated with IVT alone, EVT alone or IVT plus EVT in terms of NIHSS on arrival and 24h NIHSS. In terms of process measures time (**Figure 3**), statistically significant differences were found between the COVID and pre-COVID cohorts in the time from onset to door arrival (median 99 vs. 88 min, $p = 0.026$) and from onset to needle time (median 148 vs. 126 min, $p = 0.036$) for IVT. We did not observe significant difference in the door to CT time, CT to decision time, door to needle time for IVT and door to groin puncture time and onset to groin puncture time for EVT. The median mRS at 90 days for the patients treated with EVT (alone or combined with IVT) did not differ among the two cohorts of patients ($p = 0.403$); moreover, we did not find any statistically significant difference between the two groups of patients regarding the proportion of patients who received EVT able to achieve functional independence (mRS score of 0-2) at 90 days ($p = 0.367$) (**Table 3**).

TIA Rapid Outpatient Service

Between the 23rd March and 30th June 2019, 180 patients were referred with suspected TIA to our rapid TIA outpatient service while 136 patients were referred in same period in 2020. This represents a fall in the number of referrals by 24.44%. Patients characteristics were similar in both groups, but patients referred during the COVID-19 period had less frequently dementia ($p = 0.027$) (**Table 4**). The median symptom onset-to-first medical review time was significantly longer in the group of patients referred between the 23rd March and 30th June 2020 compared to the same period in 2019 (median = 3 vs. 0 days, $p = 0.002$).

We documented a statistically significant difference in terms of the first medical provider contact used by the TIA patients during the two study periods (**Table 4**) ($p = 0.020$). Between the

TABLE 2 | Clinical characteristics, reperfusion therapy rate and process measures of the patients with ischaemic stroke admitted in HASU during the two study periods.

	23rd March to 30th June 2020 (*n* = 235)	23rd March to 30th June 2019 (*n* = 283)	*P*
Age, y (median, IQR)	78; 72–83	80; 73–85	0.236
Male, sex (%)	127 (54.04%)	157 (55.48%)	0.468
Smoking, *n* (%)	44 (18.72%)	53 (18.72%)	0.997
Hypertension, *n* (%)	143 (60.85%)	158 (55.83%)	0.420
Diabetes, *n* (%)	66 (28.09%)	47 (16.61%)	0.031
Dementia, *n* (%)	7 (2.98%)	23 (8.12%)	0.042
Coronary artery disease, *n* (%)	19 (8.09%)	20 (7.07%)	0.867
Heart failure, *n* (%)	12 (5.11%)	18 (6.36%)	0.694
Peripheral vascular disease, *n* (%)	8 (3.40%)	6 (2.12%)	0.537
Previous ischemic stroke/TIA, *n* (%)	61 (25.96%)	85 (30.04%)	0.488
Previous ICH, *n* (%)	3 (1.27%)	22 (7.77%)	0.017
Previously known AF, *n* (%)	61 (25.96%)	51 (18.02%)	0.128
Reperfusion therapy			
IVT alone, *n* (%)	**27 (11.49%)**	**46 (16.25%)**	**0.030**
NIHSS on arrival for IVT (median, IQR)	7.5; 2–22	8; 2–25	0.546
24 h NIHSS for IVT (median, IQR)	2; 0–22	2; 0–33	0.640
EVT alone, *n* (%)	**13 (5.53%)**	**11 (3.89%)**	**0.879**
NIHSS on arrival for EVT (median, IQR)	17; 11–25	18; 2–29	0.857
24 h NIHSS for EVT (median, IQR)	18; 1–30	14.5; 1–38	0.640
IVT and EVT, *n* (%)	**44 (18.72%)**	**33 (11.66%)**	**0.043**
NIHSS on arrival for IVT and EVT (median, IQR)	18.5; 0–27	17; 7–28	0.924
24 h NIHSS for IVT and EVT (median, IQR)	12.5; 0–38	9; 0–37	0.174
Process measures			
Onset to door time for IVT, min (median, IQR)	99; 44–265	88; 15–386	0.026
Onset to needle time for IVT, min (median, IQR)	148; 46–327	126; 36–190	0.036
Door to CT time for IVT, min (median, IQR)	19; 2–50	17; 6–53	0.643
CT to decision time for IVT, min (median, IQR)	18; 1–83	12; 1–72	0.155
Door to needle time for IVT, min (median, IQR)	39; 33.5–45	40; 34–44.5	0.878
Door-to-groin puncture time for EVT, min (median, IQR)	58; 20–325	55; 21–289	0.982
Onset-to-groin puncture time for EVT, min (median, IQR)	143; 68–275	122; 71–473	0.701

TIA, transient ischemic attack; ICH, intracranial hemorrhage; AF, atrial fibrillation; IQR, interquartile range; IVT, intravenous thrombolysis; EVT, endovascular treatment; CT, computer tomography.

23rd March and 30th June 2020, 30.14% (vs. 41.67% in 2019) of the patients had their local GP as first medical provider contact while 68.38% (vs. 53.89% in 2019) of the patients self-referred to the ED of our hospital.

Finally, we observed a statistically significant difference in the final diagnosis ($p = 0.020$) (**Table 4**) after the review in our TIA service. The percentage of patients with a final diagnosis of TIA increased from 46.11% in 2019 to 58.22% during the COVID period.

Interestingly, our ambulatory rapid access TIA clinic experienced a doubling rate of ischaemic stroke diagnoses (9.56 vs. 5.0%), whilst registering a marked decrease in mimic diagnoses (35.29 vs. 48.89%) during the COVID period. Of note, 32.88% of the 2020 cohort had a final diagnosis of TIA mimic whilst in the same period in 2019 this was 48.89%.

DISCUSSION

In this observational study we explored the impact of the national lockdown measures due to the COVID-19 pandemic on our large regional tertiary stroke center. One element of novelty of our analysis is that investigated the impact of the COVID-19 outbreak on the hyper acute stroke care but also on the rapid outpatient TIA service care at a comprehensive tertiary stroke center. The main finding of our analysis is that our stroke sample presented with a lower median pre-stroke mRS combined with an increase in initial stroke severity during the national lockdown. In addition, our study showed that the proportion of patients with previous history of dementia, admitted to our HASU or assessed in our rapid outpatient TIA clinic, was statistically significantly lower during the COVID-19 outbreak compared to the same period in 2019. Several centers have described significant difference in severity at presentation of stroke patients but to date no difference in the degree of pre-stroke disability or dependence in the daily activities has been reported (11, 30, 32). Based on the available data, poor pre-admission functional status and dementia are risk factors for in-hospital mortality in patients with COVID-19 (42). Our hypothesis is that vulnerable patients and their caregivers might have intentionally avoided hospital admissions due to the risk of COVID-19 infection. Alternatively, epidemic response measures might also represent a contributing factor. Self-isolation reduces social connections, especially in the elderly and more frail population. Isolation can impact on early recognition of stroke symptoms and can lead to delayed notification of emergency services. Indeed, similar to previous studies (31), we have observed a significant delay in symptom onset-to-door review time in our sample that could support this thesis.

Another key finding is that we showed an overall significant reduction in the hospitalization rate for stroke and in the number of patients presenting with TIA. The rate of thrombolysis delivery also reduced. Our results are in line with previous observational studies and have confirmed our preliminary report (43). A survey of 81 Italian stroke centers conducted by the Italian Stroke Organization reported a reduction of about 26–30% in the hospitalization rate for minor stroke and TIA, and of about 50% for stroke acute therapies in comparison with the same period in 2019 (3, 44). In Germany the marked decrease of patients with TIA or minor stroke presenting in hospital has led the German Society of Neurology and the German Stroke Society to initiate

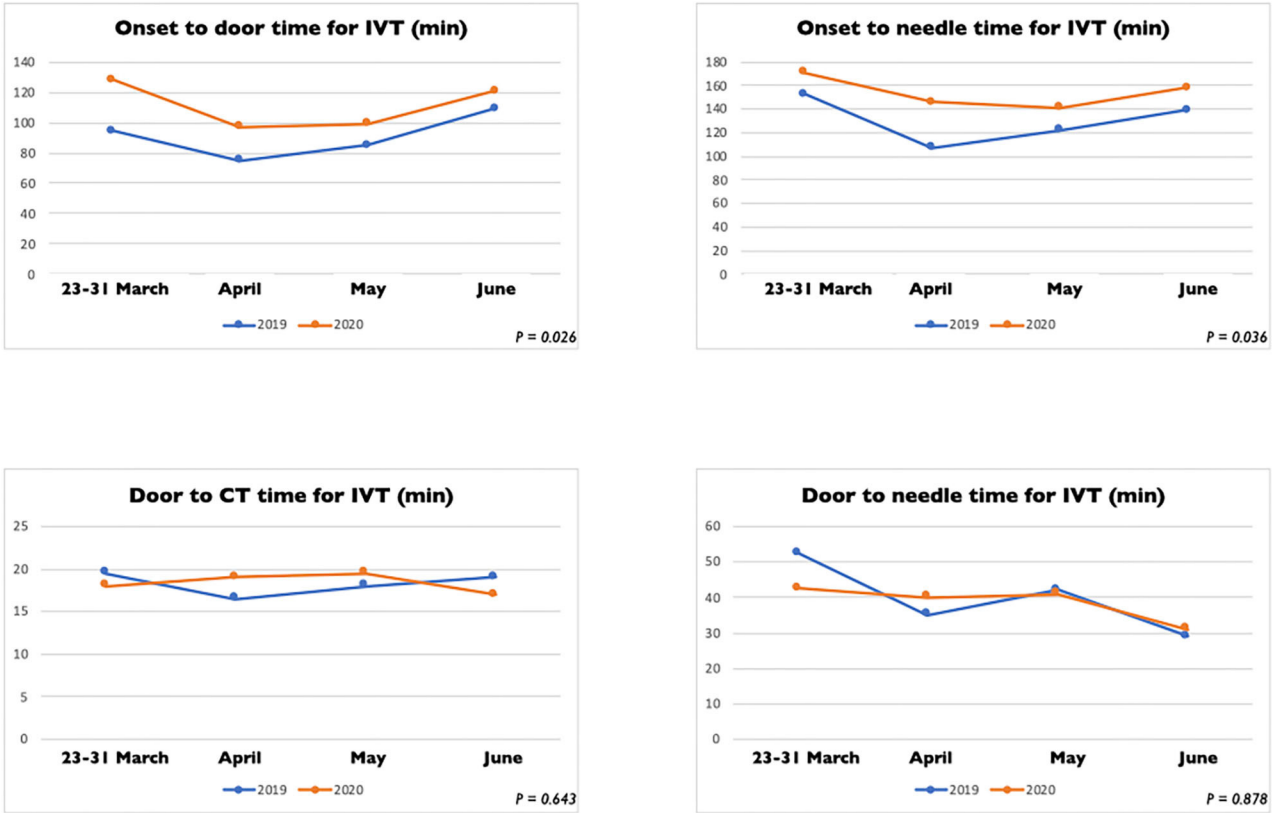


FIGURE 3 | Process measure comparison for intravenous thrombolysis between stroke patients admitted between March 23 and 30 June 2020 and between March 23 and 30 June 2019.

a publicity campaign in television and newspapers about the so-called 'phenomenon of empty stroke units' to invite patients to seek medical help (3). Similarly, in the USA (30) and in China (5) there are reports of reduction in acute stroke volume in hospitals. This concern has also been raised by the World Stroke Organization (45). There are several factors that could potentially explain this phenomenon. First, fear of in-hospital infection and advice from health authorities, media and doctors probably led patients with mild symptoms to stay at home. Interestingly, our ambulatory rapid access TIA clinic experienced a doubling rate of ischaemic stroke diagnoses, whilst registering a marked decrease in mimic diagnoses. This is in keeping with the hypothesis that milder stroke patients were avoiding hospital admissions due to fear of the pandemic, and preferred an outpatient setting where accessible. This does however delay their presentation and limit access to reperfusion therapies. For this reason, information campaigns to educate patients to present early to the ED if they have symptoms suggestive of stroke must be implemented even during this ongoing COVID-19 pandemic. Secondly, primary-care, EDs and ambulance services have undergone significant pressures due to the volume of COVID-19 patients. This might have induced additional delays and errors during patient triage and transport, thus reducing the proportion of patients eligible for acute treatment. Moreover, the COVID-19 pandemic is having implications on stroke services in all parts of the world in terms of redeployment of stroke staff, and reallocation of the stroke beds to COVID-19 patients (45). Resources management is critical during the pandemic and should be established as quickly as possible. Designated stroke centers should be assigned to maintain resources for delivery of high-quality stroke care (5).

TABLE 3 | Efficacy outcomes of the patients who underwent EVT (alone or combined with IVT) during the two study periods.

Outcome	23rd March to 30th June 2020 (*n* = 57)	23rd March to 30th June 2019 (*n* = 44)	*P*
mRS at 90 days, (median, IQR)	3; 0–6	3; 0–6	0.403
Functional independence at 90 days [mRS 0–2, *n* (%)]	20 (35.09%)	15 (34.09%)	0.367
Death at 90 days	12 (21.05%)	15 (34.09%)	0.283

mRS, modified Rankin Scale; IQR, interquartile range.

In our center, we observed a significant reduction in the proportion of patients that used the emergency medical service 999/F.A.S.T. after the onset of stroke symptoms compared to the same period in 2019. This is in line with the NHS England data showing that during the COVID-19 pandemic was a general reduction at national level in emergency admissions (46).

TABLE 4 | Baseline characteristics of the patients evaluated in the rapid outpatient TIA service during the two study periods.

	23rd March to 30th June 2020 (*n* = 136)	23rd March to 30th June 2019 (*n* = 180)	*P*
Demographics			
Age, y (median, IQR)	65; 23–96	68.5; 20–28	0.087
Male, sex, *n* (%)	99 (72.79%)	121 (67.22%)	0.227
Clinical characteristics			
Hypertension, *n* (%)	71 (52.21%)	95 (52.78%)	0.442
Diabetes mellitus, *n* (%)	27 (19.85%)	37 (20.56%)	0.645
Hypercholesterolemia, *n* (%)	65 (47.79%)	76 (42.22%)	0.638
Coronary artery disease, *n* (%)	19 (13.97%)	21 (11.67%)	0.695
Previous TIA/stroke, *n* (%)	23 (16.91%)	39 (21.67%)	0.186
Carotid stenosis, *n* (%)	3 (2.21%)	9 (5.0%)	0.164
AF, *n* (%)	15 (11.03%)	25 (13.89%)	0.334
Dementia, *n* (%)	6 (4.41%)	18 (10%)	0.027
ABCD2 score, (median, IQR)	3; 0–6	3; 0–6	0.929
Symptom onset-to-first medical review time (days), (median, IQR)	3; 0–90	0; 0–133	0.002
First healthcare provider contacts used by TIA patients			
GP, *n* (%)	41 (30.14%)	75 (41.67%)	
ED, *n* (%)	93 (68.38%)	97 (53.89%)	
Other*, *n* (%)	2 (1.48%)	6 (3.33%)	
			0.020
Final diagnosis			
TIA, *n* (%)	75 (55.15%)	83 (46.11%)	
Ischemic stroke, *n* (%)	13 (9.56%)	9 (5.0%)	
TIA mimic, *n* (%)	48 (35.29%)	88 (48.89%)	
			0.020

*IQR, interquartile range; TIA, transient ischemic attack; AF, atrial fibrillation; GP, general practitioner; ED: emergency department; *this includes referrals from other specialties consultant.*

This could probably explain the longer delay in symptom onset-to-door time and onset to needle time in stroke patients and consequently the reduced proportion of patients who presented within the therapeutic time window for thrombolysis during the COVID pandemic. Interestingly, we did not observe any significant delay to reperfusion (door-to-needle and groin-to-puncture time) for IVT and EVT, in line with other centers worldwide (11, 13, 22, 27, 30–32) and with our preliminary report (47). By contrast Meza et al. (6) and Briard et al. (7) reported an increment in their door-to-needle time likely secondary to their new in-hospital infection control measures to manage stroke patients with suspected COVID-19 that may have delayed the acute stroke management. Moreover, our analysis showed that after any reperfusion therapy (IVT, EVT and IVT plus EVT) there was no statistically significant difference in terms of early neurology outcome although patients treated during the national lockdown demonstrated to have a higher 24 h NIHSS after the treatment. Despite the unprecedented demands on emergency healthcare, early multidisciplinary efforts to adapt our acute stroke treatment process resulted in keeping the stroke quality time metrics close to the pre-pandemic levels in our center. Future research with larger sample is needed to evaluate the impact of the delayed presentation of stroke patients during the pandemic on long-term outcomes.

Our study has several limitations and strengths. It is limited by its single-center design. Our findings reflect the trend in a determined area which may not be generalized to all international healthcare practices. Although the demographics and clinical characteristics were similar between cohorts, the possibility of systemic or random bias cannot be excluded. The retrospective design is another limitation. Finally, a long-term follow up was not available for analysis. The strengths of our study include that this is the first single-center report to assess the impact of the national lockdown due to the COVID-19 pandemic on both the HASU admissions and the rapid outpatient TIA service of a comprehensive tertiary stroke center in London (UK). The strengths of our study include also our sample size and the length of the study periods.

In conclusion, the national lockdown in the UK due to the COVID-19 pandemic was associated with a significant decrease in acute stroke admission and TIA evaluations at our comprehensive stroke center. In addition, a lower proportion of acute stroke patients in the pandemic cohort benefited from reperfusion therapy, specifically intravenous thrombolysis. More minor ischaemic stroke patients presented to our rapid access TIA clinic. These findings support concerns that the current ongoing pandemic may have negative impact on the acute management of non-COVID-19-related conditions such as acute stroke. Further research is needed to evaluate the long-term effects of the pandemic on population-based acute stroke incidence, hospital stroke and TIA outpatient evaluations volume, treatment metrics, and long-term outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent of subjects was not needed as the data collected for the study were information collected as part of the routine care and only de-identified data were used in the research.

AUTHOR CONTRIBUTIONS

LD'A and SB: study concept, statistical analysis, drafting, and critical revision of manuscript. MB, SO, NE, ZB, and BD: data collection, critical revision of manuscript. OH, SJ, HJ, AM, DK, JK, and MV: critical revision of manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank for their contribution the following healthcare staff: Diane Benefer (Lead Nurse for Stroke & Neurosciences), Tsering Dolkar and Siji Joy (Stroke Clinical Nurse Specialists), Riann Kruger and Brooke Hall (data analysts for SSNAP).

REFERENCES

1. Bernard Stoecklin S, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, et al. First cases of coronavirus disease 2019 (COVID-19) in France: Surveillance, investigations and control measures. *Euro Surveill.* (2020) 25:2000094. doi: 10.2807/1560-7917.ES.2020.25.6.2000094
2. Lillie PJ, Samson A, Li A, Adams K, Capstick R, Barlow GD, et al. Novel coronavirus disease (Covid-19): the first two patients in the UK with person to person transmission. *J Infect.* (2020) 80:578–606. doi: 10.1016/j.jinf.2020.02.020
3. Bersano A, Pantoni L. Impact of the SARS-CoV-2 pandemic on stroke care: a warning message. *Eur J Neurol.* (2020) 27:1781–2. doi: 10.1111/ene.14394
4. Bersano A, Kraemer M, Touzé E, Weber R, Alamowitch S, Sibon I, et al. Stroke care during the COVID-19 pandemic: experience from three large European countries. *Eur J Neurol.* (2020) 27:1794–1800. doi: 10.1111/ene.14375
5. Klionsky DJ, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, et al. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke.* (2020) 51:1996–2001. doi: 10.1161/STROKEAHA.120.030225
6. Tejada Meza H, Lambea Gil Á, Saldaña AS, Martínez-Zabaleta M, Juez PR, Martínez EL, et al. Impact of COVID-19 outbreak on ischemic stroke admissions and in-hospital mortality in North-West Spain. *Int J Stroke.* (2020) 15:755–62. doi: 10.1177/1747493020938301
7. Neves Briard J, Ducroux C, Jacquin G, Alesefir W, Boisseau W, Daneault N, et al. Early impact of the COVID-19 pandemic on acute stroke treatment delays. *Can J Neurol Sci.* (2020) 48:1–5. doi: 10.1017/cjn.2020
8. Candelaresi P, Manzo V, Servillo G, Muto M, Barone P, Napoletano R, et al. The impact of covid-19 lockdown on stroke admissions and treatments in campania. *J Stroke Cerebrovasc Dis.* (2021) 30:105448. doi: 10.1016/j.jstrokecerebrovasdis.2020.105448
9. Tsivgoulis G, Palaiodimou L, Katsanos AH, Caso V, Köhrmann M, Molina C, et al. Neurological manifestations and implications of COVID-19 pandemic. *Ther Adv Neurol Disord.* (2020) 13:1756286420932036. doi: 10.1177/1756286420932036
10. De Filippo O, D'Ascenzo F, Angelini F, Bocchino P, Conrotto F, Saglietto A, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. *N Engl J Med.* (2020) 383:88–9. doi: 10.1056/nejmc2009166
11. Padmanabhan N, Natarajan I, Gunston R, Raseta M, Roffe C. Impact of COVID-19 on stroke admissions, treatments, and outcomes at a comprehensive stroke centre in the United Kingdom. *Neurol Sci.* (2020) 42:15–20. doi: 10.1007/s10072-020-04775-x
12. Bres Bullrich M, Fridman S, Mandzia JL, Mai LM, Khaw A, Vargas Gonzalez JC, et al. COVID-19: stroke admissions, emergency department visits, and prevention clinic referrals. *Can J Neurol Sci.* (2020) 47:693–696.
13. Paliwal PR, Tan BYQ, Leow AST, Sibi S, Chor DWP, Chin AXY, et al. Impact of the COVID-19 pandemic on hyperacute stroke treatment: experience from a comprehensive stroke centre in Singapore. *J Thromb Thrombolysis.* (2020) 50:596–603. doi: 10.1007/s11239-020-02225-1
14. Rameez F, McCarthy P, Cheng Y, Packard LM, Davis AT, Wees N, et al. Impact of a Stay-at-Home Order on Stroke Admission, Subtype, and Metrics during the COVID-19 Pandemic. *Cerebrovasc Dis Extra.* (2020) 10:159–65. doi: 10.1159/000512742
15. Paolucci M, Biguzzi S, Cordici F, Lotti EM, Morresi S, Romoli M, et al. Impact of COVID-19 pandemic on acute stroke care: facing an epidemiological paradox with a paradigm shift. *Neurol Sci.* (2020) 1–8. doi: 10.1007/s10072-020-04914-4. [Epub ahead of print].
16. Desai SM, Guyette FX, Martin-Gill C, Jadhav AP. Collateral damage – impact of a pandemic on stroke emergency services. *J Stroke Cerebrovasc Dis.* (2020) 29:104988. doi: 10.1016/j.jstrokecerebrovasdis.2020.104988
17. Diegoli H, Magalhães PSC, Martins SCO, Moro CHC, Franca PHC, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 Era. *Stroke.* (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
18. Mehrpour M, Shuaib A, Farahani M, Hatamabadi HR, Fatehi Z, Ghaffari M, et al. Coronavirus disease 2019 and stroke in Iran: a case series and effects on stroke admissions. *Int J Stroke.* (2020) 51:2315–21. doi: 10.1177/1747493020937397
19. Mag Uidhir F, Bathula R, Sivagnanaratnam A, Abdul-Saheb M, Devine J, Cohen DL. Impact of COVID-19 on stroke caseload in a major hyperacute stroke unit. *J Stroke Cerebrovasc Dis.* (2020) 29:105383. doi: 10.1016/j.jstrokecerebrovasdis.2020.105383
20. Esenwa C, Parides MK, Labovitz DL. The effect of COVID-19 on stroke hospitalizations in New York City. *J Stroke Cerebrovasc Dis.* (2020) 29:105114. doi: 10.1016/j.jstrokecerebrovasdis.2020.105114
21. Wu Y, Chen F, Wang Z, Feng W, Liu Y, Wang Y, et al. Reductions in hospital admissions and delays in acute stroke care during the pandemic of COVID-19. *Front Neurol.* (2020) 11:584734. doi: 10.3389/fneur.2020.584734
22. Chen CH, Liu CH, Chi NF, Sung PS, Hsieh CY, Lee M, et al. Maintenance of stroke care quality amid the coronavirus disease 2019 outbreak in Taiwan. *J Stroke.* (2020) 22:407–1. doi: 10.5853/jos.2020.02292
23. Katsanos AH, Palaiodimou L, Zand R, Yaghi S, Kamel H, Navi BB, et al. The impact of SARS-CoV−2 on stroke epidemiology and care: a meta-analysis. *Ann Neurol.* (2020) 89:380–8. doi: 10.1002/ana.25967
24. Hecht N, Wessels L, Werft FO, Schneider UC, Czabanka M, Vajkoczy P. Need for ensuring care for neuro-emergencies—lessons learned from the COVID-19 pandemic. *Acta Neurochir (Wien).* (2020) 162:1795–801. doi: 10.1007/s00701-020-04437-z
25. Naccarato M, Scali I, Olivo S, Ajčević M, Buoite Stella A, Furlanis G, et al. Has COVID-19 played an unexpected "stroke" on the chain of survival? *J Neurol Sci.* (2020) 414:116889. doi: 10.1016/j.jns.2020.116889
26. Yang B, Wang T, Chen J, Chen Y, Wang Y, Gao P, et al. Impact of the COVID-19 pandemic on the process and outcome of thrombectomy for acute ischemic stroke. *J Neurointerv Surg.* (2020) 12:664–8. doi: 10.1136/neurintsurg-2020-016177
27. Pop R, Quenardelle V, Hasiu A, Mihoc D, Sellal F, Dugay MH, et al. Impact of the COVID-19 outbreak on acute stroke pathways – insights from the Alsace region in France. *Eur J Neurol.* (2020) 27:1783–7. doi: 10.1111/ene.14316
28. Schirmer CM, Ringer AJ, Arthur AS, Binning MJ, Fox WC, James RF, et al. Delayed presentation of acute ischemic strokes during the COVID-19 crisis. *J Neurointerv Surg.* (2020) 12:639–42. doi: 10.1136/neurintsurg-2020-016299
29. Rudilosso S, Laredo C, Vera V, Vargas M, Renú A, Llull L, et al. Acute stroke care is at risk in the era of covid-19: experience at a comprehensive stroke center in Barcelona. *Stroke.* (2020) 51:1991–5. doi: 10.1161/STROKEAHA.120.030329
30. Agarwal S, Scher E, Rossan-Raghunath N, Marolia D, Butnar M, Torres J, et al. Acute stroke care in a New York City comprehensive stroke center during the COVID-19 pandemic. *J Stroke Cerebrovasc Dis.* (2020) 29:1–6. doi: 10.1016/j.jstrokecerebrovasdis.2020.105068
31. Frisullo G, Brunetti V, Di Iorio R, Broccolini A, Caliandro P, Monforte M, et al. Effect of lockdown on the management of ischemic stroke: an Italian experience from a COVID hospital. *Neurol Sci.* (2020) 41:2309–13. doi: 10.1007/s10072-020-04545-9
32. Rinkel LA, Prick JCM, Slot RER, Sombroek NMA, Burggraaff J, Groot AE, et al. Impact of the COVID-19 outbreak on acute stroke care. *J Neurol.* (2020) 1–6. doi: 10.1007/s00415-020-10069-1. [Epub ahead of print].
33. Kwan J, Brown M, Bentley P, D'Anna L, Hall C, Halse O, et al. Impact of COVID-19 pandemic on a regional stroke thrombectomy service in the United Kingdom. *Cerebrovasc Dis.* (2020) 1–7. doi: 10.1159/000512603. [Epub ahead of print].

34. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ (Buddy), Culebras A, et al. An updated definition of stroke for the 21st century. *Stroke.* (2013) 44:2064–89. doi: 10.1161/str.0b013e318296aeca
35. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack. *Stroke.* (2009) 40:2276–93. doi: 10.1161/strokeaha.108.192218
36. Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke.* (2015) 46:2032–60. doi: 10.1161/STR.0000000000000069
37. Saposnik G, Barinagarrementeria F, Brown RD, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2011) 42:1158–92. doi: 10.1161/STR.0b013e31820a8364
38. Nadarajan V, Perry RJ, Johnson J, Werring DJ. Transient ischaemic attacks: mimics and chameleons. *Pract Neurol.* (2014) 14:23–31. doi: 10.1136/practneurol-2013-000782
39. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke A. *Stroke.* (2019) 50:e344–418. doi: 10.1161/STR.0000000000000211
40. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med.* (2018) 378:708–18. doi: 10.1056/NEJMoa1713973
41. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med.* (2018) 378:11–21. doi: 10.1056/NEJMoa1706442
42. Ramos-Rincon J-M, Buonaiuto V, Ricci M, Martín-Carmona J, Paredes-Ruíz D, Calderón-Moreno M, et al. Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. *J Gerontol A Biol Sci Med Sci.* (2020) 220:480–94. doi: 10.1093/gerona/glaa243
43. D'Anna L, Sheikh A, Bathula R, Elmamoun S, Oppong A, Singh R, et al. Decreasing referrals to transient ischaemic attack clinics during the COVID-19 outbreak: results from a multicentre cross-sectional survey. *BMJ Open.* (2020) 10:1–4. doi: 10.1136/bmjopen-2020-041514
44. Sacco S, Ricci S, Ornello R, Eusebi P, Petraglia L, Toni D, et al. Reduced admissions for cerebrovascular events during COVID-19 outbreak in Italy. *Stroke.* (2020) 51:3746–50. doi: 10.1161/strokeaha.120.031293
45. Markus HS, Brainin M. COVID-19 and stroke—a global world stroke organization perspective. *Int J Stroke.* (2020) 15:361–4. doi: 10.1177/1747493020923472
46. The Health Foundation. *Health Foundation Analysis of NHS Monthly A & E Attendances and Emergency Admissions and Ambulance Quality Indicators 2019/20 and 2020/21*. The Health Foundation (2020).
47. Joseph K, Kyriakos L, Banerjee S. Letter by Kwan et al. regarding article, acute stroke management during the Covid-19 pandemic: does confinement impact eligibility for endovascular therapy? *Stroke.* (2020) 51: e338–e339. doi: 10.1161/STROKEAHA.120.031638

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

REVIEW
published: 18 February 2021
doi: 10.3389/fneur.2020.613832

Neurologic Care of COVID-19 in Children

*Susana Boronat**

Pediatric Neurology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Most children with SARS-CoV-2 infection have relatively mild clinical symptoms without fever or pneumonia, although severe cases with multiple-organ failure have been reported. Neurological symptoms, which have been mainly reported in adults, are very rare in children. This article will review 2 different aspects of neurological involvement related to this infection in children. In the first part, we will review the neurological abnormalities reported in children caused by this viral infection. Adults frequently report muscle pain, headache, anosmia, dysgeusia, and occasionally more severe central or peripheral nervous system damage. Neurological involvement seems infrequent in children, although some cases have been reported. In the second part, we will discuss the COVID-19 pandemic impact on the healthcare system of some countries, causing collateral damage to general pediatric care and in particular to those children affected with chronic diseases, mainly neurological conditions, including autism, intellectual disability, attention deficit and hyperactivity disorder (ADHD), neuromuscular disorders, cerebral palsy, and epilepsy, and patients needing neurosurgical procedures.

Keywords: SARS-CoV-2, seizures, epilepsy, neurocognitive, behavior, stress, child abuse

OPEN ACCESS

Edited by:
Fernando Testai,
University of Illinois at Chicago,
United States

Reviewed by:
Karin Diserens,
Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland
Alessandra Splendiani,
University of L'Aquila, Italy

****Correspondence:***
Susana Boronat
sboronat@santpau.cat

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care,
a section of the journal Frontiers in Neurology

Received: *22 October 2020*
Accepted: *31 December 2020*
Published: *18 February 2021*

Citation:
Boronat S (2021) Neurologic Care of COVID-19 in Children.
Front. Neurol. 11:613832.
doi: 10.3389/fneur.2020.613832

INTRODUCTION

The SARS-CoV-2 incubation period is usually 3–7 days, ranging from 1 to 14 days, and patients usually recover within 2 weeks. Typical clinical manifestations are dry cough and fever. Children are more frequently asymptomatic or they present with mild symptoms. Very rarely, severe pediatric cases may progress to acute respiratory failure and multiple-organ failure. The pediatric inflammatory multisystem syndrome, also referred to as Kawasaki-like SARS-CoV-2 syndrome, is a severe clinical picture that has been reported in children and shows persistent fever with multisystem organ involvement along with elevated inflammatory markers. It seems to appear in a late phase, as positive immunoglobulin G tests for SARS-CoV-2 have been reported in many cases (1–3).

In **Table 1**, we summarize the main topics of this article, including the main clinical neurological manifestations in children, current knowledge about treatment, and consequences of the COVID19 pandemic to children with neurological diseases.

NEUROLOGICAL MANIFESTATIONS RELATED TO SARS-CoV-2 INFECTION

Adults frequently report muscle pain, headache, anosmia, and dysgeusia and occasionally more severe central or peripheral nervous system damage. Within 214 patients from Wuhan reported by Mao and colleagues, 78 (36%) had neurological involvement, including neuralgic pain, myopathy,

TABLE 1 | Summary.

Neurological involvement in children related to infection with SARS-CoV-2	• Encephalopathy • Inflammatory central nervous system lesions • Seizures • Stroke • Hyposmia and hypogeusia • Muscular involvement • Guillain-Barré syndrome • Other rare manifestations
Current treatment recommendations for children with SARS-CoV-2 infection	
Consequences of the COVID19 pandemic to children with neurological diseases	• Cerebral palsy • Neuromuscular disorders • Migraines • Neurosurgical conditions • Epilepsy • Behavioral problems • Autism and intellectual disability • Attention deficit and hyperactivity disorder • Psychiatric disorders

altered states of consciousness, and stroke. These symptoms were more frequent in severe cases (46 vs. 30% in non-severe) (4).

A recent meta-analysis including 41 articles showed a wide spectrum of neurological manifestations due to SARS-CoV-2 infection. The most frequent neurological symptoms included anosmia (36–86%) and dysgeusia (33–89%). More severe cases showed inflammation of the central nervous system, stroke, or Guillain–Barré syndrome (5).

NEUROLOGICAL INVOLVEMENT IN CHILDREN RELATED TO INFECTION WITH SARS-CoV-2

Twenty-one studies (14 about non-specific and 7 about specific neurological involvement) have been included in a systematic review of neurological manifestations in children published in September 2020. Out of 3,707 children, 581 (16%) had non-specific neurological manifestations, such as headache and fatigue, and 42 (1%) had specific neurological involvement including encephalopathy (25), meningeal signs (17), and/or seizures (12), which were more common in children with severe illness. Very rarely, Guillain–Barré syndrome, cranial nerve palsies, or intracranial hemorrhage were reported (6).

Next, I will review the current literature about specific neurological abnormalities in children infected with SARS-CoV-2.

Encephalopathy

Encephalopathy of variable severity is the predominant definite neurological complication in children, usually in the setting of COVID-19 pediatric multisystem inflammatory syndrome. In these cases, aside from the infection process, septic shock or hypoxia may also play a causative role in some of these encephalopathic patients (6).

In one study, within 27 children with pediatric multisystem inflammatory syndrome related to SARS-CoV-2 infection, 4 (15%) had encephalopathy. Cerebellar and brainstem signs and muscle weakness were also detected. All patients improved and 2 showed total recovery. Interestingly, on the brain MRI, the splenium of the corpus callosum showed signal changes in all 4 patients. Other studies, including cerebrospinal fluid cells and PCR for SARS-CoV-2, oligoclonal band test or CNS autoantibodies were negative in all patients. Slow background activity was detected in the 3 patients who had EEG studies, and mild myopathic and neuropathic changes were seen in all 3 patients who were assessed by neurophysiologic studies (7). A previously healthy 16-year-old positive for SARS-CoV-2 developed seizures, encephalopathy, and syndrome of inappropriate anti-diuretic hormone (SIADH). Her CSF testing was negative for SARS-CoV-2. Although a thorough workup revealed no other infectious or autoimmune pathologies, MR imaging was not obtained (8). A lethargic 4-year-old girl with multisystem inflammatory syndrome associated with COVID19 showed aseptic meningitis and cytokine storm an low levels of BDNF (9).

Inflammatory Central Nervous System Lesions

The SARS-CoV-2-related pediatric multisystem inflammatory syndrome is characterized by a Kawasaki-like illness with persistent fever and multisystem organ involvement, including cardiac dysfunction, with elevated inflammatory markers. Consistent with other cases with encephalopathy showing slow EEG background activity and lesions in the corpus callosum (7, 10), a 2-year-old presenting with altered mental status was found also to have a moderate background slowing in the EEG, but in this case, the MRI lesions involved the bilateral lateral thalamic nuclei, showing restricted diffusion without T2 or FLAIR anomalies (11). These lesions may resemble an acute necrotizing encephalopathy (ANE), although without a hemorrhagic component in this case. ANE is a rare manifestation of some viral infections, such as influenza, leading to bilateral thalamic damage and has been related to intracranial cytokine storms, which result in blood–brain barrier breakdown. At the onset of his encephalopathy, CSF SARS-CoV-2 PCR was negative, but interleukin-6 was elevated and went down gradually as he improved. Although more frequent in children, ANE can also affect adults, and it has been reported in an adult patient with SARS-CoV-2 infection (12).

One case of acute disseminated encephalomyelitis has been reported in a 12-year-old girl with SARS-CoV-2 infection. Five days after the initial presentation with headache, rash, and fever, she had respiratory failure related to generalized motor weakness. MRI showed an extensive cervical myelopathy and restricted diffusion involving cerebral white matter, including the splenium of the corpus callosum (13). Another two children have been reported with lesions of the corpus callosum, affecting mainly splenium, in the context of SARS-CoV-2-related pediatric

inflammatory multisystem syndrome (14). These cases suggest that the splenium of corpus callosum may be a specially vulnerable area for inflammatory lesions in the context of SARS-CoV-2 infection with CNS involvement.

Recently, an international study with children with encephalopathy related to SARS-CoV-2 infection and abnormal neuroimaging findings was performed. Data were reviewed by a child neurologist, a pediatric infectious diseases expert, and a central neuroradiology panel. Neurological disease related to SARS-CoV-2 infection was reviewed in 38 children from France ($n = 13$), the UK ($n = 8$), the USA ($n = 5$), Brazil ($n = 4$), Argentina ($n = 4$), India ($n = 2$), Peru ($n = 1$), and Saudi Arabia ($n = 1$). The most common imaging abnormalities were post-infectious immune-mediated acute disseminated encephalomyelitis changes of the brain (16 patients), myelitis (8 patients), and neural enhancement (13 patients). Corpus callosum splenial lesions (7 patients) and myositis (4 patients) were predominantly observed in children with multisystem inflammatory syndrome (15).

Seizures

Pediatric seizures associated with SARS-CoV-2 infection are usually acute symptomatic seizures and mainly occur during febrile episodes (6).

Two cases of febrile status epilepticus (16, 17) and two cases of status epilepticus in the setting of multisystem inflammatory syndrome due to SARS-CoV-2 have been reported (18, 19). One of these cases showed an occipital intracerebral hemorrhage (18).

Seizures have been reported as early as the first months of life, with or without fever. A 6-week-old with positive SARS-CoV-2 PCR presented with fever, cough, and brief episodes of impaired responsiveness with upward gaze and stiffening of both legs. EEG showed intermittent delta rhythm. All the other exams, including brain MRI, were normal (20). One male infant aged 26 days with SARS-CoV-2 infection and fever had 2 episodes of generalized hypertonia. The EEG was normal (21). A 3-month-old girl was reported to present with non-febrile focal seizures with impaired consciousness during SARS-CoV-2 infection at days 6 and 9 from onset, with normal EEG and MRI. D-Dimer and ferritin levels were increased. In this case, whole-exome sequencing was performed, revealing a pathogenic frameshift mutation in the *PRRT2* gene in both the mother and the infant. The mother had two late infantile febrile convulsions with normal neurological development. The authors suggested that SARS-CoV-2 may trigger non-febrile seizures in infants with a genetic predisposition (22).

A child presenting as isolated afebrile seizure in the setting of SARS-CoV-2 infection without other symptoms has also been reported (23). An adolescent with respiratory symptoms and lethargy showed epileptic apneic episodes (24).

Stroke

Although SARS-CoV-2 predisposes to stroke in adults (4, 5), it is not the case for children, as other risk factors for stroke in children are usually absent. Angiotensin-converting enzyme 2 (ACE-2), located in the brain vascular endothelium, acts as a receptor for the virus, so clotting and infarction related to this mechanism might also be possible in children. However, stroke in children due to SARS-CoV-2 infection is exceptional, so the presence in adults of other risk factors for stroke seems to be very important for pathogenicity (25).

Coinfection by SARS-CoV-2 and tuberculous meningitis in a child was complicated by cerebral sinus venous thrombosis and arterial ischemic stroke, with elevated D-dimer, fibrinogen, and ferritin levels, suggesting that both microorganisms induced an important inflammatory prothrombotic situation leading to these complications (26).

One case with multisystem inflammatory syndrome that presented with status epilepticus showed an occipital intracerebral hemorrhage (18).

A previously healthy 14-year-old boy suffered an infarct involving middle and anterior right cerebral arteries. He developed arrhythmia with refractory shock, requiring extracorporeal life support, and died from the cerebral infarct. Postmortem microbiology was positive for SARS-CoV-2 (27).

A previously healthy 13-year-old girl who presented with loss of consciousness and was SARS-CoV-2 positive and had a ruptured pseudoaneurysm of the left middle cerebral artery (28).

Other stroke events have been associated with multisystem inflammatory syndrome in pediatric patients. A previously healthy 5-year-old who developed cardiogenic shock and required extracorporeal membrane oxygen had a right middle cerebral artery infarction, cerebral edema, and diffuse contralateral subarachnoid hemorrhage and died. A 2-month-old requiring extracorporeal membrane oxygen with refractory seizures developed multiple hemorrhagic infarctions. Although he tested negative for SARS-CoV-2 antibodies, his clinical presentation was suspicious for SARS-CoV-2 infection with elevated IL-6 levels (29).

Two children of 8 and 16 years of age suffered arterial ischemic strokes due to acute intracranial large vessel occlusion within 3–4 weeks of SARS-CoV-2 infection. One case presented with bilateral middle cerebral artery strokes and the other with multiple-organ system dysfunction. Neither patient fulfilled criteria for multisystem inflammatory syndrome in children (MIS-C) given absence of fever. These data suggest that systemic post-infectious arteritis with cerebrovascular involvement may complicate SARS-CoV-2 infection (30).

Hyposmia and Hypogeusia

Anosmia/hyposmia and dysgeusia have been reported in 30–80% cases of SARS-CoV-2 in the adult population. As the olfactory neuroepithelium expresses ACE-2, a direct invasion by the virus causing inflammatory changes locally would lead to hyposmia, usually showing in the early stages of the disease (6). In children, hyposmia with or without hypogeusia was detected in 17 out of 27 (62%) cases (31). One child presented with isolated anosmia (32) and three adolescents showed these isolated symptoms in the absence of other symptomatology (33).

Muscular Involvement

In a comparison between 7 children and 25 adults, while 13 adults (52%) complained of muscle pain, none of the children

did. However, children showed elevation of creatine kinase levels more frequently than adults (57 vs. 4%) (34).

Guillain–Barré Syndrome

Two cases of Guillain–Barré syndrome have been reported in children. An 11-year-old boy showed an acute inflammatory demyelinating polyneuropathy variant (35) and a 15-year-old boy presented with an acute motor axonal neuropathy (36). Both showed a favorable response to intravenous immunoglobulin.

Cranial Polyneuropathy

At day 21 of a hematopoietic stem cell transplantation, a 6-year-old patient with cerebral vasculopathy due to sickle cell anemia presented with dysfunction of cranial nerves V, VII, and IX. Inflammatory anomalies were detected in these nerves in the brain MRI (37).

Orbital Cellulitis With Intracranial Extension

Two adolescents with sinusitis and orbital cellulitis were reported. One had a hemorrhagic abscess, and the other an intracranial epidural abscess, with meningeal enhancement or extension in both cases (38).

Current Treatment Recommendations for Children With SARS-CoV-2 Infection

General management of children with SARS-CoV-2 infection is based on supportive therapy.

Based on findings from the RECOVERY trial, corticosteroids are recommended in adult patients who are mechanically ventilated or who require supplemental oxygen. Because only a few pediatric patients were included in this trial, it is difficult to extend these recommendations for children. Dexamethasone may be used in pediatric patients requiring mechanical ventilation, but it is generally not recommended for those who require only minimal oxygen support (39) (Coronavirus disease 19 NIH Treatment Guidelines).

In a trial of adults hospitalized with SARS-CoV-2, remdesivir, a viral RNA–dependent RNA polymerase inhibitor, was shown to decrease time to recovery, but the effects are not known in the pediatric population (40) A phase 2/3 trial of remdesivir was initiated in June 2020 for children (ClinicalTrials.gov ID: NCT04431453). Convalescent plasma, which has recently been approved by the FDA for emergency use, has shown some efficacy in reducing mortality in critically ill patients (41) A phase 1 clinical trial of convalescent plasma in children is ongoing (ClinicalTrials.gov ID: NCT04377672).

There are insufficient data in children to recommend either for or against the use of other treatments that are currently under investigation (Coronavirus disease 19 NIH Treatment Guidelines).

Given the current scarce evidence of these treatments in pediatric patients, the standard management of neurologic complications, including ischemic stroke, seizures, and inflammatory lesions, is recommended at this point (39).

CONSEQUENCES OF THE COVID19 PANDEMIC REGARDING CHILDREN HEALTH CARE

The COVID-19 pandemic has become an enormous challenge for many healthcare systems, mainly in the management of chronic patients. Children with neurological conditions are especially vulnerable to this situation.

Delayed Access to Medical Care

Measures introduced by governments to try to delay the spread of infection have impaired the access to emergency departments or primary care facilities for illnesses not related to SARS-CoV-2 infection. Evidence from previous epidemics found that hospital avoidance during outbreaks of MERS and SARS was common, but emergency departments returned early to normality following these pandemics, as they lasted 2–3 months. This is not the case scenario for the COVID-19 pandemic, with still many months of pandemic ahead of us (42). This expected prolonged reduced access to health care will be damaging to children, mainly neurologically affected children with special needs, including cerebral palsy or epilepsy.

Lazzerini et al. reported some consequences from delayed access to medical care during COVID-19 pandemic in Italy during a week in March 2020. Twelve cases of delayed access to hospital care leading to severe complications or death were detected. These complications included mainly diabetic ketoacidosis, sepsis, seizures, and bowel obstruction. Half of the children were admitted to an ICU and four died. In all cases, parents reported avoiding accessing hospital because of fear of infection with SARS-CoV-2 (43).

Children with previous neurological conditions, including cerebral palsy or severe intellectual disability or autism, may be especially vulnerable, mainly because of their inability to communicate and because their parents are used to deal at home with their chronic conditions. Two children with cerebral palsy died in the ambulance on the way to the hospital, one after 10 days of fever and the other after 3 days of bloody stools. A child with intellectual disability due to Mowat–Wilson syndrome, in dialysis for chronic renal insufficiency, arrived at the hospital after 3 days of hypoactivity and died 4 days later in the ICU (43). This data demonstrates that children with neurological disorders are specially fragile in this situation, as 3 of the 4 deaths affected patients with neurological conditions.

Changes in Modalities of Care

The COVID-19 pandemic has prompted to introduce rapidly telemedicine as one of the main modalities for patient clinic follow-ups. Visits by e-mail, telephone, or teleconference were quickly established at many hospital and primary care facilities in order to limit the spread of the virus. In some countries, including Spain, COVID-19 pandemic has accelerated the implantation of telemedicine in clinical care and it is planned to add this new modality to classical practice, during and once the pandemic is over.

Impact on Mental Health

Children are at risk of suffering the consequences of parental affected mental health driven by stress related to the COVID-19 pandemic. Also, children themselves may have problems coping with the situation, leading to hyperactivity, challenging behavior, depression, and anxiety. Children with normal development may overcome the situation only with supportive intervention, but it may be more challenging in children with previous behavioral or psychiatric problems.

An Italian study found increased anxiety in a study of 148 healthy adolescents. The items concerning breathing difficulties and sleep disorder were the most affected (44).

CONSEQUENCES TO PATIENTS WITH PREVIOUS NEUROLOGICAL DISEASES

Cerebral Palsy

Patients with cerebral palsy, who usually are prone to lung problems, may be at risk for more severe respiratory symptoms due to SARS-CoV-2 infection, requiring more frequently ICU admissions. Also, they are specially at risk of suffering consequences for delayed access to the emergency department in case of an acute illness. Also, limited access to chronic care programs, including physical therapy, botulinum toxin or chronic surveillance, has been problematic for these children. For example, orthopedic follow-ups in children with cerebral palsy try to identify early hip displacement in order to establish treatment at the right time, before the hip becomes painful. The COVID-19 pandemic has led to the cancellation of clinical appointments and elective surgeries at many hospitals, worsening the standard of care that these patients need (45).

Neuromuscular Disorders

Patients with neuromuscular disorders, including spinal muscular atrophy or muscular dystrophies, are especially at risk for respiratory complications in the setting of SARS-CoV-2. Specific consensus recommendations have been published to guide clinicians through these times of continuous adaptation of clinical care to the special needs of these patients (46, 47).

Migraines

Patients with migraine are specifically vulnerable to this situation. Disruption of sleep and dietary habits, high psychosocial stress and social isolation, may lead to worsening of headaches. A survey of 1,018 adult patients showed an increase in migraine frequency and severity, and more transformation to chronic migraine. The authors identified some risk factors for migraines worsening, including difficult access to their neurologist, chronic treatment abandonment, disruption of sleep and dietary schedules, comorbidity with anxiety and depression, and working during the pandemic (48). Two Italian studies showed a general improvement in children and adolescents with primary headaches and migraines during the lockdown. Reduction in school-related stress seems to be the main factor (49, 50). In a study of children with migraine in India during the pandemic, around 90% of caregivers were satisfied with the efficacy of telephonic consultations (51).

Neurosurgical Conditions

In general, urgent neurosurgery, for example, in cases of shunt malfunction, has not been delayed. It has been successfully performed during the pandemic with adequate measures of security in the operating room (52).

Epilepsy

The COVID-19 pandemic has an important impact in care of people with epilepsy.

A group of international epilepsy experts published a consensus statement on June 2020 in order to provide clinical guidelines for epileptic patients (53).

This situation poses a risk to good epilepsy control, as patients may be unable to get the proper information to adjust drugs or dosages, leading to self-prescription or stop of medications without physician advice.

The Pediatric Epilepsy Research Consortium and the Child Neurology Society collaborated to issue recommendations for diagnosis, treatment, and follow-up of infantile spasms in this special time (54) advocating for oral therapies as initial treatment and use of telemedicine. Also, a guideline for Chinese epileptic children has been published. The authors emphasize the use of telemedicine for care and provide a useful guideline of medications for SARS-CoV-2 that might have interactions with antiepileptic drugs (55).

A Spanish survey in April 2020 assessed the impact of the COVID-19 pandemic in patients with genetic developmental epileptic encephalopathies. Within 277 responders, 39 (14%) reported seizure frequency increase and 87 (30%) cases showed behavioral deterioration during the lockdown. In addition, nine patients experienced some degree of neurological regression and there was one case of status epilepticus. The main factors contributing to seizure or behavioral changes were inability to get the proper access to medical care, including difficulties reaching their neurologist, avoidance of seeking medical advice in the emergency department due to fear of infection, loss of regular stimulation and physical therapies, cancelation of essential medical appointments, and difficulties finding their antiepileptic drugs at a pharmacy. The oversaturation of the healthcare system was especially important in Madrid and Barcelona, the Spanish regions with the highest incidence of COVID-19. Also, new-onset depression or anxiety in caregivers, living in small homes without a terrace or yard, and economic problems were factors leading to worsening of these patients (56).

Behavioral Issues

Children with behavioral problems treated with regular psychological therapy are at high risk of worsening during the COVID-19 pandemic, due to isolation from peers, family stress, and imposed changes in routine. Some countries have implemented online therapy programs that allow to maintain physical distance and provide emotional support at the same time. Mental health of parents must be assessed, as they have direct impact on their child's behavior (57).

Autism and Intellectual Disability

Lifestyle changes imposed by the COVID-19 pandemic are hard especially for those with intellectual disability and/or autism, as they have problems with understanding the situation, communicating, and expressing their feelings, which may lead to behavioral problems, including self-aggressions. Because of their need of predictable routines, and preference for certain activities, they may feel frustrated with schedule changes. Their progress is at risk, and they may even show regression of some skills. Scheduling specific times for wake and sleep, exercise, schoolwork, and meals is important for all children and even more in individuals with neurodevelopmental problems (58).

Attention Deficit and Hyperactivity Disorder (ADHD)

Children with ADHD are also at risk in this situation. The loss of daily routine will worsen ADHD symptoms. The psychological stress lived by parents during the COVID-19 pandemic may exacerbate the children's symptoms As expected, a study among Chinese school-aged children with ADHD showed that symptoms were significantly worse during the COVID-19 outbreak compared to normal state (59). The European ADHD Guidelines Group (EAGG) has addressed these issues and developed a guideline for the management of ADHD through the pandemic (60).

Psychiatric Disorders

Individuals with mental health conditions are especially vulnerable to worsening of their symptoms during this pandemic. Some individuals manifest these mental issues as somatic complains, such as pain or breathing difficulties. Somatic symptom disorders may peak in this setting, as demonstrated by a case report of a 16-year-old adolescent, who despite testing negative for SARS-CoV-2, had an obsessive preoccupation about being infected and required an admission to the Psychiatric Unit, showing a rapid response to antidepressant and antipsychotic medications (61).

DISCUSSION

We have reviewed the neurological clinical findings in children infected with SARS-CoV-2 published at this time, but it is expected to gather more knowledge in the future, as the COVID-19 pandemic evolves.

Neurological complications of SARS-CoV-2 infection in children are much less frequent than in adult population. Around 16% of children show non-specific neurological symptoms as headache, while more severe and specific neurological complications occur only around 1% of cases.

Children with SARS-CoV-2 multisystem inflammatory syndrome are especially at risk for neurological complications. Encephalopathy is the more frequent abnormality, sometimes with symptomatic seizures, and it is usually transitory, without long-term neurological sequelae. In some patients, EEG and brain MRI show transient abnormalities, which usually resolve with time (6, 7).

The COVID-19 pandemic has supposed a struggle for healthcare systems around the world. Children with neurological conditions and their families are especially vulnerable.

Current data support the beneficial role of telemedicine in the care of these patients. Parents of children with neurological conditions need support, and they have to be encouraged to seek medical attention when needed and go to the emergency departments to avoid delay in diagnosis and treatment of potentially life-threatening conditions, such as infections, appendicitis, and shunt malfunctions. Delays in getting the adequate medical attention and other problems with neurologically affected children during the pandemic leading to severe problems and even death have been clearly documented.

Risk of abuse and neglect of children during the COVID-19 outbreak may peak due to parents' stress related to a mix of factors, including fear of illness, working from home while caring for children, financial insecurity, and lack of free time outdoors. With schools closed and families isolated in their homes, children are separated from teachers and healthcare workers, which are an important source of protection as they may detect and report suspected abuse (62, 63). A rise in pediatric blunt trauma, including skull and long bones fractures, face contusions, and intracranial hemorrhages, was reported in a hospital during the COVID-19 pandemic (64). This difficult time for some families, struggling with psychological stress and financial problems, must raise high suspicion for child abuse in some cases, mainly in behavior-challenging individuals such as those with ADHD, autism, and neurodevelopmental disorders (59, 63).

The healthcare system of every country has the obligation to assure adequate care for these children until the end of the pandemic.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

REFERENCES

1. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *N Engl J Med.* (2020) 382:1663–5. doi: 10.1056/NEJMc2005073
2. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatr Infect Dis J.* (2020) 39:355–68. doi: 10.1097/INF.0000000000002660
3. Moreno-Galarraga L, Taveras EM. COVID-19 disease in children: not as mild as we have been led to believe. *World J Pediatr.* (2020) 16:426–7. doi: 10.1007/s12519-020-00380-2
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
5. Wang L, Shen Y, Li M, Chuang H, Ye Y, Zhao H, et al. Clinical manifestations and evidence of neurological involvement in 2019 novel coronavirus SARS-CoV-2: a systematic review and meta-analysis. *J Neurol.* (2020) 267:2777–89. doi: 10.1007/s00415-020-09974-2
6. Panda PK, Sharawat IK, Panda P, Natarajan V, Bhakat R, Dawman L. Neurological complications of SARS-CoV-2 infection in children: a systematic review and meta-analysis. *J Trop Pediatr.* (2020) fmaa070. doi: 10.1093/tropej/fmaa070

7. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol.* (2020) 77:1440–5. doi: 10.1001/jamaneurol.2020.2687
8. Bhavsar SM, Agarwal S, Lewis R, Ganta A, Roshchina YS, Clouser KN, et al. Piwoz COVID-19 infection associated with encephalitis in an adolescent. *Neurol Clin Pract.* (2020). doi: 10.1212/CPJ.0000000000000911. [Epub ahead of print].
9. De Paulis M, Leal Oliveira DB, Vieira RP, Pinto IC, Machado RRG, Cavalcanti MP, et al. Multisystem inflammatory syndrome associated with COVID-19 with neurologic manifestations in a child: a brief report. *Pediatr Infect Dis J.* (2020) 39:e321. doi: 10.1097/INF.0000000000002834
10. Lin J, Lawson EC, Verma S, Peterson RB, Sidhu R. Cytotoxic lesion of the corpus callosum in an adolescent with multisystem inflammatory syndrome and SARS-CoV-2 infection. *Am J Neuroradiol.* (2020) 41:2017–19. doi: 10.3174/ajnr.A6755
11. Abel D, Shen M, Abid Z, Hennigan C, Boneparth A, Miller EH, et al. Encephalopathy and bilateral thalamic lesions in a child with MIS-C associated with COVID-19. *Neurology.* (2020) 95:745–8. doi: 10.1212/WNL.0000000000010652
12. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. *Radiology.* (2020) 296:E119–120. doi: 10.1148/radiol.2020201187
13. Miranda Henriques-Souza AM, de Melo AMG, Madeiro BAC, Freitas LF, Rocha-Filho PAS, Gonçalves FG. Acute disseminated encephalomyelitis in a COVID-19 pediatric patient. *Neuroradiology.* (2020) 63:141–5. doi: 10.1007/s00234-020-02571-0
14. Gaur P, Dixon L, Jones B, Lyall H, Jan W. COVID-19-associated cytotoxic lesions of the corpus callosum. *Am J Neuroradiol.* (2020) 41:1905–7. doi: 10.3174/ajnr.A6713
15. Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. *Lancet Child Adolesc Health.* (2020). doi: 10.1016/S2352-4642(20)30362-X. [Epub ahead of print].
16. Chegondi M, Kothari H, Chacham S, Badheka A. Coronavirus disease 2019 (COVID-19) associated with febrile status epilepticus in a child. *Cureus.* (2020) 12:e9840. doi: 10.7759/cureus.9840
17. McAbee GN, Brosgol Y, Pavlakis S, Agha R, Gaffoor M. Encephalitis associated with COVID-19 infection in an 11-year-old child. *Pediatr Neurol.* (2020) 109:94. doi: 10.1016/j.pediatrneurol.2020.04.013
18. Saeed A, Shorafa E. Status epilepticus as a first presentation of COVID-19 infection in a 3 years old boy; case report and review the literature. *IDCases.* (2020) 22:e00942. doi: 10.1016/j.idcr.2020.e00942
19. Shenker J, Trogen B, Schroeder L, Ratner AJ, Kahn P. Multisystem inflammatory syndrome in children associated with status epilepticus. *J Pediatr.* (2020) 227:300–1. doi: 10.1016/j.jpeds.2020.07.062
20. Dugue R, Cay-Martínez KC, Thakur KT, Garcia JA, Chauhan LV, Williams SH, et al. Neurologic manifestations in an infant with COVID-19. *Neurology.* (2020) 94:1100–2. doi: 10.1212/WNL.0000000000009653
21. Chacón-Aguilar R, Osorio-Cámara JM, Sanjurjo-Jimenez I, González-González C, López-Carnero J, Pérez-Moneo-Agapito B. COVID-19: fever syndrome and neurological symptoms in a neonate. *An Pediatr.* (2020) 92:373–4. doi: 10.1016/j.anpede.2020.04.001
22. García-Howard M, Herranz-Aguirre M, Moreno-Galarraga L, Urretavizcaya-Martínez M, Alegría-Echauri J, Gorría-Redondo N, et al. Case report: benign infantile seizures temporally associated with COVID-19. *Front Pediatr.* (2020) 8:507. doi: 10.3389/fped.2020.00507
23. Bhatta S, Sayed A, Ranabhat B, Bhatta RK, Acharya Y. New-onset seizure as the only presentation in a child with COVID-19. *Cureus.* (2020) 12:e8820. doi: 10.7759/cureus.8820
24. Enner S, Hormozdyaran S, Varughese R, Milillo J, Pavkovic I, Laureta E, et al. Central apnea in an adolescent with COVID-19. *Pediatr Neurol.* (2020) 110:87–8. doi: 10.1016/j.pediatrneurol.2020.05.012
25. Montalvan V, Lee J, Bueso T, De Toledo J, Rivas K. Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg.* (2020) 194:105921. doi: 10.1016/j.clineuro.2020.105921
26. Essajee F, Solomons R, Goussard P, Van Toorn R. Child with tuberculous meningitis and COVID-19 coinfection complicated by extensive cerebral sinus venous thrombosis. *BMJ Case Rep.* (2020) 13:e238597. doi: 10.1136/bcr-2020-238597
27. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* (2020) 395:1607–8. doi: 10.1016/S0140-6736(20)31094-1
28. Savić D, Alsheikh TM, Alhaj AK, Lazovic L, Alsarraf L, Bosnjakovic P, et al. Ruptured cerebral pseudoaneurysm in an adolescent as an early onset of COVID-19 infection: case report. *Acta Neurochirurg.* (2020) 162:2725–29. doi: 10.1007/s00701-020-04510-7
29. Schupper AJ., Yaeger KA, Morgenstern PF. Neurological manifestations of pediatric multi-system inflammatory syndrome potentially associated with COVID-19. *Childs Nervous Syst.* (2020) 36:1579–80. doi: 10.1007/s00381-020-04755-8
30. Appavu B, Deng D, Dowling MM, Garg S, Mangum T, Boerwinkle V, et al. Arteritis and large vessel occlusive strokes in children following COVID-19 infection. *Pediatrics.* (2020) 2020:e2020023440. doi: 10.1542/peds.2020-023440
31. Oualha M, Bendavid M, Berteloot L, Corsia A, Lesage F, Vedrenne M, et al. Severe and fatal forms of COVID-19 in children. *Archiv Pediatr.* (2020) 27:235–8. doi: 10.1016/j.arcped.2020.05.010
32. Marhaeni W, Wijaya AB, Kusumaningtyas P, Mapianto RS. Thalassemic child presenting with anosmia due to COVID-19. *Indian J Pediatr.* (2020) 87:750. doi: 10.1007/s12098-020-03370-4
33. Mak PQ, Chung K, Wong JS, Shek C, Kwan MY. Anosmia and ageusia: not an uncommon presentation of COVID-19 infection in children and adolescents. *Pediatr Infect Dis J.* (2020) 39:e199–200. doi: 10.1097/INF.0000000000002718
34. Han Y, Feng Z, Sun L, Ren X, Wang H, Xue Y, et al. A comparative-descriptive analysis of clinical characteristics in 2019-coronavirus-infected children and adults. *J Med Virol.* (2020) 92:1596–602. doi: 10.1002/jmv.25835
35. Khalifa M, Zakaria F, Ragab Y, Saad A, Bamaga A, Emad Y, et al. Guillain-Barré syndrome associated with severe acute respiratory syndrome coronavirus 2 detection and coronavirus disease 2019 in a child. *J Pediatr Infect Dis Soc.* (2020) 9:510–3. doi: 10.1093/jpids/piaa086
36. Frank CHM, Almeida VR, Marques EA, Monteiro QS, Feitoza PVS, Borba MGS, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection in a pediatric patient. *J Trop Pediatr.* (2020) fmaa044. doi: 10.1093/tropej/fmaa044
37. Roussel A, Germanaud D, Bouchoucha Y, Ouldali N, Vedrenne-Cloquet M, Castelle M, et al. Cranial polyneuropathy as the first manifestation of a severe COVID-19 in a child. *Pediatr Blood Cancer.* (2020) 68:e28707. doi: 10.1002/pbc.28707
38. Turbin RE, Wawrzusin PJ, Sakla NM, Traba CM, Wong KG, Mirani N, et al. Orbital cellulitis, sinusitis and intracranial abnormalities in two adolescents with COVID-19. *Orbit.* (2020) 39:305–10. doi: 10.1080/01676830.2020.1768560
39. Kim Y, Walser SA, Asghar SJ, Jain R, Mainali G, Kumar A. A comprehensive review of neurologic manifestations of COVID-19 and management of pre-existing neurologic disorders in children. *J Child Neurol.* (2020) 36:324–30. doi: 10.1177/0883073820968995
40. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19-final report. *N Engl J Med.* (2020) 383:1813–26. doi: 10.1056/NEJMoa2007764
41. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. *N Engl J Med.* (2021). doi: 10.1056/NEJMoa2031893. [Epub ahead of print].
42. McDonnell T, Nicholson E, Conlon C, Barrett M, Cummins F, Hensey C, et al. Assessing the impact of COVID-19 public health stages on paediatric emergency attendance. *Int J Environ Res Public Health.* (2020) 17:6719. doi: 10.3390/ijerph17186719
43. Lazzerini M, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision of care in italy resulting from fear of COVID-19. *Lancet Child Adolesc.* (2020) 4:e10–11. doi: 10.1016/S2352-4642(20)30108-5
44. Smirni P, Lavanco G, Smirni D. Anxiety in older adolescents at the time of COVID-19. *J Clin Med.* (2020) 9:3064. doi: 10.3390/jcm9103064

45. Miller S, Bone J, Mulpuri K. Suspension of hip surveillance for children with cerebral palsy during the COVID-19 outbreak: the benefit of hip surveillance does not outweigh the risk of infection. *Indian J Orthopaed.* (2020) 28:1–3. doi: 10.1007/s43465-020-00236-x
46. Veerapandiyan A, Connolly AM, Finkel RS, Arya K, Mathews KD, Smith EC, et al. Spinal muscular atrophy care in the COVID-19 pandemic era. *Muscle Nerve.* (2020) 62:46–9. doi: 10.1002/mus.26903
47. Veerapandiyan A, Wagner KR, Apkon S, McDonald CM, Mathews KD, Parsons JA, et al. The care of patients with duchenne, becker, and other muscular dystrophies in the COVID-19 pandemic. *Muscle Nerve.* (2020) 62:41–5. doi: 10.1002/mus.26902
48. Al-Hashel JY, Ismail II. Impact of coronavirus disease 2019 (COVID-19) pandemic on patients with migraine: a web-based survey study. *J Headache Pain.* (2020) 21:115. doi: 10.1186/s10194-020-01183-6
49. Papetti L, Di Loro PA, Tarantino S, Grazzi L, Guidetti V, Parisi P, et al. I stay at home with headache. a survey to investigate how the lockdown for COVID-19 impacted on headache in italian children. *Cephalalgia.* (2020) 40:1459–73. doi: 10.1177/0333102420965139
50. Dallavalle G, Pezzotti E, Provenzi L, Toni F, Carpani A, Borgatti R. Migraine symptoms improvement during the COVID-19 lockdown in a cohort of children and adolescents. *Front Neurol.* (2020) 11:579047. doi: 10.3389/fneur.2020.579047
51. Sharawat IK, Panda PK. Caregiver satisfaction and effectiveness of teleconsultation in children and adolescents with migraine during the ongoing COVID-19 pandemic. *J Child Neurol.* (2020) 36:296–303. doi: 10.1177/0883073820968653
52. Carrabba G, Tariciotti L, Guez S, Calderini E, Locatelli M. Neurosurgery in an infant with COVID-19. *Lancet.* (2020) 395:e76. doi: 10.1016/S0140-6736(20)30927-2
53. French JA, Brodie MJ, Caraballo R, Devinsky O, Ding D, Jehi L, et al. Keeping people with epilepsy safe during the Covid-19 pandemic. *Neurology.* (2020) 94:1032–7. doi: 10.1212/WNL.0000000000009632
54. Grinspan ZM, Mytinger JR, Baumer FM, Ciliberto MA, Cohen BH, Dlugos DJ, et al. Management of infantile spasms during the COVID-19 pandemic. *J Child Neurol.* (2020) 35:828–34. doi: 10.1177/0883073820933739
55. Chen B, Kessi M, Chen S, Xiong J, Wu L, Deng X, et al. The recommendations for the management of chinese children with epilepsy during the COVID-19 outbreak. *Front Pediatr.* (2020) 8:495. doi: 10.3389/fped.2020.00495
56. Aledo-Serrano Á, Mingorance A, Jiménez-Huete A, Toledano R, García-Morales I, Anciones C, et al. Genetic epilepsies and COVID-19 pandemic: lessons from the caregiver perspective. *Epilepsia.* (2020) 61:1312–4. doi: 10.1111/epi.16537
57. Wong CA, Ming D, Maslow G, Gifford EJ. Mitigating the impacts of the COVID-19 pandemic response on at-risk children. *Pediatrics.* (2020) 146:e20200973. doi: 10.1542/peds.2020-0973
58. Kong M. What COVID-19 means for non-neurotypical children and their families. *Pediatr Res.* (2020). doi: 10.1038/s41390-020-0913-7. [Epub ahead of print].
59. Zhang J, Shuai L, Yu H, Wang Z, Qiu M, Lu L, et al. Acute stress, behavioural symptoms and mood states among school-age children with attention-deficit/hyperactive disorder during the COVID-19 outbreak. *Asian J Psychiatry.* (2020) 51:102077. doi: 10.1016/j.ajp.2020.102077
60. Cortese S, Asherson P, Sonuga-Barke E, Banaschewski T, Brandeis D, Buitelaar J, et al. ADHD management during the COVID-19 pandemic: guidance from the European ADHD guidelines group. *Lancet Child Adolesc Health.* (2020) 4:412–4. doi: 10.1016/S2352-4642(20)30110-3
61. Colizzi M, Bortoletto R, Silvestri M, Mondini F, Puttini E, Cainelli C, et al. Medically unexplained symptoms in the times of Covid-19 pandemic: a case-report. *Brain Behavior Immunity Health.* (2020) 5:100073. doi: 10.1016/j.bbih.2020.100073
62. Cluver L, Lachman JM, Sherr L, Wessels I, Krug E, Rakotomalala S, et al. Parenting in a time of COVID-19. *Lancet.* (2020) 395:e64. doi: 10.1016/S0140-6736(20)30736-4
63. Brown SM, Doom JR, Lechuga-Peña S, Watamura SE, Koppels T. Stress and parenting during the global COVID-19 pandemic. *Child Abuse Negl.* (2020) 110:104699. doi: 10.1016/j.chiabu.2020.104699
64. Kovler ML, Ziegfeld S, Ryan LM, Goldstein MA, Gardner R, García AV, et al. Increased proportion of physical child abuse injuries at a level I pediatric trauma center during the Covid-19 pandemic. *Child Abuse Negl.* (2020) 104756. doi: 10.1016/j.chiabu.2020.104756

Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 22 February 2021
doi: 10.3389/fneur.2021.632036

Case Report: Decompressive Craniectomy for COVID-19 Malignant Cerebral Artery Infarction. Is Surgery a Good Option?

Miguel Sáez-Alegre[1], Pablo García-Feijoo[1], Pablo Millán[2], Catalina Vivancos Sánchez[1], Víctor Rodríguez Domínguez[1], Jorge García Nerín[2], Alberto Isla Guerrero[1] and María Luisa Gandía-González[1,3,4]*

[1] Department of Neurosurgery, Hospital La Paz Madrid, Madrid, Spain, [2] Department of Intensive Care Medicine, Hospital La Paz Madrid, Madrid, Spain, [3] Hospital La Paz Institute for Health Research, Madrid, Spain, [4] CranioSPain Research Group, Institute for Neuroscience and Sciences of the Movement, Autonomous University of Madrid, Madrid, Spain

OPEN ACCESS

Edited by:
Jordi A. Matias-Guiu, Hospital Clínico San Carlos, Spain

Reviewed by:
Borja Enrique Sanz Cuesta, Olive View-UCLA Medical Center, United States
Lina Palaiodimou, University General Hospital Attikon, Greece

***Correspondence:**
Miguel Sáez-Alegre
miksaezalegre@gmail.com

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *21 November 2020*
Accepted: *22 January 2021*
Published: *22 February 2021*

Citation:
Sáez-Alegre M, García-Feijoo P, Millán P, Vivancos Sánchez C, Rodríguez Domínguez V, García Nerín J, Isla Guerrero A and Gandía-González ML (2021) Case Report: Decompressive Craniectomy for COVID-19 Malignant Cerebral Artery Infarction. Is Surgery a Good Option? Front. Neurol. 12:632036. doi: 10.3389/fneur.2021.632036

SARS-CoV2 infection can lead to a prothrombotic state. Large vessel occlusion, as well as malignant cerebral stroke have been described in COVID-19 patients. In the following months, given the increase in COVID-19 cases, an increase in malignant cerebral SARS-CoV2 associated strokes are expected. The baseline situation of the patients as well as the risk of evolution to a serious disease due to the virus, depict a unique scenario. Decompressive craniectomy is a life-saving procedure indicated in patients who suffer a malignant cerebral stroke; however, it is unclear whether the same eligibility criteria should be used for patients with COVID-19. To our knowledge seven cases of decompressive craniectomy and malignant cerebral stroke have been described to date. We report on a 39-year-old female with no major risk factors for cerebrovascular disease, apart from oral contraception, and mild COVID-19 symptoms who suffered from left hemispheric syndrome. The patient underwent endovascular treatment with stenting and afterward decompressive craniectomy due to a worsening neurological status with unilateral unreactive mydriasis. We present the case and provide a comprehensive review of the available literature related to the surgical treatment for COVID-19 associated malignant strokes, to establish whether the same eligibility criteria for non-COVID-19 associated strokes should be used. Eight patients, including our case, were surgically managed due to malignant cerebral stroke. Seven of these patients received decompressive craniectomy, and six of them met the eligibility criteria of the current stroke guidelines. The mortality rate was 33%, similar to that described in non-COVID-19 cases. Two patients had a left middle cerebral artery (MCA) and both survived after decompressive craniectomy. Our results support that decompressive craniectomy, using the current stroke guidelines, should be considered an effective life-saving treatment for COVID-19-related malignant cerebral strokes.

Keywords: malignant stroke, large vessel occlusion, decompressive craniecotmy, middle cerebral artery, COVID-19

INTRODUCTION

The World Health Organization declared COVID-19 a pandemic on 11 March 2020. Since then, health workers have modified the way they treat their patients facing new challenges, adapting to the lack of resources, coping with uncertainty and the emergence of COVID-19 related diseases (1).

A wide sample of neurological symptoms and SARS-CoV2 infection-associated diseases have already been described—large vessel strokes being one of the most life-threatening events related to COVID-19 (2, 3).

Ischemic cerebral stroke is one of the leading causes of disability and death worldwide, especially when large vessel occlusion is present. This lack of blood supply, especially in younger patients can lead to malignant cerebral edema, which can lead to transtentorial herniation. Decompressive craniectomy represents a life-saving treatment, reducing mortality in malignant cerebral infarction (4).

We present the case of a young, previously healthy, woman with mild COVID-19 who underwent a decompressive craniectomy due to a COVID19-related malignant stroke. Cases of this type of stroke may potentially increase in the following months, and at present, it is unclear whether the same eligibility criteria could be used in this new scenario.

We also review currently available literature of large vessel strokes in COVID-19 patients who underwent decompressive craniectomy to date, with a focus on surgery eligibility criteria, to try to conclude whether these criteria should be used in decision making in COVID-19 patients.

CASE PRESENTATION

A 39-year-old healthy woman, G4P4, with mRS = 0, with a history of gestational diabetes and no major risk factors for cerebrovascular disease apart from taking oral contraception (desogestrel 75 mcg), was admitted after suffering a stroke while self-isolating at home for COVID-19. Familial history was not suggestive of a procoagulant state as no thrombotic or thromboembolic events were found in the patient's relatives. She did not smoke, drink alcohol, or take recreational drugs. She was married and unemployed and lived with her husband and his four children for whom she was the primary caregiver.

The patient contacted the health system for the first time because of a 4-day history of asthenia and ageusia. Chest radiography showed bilateral basal opacities and blood tests were normal except for a PCR of 73 mg/dl. Reverse-transcriptase polymerase chain (PCR) for SARS-CoV2 of a nasopharyngeal swab was positive. She was discharged and sent home with a diagnosis of mild bilateral SARS-CoV2 pneumonia.

On day 6 she was admitted to another hospital at 1:55 pm due to a low level of consciousness and right brachio-crural hemiparesis. Last seen, asymptomatic, at 5 am the day before, she was found unresponsive at 9 am by her husband. Global aphasia, right-side hemiplegia, right side sensory loss, gaze deviation toward the left side, and right homonymous hemianopsia were found. The National Institute Health Stroke Scale (NIHSS) scoring was 23 and no traumatic signs were found. The blood test showed LDH 293 UI/L, D-dimer 1,450 ng/mL, and C-reactive protein 17.5 mg/L. Simple head CT, CT perfusion scan, and angio-CT scans showed a left MCA and internal carotid artery (ICA) acute ischemic stroke (ASPECTS 5/10, TAN score 0-1) with 60% ischemic mismatch.

Due to lack of onset time, she was ineligible for thrombolysis but due to the perfusion scan findings, she was eligible for mechanical thrombectomy. She was transferred to our hospital, the on-call stroke center for that day, with the diagnosis of wake-up left MCA and ICA stroke in probable relation with COVID-19, arriving at 8:04 pm. At 9 pm, after obtaining consent from the patient's husband, she underwent a revascularization procedure. Left MCA recanalization was achieved. Distal unreachable thrombi in the left anterior cerebral artery (ACA) were observed, as well as a repletion defect in the extracranial internal carotid artery, suggestive of the presence of a floating thrombus or, less likely being an arterial dissection, needing the placement of a Roadsaver stent under lysine acetylsalicylate 500 mg. Double anti-aggregation was delayed until control head CT, scheduled 24 h later. The patient was admitted to the intensive care unit (ICU)

Eight hours after the thrombectomy procedure and still, under sedation and endotracheal intubation, the patient developed an unreactive dilated left pupil. Emergent head CT scan showed a left malignant middle cerebral artery stroke with a midline shift of 10 mm and she therefore underwent a left decompressive craniectomy (**Figures 1–4**).

Postoperative day 1 control head CT showed midline shift improvement and mild hemorrhagic transformation. ASA 100 mg administration was started. Forty-eight hours after surgery, sedation was withdrawn. The patient was alert, obeyed simple and complex commands, seemed to understand her current situation but persisted total motor aphasia, right hemiplegia 0/5, and severe right side sensory loss.

Serial follow-up CT showed progressive ventricular size enlargement with progressive neurological worsening, consisting of bradypsychia and drowsiness. On postoperative day 46, a left-side ventriculoperitoneal shunt (CERTAS Plus CODMAN siphonguard programmable valve) was placed electively as part of our standard hydrocephalus treatment. The patient was finally discharged on postoperative day 76 to a brain injury center. Neurological status at discharge was assessed as a NIHSS 16 and mRS4. The patient was obeying orders, had mild motor aphasia, right hemihypoesthesia, and hemiplegia (2/5 grade of strength in right inferior limb and 0/5 in upper right superior limb using the Medical Research Council Muscle Testing Scale) and right homonymous hemianopsia. Treatment at discharge consisted of ASA 100 mg/day, enoxaparin 40 mg/day, sertraline 50 mg/day, and metformin 425 mg/12 h. The patient tolerated treatment and was adherent to treatment during admission. A new surgery to replace the bone flap will be discussed on an outpatient basis.

The patient's family was informed daily and they, as well as the patient, provided consent to the different interventions. For the emergency procedures (decompressive craniectomy and neurovascular revascularization), as the patient was unresponsive, verbal consent was obtained from the patient's

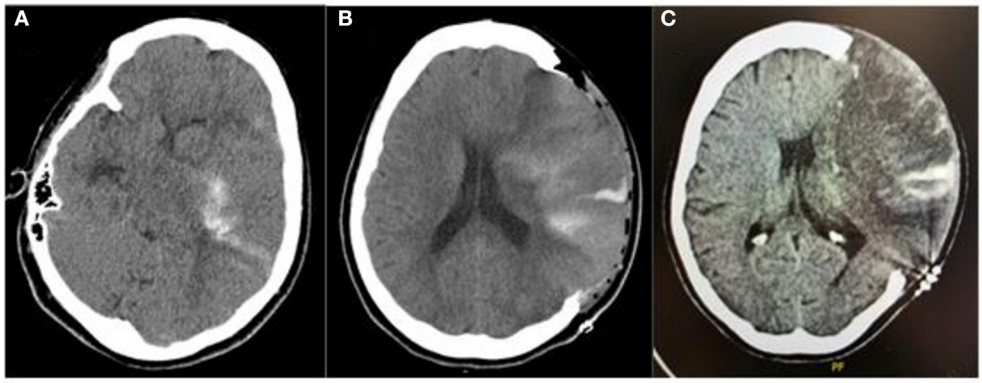


FIGURE 1 | Pre- and post-craniectomy images: **(A)** Head CT scan at admission prior to surgery with left MCA and ICA acute ischemic stroke showing hemorrhagic transformation (PH-1); **(B)** Day 1 postoperative CT scan showing improvement in midline shift and cerebral edema with foci of hemorrhagic transformation, which remained stable; **(C)** Day 10 postoperative control CT scan.

husband. After the initial surgery, the patient was alert and consented to the ventriculoperitoneal shunt, the family was also informed and provided consent.

In the presence of negative neurological symptoms in a patient, a cranial CT scan should be performed urgently to rule out bleeding. In our patient's case, the CT scan already showed data of cerebral ischemia. Although the cases associated with COVID-19 have been described, the main causes of ictus, both frequent and infrequent, must be ruled out.

The pathogenesis of SARS-CoV2-associated neurologic symptoms has been intensively studied recently. It is reported that thromboembolic events are common in SARS-CoV2 infected patients, particularly large vessel occlusion strokes. In this patient, the main differential diagnosis is an alteration in coagulation or the presence of a DVT and a permeable oval foramen. Various tests were performed to try to clarify the etiology of the stroke. EKG and transthoracic echocardiogram were within normal limits and Doppler was not suggestive of a patent foramen ovale or an atrial septal defect. Procoagulant blood tests were normal and included antithrombin, free S-protein, activated protein C resistance, homocysteine, factor V gene mutation 61691A, prothrombin gene mutation G20120A, antiphospholipid antibodies, functional factor XII, and functional activity of protein C tests. Carotid Doppler showed no atheroma plaques with preserved and symmetrical flows. Left carotid stent was permeable with symmetrical velocities. Autoimmunity tests (ANA, antiDNAds, AntiCLP IgG and IgM, c and p ANCA) were negative. Serology for SARS-CoV2, 2 months after admission, showed positive IgG and IgM.

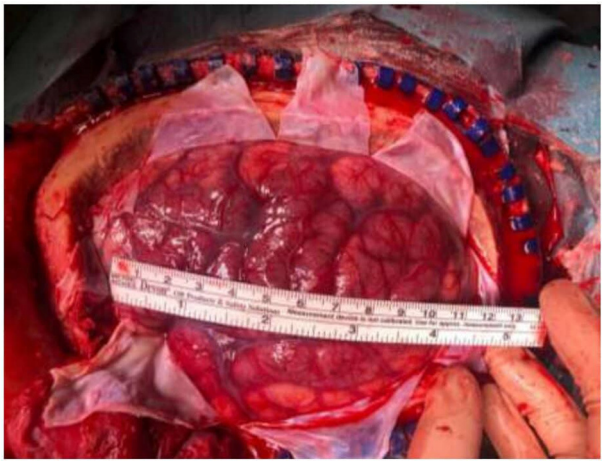


FIGURE 2 | Intraoperative image after decompression, showing a 13 × 10 cm (antero- posterior and cranio-caudal length) left hemicraniectomy. Congestive brain with herniating through the bony defect was appreciated.

DISCUSSION

The COVID-19 pandemic represents a challenge for neurologists and neurosurgeons as large vessel strokes have been associated with SARS-CoV2 disease. The question of whether our protocols for stroke management are still valid or if they should be changed, remain (5).

Our institution has been one of the hardest hit during the pandemic (6). Spain has received an important number of patients and in particular, its capital, Madrid, and more specifically our hospital has been one of the world's focal points of the pandemic, mainly in the so-called first wave (7). Despite this, we had not had to deal with a similar clinical situation.

We present the clinical outcome of a young COVID-19 stroke patient who suffered only mild COVID-19 symptoms. We followed the usual stroke protocol at our hospital, based on international consensus guidelines (7), performing a decompressive craniectomy with dural expansion if a patient deteriorates neurologically within 48 h despite medical therapy. We discuss whether AHA/ASA 2018 Stroke Guidelines should also be followed in patients with COVID-19.

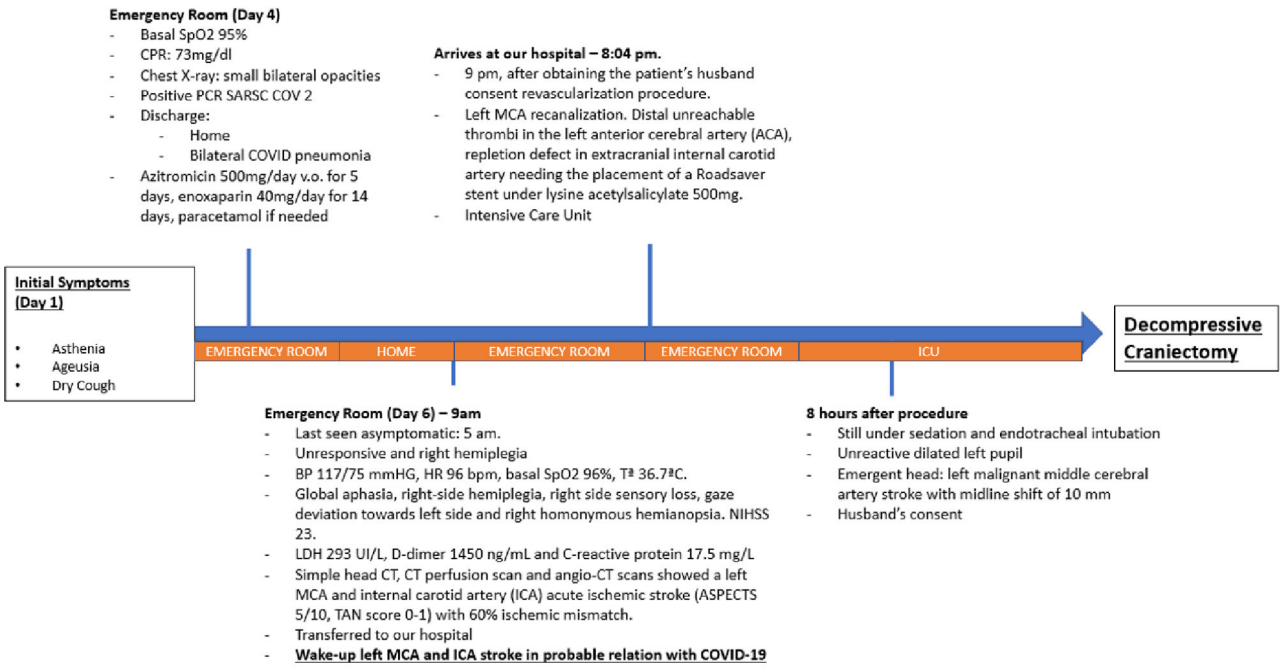


FIGURE 3 | Figure showing patient's evolution from first symptoms to decompressive craniectomy.

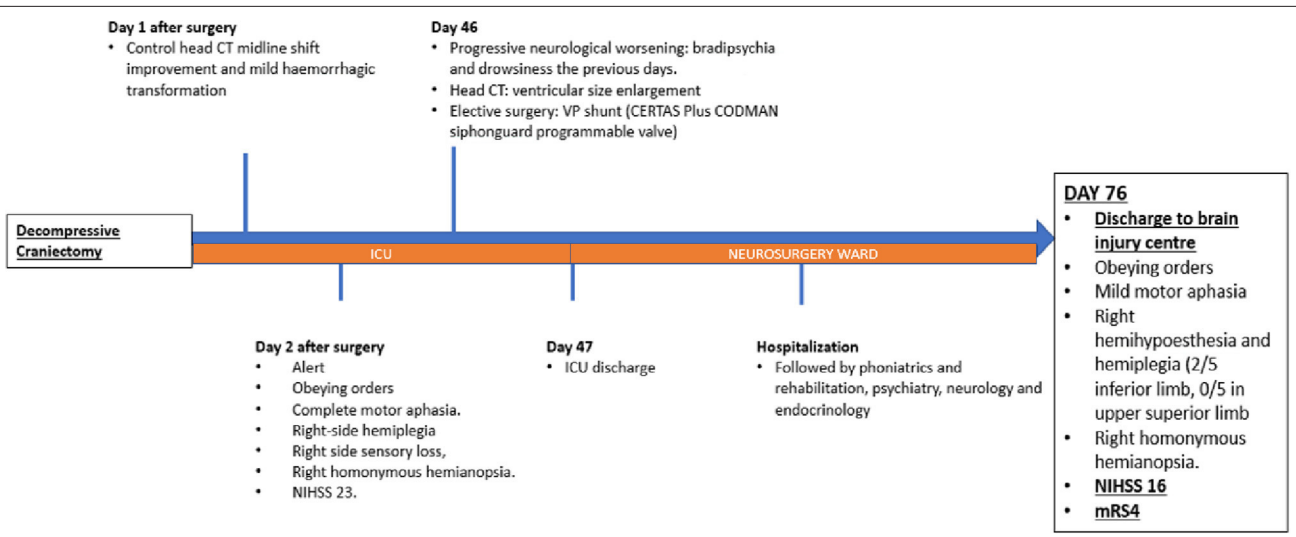


FIGURE 4 | Figure showing patient's evolution from decompressive craniectomy to discharge.

SARS-CoV2-associated neurologic symptom pathogenesis has been intensively studied. Thromboembolic events are common in SARS-CoV2 infected patients, particularly large vessel occlusion strokes (8).

Indeed, Kihira et al. (9) reported 2.4 times more risk of large vessel strokes in COVID-19 patients than in patients without COVID-19 infection. This association was not reported for small vessel strokes. They also reported on 62% of strokes involving M1-M2. This represents a risk factor to developing malignant cerebral edema. In our case the stroke was probably originally located in the left ACI and it then migrated to ipsilateral MCA and ACA. This MCA involvement was key to the development of cerebral edema.

COVID-19 patients have been shown to suffer a hypercoagulable state, increasing the risk of acute ischemic strokes, probably because some procoagulant and inflammatory pathways are activated. Mahboob et al. (10) suggested that antibody screening and immediate prophylactic anticoagulation

may have reduced the risk of those events. In our case however, we did not find major risk factors for cerebrovascular disease, and antiphospholipid antibodies and the rest of the procoagulant tests were negative. Furthermore, prophylactic enoxaparin treatment was also started before the stroke was diagnosed, as mandated by the current guidelines (11). Our patient was under oral contraception, consisting of desogestrel, a progestogen that has been shown to increase the risk of venous thromboembolism (12).

In relationship to other risk factors, our patient was young and had no major risk factors. In contrast with this, Li et al. (13) in a single-center study reported that 5% of COVID-19 hospitalized patients suffered an acute ischemic stroke and that a higher incidence was seen in older patients with stroke risk factors. There is a strong association between stroke and major risk factors in COVID-19 patients, mainly age. Briefly, Rothstein et al. (14) reviewed a large series of patients with COVID-19 and acute cerebrovascular events, reporting that 95% of patients had a previous history of hypertension, 60% had a history of diabetes mellitus, and newly positive antiphospholipid antibodies were found in 75% of patients.

It is well-known that the prognosis of patients with malignant middle cerebral artery infarction is poor, with a mortality of up to 80% when applying the best medical care (15). Moreover, as recent studies show, the association between SARS-CoV2 and stroke worsens the prognosis and has been shown to increase the mortality rate associated with stroke (16), and also worsens the management of the disease and delays medical care (17).

Although it has been described as reducing mortality and morbidity (18–23) sometimes the baseline situation of the patient, the presence of antiaggregant and anticoagulant drugs, or severe sequelae, makes it difficult to take this decision. Another special situation is the involvement of the dominant hemisphere in the infarction. Neurosurgeons have to keep special considerations in mind as global aphasia is considered to be extremely disabling, with some patients reporting at discharge that they would have preferred not to have been operated on. However, recent studies showed similar clinical outcomes at medium- and long-term follow-up and up to 55% of patients with aphasia can partially recover (24, 25). This decision should be individualized and different factors, like the patient's willingness, timing, and familial situation should be considered.

In our case, the patient met our eligibility criteria and although she was under acetylsalicylate 500 mg, and although we knew that COVID-19 could worsen the prognosis, we indicated surgery. She had no previous wills, and we contacted her family which, after discussing treatment options and prognosis, provided consent to perform the surgery.

Age is an important factor. The benefit of decompressive craniectomy after malignant MCA infarction in reducing the outcome of death, without increasing the risk if severe disability, and while also increasing independence, has been demonstrated in patients under 60 years of age (7).

We reviewed the current literature and only eight cases (**Table 1**), four female and four male, have been surgically managed due to malignant cerebral strokes that have been reported to date, including our case.

In our case, surgery was performed 9 h after deterioration and there were no complications associated with COVID-19. Liang et al. (18) described three cases, one of them underwent surgery on day 2 post-stroke and died due to concomitant ST-segment–elevation myocardial infarction. Roy et al. (19) described a case who received surgical treatment 9 h after the stroke, unfortunately, the patient developed refractory hypoxemia in the postoperative period due to extensive pulmonary embolus and died. Alkhaibary et al. (20) described a case presenting with a left common carotid artery complete occlusion and underwent surgery at least 72 h after worsening. All cases except the one presented by Alkhaibary et al. (20) were treated according to the AHA/ASA 2018 Stroke Guidelines (48 h). In our case, although the patient was admitted to the hospital after 3 days of a low level of consciousness, we support the decision of the surgery as the patient was a 31-year-old previously healthy woman.

Our patient presented hydrocephalus. Rascón-Ramírez et al. (21) described two cases, one of them a 35-year-old man with right vertebral artery hypoplasia and anatomical absence of both posterior communicating cerebral arteries that suffered a partial occlusion of the left vertebral artery and underwent extensive suboccipital craniectomy and placing

TABLE 1 | Covid19 related strokes, that required surgical treatment, described in the current medical literature.

	Authors and Year	No. patients	Vessel	Age	Sex	DT until surgery	Major risk factors	Outcomes
1	Liang et al. (2020) (18)	3	L ICA	57	F	<48H	HT, DM	Death
			R ICA	61	M	<24H	DM	Discharged
			L MCA	41	M	<24H	DM	Discharged
2	Roy et al. (2020) (19)	1	R ACA-MCA	46	F	9H	DM	Death
3	Rascón-Ramírez et al. (2020) (20)	2	L VA	35	M	<24H	None	Discharged
			R MCA	51	M	<24H	N/A	ICU
4	Alkhaibary et al. (2020) (21)	1	L CCA	31	F	72H	HT	ICU
5	Sáez-Alegre et al. (2020)	1	L MCA	39	F	8H	COCP	Discharged

ACA, anterior cerebral artery; CCA, common carotid artery; COCP, combined oral contraceptive pill; DM, diabetes mellitus; DT, deterioration time; HT, hypertension; ICA, internal carotid artery; ICU, Intensive Care Unit; L, left; MCA, middle cerebral artery; R, right; VA, vertebral artery.

of an external ventricular drainage. However, this case differs from ours. The physiopathology of hydrocephalus due to the mass effect in the posterior fossa, such as the Rascón-Ramírez et al. case, is different from post-craniectomy hydrocephalus as in our case. This allowed us to perform elective surgery, placing a ventricular peritoneal shunt valve instead of an urgent external ventricular drain.

The mean age of patients with malignant middle cerebral artery stroke ranges from 43.5 to 63.5 years (26). In our study, the mean age was 45.1 years. The mortality rate among the general population who underwent decompressive craniectomy for malignant middle cerebral artery stroke, despite receiving the best treatment, ranges from 20 to 55% in recent series (22, 27). In our review, two of the eight cases are still in ICU, two died and four have been discharged, leaving a 33% mortality rate (2/6). This analysis includes patients not only with MCA infarction but also with the involvement of other vessels. If we look only at the presence of MCA involvement, four patients remain. One of the patients was still in the ICU at the time of publication of the case, and one of the three remaining cases died, leaving the mortality rate at 33%.

Although mortality seems to be the same, it is important to mention that in all cases, mortality was essentially derived from the severe COVID-19-related comorbidities previously detailed. Therefore, we can conclude that although further studies with a large series of patients are needed to achieve statistically significant results on COVID-19, it seems that large vessel occlusion related to COVID-19 occurs in younger patients and that surgery should be indicated following the same criteria as the pre-COVID-19 era.

CONCLUSION

Our experience and our comprehensive literature review support decompressive craniectomy as a life-saving and effective treatment for patients with COVID-19 and malignant cerebral infarction. We suggest that surgery should be indicated following the same criteria as in the pre-COVID-19 era.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MS-A, PG-F, and MG-G wrote the manuscript. CV, VR, JG, and PM helped gathering information. AI helped reviewing the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Chen PM, Hemmen TM. Evolving healthcare delivery in neurology during the coronavirus disease 2019 (COVID-19) pandemic. *Front Neurol*. (2020) 11:578. doi: 10.3389/fneur.2020.00578
2. Lee KW, Yusof Khan AHK, Ching SM, Chia PK, Loh WC, Abdul Rashid AM, et al. Stroke and novel coronavirus infection in humans: a systematic review and meta-analysis. *Front Neurol*. (2020) 11:579070. doi: 10.3389/fneur.2020.579070
3. Tsivgoulis G, Palaiodimou L, Zand R, Lioutas VA, Krogias C, Katsanos AH, et al. COVID-19 and cerebrovascular diseases: a comprehensive overview. *Ther Adv Neurol Disord*. (2020) 13:1756286420978004. doi: 10.1177/17562864209 78004
4. Jüttler E, Bösel J, Amiri H, Schiller P, Limprecht R, Hacke W, et al. DESTINY II study group. DESTINY II: DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY II. *Int J Stroke*. (2011) 6:79–86. doi: 10.1111/j.1747-4949.2010.00544.x
5. Moshayedi P, Ryan TE, Mejia LLP, Nour M, Liebeskind DS. Triage of acute ischemic stroke in confirmed COVID-19: large vessel occlusion associated with coronavirus infection. *Front Neurol*. (2020) 11:353. doi: 10.3389/fneur.2020.00353
6. Gandía-González ML, Sáez-Alegre M, Roda JM. Neurosurgeons on the frontline of COVID-19: no place for surgery? *Acta Neurochir*. (2020) 162:1503−4. doi: 10.1007/s00701-020-04390-x
7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. (2018) 49:e46–110. doi: 10.1161/STR.0000000000000211
8. Khan M, Ibrahim R, Siddiqi S, Kerolos Y, Al-Kaylani MM, AlRukn SA, et al. COVID-19 and acute ischemic stroke—a case series from Dubai, UAE. *Int J Stroke*. (2020) 15:699–700. doi: 10.1177/17474930209 38285
9. Kihira S, Schefflein J, Mahmoudi K, Rigney B, Delman NB, Mocco J, et al. Association of coronavirus disease (COVID-19) with large vessel occlusion strokes: a case-control study. *AJR Am J Roentgenol*. (2020) 29:1–6. doi: 10.2214/AJR.20.23847
10. Mahboob S, Boppana SH, Rose NB, Beutler BD, Tabaac BJ. Large vessel stroke and COVID-19: case report and literature review. *eNeurologicalSci*. (2020) 20:100250. doi: 10.1016/j.ensci.2020.100250
11. Godino C, Scotti A, Maugeri N, Mancini N, Fominskiy E, Margonato A, et al. Antithrombotic therapy in patients with COVID-19? -rationale and evidence. *Int J Cardiol*. (2020) 28:S0167-527333894-8. doi: 10.1016/j.ijcard.2020.09.064
12. Abdalvand A. The risk of venous thromboembolism associated with oral contraceptive; the search is still on. *Emerg*. (2014) 2:53.
13. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. (2020) 5:279–84. doi: 10.1136/svn-2020-000431
14. Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute cerebrovascular events in hospitalized COVID-19 patients. *Stroke*. (2020) 51:e219–22. doi: 10.1161/STROKEAHA.120.030995
15. Trejo-Gabriel-Galán JM. Stroke as a complication and prognostic factor of COVID-19. *Neurologia*. (2020) 35:318–22. doi: 10.1016/j.nrleng.2020.04.013
16. Katsanos AH, Palaiodimou L, Zand R, Yaghi S, Kamel H, Navi BB, et al. The impact of SARS-CoV-2 on stroke epidemiology and care: a meta-analysis. *Ann Neurol*. (2020) 21:10.1002/ana.25967. doi: 10.1002/ana.25967
17. Tsivgoulis G, Palaiodimou L, Katsanos AH, Caso V, Köhrmann M, Molina C, et al. Neurological manifestations and implications

of COVID-19 pandemic. *Ther Adv Neurol Disord*. (2020) 13:1756286420932036. doi: 10.1177/1756286420932036
18. Liang JW, Reynolds AS, Reilly K, Lay C, Kellner CP, Shigematsu T, et al. COVID-19 and decompressive hemicraniectomy for acute ischemic stroke. *Stroke*. (2020) 51:e215–8. doi: 10.1161/STROKEAHA.120.030804
19. Roy D, Hollingworth M, Kumaria A. A case of malignant cerebral infarction associated with COVID-19 infection. *Br J Neurosurg*. (2020) 5:1–4. doi: 10.1080/02688697.2020.1779180
20. Alkhaibary A, Abbas M, Ahmed ME, Khatri IA, Alkhani A. Common carotid artery occlusion in a young patient: can large-vessel stroke be the initial clinical manifestation of coronavirus disease 2019? *World Neurosurg*. (2020) 144:140–2. doi: 10.1016/j.wneu.2020.08.154
21. Rascón-Ramírez FJ, Carrascosa-Granada ÁM, Vargas-Jiménez AC, Ferrández-Pujante B, Ortuño-Andériz F. Supra and infratentorial massive strokes in previously healthy young patients with SARS-CoV-2. The role of neurosurgery. *Neurocirugia*. (2020) 6:S1130-147330098-1. doi: 10.1016/j.neucir.2020.08.001
22. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke*. (2007) 38:2506–17. doi: 10.1161/STROKEAHA.107.485235
23. Neugebauer H, Creutzfeldt CJ, Hemphill JC 3rd, Heuschmann PU, Jüttler E. DESTINY-S: attitudes of physicians toward disability and treatment in malignant MCA infarction. *Neurocrit Care*. (2014) 21:27–34. doi: 10.1007/s12028-014-9956-0
24. García-Feijoo P, Isla A, Díez-Tejedor E, Mansilla B, Palpan Flores A, Sáez-Alegre M, et al. Decompressive craniectomy in malignant middle cerebral artery infarction: family perception, outcome and prognostic factors. *Neurocirugia*. (2020) 31:7–13. doi: 10.1016/j.neucie.2019.07.002
25. Godoy D, Piñero G, Cruz-Flores S, Alcalá Cerra G, Rabinstein A. Malignant hemispheric infarction of the middle cerebral artery. Diagnostic considerations and treatment options. *Neurologia*. (2016) 31:332–43. doi: 10.1016/j.nrleng.2013.02.009
26. Wei H, Jia FM, Yin HX, Guo ZL. Decompressive hemicraniectomy versus medical treatment of malignant middle cerebral artery infarction: a systematic review and meta-analysis. *Biosci Rep*. (2020) 40:BSR20191448. doi: 10.1042/BSR20191448
27. Das S, Mitchell P, Ross N, Whitfield PC. Decompressive hemicraniectomy in the treatment of malignant middle cerebral artery infarction: a meta-analysis. *World Neurosurg*. (2019) 123:8–16. doi: 10.1016/j.wneu.2018.11.176

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 26 February 2021
doi: 10.3389/fneur.2021.621495

COVID-19 Pandemic Impact on Care for Stroke in Australia: Emerging Evidence From the Australian Stroke Clinical Registry

Dominique A. Cadilhac[1,2], Joosup Kim[1,2], Emma K. Tod[2], Julie L. Morrison[2], Sibilah J. Breen[2], Katherine Jaques[3], Rohan Grimley[1,3], Brett Jones[4], Geoffrey C. Cloud[5,6], Timothy Kleinig[7], Susan Hillier[8], Helen Castley[9], Richard I. Lindley[10], Natasha A. Lannin[5,6], Sandy Middleton[11,12], Bernard Yan[13], Kelvin Hill[14], Benjamin B. Clissold[1,15], Peter J. Mitchell[13], Craig S. Anderson[16,17], Steven G. Faux[12,18], Bruce C. V. Campbell[2,13] and the AuSCR COVID-19 Reporting Consortium Group*

[1] Stroke and Ageing Research School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia, [2] Stroke Division, The Florey Institute of Neuroscience and Mental Health, Heidelberg, VIC, Australia, [3] Statewide Stroke Clinical Network, Healthcare Improvement Unit, Clinical Excellence, Queensland Health, Brisbane, QLD, Australia, [4] Canberra Hospital, Canberra, ACT, Australia, [5] Department of Neuroscience, Central Clinical School, Monash University, Clayton, VIC, Australia, [6] Alfred Health, Prahran, VIC, Australia, [7] Royal Adelaide Hospital, Adelaide, SA, Australia, [8] Division of Health Sciences, University of South Australia, Adelaide, SA, Australia, [9] Royal Hobart Hospital, Hobart, TAS, Australia, [10] Westmead Clinical School, University of Sydney, Darlington, NSW, Australia, [11] Nursing Research Institute, Australian Catholic University, Sydney, NSW, Australia, [12] St Vincent's Hospital Sydney, Darlinghurst, NSW, Australia, [13] Department of Radiology, The Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia, [14] Stroke Foundation, Melbourne, VIC, Australia, [15] Monash Health, Clayton, VIC, Australia, [16] Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia, [17] The George Institute for Global Health, Camperdown, NSW, Australia, [18] University of New South Wales, Kensington, NSW, Australia

OPEN ACCESS

Edited by:
Tomohisa Nezu,
Hiroshima University, Japan

Reviewed by:
Atilla Ozcan Ozdemir,
Eskişehir Osmangazi University, Turkey
Thabele Leslie-Mazwi,
Massachusetts General Hospital and Harvard Medical School,
United States

***Correspondence:**
Dominique A. Cadilhac
dominique.cadilhac@monash.edu

Specialty section:
This article was submitted to Stroke,
a section of the journal Frontiers in Neurology

Received: 26 October 2020
Accepted: 04 February 2021
Published: 26 February 2021

Citation:
Cadilhac DA, Kim J, Tod EK, Morrison JL, Breen SJ, Jaques K, Grimley R, Jones B, Cloud GC, Kleinig T, Hillier S, Castley H, Lindley RI, Lannin NA, Middleton S, Yan B, Hill K, Clissold BB, Mitchell PJ, Anderson CS, Faux SG, Campbell BCV and the AuSCR COVID-19 Reporting Consortium Group (2021) COVID-19 Pandemic Impact on Care for Stroke in Australia: Emerging Evidence From the Australian Stroke Clinical Registry. Front. Neurol. 12:621495. doi: 10.3389/fneur.2021.621495

We present information on acute stroke care for the first wave of the COVID-19 pandemic in Australia using data from the Australian Stroke Clinical Registry (AuSCR). The first case of COVID-19 in Australia was recorded in late January 2020 and national restrictions to control the virus commenced in March. To account for seasonal effects of stroke admissions, patient-level data from the registry from January to June 2020 were compared to the same period in 2019 (historical-control) from 61 public hospitals. We compared periods using descriptive statistics and performed interrupted time series analyses. Perceptions of stroke clinicians were obtained from 53/72 (74%) hospitals participating in the AuSCR (80% nurses) *via* a voluntary, electronic feedback survey. Survey data were summarized to provide contextual information for the registry-based analysis. Data from the registry covered locations that had 91% of Australian COVID-19 cases to the end of June 2020. For the historical-control period, 9,308 episodes of care were compared with the pandemic period (8,992 episodes). Patient characteristics were similar for each cohort (median age: 75 years; 56% male; ischemic stroke 69%). Treatment in stroke units decreased progressively during the pandemic period (control: 76% pandemic: 70%, $p < 0.001$). Clinical staff reported fewer resources available for stroke including 10% reporting reduced stroke unit beds. Several time-based metrics

were unchanged whereas door-to-needle times were longer during the peak pandemic period (March-April, 2020; 82 min, control: 74 min, $p = 0.012$). Our data emphasize the need to maintain appropriate acute stroke care during times of national emergency such as pandemic management.

Keywords: stroke, COVID-19, healthcare quality, survey, clinical registry

INTRODUCTION

Stroke is a time critical emergency and is a leading cause of death and disability. Better outcomes are achievable with early presentation to hospital and treatment in a specialized stroke unit (1). Worldwide, there have been reports that the Coronavirus Disease 2019 (COVID-19) pandemic has impacted presentations to hospital and the ability to provide the same standard of acute stroke care as prior to the pandemic. During this time, national organizations for stroke have issued statements to encourage people with suspected stroke to avoid delays in seeking medical attention and to promote and preserve best practice management in hospitals (2).

The impacts on emergency department presentations and admissions to hospitals for acute stroke during the COVID-19 pandemic have been reported (3–13). The steepest declines in presentations have been noted to immediately follow implementation of lockdown or stay at home orders (10–12). Several authors have reported a change in symptom severity of people presenting with stroke or transient ischemic attack (TIA). In some studies, presentations of minor strokes and TIAs have reduced by 31–45% (3, 4, 7, 10, 11, 13). The impacts on patient arrival times to hospital (3, 6, 7, 12–14) and the delivery of stroke care that have been reported has differed between studies (4). Reported changes have included altered transportation protocols, changes to triage processes and stroke pathways, and fewer multidisciplinary team rounds (15, 16). Provision of reperfusion treatments and the timeliness of these have decreased or remained stable (3, 5, 6, 8, 12, 17, 18).

Within Australia, social distancing restrictions and community lockdowns commenced on March 24, 2020; and almost uniquely in the developed world, were followed by extremely low COVID-19 transmission rates. Guidance on the use of personal protective equipment at hospitals was regularly updated by the Australian Government. The first case of COVID-19 in Australia was recorded on January 25th and by June 30th 2020, there were 7,833 cases (307 per 1,000,000 population) and 104 deaths (19), with the majority of cases (69%) occurring in two Australian states (**Supplementary Table 1**). Since the experience in each country to COVID-19 and its impact on stroke is likely to differ, we provide this brief report to illustrate the unintended and indirect consequences from an Australian perspective.

AIMS

The aim of this paper is to describe the impact of the COVID-19 pandemic on stroke services from the perspective of hospitals participating in the Australian Stroke Clinical Registry (AuSCR) up until the end of June 2020.

METHODS

The impacts of the COVID-19 pandemic on stroke services were captured through our collaborative work on the AuSCR. The AuSCR is a clinical quality registry that was established in 2009 to monitor and improve the quality of stroke care in Australia. Participating hospitals capture data on patients admitted with acute stroke and TIAs. Public hospitals from six Australian states and territories contribute data to the AuSCR and it is funded primarily by state governments. The AuSCR captures a minimum dataset on patient characteristics, clinical indicators, and patient outcomes. The data for the analysis were extracted from AuSCR on the 17th September 2020. For further information see www.auscr.com.au.

Study Design

Mixed methods design using (i) patient-level data from the registry and (ii) a survey of clinicians working in the hospitals that participate in the AuSCR.

To avoid the effect of season on stroke admissions, patient-level data from the registry from January to June 2020 were compared to data for the same period in 2019 prior to the pandemic (the historical control cohort for this analysis). We also compared the 2 months when we had the peak of cases in the first wave of COVID within Australia occurred between March and April (https://covid-19-au.com/, accessed 21 September 2020) to the historical, non-pandemic control period.

Setting

Public hospitals from six Australian states and territories that contribute data to the AuSCR.

Survey Design and Distribution

A voluntary, feedback survey was designed to capture the impacts of COVID-19 from the perspective of hospital clinicians working in on acute stroke care using a standardized approach. Several members of the AuSCR team (EKT, JLM, SJB, DAC) developed the set of 23 closed or open-ended questions based on informal feedback and information being circulated by the Stroke Foundation and World Stroke Organization. The questionnaire was reviewed and approved for distribution by the Chair of the Management (NAL) and Steering committees (SM). A copy of the survey is in the **Supplementary Material**.

The survey was distributed electronically to the AuSCR hospital mailing list and *via* the AuSCR Newsletter on the first of May 2020 and was left open until the 31st of May 2020. More than

one response from each participating hospital was acceptable. Participation was voluntary.

Data Analysis

Quantitative and qualitative methods of analyses were used as outlined below. Results of the survey were contrasted to the findings from the comparison of patient data from the registry to provide context.

Analysis of Patient Cohort Data From the Australian Stroke Clinical Registry

Hospitals contributing data between January and June 2019 (historical-control period) and between January and June 2020 (pandemic period) were included in a matched analysis. Patient characteristics (stroke numbers, type, severity, age) and quality of care indicators (treatment in a stroke unit, provision of reperfusion and time to reperfusion), and other process metrics (i.e., length of stay and discharge destination) were compared. Descriptive statistics were generated based on the type and distribution of the data. Differences between time periods were assessed using Chi^2 and Kruskal-Wallis tests. In the case where a specific process of care (i.e., clinical indicator) for any individual hospital contained >30% missing data, these hospitals were excluded from the analysis of that specific process of care. Data on the provision of stroke unit care was excluded from one hospital contributing 86 cases between 1/1/2019 and 17/9/2020.

Data on all episodes between 1/1/2019 and 17/9/2020 at the hospitals included in the matched analysis were used in an interrupted time series (ITS) analyses. Data points are presented per week. For the ITS analyses related to reperfusion, predicted values were adjusted for the number of patients with ischemic stroke. All other ITS analyses were adjusted for the numbers of patients with different diagnoses (ischemic stroke, intracerebral hemorrhage, transient ischemic attack, and undetermined stroke). Trends were compared before and after 1/3/2020 (week 61 in the model), which coincided with the first COVID-19 related death in Australia. A State of Emergency was declared in Victoria on 16/3/2020 and there were nationwide restrictions imposed on 21/3/2020. Seasonality was considered by using a lag period of 53 weeks for correlations. The last 2 weeks of data were removed due to low case numbers entered into the AuSCR (**Supplementary Figure 1**).

Analysis of Survey From Clinicians That Participate in the Australian Stroke Clinical Registry

Descriptive statistics were compiled for closed questions and inductive thematic analysis for open-ended responses.

RESULTS

Comparison of Patient-Level Registry Data

Sixty-two hospitals from five states (New South Wales, Victoria, Queensland, South Australia, and Tasmania) contributed patient data between January and June in both 2019 and 2020. We did not include data from a children's hospital, therefore the data used in the analysis was from 61 hospitals (**Supplementary Table 1**).

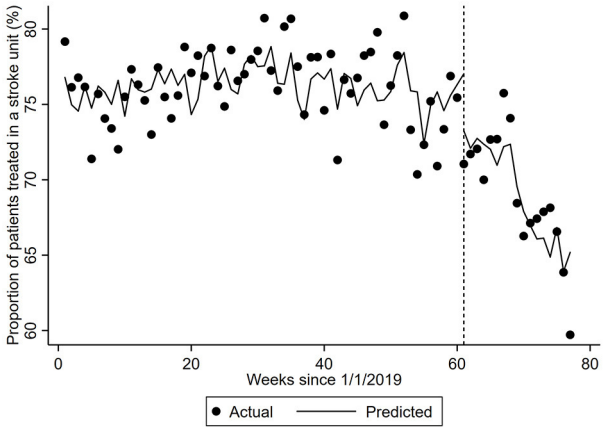


FIGURE 1 | Proportion of patients treated in a stroke unit. The dots represent the proportion of patients provided treatment in a stroke unit per week. The predicted proportion is the expected proportion is adjusted for the number of patients with different diagnoses and the corresponding number from the previous year (seasonality). Vertical hatched line represents week 61 of the interrupted time-series model with trends compared before and after this date, which coincides with the first COVID-19 related death. Coefficient −0.2457 (95% CI −0.4216, −0.0697, p-value = 0.0069).

Data from the registry covered locations that had 91% of Australian COVID-19 cases to the end of June 2020.

A sample of 9,308 pre-COVID 2019 AuSCR episodes were compared to a 2020 sample of 8,992 episodes (**Supplementary Table 2**). The demographic characteristics and stroke type distributions were similar for each cohort (median age: 75 years; 56% male; ischemic stroke 69%).

There were several changes in clinical processes over the first half of 2020 (**Table 1**). Compared to the pre-pandemic period, more patients arrived to hospital by ambulance in March–April 2020 ($p < 0.001$) and May–June ($p = 0.001$) and there was a shorter time between hospital arrival and brain scan ($p < 0.001$ and $p = 0.041$, respectively). The proportion of patients treated in a stroke unit in the first half of 2020 was significantly less than those in the control period ($p < 0.001$ for each period) and appeared to decline over the first half of 2020 (from 73 to 65%, $p < 0.001$). Using ITS analysis, the proportion of patients treated in a stroke unit decreased by 2.85% (95%CI −4.19, −1.51) in the week including 1/3/2020 followed by a continued decline of 0.25% per week (**Figure 1**).

During the week including 1/3/2020, the proportion of patients with ischemic stroke provided thrombolysis increased by 1.09% (**Table 2**). There was a 0.03% per week decrease in thrombolysis provision per week prior to this point and a significantly greater 0.23% per week decrease (95% CI −0.35, −0.10) from the week including 1/3/2020. Median door-to-needle times increased by 0.10 (95% CI 0.03, 0.18) minutes per week prior to the 1/3/2020, followed by a 12.15 minute (95% CI 9.35, 14.95) increase during the week including 1/3/2020 (**Figure 2**). Median door-to-needle times decreased by 2.05 (95%CI −2.36, −1.73) minutes per week from the week including 1/3/2020. When data from Victoria and Queensland were

TABLE 1 | Comparison of patient characteristics and clinical care for the historical-control period and different stages of the pandemic in 2020.

	2019	2020					
	January–June 2019 (control period)	January/February (pandemic period 0)		March/April (pandemic period 1)		May/June (pandemic period 2)	
Number of episodes	9,308	3,180		3,017		2,795	
Number of patients	9,116	3,080		2,912		2,737	
	n (%)*	*n* (%)*	*p*-value†	*n* (%)*	*p*-value†	*n* (%)*	*p*-value†
Median age (IQR)	75 (64–83)	75 (64–83)	0.961	74 (64–83)	0.094	76 (66–84)	0.014
Male	5,102 (56)	1,767 (57)	0.373	1,670 (56)	0.810	1,516 (55)	0.229
Diagnosis			0.060		0.636		<0.001
Intracerebral hemorrhage	1,124 (12)	326 (10)		350 (12)		331 (13)	
Ischemic stroke	6,393 (69)	2,219 (71)		2,058 (70)		1,628 (65)	
Transient ischemic attack	1,521 (16)	502 (16)		468 (16)		505 (20)	
Undetermined stroke	201 (2)	71 (2)		55 (2)		58 (2)	
Ability to walk on admission	3,772 (43)	1,230 (44)	0.704	1,061 (42)	0.091	868 (41)	0.082
Arrival by ambulance	6,802 (77)	2,177 (77)	0.816	2,110 (81)	<0.001	1,840 (80)	0.001
Median minutes from onset to arrival (IQR)	337 (100–1,127)	364 (105–1,192)	0.317	340 (98–1,074)	0.622	344 (101–1,013)	0.673
Median minutes from door to brain scan (IQR)	57 (24–155)	57 (24–153)	0.768	48 (22–120)	<0.001	51 (24–139)	0.041
Thrombolysis if ischemic stroke	808 (13)	246 (11)	0.082	247 (12)	0.545	178 (11)	0.066
Median minutes from door to needle (IQR)	74 (54–101)	76 (56–104)	0.395	82 (59–116)	0.012	71 (52–103)	0.882
Door to needle time under 60 min	218 (27)	65 (26)	0.863	56 (23)	0.177	46 (26)	0.756
Endovascular thrombectomy if ischemic stroke	535 (18)	183 (20)	0.400	159 (18)	0.992	144 (20)	0.266
Median door to groin puncture (minutes IQR)	76 (32–122)	81 (31–126)	0.643	84 (38–123)	0.504	89 (48–122)	0.074
Treated in a stroke unit	7,059 (76)	2,307 (73)	<0.001	2,126 (70)	<0.001	1,822 (65)	<0.001

*IQR, interquartile range; *number and proportion of the number of episodes unless otherwise specified; †P-value is for the differences between pandemic periods in 2020 compared to historical control period January to June 2019.*
Missing data: age 2.7%, sex 1.8%, diagnosis 2.8%, ability to walk on admission 11.9%, arrival by ambulance 9.3%, onset to arrival 14.2%, door to brain scan 9.8%, thrombolysis 2.6%, door to needle 11.1%, endovascular thrombectomy 3.1%, door to groin 12.7%, treated in a stroke unit 3.4%.

explored using ITS analysis, given these two states of Australia provided 75% of the AuSCR data in this analysis and had 40% of the COVID-19 cases (**Supplementary Table 1**), the only notable difference was that Victoria had a more pronounced reduction in stroke unit care in the interruption week [Victoria ∼6% drop, Queensland ∼4% increase (**Supplementary Table 3**)].

Fewer patients were discharged to rehabilitation in January–February 2020 ($p = 0.020$) but this improved to pre-pandemic levels from March onwards (**Table 3**). The median length of stay was 3 days between March and April 2020, lower than a median of 4 days in other months in the first half of 2020 and significantly shorter than pre-pandemic period ($p < 0.001$). There was evidence of fewer patients receiving their secondary prevention medications at time of discharge (**Table 3**).

Survey Results

Responses were received from 53/72 (74%) hospitals participating in the AuSCR; 80% of respondents had a nursing background. About half reported reduced presentations, in particular for mild stroke and transient ischemic attacks (44%). Changes to patient flow and management in emergency departments were reported by 36%; 26% had their stroke unit relocated with 10% reporting reduced capacity, and 28% reporting that stroke service staff were redeployed to other hospital work. Staff described the impact on patients having less access to visitors creating reduced opportunities for support and education and information sharing with relatives by the stroke team. Communication about redeployment of services or patient flow policy changes was reported to be less than optimal at some hospitals. Delays to time-critical stroke treatment were identified due to COVID-19 screening/triage processes, and nursing staff ratios and the interdisciplinary team skill base were adversely impacted.

DISCUSSION

Despite Australia's relatively low rates of COVID-19 in the population [4.5 times fewer cases per million than the global

TABLE 2 | Comparison of discharge care and length of stay for the historical-control period and different stages of the pandemic in 2020.

	2019			2020			
	January–June 2019 (control period)	January/February (pandemic period 0)	*p*-value†	March/April (pandemic period 1)	*p*-value†	May/June (pandemic period 2)	
Median length of stay (IQR)	4 (2–7)	4 (2–7)	0.001	3 (2–6)	<0.001	4 (2–7)	<0.001
Discharged home	4,593 (50)	1,602 (52)	0.062	1,430 (49)	0.394	1,193 (49)	0.231
Discharged to inpatient rehabilitation	2,027 (22)	619 (20)	0.020	679 (23)	0.160	558 (23)	0.468
Provided a discharge care plan if discharged to the community	3,127 (66)	1,127 (68)	0.052	940 (64)	0.412	810 (66)	0.756
Discharged with an antihypertensive medication	5,893 (74)	1,892 (70)	<0.001	1,751 (69)	<0.001	1,435 (62)	<0.001
Discharged with an antithrombotic medication (excludes ICH)	6,704 (91)	2,229 (87)	<0.001	2,010 (85)	<0.001	1,605 (75)	<0.001
Discharged with a lipid-lowering medication (excludes ICH)	5,674 (77)	1,954 (77)	0.669	1,754 (74)	0.001	1,369 (64)	<0.001

†P-value is for the differences between pandemic periods in 2020 compared to historical control period January–June 2019; IQR, interquartile range; ICH, intracerebral hemorrhage. Missing data: length of stay 3.1%, discharge destination 4.2%, provided a discharge care plan 6.7%, discharged with an antihypertensive medication 11.4%, discharged with an antithrombotic medication 7.7%, discharged with a lipid-lowering medication 7.9%.

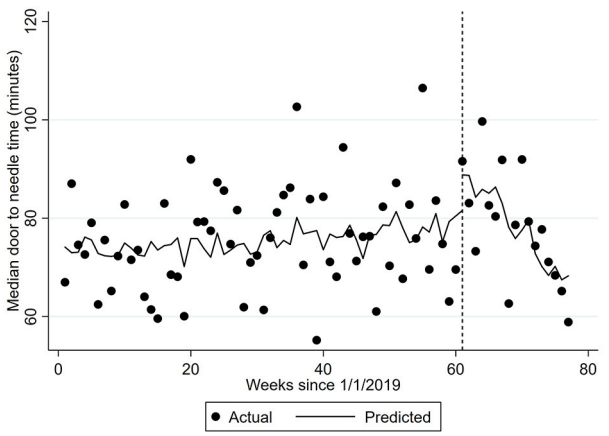


FIGURE 2 | Median door-to-needle time. The dots represent the median door-to-needle per week. The predicted time is adjusted for the number of patients with ischemic stroke and the corresponding number from the previous year (seasonality). Vertical hatched line represents week 61 of the interrupted time-series model with trends compared before and after this date, which coincides with the first COVID-19 related death. Coefficient −2.0476 (95% CI −2.36, −1.73) $p < 0.0001$.

TABLE 3 | Changes in the provision of acute stroke care assessed using interrupted time series analysis.

	Trend before 1/3/2020	Change during the week of 1/3/2020 (interruption week)*	Trend from 1/3/2020
Proportion provided thrombolysis if an ischemic stroke	−0.03 (−0.05, −0.02)	1.09 (0.05, 2.14)	−0.23 (−0.35, −0.10)
Median door to needle time (minutes)	0.10 (0.03, 0.18)	12.15 (9.35, 14.95)	−2.05 (−2.36, −1.73)
Proportion treated in a stroke unit	−0.01 (−0.04, 0.02)	−2.85 (−4.19, −1.51)	−0.25 (−0.42, −0.07)

*Coefficient and 95% confidence intervals presented. *week 61 of the interrupted time-series model with trends compared before and after this date, which coincides with the first COVID-19 related death.*

average (20)], we have demonstrated that stroke care nationally was negatively impacted by the pandemic. This may have been brought on by the need to prepare for a potential influx of infected cases needing hospital management and additional screening processes for triage in emergency departments. In our study, significantly fewer patients had access to stroke unit care at all three post-pandemic timepoints analyzed, an important finding given that patients treated in a stroke unit are more likely to be alive, independent, and living at home 1 year after the stroke than if cared for in other settings (1, 21). Length of stay significantly decreased and fewer patients were discharged with secondary stroke prevention medications across the pandemic timepoints. Other care processes such as discharge to rehabilitation and door-to-needle times under 60 minutes for thrombolysis quickly returned to pre-pandemic levels. Interestingly, an increased proportion of strokes arrived by ambulance in the post-pandemic period, which coincided with a concomitant decrease in the median time to brain scan following arrival. There was little evidence to indicate that one region fared worse than others during this first wave of the pandemic.

Care in organized, dedicated stroke units by expert, interdisciplinary clinicians is the hallmark of best-practice stroke care that is universally applicable to all patients with stroke (21). Our major findings were that stroke unit access decreased, fewer

patients were discharged to inpatient rehabilitation in the early phases of the pandemic, patients were being discharged earlier, and discharged without secondary prevention medications more often than the pre-pandemic period. This may have occurred due to resource redistribution between units, demand for hospital beds or clinician perception of increased risk of patients contracting COVID-19 in hospitals. Our quantitative findings mirror the feedback about service impacts reported by the stroke clinicians. These findings are concerning, since without the care provided in dedicated stroke units, patients experience more complications, disability and mortality (21–23). Disaster planning should incorporate the necessity of maintaining stroke services so that access to evidence-based care processes, such as stroke unit access, are sustained and the "collateral damage" of disaster responses is limited.

Interestingly, although clinicians reported that milder strokes were not presenting to hospital, we were unable to substantiate this perception of a clinically meaningful difference in severity based on the ability to walk on admission or the proportion admitted with final diagnosis of TIA. Evidence around symptom onset to arrival time to hospital has been mixed with reports of maintenance of usual onset to arrival time or delays, particularly with the proportion of ischemic strokes arriving within 4.5 h of onset (3, 6, 7, 12–14). In our study we did not detect a change in median arrival times to hospital from symptom onset. However, more patients used ambulance services. We have described the impact of the COVID-19 pandemic on stroke services from the perspective of hospitals participating in the AuSCR up until the end of June 2020. Although most jurisdictions in Australia were successful in containing the COVID-19 pandemic by the end of April 2020, community and hospital responses led to significant differences in stroke system organization and stroke care. Here we have provided an analysis of the first 6 months of the pandemic prior to the "second wave" of COVID-19 that was limited to Victoria and led to a large number of community transmissions with many health workers being infected (24).

Stroke symptom recognition, rapid diagnosis and subsequent treatment requires streamlined management across multiple hospital departments that is guided by an interdisciplinary team (25). The reported changes to the delivery of stroke services from different countries have not been uniform. While delivery of care in some hospitals and systems has not been significantly restructured, others have experienced redeployment of specialist staff and repurposing of dedicated stroke beds to meet the demands of increased patients requiring treatment for COVID-19 (4, 26, 27). Changes have included the necessity of establishing different triaging protocols for presentations with respiratory symptoms or other signs of COVID-19, altered transportation protocols, changes to stroke pathways and fewer multidisciplinary team rounds (15, 16).

Authors of studies conducted in other countries have reported changes to emergency department workflows associated with the COVID-19 pandemic whereby prevention strategies may delay referrals to the stroke team, and additional brain scanner decontamination processes have also created delays (8, 25, 27, 28). Treatment delays for those eligible for reperfusion therapies lead to worse outcomes including greater disability (29, 30). Our results are reassuring in that many time-based metrics were not negatively impacted. In our cohort, it was found that door-to-scan times were faster during the pandemic period compared to the control period, which may reflect decreased workload in the emergency department at the time, or the increased proportion of patients arriving by ambulance. Although door-to-needle times initially rose by 12.15 (95% CI 9.35, 14.95) minutes with commencement of the pandemic period, these subsequently declined progressively thereafter with evidence of returning to pre-pandemic trends after April. A trend for increased door-to-groin puncture times did not reach significance. Internationally, there have been reports of reduced total numbers of thrombolysis and endovascular thrombectomy procedures due to fewer presentation volumes which was not reflected in these Australian data. Rates of provision of reperfusion therapies among patient with ischemic strokes has been relatively stable (3, 5, 6, 8, 17, 18) both in this study and elsewhere, along with associated time metrics (5, 6, 12, 31).

The strengths of our study include the standardized data from the AuSCR on 18,300 stroke and TIA admissions to the majority of participating hospitals ($n = 61$), and obtaining clinician perspectives prior to the analysis. Further we used a historical control period matched to the pandemic period including comparisons with different phases of the first national wave to account for potential differences in stroke admission related to season. We also performed interrupted time series analysis to comprehensively understand the influence of trends in our prospectively collected patient data adjusting for seasonality and changes in the distribution of diagnosis. The analysis of the survey data was undertaken by different authors (EKT, DAC) to the author who analyzed the AuSCR data (JK). A limitation is the potentially incomplete data for 2020, and the potential for selection bias if not all AuSCR cases were captured because of constrained resources in hospitals to collect data. However, given that the number of 2020 episodes is similar to those collected in the 2019 pre-pandemic period, we are reasonably confident that 2020 dataset is a representative sample from the time of data extraction and analysis. Further, we were unable to report on whether any of the patients in our sample experienced stroke as a result of contracting COVID-19. There is emerging evidence that COVID-19 exhibits neurotropic properties and causes neurological diseases (32) and it is estimated that 1.5% of patients with emergency department visits or hospitalizations with COVID-19 have experienced ischemic stroke (33).

Future data from the registry will enable analysis of the long-term outcomes for patients with stroke who received care in the pandemic period when compared with the pre-pandemic period, including mortality and self -reported morbidity at 90–180 days following admission. A larger second wave of COVID-19 also occurred in the state of Victoria from June 2020 onwards, and future analyses will focus on this time period and comparisons between different regions of Australia. Linkage of AuSCR data with other datasets, to include confirmed diagnoses of COVID-19 positive patients, will also broaden our understanding of the relationship between COVID-19 and stroke.

During disruptions such as a pandemic, efforts to ensure that people with suspected stroke are provided with rapid

triage, acute diagnosis and reperfusion treatment where relevant, and are provided with secondary prevention medications when discharged are required. Access to specialized stroke unit care and rehabilitation should not be compromised. Such concerns have resulted in the Stroke Society of Australasia's appeal to hospital executives to protect the integrity of stroke services (34).

CONCLUSIONS

We highlight the consequences of community and health system COVID-19 responses on hospital care for acute stroke. These impacts occurred despite the predicted hospital overload from COVID-19 patients being averted in Australia during the first half of 2020. The continued decreased access to specialized stroke units is of grave concern given treatment in a stroke unit improves outcomes. Future studies of longer-term outcomes following significant changes to access to stroke unit care, accompanied by decreased length of stay, will be crucial. It is imperative that solutions are identified to maintain appropriate acute stroke care during times of national emergency such as pandemic management. These might include alternate models of providing support to patients immediately after stroke and without comprising access to best-practice in-patient care. As Australia cycles out of the initial phase of the COVID-19 pandemic we will need to ensure there is resilience within the health system to similar events in the future.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Florey Institute of Neuroscience and Mental Health. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the corresponding author with the permission of the Florey Institute of Neuroscience and Mental Health acting on behalf of the AuSCR Consortium. Requests to access these datasets should be directed to admin@auscr.com.au.

ETHICS STATEMENT

This study was approved by the Monash University Human Research Ethics Committee (project ID number 26558). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DAC and JK: study design, data analysis and interpretation, and drafting of the article. ET, JM, and SB: study design, data collection, interpretation of data, and drafting of the article. KJ, RG, BJ, GC, TK, HC, RL, BCl, PM, and BCa: data collection, interpretation of data, and critical revision of the article. SH, NL, SM, BY, KH, CA, and SF: interpretation and critical revision of the article. All authors provided final approval of the version to the article to be published.

FUNDING

The Australian Stroke Clinical Registry was funded from various grants obtained from Stroke Foundation, Queensland Health, Victorian government, Tasmania Government, South Australian government. The following authors receive Research Fellowship support from the National Health and Medical Research Council: DC (1154273) and the National Heart Foundation of Australia: NL (102055).

ACKNOWLEDGMENTS

We acknowledge Prof. Helen Dewey, Prof. Mark Parsons, Ms. Jot Ghuliani, and other members of the AuSCR office team, governance committees, and data contributors to the AuSCR (see **Supplementary Material**).

AuSCR COVID-19 REPORTING CONSORTIUM GROUP

The following authors contributed to the interpretation of data, critical revision of the article, and/or collection of data.

Alaa Alghamry (The Prince Charles Hospital, Queensland, Australia)

Lauren Arthurson (Echuca Regional Health, Victoria, Australia)

Jonnel Boco (Caboolture, Queensland, Australia)

Melanie Brown (Goulburn Valley Health, Victoria, Australia)

Helen Brown (Princess Alexandra Hospital, Queensland, Australia)

Ernie Butler (Peninsula Health, Victoria, Australia)

Greg Cadigan (Queensland Health, Queensland, Australia)

Anna Clissold (South West Healthcare, Victoria, Australia)

Janell Cole (North West Regional Hospital, Tasmania, Australia)

Douglas Crompton (Northern Health, Victoria, Australia)

Vanessa Crosby (Albury Wodonga Health, Victoria & New South Wales, Australia)

Geoffrey Donnan (University of Melbourne, Parkville, Australia)

Angela Dos Santos (Alfred Health, Victoria, Australia)

Ramesh Durairaj (Cairns Hospital, Queensland, Australia)

Chris Ebersohn (Wimmera Base Hospital, Victoria, Australia)

Andrew Evans (Westmead Hospital, New South Wales, Australia)

Brett Forge (West Gippsland Hospital, Victoria, Australia)

Karen Fuller (Wollongong Hospital, New South Wales, Australia)

Nisal Gange (Toowoomba Hospital, Queensland, Australia)

Yash Gawarikar (Calvary Hospital, Australian Capital Territory, Australia)

Richard Geraghty (Redcliffe Hospital, Queensland, Australia)

Kate Jackson (Agency for Clinical Innovation, New South Wales, Australia)

Martin Jude (Wagga Wagga Hospital, New South Wales, Australia)

Salman Khan (Nepean Hospital, New South Wales, Australia)
Monique Kilkenny (Monash University, Victoria, Australia)
Thomas Kraemer (Ballarat Base Services, Victoria, Australia)
Alex Lau (Logan Hospital, Queensland, Australia)
Henry Ma (Monash Health, Victoria, Australia)
Krishna Mandaleson (Central Gippsland Health Service)
Romesh Markus (St Vincent's Hospital, Sydney, New South Wales, Australia)
Stephen Moore (Lismore Base Hospital, New South Wales, Australia)
Neha Nandal (Mackay Base Hospital, Queensland, Australia)
Kim Parrey (Port Macquarie Hospital, New South Wales, Australia)
Lauren Pesavento (Melbourne Health, Victoria, Australia)
Juan Rois-Gnecco (Ipswich, Queensland, Australia)
Darshan Shah (Gold Coast University Hospital, Queensland, Australia)
Daniel Schweitzer (Mater Hospital Brisbane, Queensland, Australia)
Amanda Siller (Queen Elizabeth II Jubilee Hospital, Queensland, Australia)
Jenni Steel (Port Macquarie Hospital, New South Wales, Australia)
Karen Stephens (Eastern Health, Victoria, Australia)
Louise Starkie (Hamilton Base Hospital, Victoria, Australia)
Meng Tan (Gold Coast University Hospital and Robina Hospital, Queensland, Australia)
Vincent Thijs (Austin Health, Victoria, Australia)
Dinesh Tryambake (Launceston General Hospital, Tasmania, Australia)
Rebecca Weir (Northeast Health Wangaratta, Victoria, Australia)
Leanne Whiley (Rockhampton Hospital, Queensland, Australia)
Richard White (Townsville Hospital, Queensland, Australia)
Tissa Wijeratne (Western Health, Victoria, Australia)
Matt Willcourt (Flinders Medical Centre, South Australia, Australia)
Nigel Wolfe (Blacktown Hospital, New South Wales, Australia)
Andrew Wong (Royal Brisbane and Women's Hospital, University of Queensland, Queensland, Australia)
Peter Wood (Bundaberg Hospital & Hervey Bay Hospital, Queensland, Australia)
Jorge Zavala (Alfred Health, Victoria, Australia).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.621495/full#supplementary-material

REFERENCES

1. Langhorne P, Ramachandra S, Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke: network meta-analysis. *Cochrane Database Syst Rev*. (2020) 4:CD000197. doi: 10.1002/14651858.CD000197.pub4
2. Brainin M. *Stroke Care and the COVID19 Pandemic: Words From Our President*. World Stroke Organization (2020). Available online at: https://www.world-stroke.org/news-and-blog/news/stroke-care-and-the-covid19-pandemic.
3. Agarwal S, Scher E, Rossan-Raghunath N, Marolia D, Butnar M, Torres J, et al. Acute stroke care in a New York city comprehensive stroke center during the COVID-19 pandemic. *J Stroke Cerebrovasc Dis*. (2020) 29:105068. doi: 10.1016/j.jstrokecerebrovasdis.2020.105068
4. Bersano A, Kraemer M, Touzé E, Weber R, Alamowitch S, Sibon I, et al. Stroke care during the COVID-19 pandemic: experience from three large European countries. *Eur J Neurol*. (2020) 27:1794–800. doi: 10.1111/ene.14375
5. Jasne AS, Chojecka P, Maran I, Mageid R, Eldokmak M, Zhang Q, et al. Stroke code presentations, interventions, and outcomes before and during the COVID-19 pandemic. *Stroke*. (2020) 51:2664–73. doi: 10.1161/STR.0000000000000347
6. Rudilosso S, Laredo C, Vera V, Vargas M, Renú A, Llull L, et al. Acute stroke care is at risk in the era of COVID-19: experience at a comprehensive stroke center in Barcelona. *Stroke*. (2020) 51:1991–5. doi: 10.1161/STROKEAHA.120.030329
7. Sharma M, Lioutas VA, Madsen T, Clark J, O'Sullivan J, Elkind MSV, et al. Decline in stroke alerts and hospitalisations during the COVID-19 pandemic. *Stroke Vasc Neurol*. (2020) 5:403–5. doi: 10.1136/svn-2020-000441
8. Zhao J, Li H, Kung D, Fisher M, Shen Y, Liu R. Impact of the COVID-19 epidemic on stroke care and potential solutions. *Stroke*. (2020) 51:1996–2001. doi: 10.1161/STROKEAHA.120.030225
9. Rinkel LA, Prick JCM, Slot RER, Sombroek NMA, Burggraaff J, Groot AE, et al. Impact of the COVID-19 outbreak on acute stroke care. *J Neurol*. (2021) 268:403–8. doi: 10.1007/s00415-020-10069-1
10. Gittins M, Ashton C, Holden N, Cross S, Meadipudi S, Kawafi K, et al. Environmental factors and hyperacute stroke care activity during the COVID-19 pandemic: an interrupted time-series analysis. *J Stroke Cerebrovasc Dis*. (2020) 29:105229. doi: 10.1016/j.jstrokecerebrovasdis.2020.105229
11. Hoyer C, Ebert A, Huttner HB, Puetz V, Kallmünzer B, Barlinn K, et al. Acute stroke in times of the COVID-19 pandemic: a multicenter study. *Stroke*. (2020) 51:2224–7. doi: 10.1161/STROKEAHA.120.030395
12. Nguyen-Huynh MN, Tang XN, Vinson DR, Flint AC, Alexander JG, Meighan M, et al. Acute stroke presentation, care, and outcomes in community hospitals in Northern California during the COVID-19 pandemic. *Stroke*. (2020) 51:2918–24. doi: 10.1161/STROKEAHA.120.031099
13. Diegoli H, Magalhães PSC, Martins SCO, Moro CHC, França PHC, Safanelli J, et al. Decrease in hospital admissions for transient ischemic attack, mild, and moderate stroke during the COVID-19 era. *Stroke*. (2020) 51:2315–21. doi: 10.1161/STROKEAHA.120.030481
14. Teo KC, Leung WCY, Wong YK, Liu RKC, Chan AHY, Choi OMY, et al. Delays in stroke onset to hospital arrival time during COVID-19. *Stroke*. (2020) 51:2228–31. doi: 10.1161/STROKEAHA.120.030105
15. Venketasubramanian N. Stroke care services in Singapore during COVID-19 pandemic-a national perspective. *Front Neurol*. (2020) 11:780. doi: 10.3389/fneur.2020.00780
16. Aguiar de Sousa D, van der Worp HB. Stroke care in Europe during the COVID-19 pandemic. *Eur J Neurol*. (2020) 27:1793. doi: 10.1111/ene.14401
17. Kerleroux B, Fabacher T, Bricout N, Moïse M, Testud B, Vingadassalom S, et al. Mechanical thrombectomy for acute ischemic stroke amid the COVID-19 outbreak: decreased activity, and increased care delays. *Stroke*. (2020) 51:2012–7. doi: 10.2139/ssrn.3571545
18. Tejada Meza H, Lambea Gil Á, Saldaña AS, Martínez-Zabaleta M, Juez PR, Martínez EL, et al. Impact of COVID-19 outbreak on ischemic stroke admissions and in-hospital mortality in North-West Spain. *Int J Stroke*. (2020) 15:755–62. doi: 10.1177/1747493020938301
19. Wang H, Wu C, Singh P, Boxuan L, Zhang A, Bhatia S. *COVID-19 in Australia: Real-Time Report*. GitHuB (2020). Available online at: https://covid-19-au.com/.

20. World Health Organization. *WHO Coronavirus Disease (COVID-19) Dashboard*. (2020) Available online at: https://covid19.who.int/.
21. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. (2013) 2013:CD000197. doi: 10.1002/14651858.CD000197.pub3
22. Cadilhac DA, Ibrahim J, Pearce DC, Ogden KJ, McNeill J, Davis SM, et al. Multicenter comparison of processes of care between stroke units and conventional care wards in Australia. *Stroke*. (2004) 35:1035–40. doi: 10.1161/01.STR.0000125709.17337.5d
23. Cadilhac DA, Andrew NE, Lannin NA, Middleton S, Levi CR, Dewey HM, et al. Quality of acute care and long-term quality of life and survival: the Australian stroke clinical registry. *Stroke*. (2017) 48:1026–32. doi: 10.1161/STROKEAHA.116.015714
24. Smith P. Covid-19 in Australia: most infected health workers in Victoria's second wave acquired virus at work. *BMJ*. (2020) 370:m3350. doi: 10.1136/bmj.m3350
25. Coote S, Cadilhac DA, O'Brien E, Middleton S, on behalf of the Acute Stroke Nurses Education Network (ASNEN) Steering Committee. Critical considerations for stroke management during COVID-19 pandemic. *Heart Lung Circ*. (2020) 29:1263–7. doi: 10.1016/j.hlc.2020.09.925
26. Inglis SC, Naismith C, White K, Hendriks JM, Bray JE, Hickman LD, et al. CSANZ COVID-19 cardiovascular nursing care consensus statement: executive summary. *Heart Lung Circ*. (2020) 29:1263–7. doi: 10.1016/j.hlc.2020.08.001
27. Markus HS, Brainin M. COVID-19 and stroke - a global World Stroke Organization perspective. *Int J Stroke*. (2020) 15:361–4. doi: 10.1177/1747493020923472
28. Schirmer CM, Ringer AJ, Arthur AS, Binning MJ, Fox WC, James RF, et al. Delayed presentation of acute ischemic strokes during the COVID-19 crisis. *J NeuroInterv Surg*. (2020) 12:639–42. doi: 10.1136/neurintsurg-2020-016299
29. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. (2010) 375:1695–703. doi: 10.1016/S0140-6736(10)60491-6
30. Goyal M, Menon BK, van Zwam WH, Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. (2016) 387:1723–31. doi: 10.1016/S0140-6736(16)00163-X
31. Mitra B, Mitchell RD, Cloud GC, Stub D, Nguyen M, Nanayakkara S, et al. Presentations of stroke and acute myocardial infarction in the first 28 days following the introduction of state of emergency restrictions for COVID-19. *Emerg Med Australas*. (2020) 32:1040–5. doi: 10.1111/1742-6723.13621
32. Payus AO, Liew Sat Lin C, Mohd Noh M, Jeffree MS, Ali RA. SARS-CoV-2 infection of the nervous system: a review of the literature on neurological involvement in novel coronavirus disease-(COVID-19). *Bosn J Basic Med Sci*. (2020) 20:283–92. doi: 10.17305/bjbms.2020.4860
33. Merkler AE, Parikh NS, Mir S, Gupta A, Kamel H, Lin E, et al. Risk of ischemic stroke in patients with Covid-19 versus patients with influenza. *JAMA Neurol*. (2020) 77:1–7. doi: 10.1001/jamaneurol.2020.2730
34. Yan B. *SSA Statement of Stroke Care During the COVID-19 Stroke Society of Australasia*. (2020). Available online at: https://www.strokesociety.com.au/news-item/4530/ssa-statement-on-stroke-care-during-covid-19.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 26 February 2021
doi: 10.3389/fneur.2021.640581

The Impact of COVID-19 Lockdown on People With Epilepsy and Vagal Nerve Stimulation

Eleonora Grande[1], Tommaso Tufo[2], Marco Ciavarro[3], Ines Di Muccio[4], Filomena Fuggetta[2], Martina Silvestri[2], Giuseppina Bevacqua[5], Jacopo Lanzone[6] and Giovanni Assenza[6]*

[1] Department of Neuroscience, Imaging and Clinical Sciences, University "Gabriele d'Annunzio" of Chieti-Pescara, Chieti, Italy, [2] Neurosurgery, Policlinico A. Gemelli Foundation Istituto di Ricovero e Cura a Carattere Scientifico, Catholic University, Rome, Italy, [3] Neuromed for Istituto di Ricovero e Cura a Carattere Scientifico, Pozzilli, Italy, [4] Neurosurgery, A.O.S.G Moscati, Avellino, Italy, [5] Department of Human Neurosciences, "Sapienza" University of Rome, Rome, Italy, [6] Neurology, Neurophysiology and Neurobiology Unit, Department of Medicine, Università Campus Bio-Medico di Roma, Rome, Italy

OPEN ACCESS

Edited by:
Fernando Cendes,
State University of Campinas, Brazil

Reviewed by:
Veriano Alexandre,
University of São Paulo, Brazil
Cristine Cukiert,
Santa Casa of São Paulo, Brazil

***Correspondence:**
Jacopo Lanzone
jacopo.lanzone@gmail.com

Specialty section:
This article was submitted to Epilepsy, a section of the journal Frontiers in Neurology

Received: 11 December 2020
Accepted: 27 January 2021
Published: 26 February 2021

Citation:
Grande E, Tufo T, Ciavarro M, Di Muccio I, Fuggetta F, Silvestri M, Bevacqua G, Lanzone J and Assenza G (2021) The Impact of COVID-19 Lockdown on People With Epilepsy and Vagal Nerve Stimulation. Front. Neurol. 12:640581. doi: 10.3389/fneur.2021.640581

Objectives: Restrictive measures adopted during the COVID-19 pandemic, in order to limit contagion, have had a severe impact on mental health. The burden of lockdown has been particularly heavy on patients with chronic neurologic diseases such as People with Epilepsy (PwE). Our survey aims to describe the struggles and needs of Drug-Resistant (DR) PwE with implanted Vagal Nerve Stimulator (VNS) during the first wave of the COVID-19 lockdown in order to find strategies that help patients cope with present or future periods of restriction.

Methods: We collected answers from 30 respondents who underwent an online survey including socio-demographic and clinical information and COVID-19-related information. Depression, anxiety symptoms, and sleep quality were investigated in patients through BDI II, GAD-7, and the PSQI scale.

Results: In all, 46% of our sample reported an increase in the number of seizures; the entire sample complained of epilepsy-related issues (medication availability, VSN adjustments, anxiety, sleep disturbance); one out of three participants reported major epilepsy issues felt urgent; 30% had to postpone scheduled examination. Significantly higher scores for depression and anxiety scales were found in patients who perceived seizure frequency worsening and reported major epilepsy-related issues.

Conclusion: Preliminary findings showed that the first lockdown influenced the clinical and psychological status of PwE and was related to seizures worsening. The lack of medical assistance and control on VNS therapy left patients to cope with the situation without a chance to contact a specialist. We discuss how a wider implementation of telemedicine programs could facilitate remote assistance of PwE with a VNS implant.

Keywords: epilepsy, vagal nerve stimulator, COVID-19, mental health, telemedicine

INTRODUCTION

Coronavirus infection (COVID-19) rapidly spread worldwide during the early months of 2020 (1) to the point of being declared a pandemic by the World Health Organization (WHO) in March. Early on, imposing lockdown measures was the most widespread strategy to limit the diffusion of the disease, alleviating the burden on healthcare systems. Restrictive measures severely affected the social and mental health of individuals, and thus, lockdown was associated with an increase in mental health-related issues, such as anxiety, depression, and sleep disorders, as was shown by a national cross-sectional study on the general Italian population (2). Patients with chronic neurologic diseases suffered even more from the hardships of lockdown (3–6). Restrictive measures imposed during the first wave of COVID-19 caused a decrease in availability of neurological assistance in Italy (5). This affected, among others, PwE, given that most healthcare services or hospitals were not ready to implement telemedicine, which had been proposed as a potential solution during the time of restrictions (7). In particular, more frail patients, such as DR-PwE with implanted VNS, were not able to attend scheduled visits fundamental to titrate stimulation's parameters to optimize efficacy and tolerability. VNS is implanted in DR-PwE as palliative therapy to reduce seizure frequency, when pharmacological and surgical approaches fail (8, 9), and once implanted, it repeatedly needs to be regulated, to slowly reach the target stimulus intensity, possibly with minimal adverse effects (10). Adverse events (mainly hoarseness, cough, paresthesia during the ON phase of VNS) can be easily overcome by frequency, duration, and intensity adjustments. Unfortunately, VNS devices cannot be remotely controlled but require a physical intervention of the clinicians. For these reasons, VNS patients need continuous and cadenced follow-up visits, which are difficult to guarantee during the COVID-19 lockdown. Since VNS patients carry an implanted device upon which they do not have direct control, they are vulnerable to the reduced availability of neurological assistance during lockdown. Thus, we designed a survey targeting PwE patients with VNS. With this study, we aimed at identifying and discussing the special needs of PwE with VNS implant during periods of reduced availability of follow-up and propose helpful strategies to implement during this new wave of contagion.

MATERIALS AND METHODS

Data were collected from PwE with implanted VNS attending the outpatient epilepsy clinics in two major hospitals in Rome (Italy), the "Policlinico Universitario Fondazione Agostino Gemelli—Roma" and "Policlinico Universitario Campus Bio-Medico di Roma." All patients gave their consent to be contacted for research purposes at the moment of their hospitalization for VNS surgery.

Experimenters contacted all PwE with implanted VNS (by phone) from the joint database to assess their consent to receive an online questionnaire before it was sent to patients and their caregivers through mail or WhatsApp® contact. **Figure 1** shows the database features. The inclusion criteria involve an implanted VNS device regardless of the etiology and consent to take part in the study; the exclusion criteria involve duplicated answers (i.e., participants with the same birth date answer twice) and unreliable answers.

The survey was performed during the months of April and May 2020, which was at the maximum of the Italian contagion curve. Given the neurocognitive impairment experienced by many PwE with VNS implant, if the patient was not able to independently answer our survey, the caregiver provided the response with clinical information, referring to the patient. The questionnaire contains a brief description of the study. They electronically consented to complete the questionnaire after reading an informed consent on their devices, and data were stored anonymously. Clinical information on epilepsy, such as seizure frequency and type, anti-seizure medications (ASMs), and duration of the disease, was collected. In addition, participants were asked COVID-19-related information (symptoms, fever, hospitalization) and VNS-related questions (the seizure frequency reduction and seizure intensity reduction induced by VNS). Participants had to accurately report the number of monthly seizures occurring in the 50 days during the first lockdown (referred to as the "COVID-19 period") and in the 50 days before March 11 (start of the first lockdown in Italy; referred to as the "pre-COVID-19 period"). Most patients and their caregivers have a long-standing story of epilepsy, are accustomed to their subjective semiology, and are instructed in identifying symptoms. They keep a daily seizures diary; thus, their report is considered to be reliable. Finally, participants were asked information on major (i.e., clinical issues were felt to be urgent with the inability to contact a specialist; clinical problems that in normal situations would make the patient look for a specialist's opinion) and minor complications (i.e., ASM availability, VNS adjustment, anxiety, and sleep disturbance) due to COVID-19 restrictions.

Mental health status was investigated only when the respondent was the PwE in person. We used the Beck Depression Inventory scale II (BDI-II) (11), a 21-item scale (scored 0–3), as a self-report measure of common depressive symptoms. Anxiety symptoms were assessed through use of the General Anxiety Disorder-7 (GAD-7) (12). Pittsburg Sleep Quality Index (PSQI) (13) was administered to evaluate sleep quality. Previous items (clearly showed in **Supplementary Table 2**) were included in an online survey questionnaire created using the free open-access Google™ Forms (https://www.google.com/forms/about/) application, as in a prior study on COVID-19 consequences (6). Data were treated according to the European regulation GDPR n. 2016/679. Our ethics committee was involved in the development of the study, and the local Ethics committee was officially notified of the study as a prospective observational study with anonymous data sampling. Proper ethical committee approval was not necessary for this type of study.

We applied this protocol in an emergency phase of the COVID-19 pandemic with the hope that the preliminary data received, in the future, could be expanded through national and international collaboration to better depict the needs of the special population of VNS PwE.

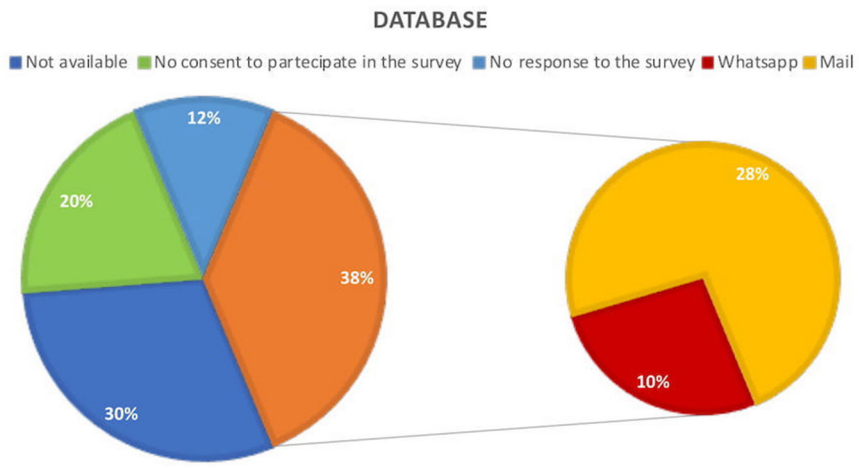


FIGURE 1 | Participants in the joint database who consent to take part in the survey and those who did not; reception of the online questionnaire.

Statistical Analysis

We performed statistical analysis using R studio software 1.3.1. The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. Normally distributed data are reported as Mean ± SD, and their differences are described with a Student *t*-test; nonnormally distributed data are reported as Median and Interquartile Range (IQR), with their differences analyzed by Wilcoxon's test. The alpha level was set at 0.05 for statistical significance.

RESULTS

Demographic and Clinical Data

We collected responses to the questionnaire from 30 participants. The whole sample came from central/southern Italy. The sample comprised 30 PwE (13 patients and 17 caregivers), with 11 females of a mean age of 45.6 ± 13.8. The whole sample has an implanted VNS in the active phase. Demographic information was displayed in **Table 1** while education, marital, and working status are reported in **Supplementary Table 1**. **Table 1** also includes epilepsy clinical data, such as etiology, ASM, types of seizures, and non-pharmacological therapies. All the patients were under ASMs, and only 3 (10%) of these did not receive a neurological examination during the last year. Furthermore, **Table 1** reports data concerning the number of seizures that occurred during the 3 months prior to the interview, specifically, the number of all seizures (focal and tonic-clonic generalized seizure, median number 38.5, IQR 110.7) and the number of generalized tonic-clonic seizures exclusively (median number: 1.5, IQR: 20). Moreover, the number of seizures before and during the COVID-19 period were registered. Finally, **Table 1** includes information about the benefit of VNS and outcomes of VNS with respect to seizure frequency and intensity.

COVID-19 Data

Symptoms of COVID-19 infection were specifically investigated. Two participants reported fever, and two underwent a nasopharyngeal swab test for SARS-CoV-2 (no positive and no hospitalization).

Epilepsy During the COVID-19 Lockdown

Seizure Number Report

For the whole sample preliminary findings showed no significant difference in the number of seizures during the pre-COVID-19 period and COVID-19 pandemic: the median number of seizures during the COVID-19 period was 26 (IQR 39.75) and 26 (IQR 41.5) during the pre-COVID-19 pandemic period ($p > 0.05$).

Epilepsy-Related Issues

Due to COVID-19 restrictions, eight participants of the whole sample (27%) reported major epilepsy-related issues, while all participants reported minor problems as displayed in **Figure 2A**. **Figure 2B** highlights that 16 participants (53%) achieved to get in touch with their neurologist during the COVID-19 period (9, 56% personal mobile calls; 4, 25% short text messages/WhatsApp messages; 2, 16% mail; 1, 6% doctor's office calls). Ten patients (33%) had to postpone a scheduled medical visit, and nine participants (30%) did not manage to solve their problems (**Figure 2C**). No patient was hospitalized for epilepsy-related problems.

Psychometric Assessment

In the last section of the questionnaire, anxiety, depressive symptoms, and sleep quality were investigated in the patients' group ($n = 13$). The BDI II median score was 6 (IQR 13.5), with three patients (23%) reporting out of normal range values. The GAD-7 median score was 5 (IQR 4.5), and seven patients (54%) reported out of normal range value. The PSQI index median score was 4 (IQR 5), with five patients (38%) showing out of normal range scores.

TABLE 1 | Demographic and clinical data of the whole sample.

Patients	Epilepsy etiology	Surgery	Year	Sex	Years of epilepsy	ASM number	Specific ASM	Years VNS	Type of seizures	Non Pharmaco logical therapies	N of seizures (3 months)	N of tonico-clonic seizures (3 months)	N of seizures pre Covid-19	N of seizures during Covid-19	VNS benefit	VNS N of seizures reduction	VNS % frequency reduction	VNS intesity reduction
1	Unknown		58	M	11	3	CBZ TPM PER	12	FS FBTC		12	0	8	4	Yes	Yes	>50%	Yes
2	Unknown		46	F	12	3	LEV CBZ PB	8	FS FBTC		178	5	91	133	Yes	Yes	>25%	Yes
3	Structural		45	F	10	3	ZNS CBZ PB	7	GTC		87	0	34	44	N/A	N/A	N/A	N/A
4	Structural		52	M	20	4	CBZ VPA LEV PER	22	FS FBTC		15	0	8	9	Yes	Yes	>75%	Yes
5	Genetic		25	F	24	2	VPA CBZ	15	FS FBTC	Ketogenic diet	45	6	28	28	Yes	Yes	>75%	Yes
6	Unknown		71	M	36	2	LEV LTG	10	AA GTC		16	0	12	23	No	Yes	<25%	Yes
7	Unknown		44	M	44	3	OXC ZNS PB	8	GTC T		32	20	34	26	Yes	Yes	>50%	No
8	Unknown		51	M	21	2	VPA BRV	12	GTC		6	0	2	1	Yes	Yes	<25%	Yes
9	Unknown		56	F	12	3	ZNS LAC BRV	11	GTC		60	0	50	30	Yes	Yes	>50%	No
10	Unknown		46	M	18	4	TPM PER CBZ LTG	9	FS FBTC		181	0	50	70	N/A	N/A	N/A	N/A
11	Structural		34	M	3	3	PB RAC BRV	11	FS FBTC		30	0	14	16	Yes	Yes	>50%	Yes
12	Unknown		51	M	1	2	CBZ GBP	12	GTC		7	3	2	5	Yes	Yes	<25%	Yes
13	Unknown		56	M	25	3	OXC PER LAC	14	FS FBTC		13	13	7	7	N/A	N/A	N/A	N/A
14	Unknown		38	M	1	2	CBZ PB	15	GTC		275	90	155	147	Yes	Yes	>50%	Yes
15	Anterior Temporal Lobectomy	Yes	29	M	1	2	OXC FBN	15	FS FBTC		90	30	30	30	Yes	Yes	>25%	No
16	Unknown		38	M	5	4	CBZ ZNS TPM CLN	13	FS FBTC		N/A	N/A	N/A	N/A	No	No	<25%	No
17	Unknown		76	F	24	1	VPA	14	FS FBTC		3	0	2	3	Yes	Yes	>75%	Yes
18	Unknown		41	F	6	3	VPA FBN CBZ	16	GTC		100	20	60	45	Yes	Yes	<25%	Yes
19	Unknown		34	M	8	3	OXC CBZ PER	10	FS FBTC		4	12	8	6	Yes	Yes	>25%	Yes
20	Anterior Temporal Lobectomy	Yes	27	F	0	3	VPA CBZ PER	4	GTC		120	0	40	60	No	No	<25%	No

(Continued)

TABLE 1 | Continued

Patients	Epilepsy etiology	Surgery	Year	Sex	Years of epilepsy	ASM number	Specific ASM	Years VNS	Type of seizures	Non Pharmaco logical therapies	N of seizures (3 months)	N of tonico-clonic seizures (3 months)	N of seizures pre Covid-19	N of seizures during Covid-19	VNS benefit	VNS N of seizures reduction	VNS % frequency reduction	VNS intesity reduction
21	Unknown		44	M	44	3	OXC PB ZNS	13	FS FBTC		32	27	24	26	No	Yes	<25%	Yes
22	Unknown		23	M	7	3	VPA CBZ PB	3	GTC AA	Ketogenic diet	500	150	45	50	No	No	N/A	No
23	Unknown		30	M	1	4	FBN OXC TPM CLN	5	FS FBTC		400	12	60	135	No	No	<25%	No
24	Genetic		69	F	29	3	TPM PB SL	29	FS FBTC		3	3	4	5	Yes	Yes	>90%	Yes
25	Unknown		55	F	13	3	ZNS LAC BRV	12	GTC		60	0	33	33	Yes	Yes	>90%	Yes
26	Unknown		50	M	21	2	VPA BRV	11	GTC		10	23	1	1	Yes	Yes	>25%	No
27	Structural		44	M	5	4	CBZ LTG ZNS CBZ	22	FS FBTC		4	0	2	2	N/A	N/A	N/A	N/A
28	Unknown		55	F	4	3	CLN CBZ PB	15	FS FBTC		N/A	N/A	N/A	N/A	Yes	Yes	>50%	Yes
29	Unknown		56	F	1	5	TPM BRV LAC PER CBZ	12	FS FBTC		48	0	20	7	Yes	Yes	>25%	No
30	Structural		25	M	6	3	LEV PER CLN	16	GTC	Ketogenic diet	120	20	80	45	Yes	Yes	<25%	No

GTC, Generalized tonic-clonic seizures; FS, focal seizures; FBTC, focal to bilateral tonic-clonic; AA, atypical absence; T, tonic seizures; N/A, no answer; CBZ, Carbamazepine; ESL, Eslicarbamazepine; OXC, Oxcarbamazepine; VPA, Valproic Acid; ZNS, Zonisamide; TPM, Topiramate; LEV, Levetiracetam; BRV, Brivaracetam; CLN, Clonazepam; CBZ, Clobazam; PB, Phenobarbital; LTG, Lamotrigine; LAC, Lacosamide; PER, Perampanel; FBM, Felbamate.

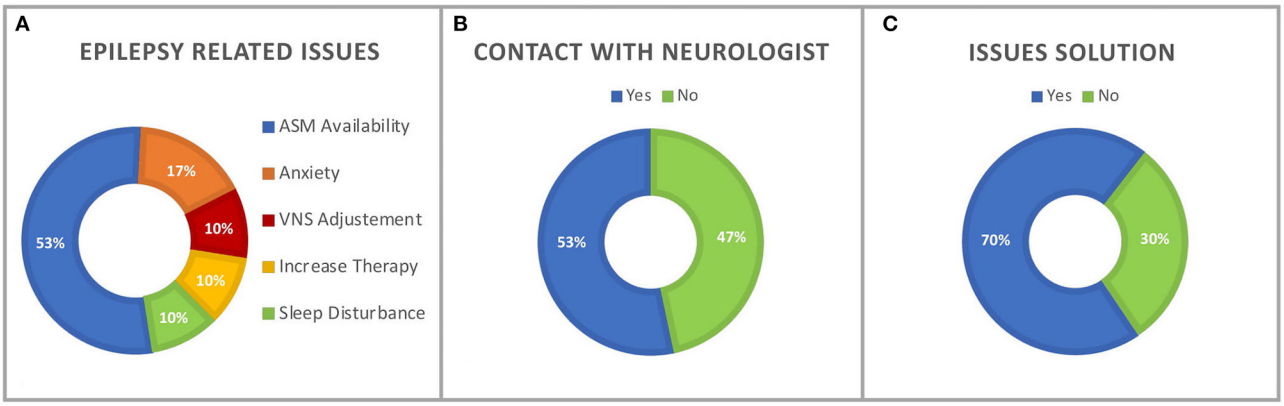


FIGURE 2 | (A) Percentage of epilepsy-related issues experienced during the COVID-19 period. **(B)** Percentage of participants who reached a neurologist during the COVID-19 period. **(C)** Percentage of participants who managed to solve epilepsy-related issues.

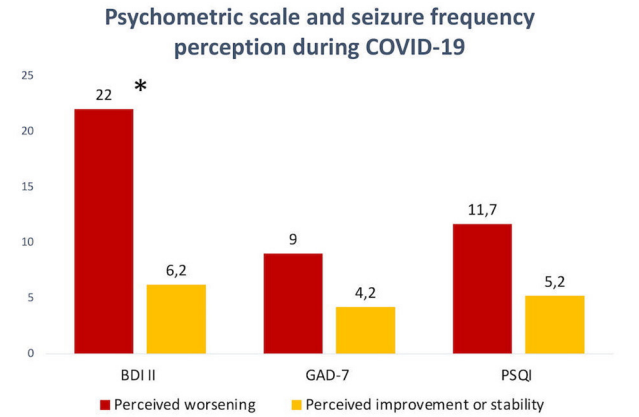


FIGURE 3 | Differences in psychometric scales scores between patients who perceived seizure frequency worsening during the COVID-19 period and patients who perceived seizure frequency stability or improvement. Significant difference in the BDI II scale value (*$p < 0.05$).

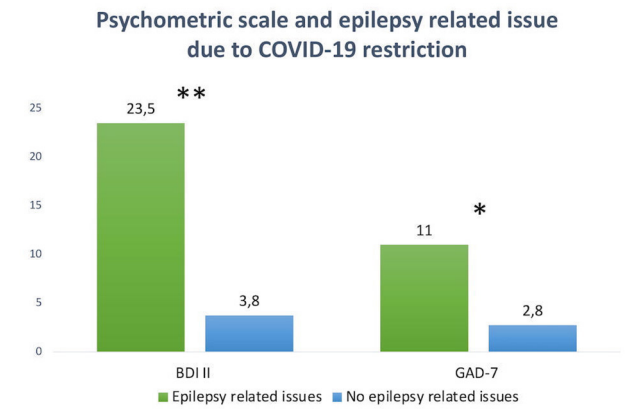


FIGURE 4 | Significant differences in BDI II scale value (**$p < 0.01$) and GAD-7 value (*$p < 0.05$) between the group who experienced major epilepsy-related issues during the COVID-19 pandemic and the group who did not.

Our preliminary results exhibited a significant difference ($p < 0.05$) on the depression scale between patients who perceived an increase in seizure frequency (3, 23%; BDI II: 22 ± 26) and patients who reported reduction or stability (10, 76%; BDI II: 6.2 ± 7.49) (**Figure 3**). These exploratory results suggest higher depressive symptoms in patients who perceived seizure frequency worsening during the COVID-19 period.

To address major epilepsy-related issues during the COVID-19 period, a prior comparison between the group who experienced major epilepsy-related issues (4, 31%) and those who did not (9, 69%) was performed. In the group with epilepsy-related issues during the COVID-19 period, the BDI II score (23.5 ± 19.89) and GAD-7 score (11 ± 7.11) were significantly greater ($p < 0.01$; $p < 0.05$, respectively) (**Figure 4**) than the group who did not report major epilepsy-related issues (BDI II: 3.8 ± 4.6; GAD-7: 2.8 ± 1.78), indicating increasing symptoms of anxiety and depression in the group who experienced global epilepsy-related adverse event due to COVID-19 restrictions.

DISCUSSION

We designed the present survey to explore the impact that the COVID-19 lockdown had on the PwE with VNS implant, one of the frailest group of patients with epilepsy. During COVID-19, a recent wider survey on PwE evidenced that they face many difficulties. Thus, we expected that PwE with VNS, that need more frequent medical examinations, might also face major clinical issues.

COVID-19 Lockdown Impact on Epilepsy

The whole sample has an implanted VNS in the active phase, and about half of the participants report a benefit in seizure frequency > 50%, as commonly presented in the literature (14). According to our preliminary findings, we did not find

significant changes in seizures during the COVID-19 lockdown. On the other hand, up to a third of respondents encountered major disease-related issues during the lockdown period. The entire sample complained of minor issues, such as postponed scheduled medical visits, reduced ASM availability, need of VNS adjustments, anxiety, and sleep disturbance. Nearly half of the respondents could not contact a specialist, leading to a third of them not being able to find a solution to major or minor complications. These data closely replicate previously reported findings from a larger Italian survey (6), confirming that restrictive measures of the first wave of COVID-19 resulted in a medical care reduction for PwE and also insufficient service in the antiseizure medications supply chain. Furthermore, it is worth mentioning that our population often reported specific problems with VNS devices that are not solvable without the assistance of specialists, thus exposing PwE with VNS to a significant discomfort and clinical risk during lockdown. These data underscore the urgency of the implementation of remote assistance with VNS devices, in order to reduce malfunctions or to provide specialistic assistance and to help patients to alleviate adverse events in case of isolation.

Epilepsy and Psychometric Reports

Early results of psychometric scales showed that half of the patients reported abnormal values on the anxiety symptoms scales, and one out of four showed abnormal values in the assessment of depressive symptoms. Poor sleep quality was observed in 4 out of 10 PwE. Prior depressive and anxiety symptoms emerged among our PwE with VNS sample confirmed the previous results in a larger PwE sample and seems strictly related to both a reported increase in seizure frequency and the presence of epilepsy-related issues. Our preliminary findings showed that PwE reporting worsening of seizures and epilepsy-related issues had worse depressive and anxiety symptoms than PwE who did not.

The format of our questionnaire cannot proove the directionality of the relationship among seizure worsening, depressive/anxiety symptoms, and clinical issues complaints; we nonetheless want to underscore the need for assistance of these frail patients. One interpretation of our preliminary results is the hypothesis that the combination of epilepsy-related issues and seizure worsening might have negatively influenced the psychological status of PwE. However, we cannot rule out the possibility that the reported worsening could be the result of poorer scores in depression and anxiety scales affecting self-perception and the perception of each respondent's own disease. In fact, PwE often demostrate incongruence confronting to their own disease consistently with the fact that patients with long-standing epilepsy are often found to be alexithymic, meaning they have scarce insight into their condition both physical and psychological (15).

It is not surprising that more severe patients, such as those PwE with VNS, exposed to factors directly influencing quality of life, such as the perception of stigma and the number of medications (15, 16), report more anxiety and depression. Thus, our purpose is to highlight the need for assistance in PwE with VNS, in whom depression is very frequent comorbidity and who constantly have to cope with the anxiety derived from having an implanted device that they cannot directly control, along with the fear of unfathomed adverse effects or of the abrupt stop of the titration plan during the lockdown period. For many of them, this translates into trying to contact a specialist because of the need for information.

Italy was completely unprepared to assist chronic patients with telemedicine, and telemedicine was often implemented only on account of a personal initiative of doctors who were directly contacted by patients (7). In most cases, a simple phone call with a neurologist would reassure patients or help them cope with their situation. We advise services caring for people with chronic diseases such epilepsy to implement some official form of telemedicine. This will reduce the cost of needed follow-up visits and might be suitable for reducing patients' distress during the current new wave of COVID-19. Technology-driven therapies, such as VNS, should facilitate the remote assistance of our patients. Actually, recent developments in VNS technology allow auto-titration to the target intensity and duty cycle (17). Auto-titration changes VNS stimulation parameters at defined intervals; within the therapeutic range, it is usually well-tolerated, and patients feel they have some control since they know on which day the titration will happen. This method makes it possible to reach the target stimulation intensity and duty cycle, avoiding several visits to the outpatient clinic. In the unlikely event that adverse effects (cough, pain, hoarseness) are reported, the patients could temporally stop stimulation using the magnet and consult their neurologist. This feature is very useful, both for clinicians and patients, in periods of reduced disposal of follow-up with a specialist since it spares many ambulatory visits that have the sole purpose of causing a small increase in VNS parameters. We think that a more direct interaction of the patient with VNS devices, such as a patient dedicated app showing the status of stimulation, could help alleviate the preoccupations and anxiety related to the implant. Currently, the only control that a patient has of a VNS device is the possibility to turn on extra-stimulation or temporally stop the device, using a magnetic wristband. Furthermore, remote control for the VNS device (by telephone or internet) is desirable to allow clinicians to intervene in case of urgency (severe adverse effect or catastrophic seizure frequency modification) to modify stimulation parameters.

Present exploratory results, derived from an emergency situation, also offer new ideas to reflect about the protocols of follow-up used for PwE in general. Chronic follow-up of PwE should be mostly guaranteed by a remote service assessing seizure features (frequency, severity, related injuries, post-ictal phenomena), ASM tolerability, quality of life, and psychometric tests and instrumental results (blood, EEG, MRI). As a matter of fact, most PwE with chronic epilepsy do not undergo neurological clinical examination during their controls. Since epilepsy is not usually clinically manifest at the moment of the visit, the neurologist bases his/her decisions mostly on data such as EEG, MRI, and blood tests. All these data can be informatically transferred to the clinician, using coding such as blockchain, which guarantees privacy and traceability of health care data (18), who will reserve the visit only for those cases with critical issues or new problems requiring a physical evaluation. For the rest

of PwE, the chronic follow-up might be guaranteed by sporadic physical (yearly) examination.

The present study has some limitations. The small size of the sample reduces its statistical power. Another limitation of our research is that this population, treated with VNS, suffered from a different form of drug-resistant epilepsy, making it hard to reach a homogeneous population, as is done commonly when researchers study a severe form of epilepsy. However, we designed this study to obtain preliminary data for a bigger future multicenter study. Using an online questionnaire did not allow patients with moderate to severe cognitive impairment to answer, and this explains the involvement of caregivers participating in the survey. Anyway, it must be said that the online survey offered the opportunity to reach as many patients as possible during the lockdown phase, allowing the possibility to get in touch with them during isolation. We are aware that the online survey we elaborated on provides low strength of scientific evidence, but it allowed us to understand the needs of patients and caregivers despite the limitations imposed by the lockdown.

CONCLUSION

The first wave of the COVID-19 pandemic and the related social restrictions apparently did not impact seizure frequency; however, they caused psychological distress in PwE with implanted VNS. The preliminary findings reported a lack of assistance in patients and showed that many VNS-treated PwE and their caregivers faced problems due to the chronic disease and reported anxiety and depressive symptoms during the pandemic. Disease-related issues were amplified by the lack of telemedicine assistance and the lack of control/information about VNS therapy at the disposal of PwE. These issues should be systematically addressed in order to improve the quality of life of PwE with VNS, especially during periods of lockdown.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GA, TT, and MC designed and conceptualized the study. EG had a major role in the statistical analysis. GA, EG, and JL provided interpretation and wrote the paper. ID, FF, and MS provided database implementation. ID, EG, GB, and MS played a major role in the acquisition of data. MC, GB, GA, TT, and JL revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.640581/full#supplementary-material

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382-18:1708–20. doi: 10.1056/NEJMoa2002032
2. Gualano MR, Lo Moro G, Voglino G, Bert F, Siliquini R. Effects of Covid-19 lockdown on mental health and sleep disturbances in Italy. *Int J Environ Res Public Health.* (2020) 17:4779. doi: 10.3390/ijerph17134779
3. Motolese F, Magliozzi A, Puttini F, Rossi M, Capone F, Karlinsky K, et al. Parkinson's disease remote patient monitoring during the COVID-19 lockdown. *Front Neurol.* (2020) 11:1190. doi: 10.3389/fneur.2020.567413
4. Lanzone J, Cenci C, Tombini M, Ricci L, Tufo T, Piccioli M, et al. Glimpsing the impact of COVID19 lock-down on people with epilepsy: a text mining approach. *Front Neurol.* (2020) 19:11–870. doi: 10.3389/fneur.2020.00870
5. Assenza G, Lanzone J, Ricci L, Boscarino M, Tombini M, Galimberti CA, et al. Electroencephalography at the time of Covid-19 pandemic in Italy. *Neurol Sci.* (2020) 41:1999–2004. doi: 10.1007/s10072-020-04546-8
6. Assenza G, Lanzone J, Brigo F, Coppola A, Di Gennaro G, Di Lazzaro V, et al. Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening. *Front Neurol.* (2020) 3:11–737. doi: 10.3389/fneur.2020.00737
7. Omboni S. Telemedicine during the COVID-19 in Italy: a missed opportunity? *Telemed J E Health.* (2020) 26:973–5. doi: 10.1089/tmj.2020.0106
8. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs a 30-year longitudinal cohort study. *JAMA Neurol.* (2018) 75:279–86. doi: 10.1001/jamaneurol.2017.3949
9. Assenza G. Diagnosis and treatment of drug-resistant epilepsy: present and future perspectives. *Brain Sci.* (2020) 10:779. doi: 10.3390/brainsci10110779
10. Yamamoto T. Vagus nerve stimulation therapy: indications, programing, and outcomes. *Neurol Med Chir.* (2015) 55:407–15. doi: 10.2176/nmc.ra.2014-0405
11. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II.* San Antonio, TX: Psychological Corporation (1996).
12. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092
13. Curcio G, Tempesta D, Scarlata S, Marzano C, Moroni F, Rossini PM, et al. Validity of the Italian version of the Pittsburgh sleep quality index (PSQI). *Neurol Sci.* (2013) 34:511–9. doi: 10.1007/s10072-012-1085-y
14. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg.* (2011) 115:1248–55. doi: 10.3171/2011.7.JNS11977
15. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, Ulivi M, et al. Depressive symptoms and difficulties in emotion regulation in adult patients with epilepsy: association with quality of life and stigma. *Epilepsy Behav.* (2020) 107:107073. doi: 10.1016/j.yebeh.2020.107073
16. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, De Mojà R, et al. Epilepsy-associated stigma from the perspective of people with epilepsy and the community in Italy. *Epilepsy Behav.* (2019) 98:66–72. doi: 10.1016/j.yebeh.2019.06.026
17. Boon P, Vonck K, van Rijckevorsel K, El Tahry R, Elger CE, Mullatti N, et al. A prospective, multicenter study of cardiac-based seizure

detection to activate vagus nerve stimulation. *Seizure*. (2015) 32:52–61. doi: 10.1016/j.seizure.2015.08.011

18. Agbo CC, Mahmoud QH, Eklund JM. Blockchain technology in healthcare: a systematic review. *Healthcare*. (2019) 4:7–56. doi: 10.3390/healthcare7020056

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 08 March 2021
doi: 10.3389/fneur.2021.613769

Multiple Sclerosis Patient Management During the COVID-19 Pandemic: Practical Recommendations From the Portuguese Multiple Sclerosis Study Group (GEEM)

João J. Cerqueira[1], Ana F. Ladeira[2], Ana M. Silva[3], Ângela Timóteo[4], José Vale[4], Lívia Sousa[5], Marta Arenga[6], Pedro Abreu[7], Rui Guerreiro[8] and João de Sá[9]*

[1] Life and Health Sciences Research Institute (Instituto de Investigação em Ciências da Vida e Saúde), School of Medicine, University of Minho, Braga, Portugal, [2] Neurology Department, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal, [3] Department of Neurology, Centro Hospitalar e Universitário Do Porto, Porto, Portugal, [4] Department of Neurology, Hospital Beatriz Ângelo, Loures, Portugal, [5] Department of Neurology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal, [6] Department of Neurology, Centro Hospitalar da Cova da Beira, Lisbon, Portugal, [7] Department of Neurology, Centro Hospitalar São João, Porto, Portugal, [8] Department of Neurology, Centro Hospitalar de Setúbal, Setúbal, Portugal, [9] Department of Neurology, Centro Hospitalar Lisboa Norte, Lisbon, Portugal

OPEN ACCESS

Edited by:
Jesús Porta-Etessam, Hospital Clínico San Carlos, Spain

Reviewed by:
Moussa Antoine Chalah, Hôpitaux Universitaires Henri Mondor, France
Lamberto Landete Pascual, Doctor Peset University Hospital, Spain

***Correspondence:**
João J. Cerqueira
jcerqueira@med.uminho.pt

Specialty section:
This article was submitted to Multiple Sclerosis and Neuroimmunology, a section of the journal Frontiers in Neurology

Received: *03 October 2020*
Accepted: *08 February 2021*
Published: *08 March 2021*

Citation:
Cerqueira JJ, Ladeira AF, Silva AM, Timóteo Â, Vale J, Sousa L, Arenga M, Abreu P, Guerreiro R and de Sá J (2021) Multiple Sclerosis Patient Management During the COVID-19 Pandemic: Practical Recommendations From the Portuguese Multiple Sclerosis Study Group (GEEM). Front. Neurol. 12:613769. doi: 10.3389/fneur.2021.613769

The spread of the COVID-19 pandemic has imposed significant challenges on healthcare provision, requiring changes in the conventional patient management, particularly in chronic diseases like multiple sclerosis (MS). To increase patient safety and reduce the risk of infection, while ensuring an appropriate and regular follow-up, tele-medicine gained prominence as a valid alternative to face-to-face appointments. However, the urgency of the implementation and the lack of experience in most MS centers led to "*ad hoc*" and extremely diverse approaches, which now merit to be standardized and refined. Indeed, while tele-consultation cannot fully replace face-to-face visits, it certainly can, and will, be incorporated as part of the routine care of MS patients in the near future. Bearing this in mind, the Portuguese Multiple Sclerosis Study Group (GEEM) has developed a set of recommendations for the usage of tele-medicine in the management of MS patients, both during the pandemic and in the future. The consensus was obtained through a two-step modified Delphi methodology, resulting in 15 recommendations, which are detailed in the manuscript.

Keywords: telehealth, virtual consultation, monitoring, remote assessment, consensus

INTRODUCTION

Multiple sclerosis (MS) is a chronic degenerative disorder of the central nervous system of auto-immune origin (1) that affects 2.8 million persons worldwide and 0.142% of Europeans (2). Optimal management of MS includes early diagnosis and treatment as well as regular monitoring and follow-up, since patients often need their treatments to be adjusted for lack of efficacy, tolerability, or safety issues (3). In general, patients with MS are followed periodically in specialized MS clinics (approximately every 6 months) with visits that include, as a minimum, a clinical interview for any new

symptoms, adverse events and relapses, a neurological examination, and a review and discussion of any ancillary examinations performed (4). In addition, given their importance for the optimal control of the disease, patient education regarding diet, physical exercise, smoking, and other lifestyle factors should also take place at each visit (4).

The infection by the new respiratory agent SARS-CoV-2 was firstly identified in China in December 2019 (5). On March 11, 2020, the World Health Organization declared COVID-19 (as the disease caused by SARS-CoV-2 was named) a pandemic (6). In Portugal, the first case was registered on March 2, and 14 days later, the Ministry of Health determined that all non-urgent care provision should be canceled, redirecting all efforts to fight COVID-19 (7). This suspension was lifted at the beginning of May (8), but by then, thousands of appointments and exams had been canceled and had to be rescheduled. Moreover, mandatory safety measures, such as limiting the presence of patients in the waiting rooms and introducing "empty periods" in the schedule to accommodate delays in face-to-face visits, significantly limited the availability of healthcare services. This was further complicated by the fact that many MS patients avoided going to healthcare facilities, for fear of acquiring SARS-CoV-2 (9).

From the beginning of the pandemic, tele-medicine has emerged in several countries as a possible solution for balancing the need to prevent infection with the need to keep an appropriate follow-up (10–20). Tele-medicine enables the regular and close contact between patient and physician while lowering the need for patient's physical presence in Health Units, and hence the risk of exposure to SARS-CoV-2 (14, 20). The implementation of tele-medicine, in particular tele-consultations, should not rely on *ad hoc* approaches by individual physicians, but rather be based in internationally recognized best practices and, as much as possible, standardized (14). In the last year, many publications addressed the care of MS under a global pandemic, describing cases of success (16, 17, 19), giving practical recommendations (11–14), and sometimes focusing on particular aspects of the teleconsultation (15). However, clear, systematic, consensus-based recommendations that reflect the opinion of diverse group of practitioners and can be widely adopted are largely missing, with two notable exceptions coming from Latin America (18, 20) and Italy (21). Moreover, while attention has been paid to the content of the tele-consultation (18, 20, 21), there is a gap regarding the entire tele-consultation organization and management. Recognizing this gap, the Portuguese Multiple Sclerosis Study Group has developed a document with recommendations for using tele-consultation/telemedicine to manage MS patients. This document is a collection of best practices developed by neurologists with strong expertise in MS and was developed bearing in mind that tele-medicine will inevitably be, to a greater or lesser extent, incorporated in the routine care of MS patients in the near future.

Although this is not a formal and exhaustive guideline document, it is expected that this expert consensus may provide some guidance to physicians in the best approach to use tele-medicine in MS patients.

TABLE 1 | Organization of topics for the development of recommendations.

Section	Addressed topics
Triage	Relevance of tele-screening Data collection
Appointment	Importance of tele-medicine Eligibility criteria for non-face-to-face appointment Barriers for tele-medicine
Follow-up	Patient monitoring changes Disease dashboards Self-reporting monitoring tools Relapse procedure
Nursing	Nursing role Nurse non-face-to-face appointment
Communication	Communication channels Information sharing

METHODS

The consensus was obtained through a two-step modified Delphi methodology that took place between June and July 2020 and consisted of one round of online questionnaire followed by a virtual consensus meeting.

A comprehensive list of items for evaluation was initially developed, aligned with the five fundamental steps in patient management: triage, appointment, follow-up, nursing, and communication (as presented in **Table 1**).

The questionnaire was developed aligned with this topic list, considering both open-ended questions (like *"which are the main benefits of tele-medicine?"*) and closed-ended questions (such as *"of the following, which are the relevant criteria for tele-appointment eligibility?"*). The questionnaire is presented as **Supplementary Material**.

A total of 158 neurologists were invited for the online questionnaire round. Thirty different responses were obtained, from respondents that had, on average, 15 years of experience in MS management. These physicians followed at least 150 patients and were evenly split among the three main health regional administrations (North, Center, and "Lisboa and Vale do Tejo" —LVT), with additional colleagues from the autonomous regions of Azores (1) and Madeira (2). The latter were invited to increase the generalizability of the recommendations. While the provision of care to persons with MS in Madeira and Azores is broadly similar to that of mainland Portugal, the two regions have their own regional health services with corresponding specificities that should be taken into consideration.

Questionnaire results were translated into a report with a preliminary set of recommendations. Resulting statements progressed to the second round of Delphi consensus regardless of the agreement level, but with the indication of the percentage of agreement between experts, to be further considered. These were discussed in a virtual consensus meeting with eight experts, and final recommendations were developed and sent for validation.

The Delphi panel was considered an appropriate methodology for obtaining practical guidelines on MS patients' management as it ensures anonymity between participants, iteration with controlled feedback of group opinion, statistical aggregation of group response, and expert input (22).

SECTION 1: TRIAGE

Triage is a very important and often disregarded activity. An effective triage may highly increase the effectiveness of the appointment, enabling an adequate preparation while saving physicians' time (13).

Participants were asked about distinct procedures to optimize the triage process, mainly related to tele-triage and patient data collection prior to the specialist appointment.

Actionable Recommendations

1. The implementation of a system to collect patient information before the appointment is highly recommended. Data collection should be performed through a tele-screening process with the specialized nurse, or a specific and certified tool, accessible to both patients and healthcare professionals.

   The collected data should include new symptoms, relapses, exams results, ability to perform daily tasks, and current therapy.

SECTION 2: APPOINTMENT

Health systems are trying to adapt themselves to this new reality: creating distinct circuits for COVID-19 and non-COVID-19 patients and adjusting both facilities and procedures to the safety recommendations. This adaption has caused some disruption in the regular healthcare provision, delaying appointments, exams, and procedures. Although tele-medicine (and particularly phone contacts) has been widely used to mitigate the limitation in physical availability, there is a need to define an appropriate framework for non-face-to-face appointment, ensuring its effectiveness (14).

Most of the Delphi questionnaire was related to the appointment. Participants were asked to evaluate the importance of tele-medicine and its suitability to the MS context. From a list of possible criteria for non-face-to-face appointments (that included disability status, relapses, therapy, geographic location, risk profile, and age, among others), physicians rated the importance of each variable and defined the necessary conditions, reaching a consensus on the eligibility for a non-face-to-face appointment. As non-face-to-face appointment effectiveness is often limited by both infrastructural and personal constraints, participants discussed the required steps to ensure tele-medicine adoption.

Actionable Recommendations

2. Non-face-to-face appointment (tele-appointment or video-appointment) is a good alternative to face-to-face appointment, as it reduces the risk of exposure to the virus, facilitates physician access, and could be more convenient to patients and caregivers, preventing a hospital visit. However, non-face-to-face appointments should only be an alternative during a limited time period, since physicians still need to physically examine MS patients on a regular basis.
3. The ideal follow-up frequency for previously diagnosed and stable patients should be every 6 months, with at least one face-to-face appointment per year.
4. The following criteria should be met to determine the eligibility for a non-face-to-face appointment:
   - Diagnosed patients, coming for follow-up and treatment monitoring; non-face-to-face appointments should not be used to establish or discuss a new MS diagnosis
   - Stable patients, without current or recent relapse suspicion; patients with a suspected or recent relapse should be examined in person

     In addition, the patients living far from the hospital, or with accessibility constraints, and patients with high disability level are most likely to benefit from non-face-to-face appointments.
5. During non-face-to-face appointments, as in face-to-face appointments, a set of relevant information should be evaluated and recorded in the patient registry:
   - New symptoms and relapses;
   - Treatment adverse effects/changes to the current therapy;
   - Other comorbidities;
   - Urinary/intestinal complaints;
   - Ability to walk;
   - Cognitive complaints;
   - Remote neurological examination (in case of video-appointment).

   Besides these vital data, other aspects should also be evaluated, such as fever/infection, fatigue, depression, risk of social isolation, plans to start a family, and information about labor activity.
6. Video-appointment is preferable to tele-appointment, as it enables a stronger and closer connection between patient and physician. Moreover, visual evaluation provides additional clinical information.
7. To reduce the difficulties and resistance that are often associated with digital and tele-medicine, ensuring healthcare professionals' adoption to digital appointments, hospitals should:
   - Provide adequate means for video-appointments: setup videoconferencing platforms (Teams, Zoom), acquire the necessary devices (cameras, computers with adequate capacity, appropriate internet connection), and make platforms for document sharing available;
   - Train the clinical team;
   - Ensure the prior patient preparation for this type of appointment.
8. Patient acceptance of tele-appointments should be ensured by:
   - Regularly updating patients' contact information;

- Raising awareness for the effectiveness of non-face-to-face appointments (this should be performed by all relevant stakeholders: clinical team, nursing team, hospital, patients' association and the Portuguese MS Study group);
- If necessary, requiring the presence of a caregiver on non-face-to-face appointments to support patients (to hold the phone during coordination exercises, record walking exercise, etc.), particularly when there is a high disability level.

SECTION 3: FOLLOW-UP

Besides follow-up appointments, MS patients require regular monitoring to evaluate relapses and disease progression (4). The limitation in the availability of ancillary exams induced by the pandemic has created some variability in the way different physicians and hospitals manage their patients.

Participants discussed monitoring frequency and procedures and required exams for an adequate MS patient management. Additional tele-monitoring tools were also evaluated and deemed relevant, although there was no consensus on the most appropriate tool.

Actionable Recommendations

9. Due to restrictions in healthcare facilities, MS monitoring protocol may be adjusted. It is recommended to:
   - Postpone exams that are not related to the disease safety protocol;
   - Increase the interval of routine exams, such as blood and MRI tests in stable patients. However, the safety protocol exams are still vital for patients' follow-up, regardless of the pandemic context. Similarly, in urgent situations, all procedures deemed necessary should not be postponed.

In addition, patients should send the exams results (performed outside the hospital) to the institutional e-mail of the attending physician, avoiding an unnecessary hospital visit.

10. As a follow-up complement, online questionnaires such as PDDS (*Patient Determined Disease Steps*), MSQol-54 (*MS Quality of Life*), MSIS-29 (*MS Impact Scale*), MSWS-12 (*MS Walking Scale*), and other monitorization tools (such as apps for cognitive evaluation and wearables) may also be used.
11. If there is a suspected relapse, the procedure should be the same as before the pandemic:
    - Tele-screening should be used to evaluate the symptoms and clinically validate the relapse;
    - Corticosteroids should still be administered, if there is clinical justification;
    - Intravenous administration should be maintained, as in the pre-pandemics context. However, for certain mild relapses, oral corticosteroids can be prescribed, reducing patient visits to the hospital.
    - These situations should be individually analyzed considering the patient profile. The decision to request the patient presence in the hospital due to a suspicion/occurrence of a relapse or the decision to continue the corticosteroid therapy should be taken by the physician balancing the benefits and the risks of each option.

SECTION 4: NURSING

Nursing care is crucial to adequate patient management, both in a face-to-face and in a non-face-to-face context. In the latter, a nurse role may be even more relevant, as counseling and education are vital to ensure that patients can adequately manage their disease in their homes.

Participants discussed the necessary coordination between physicians and nurses and the relevance of specialized staff.

Actionable Recommendations

12. Nurses also play a fundamental role in non-face-to-face appointments, due to the relevance of counseling and education. A useful and effective non-face-to-face nursing appointment should:
    - Be scheduled in the interval of physicians' appointments;
    - Occur as a video-appointment, focused on the patients' education.
13. The hospital should ensure the presence of nursing staff specialized in MS. Nurses' training is fundamental, and an appropriate task division (considering roles, data to collect, and disease scales to assess) should be performed, ensuring there is no overlap and duplication between physicians and nursing appointments.

SECTION 5: COMMUNICATION

Communication is key in healthcare provision—an effective communication promotes patients' knowledge, reassures patients and caregivers, fosters patients' compliance with the treatment plan and can immediately increase patient perception on the quality of care provided (4).

The communication with the patient is even more important in this pandemic context—patients must be informed of the necessary care procedures and treatment continuity, so they feel confident in their disease management even if they are not able to go to the hospital.

Participants were asked to evaluate the importance of different communication channels, discussing the type of information to be shared with patients to ensure appropriate communication flow.

Actionable Recommendations

14. It is critical to reinforce an effective transmission of information to the patient by:
    - Sharing relevant information with patients by e-mail or message;
    - Communicating relevant information through Patients' Associations and the Portuguese MS Study Group—promotion of a healthy lifestyle and reliable information update;

- Creating a support line for patients with MS.

15. It is important that physicians are truly available to answer patients' doubts when they have a chronic disease like MS. Patients' direct contact with their care team (healthcare professionals that follow them in a regular basis) should be privileged.

DISCUSSION

The set of recommendations reflects the experience of relevant physicians in MS management in Portugal. While the scientific investigation on COVID-19 is moving forward and there is low evidence regarding the appropriate patient management in the pandemic context, the follow-up of MS patients should be based on the above-mentioned recommendations.

These recommendations are meant to reduce patient risk of contagion, by avoiding unnecessary hospital visits and fostering the usage of tele-medicine, while ensuring a standardization of MS patient management. These measures also consider this context of reduced healthcare services availability.

Some of these measures are easy to implement, while others require infrastructure changes or investments. Additionally, clinical judgement is paramount, and these recommendations should only be applied to patients that meet the defined criteria and when the usage of digital channels will not reduce the effectiveness of patient follow-up. These recommendations should be enforced in alignment with patient-specific factors and hospital procedures.

With the advance of research on both COVID-19 and the impact of this disease in MS patients, it is expected that further updates and more substantive guidelines can be developed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JJC and JdS had the initial idea and developed the work plan. JJC coordinated the project. JJC and AFL wrote the first draft of the paper. JJC, AFL, AMS, AT, JV, LS, MA, PA, RG, and JdS participated in the consensus meeting, where the final recommendations were produced, and contributed to the manuscript. All authors reviewed and approved the manuscript.

FUNDING

The consensus and the publication of this manuscript were supported by an educational grant from Novartis Portugal to the Grupo de Estudos de Esclerose Múltipla. These funds were used to pay the work of the consultancy MOAI, which set up the online questionnaire and helped with writing the summary of the meeting and the first draft of the consensus, and the publishing fee (article processing charge). The funding source had no role in the process and did not influence, by any means, the content of the consensus or the present manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.613769/full#supplementary-material

REFERENCES

1. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. *Lancet*. (2018) 391:1622–36. doi: 10.1016/S0140-6736(18)30481-1
2. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. *Mult Scler*. (2020) 26:1816–21. doi: 10.1177/1352458520970841
3. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler*. (2018) 24:96–120. doi: 10.1177/1352458517751049
4. Hobart J, Bowen A, Pepper G, Crofts H, Eberhard L, Berger T, et al. International consensus on quality standards for brain health-focused care in multiple sclerosis. *Mult Scler*. (2019) 25:1809–18. doi: 10.1177/1352458518809326
5. World Health Organization. *Pneumonia of Unknown Cause—China: Disease Outbreak News*. Geneva: World Health Organization. (2020). Available online at: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/ (accessed February 24, 2021).
6. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed*. (2020) 91:157–60. doi: 10.23750/abm.v91i1.9397
7. Gabinete da Ministra da Saúde. Available online at: https://www.sns.gov.pt/noticias/2020/03/16/covid-19-orientacoes-para-os-hospitais/
8. Gabinete da Ministra da Saúde. *Despacho 5314/2020. Diário da República n.° 89/2020, Série II de 2020-05-07* Lisbon. (2020).
9. Salama S, Giovannoni G, Hawkes CH, Lechner-Scott J, Waubant E, Levy M. Changes in patient and physician attitudes resulting from COVID-19 in neuromyelitis optica spectrum disorder and multiple sclerosis. *Mult Scler Relat Disord*. (2020) 42:102259. doi: 10.1016/j.msard.2020.102259
10. Yeroushalmi S, Maloni H, Costello K, Wallin MT. Telemedicine and multiple sclerosis: a comprehensive literature review. *J Telemed Telecare*. (2020) 26:400–13. doi: 10.1177/1357633X19840097
11. Temesgen ZM, DeSimone DC, Mahmood M, Libertin CR, Varatharaj Palraj BR, Berbari EF. Health care after the COVID-19 pandemic and the influence of telemedicine. *Mayo Clin Proc*. (2020) 95:S66–8. doi: 10.1016/j.mayocp.2020.06.052
12. Capra R, Mattioli F. Tele-health in neurology: an indispensable tool in the management of the SARS-CoV-2 epidemic. *J Neurol*. (2020) 267:1885–6. doi: 10.1007/s00415-020-09898-x
13. Bonavita S, Tedeschi G, Atreja A, Lavorgna L. Digital triage for people with multiple sclerosis in the age of COVID-19 pandemic. *Neurol Sci*. (2020) 41:1007–9. doi: 10.1007/s10072-020-04391-9
14. Matthews PM, Block VJ, Leocani L. E-health and multiple sclerosis. *Curr Opin Neurol*. (2020) 33:271–6. doi: 10.1097/WCO.0000000000000823
15. Moccia M, Lanzillo R, Brescia Morra V, Bonavita S, Tedeschi G, Leocani L, et al. Assessing disability and relapses in multiple sclerosis on tele-neurology. *Neurol Sci*. (2020) 41:1369–71. doi: 10.1007/s10072-020-04470-x
16. Sastre-Garriga J, Tintoré M, Montalban X. Keeping standards of multiple sclerosis care through the COVID-19 pandemic. *Mult Scler*. (2020) 26:1153–6. doi: 10.1177/1352458520931785

17. Ciampi E, Uribe-San-Martin R, Cárcamo C. COVID-19 pandemic: the experience of a multiple sclerosis centre in Chile. *Mult Scler Relat Disord*. (2020) 42:102204. doi: 10.1016/j.msard.2020.102204
18. Apóstolos-Pereira SL, Silva GD, Disserol CCD, Feo LB, Matos AMB, Schoeps VA, et al. Management of central nervous system demyelinating diseases during the coronavirus disease 2019 pandemic: a practical approach. *Arq Neuropsiquiatr*. (2020) 78:430–9. doi: 10.1590/0004-282x20200056
19. Derache N, Hauchard K, Seguin F, Ohannessian R, Defer G. Retrospective evaluation of regional telemedicine team meetings for multiple sclerosis (MS) patients: experience from the Caen MS expert center in Normandy, France. *Rev Neurol*. (2020) 30:S0035-378730716-5. doi: 10.1016/j.neurol.2020.06.020
20. Alonso R, Carvajal R, Boaventura M, Galleguillos L. Experience of South American MS and/or NMOSD experts in practice during the COVID-19 pandemic: focus on telemedicine. *Mult Scler Relat Disord*. (2020) 48:102702. doi: 10.1016/j.msard.2020.102702
21. Dubbioso R, Nobile-orazio E, Manganelli F, Santoro L, Briani C, Cocito D, et al. Dealing with immune-mediated neuropathies during COVID-19 outbreak: practical recommendations from the task force of the Italian Society of Neurology (SIN), the Italian Society of Clinical Neurophysiology (SINC) and the Italian Peripheral Nervous System. *Neurol Sci*. (2020) 41:1345–8. doi: 10.1007/s10072-020-04448-9
22. Trevelyan EG, Robinson N. Delphi methodology in health research: how to do it? *Eur J Integr Med*. (2015) 7:423–8. doi: 10.1016/j.eujim.2015.07.002

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 22 March 2021
doi: 10.3389/fneur.2021.635856

Clinical and Radiological Characteristics of Acute Cerebrovascular Diseases Among Egyptian Patients With COVID-19 in Upper Egypt

Eman M. Khedr[1], Radwa K. Soliman[2], Noha Abo-Elfetof[1], Mariam Amin[3], Ossama Yassin Mansour[4]*, Ahmed Aly[5], Ahmed F. Zaki[6] and Mostafa Saber[7]*

[1] Department of Neuropsychiatry, Faculty of Medicine, Assiut University Hospital, Asyut, Egypt, [2] Department of Diagnostic and Interventional Radiology, Faculty of Medicine, Assiut University Hospital, Asyut, Egypt, [3] Department of Public Health and Community Medicine, Faculty of Medicine, Assiut University Hospital, Asyut, Egypt, [4] Department of Neurology Stroke and Neuro-Intervention Section, Faculty of Medicine, Alexandria University, Alexandria, Egypt, [5] Department of Neurosurgery, Faculty of Medicine, Aswan University Hospital, Aswan, Egypt, [6] Department of Neuropsychiatry, Faculty of Medicine, South Valley University, Qena, Egypt, [7] Department of Neuropsychiatry, Faculty of Medicine, Aswan University Hospital, Aswan, Egypt

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh, Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Adam A. Dmytriw, Brigham and Women's Hospital and Harvard Medical School, United States
Haokuang Wang, Eda Hospital, Taiwan
Lung Chan, Taipei Medical University, Taiwan

***Correspondence:**
Eman M. Khedr
emankhedr99@yahoo.com; Emankhedr99@aun.edu.eg
Ossama Yassin Mansour
chairman@mena-sino.com

Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *30 November 2020*
Accepted: *02 February 2021*
Published: *22 March 2021*

Citation:
Khedr EM, Soliman RK, Abo-Elfetof N, Amin M, Mansour OY, Aly A, Zaki AF and Saber M (2021) Clinical and Radiological Characteristics of Acute Cerebrovascular Diseases Among Egyptian Patients With COVID-19 in Upper Egypt. Front. Neurol. 12:635856. doi: 10.3389/fneur.2021.635856

Background and Purpose: There is little information on the acute cerebrovascular complications of coronavirus disease 2019 (COVID-19) in Egypt. The aim of this study was to estimate the proportion of acute cerebrovascular disease (CVD) among COVID-19 patients and evaluate their clinical and radiological characteristics in comparison with non-COVID-19 CVD.

Materials and Methods: In a retrospective study, COVID-19 patients whom presented with CVD in Assiut and Aswan University Hospitals were compared with non-COVID-19, CVD patients, admitted to Qena University Hospital, prior to the pandemic. The following data were collected: clinical history and presentation, risk factors, comorbidities, brain imaging (MRI or CT), chest CT, and some laboratory investigations.

Results: Fifty-five (12.5%) of the 439 patients with COVID-19 had acute CVD. Of them, 42 (9.6%) had ischemic stroke while 13 patients (2.9%) had hemorrhagic CVD. In the 250 cases of the non-COVID-19 group, 180 had ischemic stroke and 70 had hemorrhagic stroke. A large proportion of patients with COVID-19 who presented with ischemic stroke had large vessel occlusion (LVO), which was significantly higher than in non-COVID-19 patients with CVD (40 vs. 7.2%, $P < 0.001$). Comorbidities were recorded in 44 (80%) cases. In COVID-19 ischemic stroke patients, risk factors [hypertension and ischemic heart disease (IHD)] and comorbidities (hepatic and renal) were significantly higher than those in non–COVID-19 patients. In addition, 23.5% had hemorrhagic CVD, and six patients with LVO developed hemorrhagic transformation.

Conclusion: Acute CVD among patients with COVID-19 was common in our study. LVO was the commonest. Hypertension, IHD, and anemia are the most common risk factors and could contribute to the worsening of clinical presentation. Comorbidities

were common among patients with CVD, although a large number had elevated liver enzymes and creatinine that were partially due to COVID-19 infection itself. The current results begin to characterize the spectrum of CVD associated with COVID-19 in patients in Upper Egypt.

Registration ID: The ID number of this study is IRB no: 17300470.

Keywords: COVID-19, cerebrovascular stroke, central nervous system, anosmia, large vessel occlusion, hemorrhagic infarction

INTRODUCTION

In most patients, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection presents with a flu-like illness; neurological symptoms are most usually seen in patients with other comorbidities. Recently, some studies (1, 2) and case reports (3–6) have reported a small number of COVID-19 patients with concurrent stroke, the majority of whom had ischemic rather than hemorrhagic strokes. The World Health Organization (WHO) reported that the risk of ischemic stroke associated with COVID-19 is around 5% (7). There have also been a few cases, in patients with mild symptoms, of macrothrombosis in the internal carotid artery (8, 9). Most of the strokes occurred in young adults without cardiovascular risk factors. For example, Gunasekaran et al. (10) described a case of cerebrovascular stroke in a COVID-19 patient younger than 50 years with few risk factors for stroke. At the present time, there is little knowledge about the clinical and radiological criteria of acute cerebrovascular complications of COVID-19 in Egypt.

This retrospective study analyzes data from COVID-19 patients with acute cerebrovascular disease (CVD) who were admitted into the two largest university hospitals in Upper Egypt. We estimate the proportion of acute CVD among COVID-19 patients and evaluate their clinical and radiological characteristics in comparison to a group of patients with acute CVD without COVID-19 who had been observed 3 years prior to the pandemic in Qena University Hospital (Upper Egypt).

MATERIALS AND METHODS

Patients with suspected COVID-19 were admitted from June 1 to August 10, 2020, to two university hospitals in Upper Egypt (Assiut and Aswan), which served as quarantine areas (11). Then, all patients with COVID-19 infection, whom presented with acute CVD, were transferred to the intensive care unit (ICU) of the Neurology, Neurosurgery Hospital of Assiut and the ICU in Aswan University hospital. We used the World Health Organization (WHO) definition of stroke as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than of vascular origin" (12). We documented the latter using either computed tomography (CT) or magnetic resonance imaging (MRI) with additional data regarding demographic data, risk factors, and comorbidities. Clinical assessment was made using the National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), and chest CT. Laboratory investigations included blood picture and gases, renal and liver function, and coagulation profile [prothrombin time and concentration and international normalized ratio (INR)]. D-dimer and ferritin levels were measured for a few patients when available.

Our control group was taken from retrospective data of all patients diagnosed with acute CVD within 72 h of onset and admitted to Qena University Hospital from October 1, 2015, to the end of March 2016. Qena is a Nile Valley governorate and one of the largest cities in Upper Egypt, lying midway between Assiut and Aswan governorates where they share a common culture and climate.

CT scanners included GE Bright Speed Elite 16 slice, Siemens-Somatom go UP32 slice, and Toshiba Aquilion PRIME, while MRI scanners included Philips Achieva, 1.5 T, Siemens Avanto 1.5 T, and Toshiba Ventage 1.5 T.

Only cases with imaging-confirmed stroke were included in the study. For ischemic insult, vascular territories were identified (whether venous or arterial/large or small vessel occlusion), while hemorrhagic insults were classified into intra-parenchymal (lobar, deep, and infra-tentorial) and extra-parenchymal hemorrhage (intraventricular and subarachnoid), as well as mixed intra-parenchymal and extra-parenchymal hemorrhage. A chest CT was also obtained.

The raw data supporting the findings of this study are available upon request from the corresponding authors.

Consent and Ethics

Each patient or relative gave a written informed consent. Approval of the study was obtained from the local ethics committee of Assiut University Hospital.

Infection of COVID-19 Was Defined as

1-Definite COVID-19 if patients came with clinical symptoms of infection and had a positive reverse transcription polymerase chain reaction (PCR) test of respiratory samples (e.g., nasopharyngeal swab).

2-Suspected COVID-19 if the usual clinical symptoms of COVID-19 infection but PCR were not available. Diagnosis was based on chest CT and one of the following laboratory data was positive: lymphopenia and/or ferritin level, D-dimer.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 25). Number and percent or means ± standard deviation (SD) were used to represent data. Demographic,

risk factors, comorbidities, and other variables were compared between COVID-19 CVD patients versus non-CVD patients and also between COVID-19 CVD patients and non-COVID-19 CVD patients with the χ^2 test. The level of significance was set at $P < 0.05$.

RESULTS

Out of 439 patients with confirmed/suspected COVID-19, acute CVD was recorded in 55 cases (12.5%). Cases were classified using neuroimaging data. Here, 42 (9.6%) patients were diagnosed with ischemic arterial/venous stroke (40/2); 11 (2.5%) cases were diagnosed with hemorrhagic stroke; one case (0.2%) had combined subdural hematoma and intracerebral hematoma; and the remaining case (0.2%) had subarachnoid hemorrhage (see **Figure 1** flowchart).

The mean age of the patients with COVID-19–CVD was 62.8 ± 14.1 years (range 35–90 years), with 30 (54.5%) males and 25 (45.5%) females. Twelve patients (21.8%) had a positive PCR and were diagnosed as definite COVID-19; the remaining 43 cases (78.2%) were diagnosed as suspected COVID-19 because they had fever and pulmonary symptoms plus chest CT findings of bilateral ground-glass opacities with consolidation (GGO) in addition to lymphopenia and/or elevated ferritin level or D-dimer.

Fifty-one (92.7%) out of 55 COVID-19 patients had bilateral ground-glass appearance with consolidation in CT chest. Among the constitutional symptoms of COVID-19 in the CVD group, we found that fever (89.1%) and respiratory symptoms (81.9%) were the most common manifestations, followed by headache (30.9%) and gastrointestinal tract (GIT) (21.8%) symptoms. Fatigue and malaise (9.3%) as well as dizziness and vertigo (3.6%) were least frequent. In the CVD group with COVID-19, 44 (80%) had risk factors and/or comorbidities. Comparison of demographic, clinical data, risk factors, and comorbidities between COVID-19 patients with CVD (55 cases) vs. without CVD (384 cases) showed a significantly higher mean age of COVID-19 patients with CVD than those without CVD. The percentages of fever, headache, and disturbed consciousness were significantly higher in COVID-19 with CVD than without, while fatigue, myalgia, malaise, dizziness, and vertigo were significantly lower in COVID-19 with CVD than without. In general, risk factors and comorbidities were significantly higher in COVID-19 with CVD than without (**Table 1**).

Table 2 compares demographics, clinical, and risk factors and comorbidities of COVID-19 ischemic stroke patients (42 patients) and non-COVID-19 ischemic stroke patients (180 patients). The mean age of COVID-19 patients was significantly higher than that of non-COVID-19 patients, while no significant difference was found in terms of sex. Hypertension and ischemic

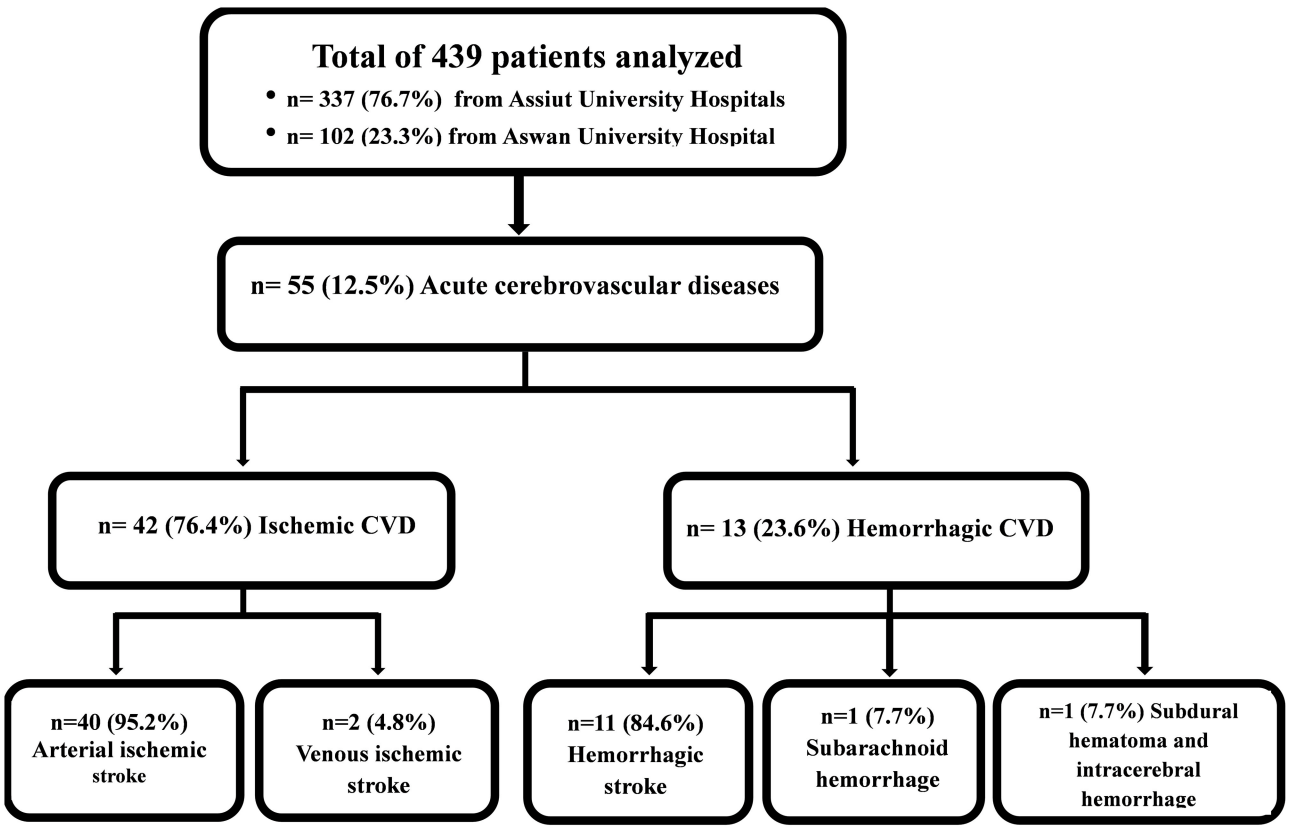


FIGURE 1 | Flowchart.

TABLE 1 | Demographic and clinical data of COVID patients with CVD vs. without CVD.

Demographics	CVD patients (*n* = 55)	Non-CVD (*n* = 384)	*P*-value
Age (years)			
Mean ± SD	62.8 ± 14.1	49.5 ± 16.9	<0.001
Range	35–90	18–86	
≤50 n (%)	12 (21.8 %)	183 (47.7%)	<0.001
>50 n (%)	43 (78.2%)	201 (52.3%)	
Sex *n* (%)			
Male	30 (54.5%)	194 (50.5%)	0.577
Female	25 (45.5%)	190 (49.5%)	
Presenting symptoms *n* (%)			
Fever	49 (89.1%)	278 (72.4%)	0.008
Respiratory symptoms	45 (81.9%)	283 (73.7%)	0.195
Headache	17 (30.9%)	67 (17.4%)	0.018
GIT symptoms	12 (21.8%)	81 (21.1%)	0.902
Fatigue, myalgia and malaise	5 (9.1%)	170 (44.3%)	<0.001
Dizziness and vertigo	2 (3.6%)	61 (15.9%)	0.015
Disturbed consciousness	27 (49.1%)	17 (4.4%)	<0.001
Comorbid risk factor and comorbidities *n* (%)			
Hypertension	32 (58.2%)	140 (36.5%)	0.002
Ischemic heart disease	14 (25.4%)	42 (10.9%)	0.003
Rheumatic heart disease	2 (3.6%)	1 (0.26%)	0.005
Atrial fibrillation	1 (1.8%)	2 (0.52%)	0.275
Diabetes mellitus	17 (30.9%)	130 (33.9%)	0.665
Liver disease	5 (9.1%)	10 (2.6%)	0.013
Renal disease	8 (14.5%)	16 (4.2%)	0.001
Chronic pulmonary disease	1 (1.8%)	29 (7.6%)	0.115
No risk factor or comorbidities	11 (20.0%)	159 (41.4%)	0.002

TABLE 2 | Comparison between Covid-19 and non-covid-19 ischemic stroke patients in demographic, risk factors, comorbidities, and clinical presentation.

Demographic, risk factors clinical presentation and comorbidities	COVID-19 ischemic stroke (*n* = 42)	Non-COVID-19 ischemic stroke (*n* = 180)	*P*-value*
Age (years)			
Mean ± SD	64.8 ± 13.7	56.1 ± 1.5	<0.001
Range	37–90	33–85	
Age ≤50 n (%)	8 (19.0%)	56 (31.1%)	0.120
Age >50 n (%)	34 (81.0%)	124 (68.9%)	
Sex *n* (%)			
Male	22 (52.4%)	84 (46.7%)	0.562
Female	20 (47.6%)	96 (53.3%)	
Stroke risk factors and comorbidities *n* (%)			
Hypertension	23 (54.7%)	52 (28.8%)	0.001
Ischemic heart disease	13 (30.9%)	15 (8.3%)	0.001
Rheumatic heart disease	2 (4.7%)	6 (3.3%)	0.654
Diabetes mellitus	14 (33.3%)	53 (29.4%)	0.621
Atrial fibrillation	2 (4.7%)	19 (10.6%)	0.247
Hepatic disease	3 (7.1%)	2 (1.1%)	0.017
Renal diseases	8 (19%)	5 (2.8%)	0.001
No risk factor or comorbidities	10 (23.8%)	35(19.4%)	0.526
Clinical presentation			
NIHSS Mean ± SD (range)	13.8 ± 5.6 (4–24)	9.2 ± 5.4	<0.001
GCS Mean ± SD (range)	9.5 ± 4.5 (0–15)	13.3 ± 1.9	<0.001
DCL n (%)	15 (35.7%)	3 (1.7%)	<0.001

*National Institutes of Health Stroke Scale, GCL, Glasgow Coma Scale; DCL, Disturbed Conscious Level. *Students' T-test and Chi-square test were used.*

heart disease (IHD) were significantly higher in COVID-19 than those in non-COVID-19 patients as risk factors for stroke. Also, comorbidities (hepatic and renal disease) were significantly higher in COVID-19 than non-COVID-19. NIHSS and GCS were significantly worse in COVID-19 compared with non-COVID-19 ischemic stroke patients with a higher percentage of patients presenting with a disturbed level of consciousness. **Table 3** shows the comparison between hemorrhagic stroke in COVID-19 and non-COVID-19 patients. There were no significant differences between groups in demographics, risk factors, and comorbidities, or in clinical presentation. However, there were significantly higher National Institutes of Health Stroke Scale/Score (NIHSS) and lower Glasgow Coma Scale (GCS) scores in the COVID-19 group than the non-COVID-19 group, with a higher percentage of disturbed consciousness in the COVID-19 group.

Laboratory Data

Regarding the blood picture: 24 (43.6%) cases had leukocytosis (19 ischemic and five hemorrhagic), 26 (47.3%) cases had lymphopenia (19 in ischemic and seven in hemorrhagic stroke), and 26 patients (47.3%) had microcytic hypochromic anemia (23 ischemic and three hemorrhagic). Eight (15.5%) had prolonged prothrombin time (PTT), and five (9.1%) had decreased prothrombin concentration (five in ischemic stroke and three in hemorrhagic).

Interestingly, in ischemic stroke (42 cases), only three patients had a history of liver disease among COVID-19 patients. However, during admission, 16 (38.1%) cases had elevated liver enzymes of whom three had increased PTT and decreased prothrombin concentration. Eight patients (19%) had a history of kidney diseases. Yet, 16 cases (38.1%) had elevated blood urea and creatinine (renal impairment) during admission.

In hemorrhagic stroke (13 cases), only two patients had a history of liver disease. However, during admission, four (36.4%) cases had elevated liver enzymes of whom three had increased PTT and decreased prothrombin concentration. There were no patients with a history of kidney disease. Yet, during admission, four cases had elevated blood urea and creatinine (renal impairment). In total, six patients had both impaired renal and elevated liver enzymes.

Neuroimaging

Based on radiological findings, there were no significant differences between COVID-19 and non-COVID-19 patients in

TABLE 3 | Difference between Covid-19 and non-covid-19 hemorrhagic stroke patients in demographic, risk factors and comorbidities.

Demographic, Stroke risk factors and comorbidities and clinical presentation	COVID-19 hemorrhagic CVD ($n = 13$)	Non-COVID-19 hemorrhagic CVD ($n = 70$)	*P*-value
Age (years)			
Mean ± SD	57.4 ± 13.5	50.4 ± 13.3	0.204
Range	35–80	19–99	
Age ≤50 n (%)	5 (38.5%)	38 (54.3%)	0.294
Age >50 n (%)	8 (61.5%)	32 (45.7%)	
Sex *n* (%)			
Male	8 (61.5%)	32 (45.7%)	0.294
Female	5 (38.5%)	38 (54.3%)	
Stroke risk factors and comorbidities *n* (%)			
Hypertension	8 (61.5%)	46 (65.7%)	0.771
Ischemic heart disease	1 (7.7%)	1 (4.2%)	0.176
DM	3 (23.1%)	23 (2.9%)	0.485
Atrial fibrillation	1 (7.7%)	1 (1.4%)	0.176
Chronic pulmonary disease	1 (7.7%)	1 (1.4%)	0.176
Hepatic disease	2 (15.4%)	4 (5.7%)	0.216
Renal disease	0	1(1.4%)	–
No risk factor or comorbidities	1 (7.7%)	5 (7.1%)	0.891
Clinical presentation			
NIHSS Mean ± SD (range)	16.1 ± 3.2 (9–22)	10.6 ± 6.2	<0.001
GCS Mean ± SD (range)	8.7 ± 3.4 (5–159)	12.3 ± 2.6	<0.001
DCL n (%)	6 (46.1%)	2 (2.8%)	<0.001

DM, Diabetes Mellites; HCV, Hepatitis C Virus; RHD, Rheumatic Heart Disease; NIHSS, National Institutes of Health Stroke Scale; GCL, Glasco Coma Scale; DCL, Disturbed Conscious Level.

TABLE 4 | Radiological findings of 55 COVID-19 patients with cerebrovascular diseases (CVD).

Radiological findings	COVID-19 CVD ($n = 55$)	Non-COVID-19 CVD ($n = 250$)	*P*-value
I-*Arterial/venous ischemic stroke	**42 (76.4%)**	**180 (72%)**	**0.510**
1-Anterior circulation	31 (56.4%)	125 (50%)	0.393
A-Large artery occlusion	22 (40.0%)	18 (7.2%)	<0.001
B-Small vessels occlusion (Territories of MCA)	9 (16.4%)	107 (42.85)	<0.001
2-Posterior circulation	9 (16.4%)	47 (29.6%)	0.673
A-large vessel occlusion	2 (3.6%)	2 (0.8%)	0.094
B-Small vessels occlusion	7 (12.7%)	45 (18%)	0.347
3-Mixed anterior and posterior circulation	0	6 (2.4%)	–
4-Venous stroke:	2 (3.6%)	2 (0.8%)	0.094
II-Hemorrhagic CVD	13 (23.6%)	70 (28%)	0.510
1-Intra-parenchymal	6 (10.9%)	49 (19.6%)	0.129
Deep	2 (3.6%)	28 (11.2%)	0.088
Lobar	2 (3.6%)	12 (4.8%)	0.998
Lobar and deep	0	2 (0.8%)	–
Infra-tentorial	2 (3.6%)	7 (2.8%)	0.740
2-Extra-parenchymal	3 (5.5%)	6 (2.4%)	0.226
Intra-ventricular	2 (3.6%)	3 (1.2%)	0.198
Subarachnoid	1 (1.8%)	3 (1.2%)	0.715
3-Mixed intra and extra- parenchymal	4 (7.2%)	15 (6%)	0.724

**Hemorrhagic transformation was observed in 6 cases, one internal carotid artery, 3 out of 13 right middle cerebral artery occlusion (MCAO), and 2 left middle cerebral artery occlusion (MCAO), while only 3 cases out of 180 non-COVID ischemic stroke had Hemorrhagic transformation with significant difference (P < 0.001). 4 young adult had large vessel occlusion.*
CVD, cerebrovascular diseases; MCA, middle cerebral artery.

terms of the incidence of either ischemic or hemorrhagic CVD (details are provided in **Table 4**). However, COVID-19 patients had a significantly higher rate of large vessel occlusion compared to non-COVID-19 patients [40% in COVID-19 patients vs. 7.2% in non-COVID-19 patients ($P < 0.001$)]. Furthermore, there was a significantly higher rate of hemorrhagic transformation (of arterial ischemic stroke) in COVID-19 patients (14.3%) compared to non-COVID-19 patients (1.6%), with $P < 0.001$.

In total, 42 (76.4%) COVID-19 cases had ischemic CVD, which was arterial in 40 (72.7%) cases and cerebral sinus venous thrombosis (CSVT) in two cases (3.6%). The anterior circulation was affected in 31 (56.4%) cases, while 22 (40%) had large vessel occlusion. Out of the latter, eight (14.5%) patients had occlusion of the left middle cerebral artery (MCA), 13 (23.6%) had right MCA occlusion, and one patient (1.8%) had occlusion of the left internal carotid artery. Hemorrhagic transformation developed in six (10.9%) patients (**Figure 2**). Large vessel occlusion occurred in four young patients. Small vessel occlusion (MCA territories) was observed in nine (16.4%) cases. The posterior circulation was affected in nine (16.4%) patients, of whom two (3.6%) had LVO (basilar artery) (**Figure 3**).

With regard to venous stroke, one patient had a deep cerebral vein thrombosis with bilateral thalamic and basal ganglia infarction (**Figure 4**), and the other patient had left transverse and sigmoid sinus thrombosis with parenchymal infarction.

Hemorrhagic CVD was observed in 13 (23.6%) cases. Intra-parenchymal hemorrhage (**Figure 5**) occurred in six (10.9%) patients, two of which (3.6%) had deep (basal ganglionic) hemorrhage, two (3.6%) had lobar (frontotemporal and left inferior frontal lobe) hemorrhage, and two (3.6%) had infratentorial (pontine) hemorrhage. Extra-parenchymal hemorrhage occurred in three (5.5%) cases in which there was no CT angiography evidence of aneurysm or arteriovenous malformation. Of these, two (3.6%) had intraventricular hemorrhage, and one (1.8%) had subarachnoid hemorrhage. In addition, mixed intraventricular and basal ganglia hemorrhage

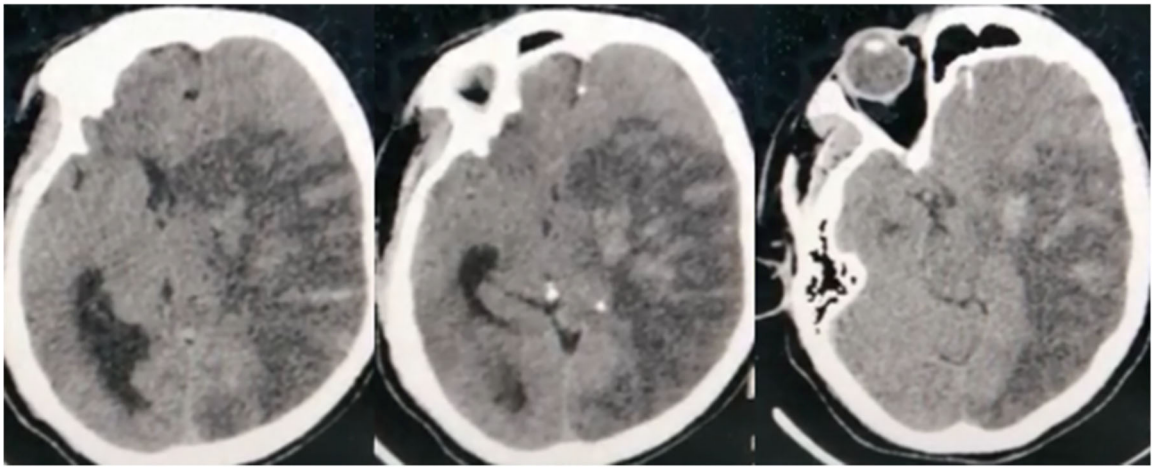


FIGURE 2 | Non-contrast CT brain of a 45-year-old male shows subacute left middle cerebral artery (MCA) territory infarct (large vessel occlusion), associated with marked edema excreting mass effect on the lateral ventricle, and midline shift. Noted multiple hyperdense patches within the infarct representing hemorrhagic transformation.

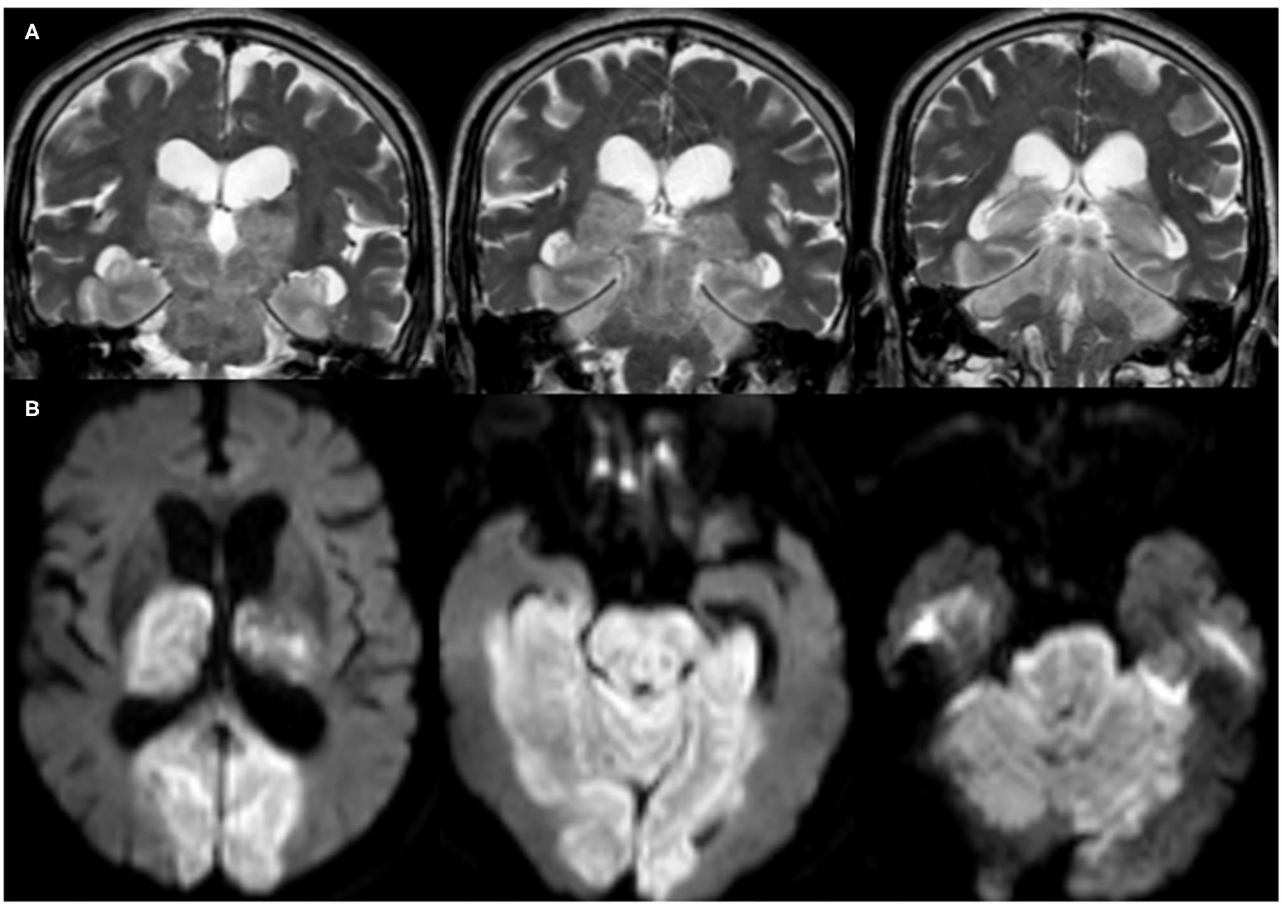


FIGURE 3 | Brain MRI, **(A)** coronal T2-weighted imaging (T2WI), and **(B)** axial diffusion-weighted imaging (DWI) of a 76-year-old male patient show acute infarct (large vessel occlusion) involving the basilar artery territories (brain stem, bilateral thalami, occipital and inferior temporal lobes, as well as the cerebellum).

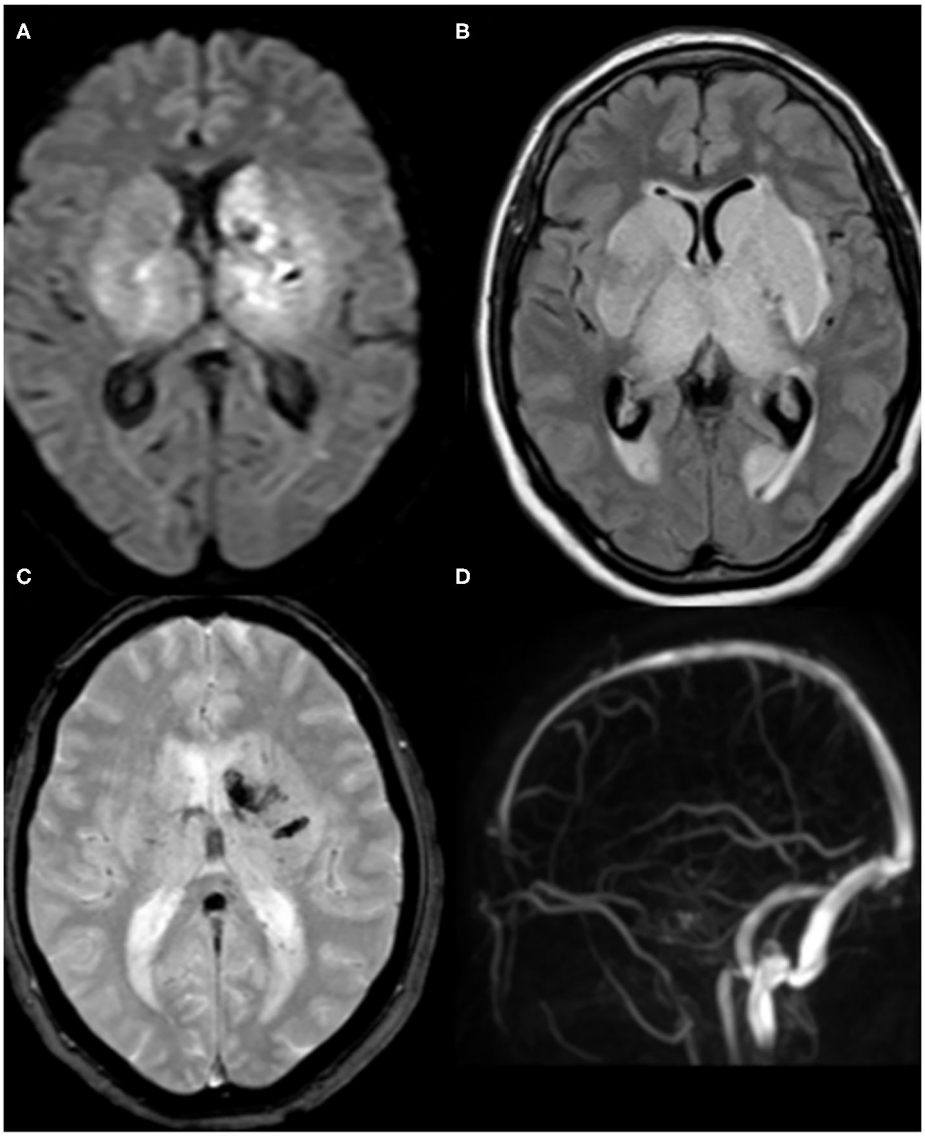


FIGURE 4 | Brain MRI of a 62-year-old female patient. **(A)** axial DWI and **(B)** Fluid-attenuated inversion recovery (FLAIR) demonstrate acute infarction involving bilateral thalami and basal ganglia. **(C)** T2*-weighted imaging (T2*WI) shows associated hemorrhagic foci at the left side. **(D)** The corresponding magnetic resonance venography (MRV) reveals the absence of the normal flow in the deep cerebral veins. Findings are consistent with venous infarction secondary to deep cerebral venous thrombosis.

occurred in three (5.4%) cases, while one patient (1.8%) had mixed subdural and inter-parenchymal hematoma, with no history of trauma (details illustrated in **Table 4**).

DISCUSSION

The main finding of this study is the high frequency of CVD in comparison to previous studies (13, 14): 55 out of 439 COVID-19 patients had CVD (12.5%). However, this is likely to be an overestimate of general prevalence, since patients with mild symptoms were asked to isolate at home, and only patients with moderate to severe symptoms or those with complications or comorbidities were admitted. Most of the strokes were ischemic, but hemorrhagic strokes and cerebral sinus venous thrombosis (CSVT) were observed.

Previous papers generally reported a lower frequency of CVD. In a Chinese cohort of 214 confirmed COVID-19 patients, CVD was seen in six patients (2.8%) (2). Requena et al. (15) reported 21 (1.02%) cases with an acute ischemic stroke and four (0.2%) with an intracranial hemorrhage in a sample of 2,050 patients with confirmed SARS-CoV-2. In a systematic review of 80 COVID-19 articles, Fraiman et al. (16) found a total of 226 cases of ischemic stroke, 35 cases of intracranial bleeding, and 14 cases of venous sinus thrombosis. The same distribution was observed

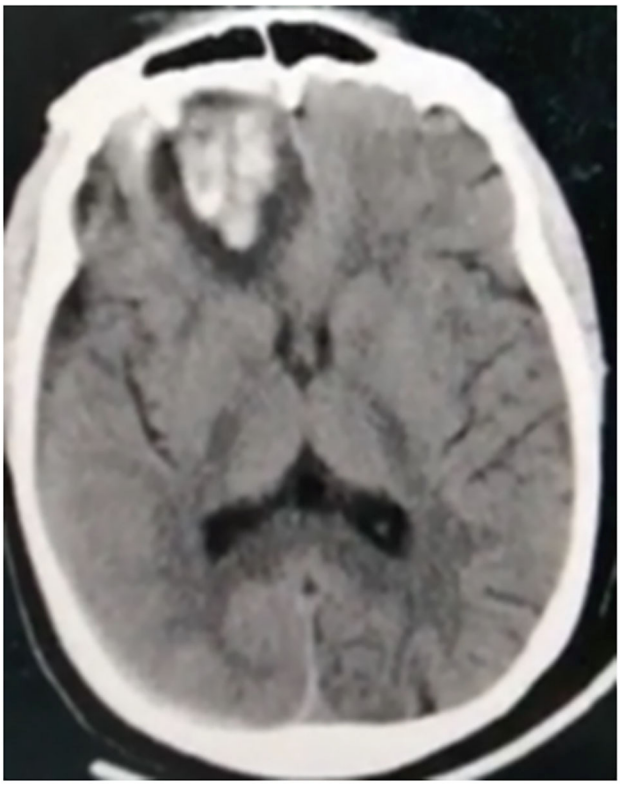


FIGURE 5 | Non-contrast CT of a 38-year-old male patient shows intra-parenchymal right inferior frontal hematoma.

in the current study: 42 cases had ischemic stroke (9.6% of 439) and 13 patients (2.5% of 439) had hemorrhagic CVD. Li et al. (13) reported only 13 cases (5.9%) of CVD out of 221 COVID-19 patients; 11 (84.6%) were diagnosed as ischemic stroke, one (7.7%) had cerebral hemorrhage, and the other (7.7%) had CSVT. In the case series of Reddy et al. (14) (12 cases) 10 patients had an ischemic stroke, of whom one suffered from hemorrhagic transformation and only two had intracerebral hemorrhage. Few other studies have reported cerebrovascular complications in COVID-19 (1, 2). A small number of case series have also described patients with COVID-19 and concurrent stroke (3, 5).

Four Interesting Findings in the Current Study

First, our COVID-19 patients with ischemic stroke had a significantly higher mean age than non-COVID-19 patients. The same result was observed by Katz et al. (17), who reported that 68 COVID-19-positive stroke patients were older than 449 non-COVID-19 stroke patients. In contrast, Wang et al. (18) found that the mean age of patients in several thrombectomy case series of COVID-19 in New York City was 52.8 years. Another large medical center in New York reported that patients with COVID-19 who presented with stroke were younger than a control group of patients with stroke without SARS-CoV-2 infection (19). In contrast, Fraiman et al. (16) in their systematic review found that the mean age of COVID-19 patients with ischemic stroke was 64.16 ± 14.73 years, similar to the present data.

Second, the frequency of patients with a positive history of hypertension and IHD as well as hepatic and renal disease was significantly higher in COVID-19 than non-COVID-19 ischemic stroke patients. In total, 76.2% of COVID-19 ischemic stroke patients had preexisting risk factors. Consistent with our findings, Tiwari et al. (20) also reported that 81% of COVID-19 patients presenting with ischemic stroke had previous known vascular risk factors. COVID-19 cases are also more commonly associated with diabetes mellitus (DM), arterial hypertension (AH), and atrial fibrillation (AF) (16).

The occurrence of ischemic stroke in patients with COVID-19 may be due to competitive blockage of the angiotensin-converting enzyme 2 (ACE2) by the SARS-CoV-2 virus (21). This downregulates ACE2 expression, leading to fluctuations in blood pressure and an increase in the possibility of cerebrovascular accidents. This explanation is compatible with the significantly higher number of patients with COVID-19 who presented with hypertension (54.7%) in comparison to non-COVID-19 patients (28.8%). In addition, preexisting IHD seems to be linked with worse clinical presentation similar to the results of Guan et al. (22) and Wang et al. (23). COVID-19 itself can also induce myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism (24, 25).

A large number of patients [26 or 47.3%; 23 (54.8%)] with ischemic stroke and three with hemorrhagic stroke had microcytic hypochromic anemia. Unfortunately, this was not recorded in our non-COVID-19 patients. Nevertheless, our results are consistent with those of Chen et al. (26) who found that 51% of 99 COVID-19 patients transferred to Jinyintan Hospital showed a decreasing tendency in hemoglobin levels. Another study on 1,099 laboratory-confirmed COVID-19 cases found that severe patients had significantly lower hemoglobin levels than those diagnosed as non-severe cases (22). Anemia is considered a hyperkinetic state that disturbs endothelial adhesion molecule genes that may lead to thrombus formation. Furthermore, blood flow augmentation and turbulence may result in the migration of this thrombus, thus producing artery-to-artery embolism.

An Important aspect of the present study was the number of COVID-19–stroke patients who had elevated liver enzymes and elevated blood urea and creatinine compared with the number of patients with history of no comorbidities. This confirms the assumption that COVID-19 infection can lead to multiorgan symptoms (affecting liver and kidney), which may worsen the clinical presentation (as measured by NIHSS) and lead to the higher percentage of patients presenting with disturbed consciousness and lower GCS in comparison to non-COVID-19 stroke patients. Our results are supported by a study of Dmytriw et al. (27) who reported that the mortality rate of patients with stroke who were COVID-19 positive was greater than that previously reported in acute ischemic stroke alone, suggesting an interaction that needs further investigation (28).

In the present study, 11 out of the 55 patients had no apparent risk factors for CVD and no associated comorbidities suggesting

that mechanisms peculiar to COVID-19 may be responsible. These could be related to direct viral invasion and inflammation of the blood vessel walls leading to endotheliitis (6, 29), as well as induction of a "cytokine storm" as explained by Mangalmurti and Hunter in 2020 (30).

The third significant finding was the large proportion of COVID-19 patients who presented with ischemic stroke and large vessel occlusion, which was significantly higher compared with non-COVID-19 patients (40 vs. 7.2%, $P < 0.001$). These results are consistent with findings reported recently by Kihira et al. (31) who focused mainly on large vessel occlusion in COVID-19. Furthermore, Fraiman et al. (16) in their systematic review of COVID-19 stroke patients found that 105/226 (46.5%) patients had LVO. As mentioned above, an increase in the risk of vascular thrombosis and embolism is likely responsible for such a high incidence of large vessel occlusion. Overall, our analyses indicate that COVID-19 patients are more liable to serious CVD complications. Therefore, they should be monitored closely.

A final point of interest is that 23.5% of our patients had hemorrhagic CVD, and six patients with large vessel occlusion developed hemorrhagic transformation.

The pathogenesis of hemorrhagic stroke in the setting of COVID-19 may be related to the fluctuations in blood pressure as previously described and by the affinity of the SARS-CoV-2 for ACE2 receptors, which are expressed in endothelial and arterial smooth muscle cells in the brain and allow the virus to damage intracranial blood vessels and rupture the wall (32). The secondary hemorrhagic transformation of ischemic strokes observed in the present study may also relate to endothelial damage accompanying COVID-19 (33).

CONCLUSION

COVID-19-associated CVD was common in our study, with LVO as the commonest type of stroke. Hypertension, IHD, and anemia were the most common risk factors and could potentially worsen clinical presentation. Comorbidities were common among patients with CVD; however, elevated liver enzymes and creatinine in a large number of cases may be partially due to COVID-19 infection itself. The current results begin to characterize the spectrum of CVD associated with COVID-19 patients in Egypt.

Limitation of the Study

One of the main limitations of this study is the large number of patients who had not received a PCR test.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethical Committee of Assiut University Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EK contributed to the study conception, design of the work, statistical analysis, and critical revision of the manuscript. NA-E and MS contributed to the study conception, design of the work, and drafting of the manuscript. RS contributed to the study conception, interpretation of neuroimaging, preparing the radiological figures, and drafting of the manuscript. AZ recruited data of non-COVID-19 stoke patients from Qena University Hospital. MA recruited the COVID-19 stoke cases and performed the analysis. OM and AA contributed to the drafting and critical revision of the manuscript. All authors gave final approval of the version to be published.

ACKNOWLEDGMENTS

Thank you to Professor John C. Rothwell for his revision of the language, Sobell Department of Motor Neuroscience and Movement Disorders, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*. (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
3. Avula A, Nalleballe K, Narula N, Sapozhnikov S, Dandu V, Toom S, et al. COVID-19 presenting as stroke. *Brain Behav Immun*. (2020) 87:115–9. doi: 10.1016/j.bbi.2020.04.077
4. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. (2020) 91:889–91. doi: 10.1136/jnnp-2020-323586
5. Oxley TJ, Mocco J, Majidi S, Kellner CP. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. (2020) 382:e60. doi: 10.1056/NEJMc2009787
6. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. (2020) 382:e38. doi: 10.1056/NEJMc2007575
7. Qureshi AI, Abd-Allah F, Al-Senani F, Aytac E, Borhani-Haghighi A, Ciccone A, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. *Int J Stroke*. (2020) 15:540–54. doi: 10.1177/1747493020923234
8. Fara MG, Stein LK, Skliut M, Morgello S, Fifi JT, Dhamoon MS. Macrothrombosis and stroke in patients with mild Covid-19 infection. *J Thromb Haemost*. (2020) 18:2031–3. doi: 10.1111/jth.14938

9. Mohamud AY, Griffith B. Intraluminal carotid artery thrombus in COVID-19: another danger of cytokine storm? *AJNR Am J Neuroradiol*. (2020) 41:1677–82. doi: 10.3174/ajnr.A6674
10. Gunasekaran K, Amoah K, Rajasurya V, Buscher MG. Stroke in a young COVID-19 patient. *QJM*. (2020) 113:573–4. doi: 10.1093/qjmed/hcaa177
11. Khedr EM, Abo-Elfetoh N, Deaf E, Hassan HM, Amin MT, Soliman RK, et al. Surveillance study of acute neurological manifestations among 439 Egyptian patients with COVID-19 in Assiut and Aswan University Hospitals. *Neuroepidemiology*. (2021) 1–10. doi: 10.1159/000513647 [Epub ahead of print].
12. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. (1980) 58:113–30.
13. Li Y, Wang M, Zhou Y. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study (3/3/2020). *Stroke Vasc Neurol*. (2020) 5:279–84. doi: 10.2139/ssrn.3550025
14. Reddy ST, Garg T, Shah C, Nascimento FA, Imran R, Kan P, et al. Cerebrovascular disease in patients with COVID-19: a review of the literature and case series. *Case Rep Neurol*. (2020) 12:199–209. doi: 10.1159/000508958
15. Requena M, Olivé-Gadea M, Muchada M, García-Tornel Á, Deck M, Juega J, et al. COVID-19 and stroke: incidence and etiological description in a high-volume center. *J Stroke Cerebrovasc Dis*. (2020) 29:105225. doi: 10.1016/j.jstrokecerebrovasdis.2020.105225
16. Fraiman P, Godeiro Junior C, Moro E, Cavallieri F, Zedde M. COVID-19 and cerebrovascular diseases: a systematic review and perspectives for stroke management. *Front Neurol*. (2020) 11:574694. doi: 10.3389/fneur.2020.574694
17. Katz JM, Libman RB, Wang JJ, Sanelli P, Filippi CG, Gribko M, et al. Cerebrovascular complications of COVID-19. *Stroke*. (2020) 51:e227–e31. doi: 10.1161/STROKEAHA.120.031265
18. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg*. (2020) 12:648–53. doi: 10.1136/neurintsurg-2020-016220
19. Yaghi S, Ishida K, Torres J, Mac Grory B, Raz E, Humbert K, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. *Stroke*. (2020) 51:2002–11. doi: 10.1161/STROKEAHA.120.030335
20. Tiwari A, Berekashvili K, Vulkanov V, Agarwal S, Khaneja A, Turkel-Parella D, et al. Etiologic subtypes of ischemic stroke in SARS-CoV-2 patients in a cohort of New York city hospitals. *Front Neurol*. (2020) 11:1004. doi: 10.3389/fneur.2020.01004
21. Zhu H, Rhee JW, Cheng P, Waliany S, Chang A, Witteles RM, et al. Cardiovascular complications in patients with COVID-19: consequences of viral toxicities and host immune response. *Curr Cardiol Rep*. (2020) 22:32. doi: 10.1007/s11886-020-01302-4
22. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *medicine Engl J Med*. (2020) 382:1708–20. doi: 10.1056/NEJMoa2002032
23. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. (2020) 323:1061–9. doi: 10.1001/jama.2020.1585
24. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. (2020) 5:811–8. doi: 10.1001/jamacardio.2020.1017
25. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J*. (2020) 41:2070–9. doi: 10.1093/eurheartj/ehaa408
26. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)*. (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
27. Dmytriw AA, Phan K, Schirmer C, Settecase F, Heran MKS, Efendizade A, et al. Ischaemic stroke associated with COVID-19 and racial outcome disparity in North America. *J Neurol Neurosurg Psychiatry*. (2020) 91:1362–4. doi: 10.1136/jnnp-2020-324653
28. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, et al. From SARS to MERS, thrusting coronaviruses into the spotlight. *Viruses*. (2019) 11:59. doi: 10.3390/v11010059
29. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet (London, England)*. (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5
30. Mangalmurti N, Hunter CA. Cytokine storms: understanding COVID-19. *Immunity*. (2020) 53:19–25. doi: 10.1016/j.immuni.2020.06.017
31. Kihira S, Schefflein J, Mahmoudi K, Rigney B, B ND, Mocco J, et al. Association of coronavirus disease (COVID-19) with large vessel occlusion strokes: a case-control study. *AJR Am J Roentgenol*. (2021) 216:150–6. doi: 10.2214/AJR.20.23847
32. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. *Rev Neurol*. (2020) 70:311–22. doi: 10.33588/rn.7009.2020179
33. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe acute respiratory syndrome coronavirus 2 infection and ischemic stroke. *Stroke*. (2020) 51:e124–e7. doi: 10.1161/STROKEAHA.120.030153

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

MINI REVIEW
published: 24 March 2021
doi: 10.3389/fneur.2021.607790

Care for Patients With Neuromuscular Disorders in the COVID-19 Pandemic Era

Yung-Hao Tseng[1] *and Tai-Heng Chen*[1,2]*

[1] Department of Pediatrics, Division of Pediatric Emergency, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [2] School of Post-Baccalaureate Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

The coronavirus disease 2019 (COVID-19) pandemic has prompted a rapid and unprecedented reorganization of medical institutions, affecting clinical care for patients with chronic neurological diseases. Although there is no evidence that patients with neuromuscular disorders (NMD) confer a higher infection risk of COVID-19, NMD and its associated therapies may affect the patient's ability to cope with infection or its systemic effects. Moreover, there is a concern that patients with chronic NMD may be at increased risk of manifesting severe symptoms of COVID-19. In particular, as respiratory compromises account for the major cause of mortality and morbidity in NMD patients, newly emerging data also show that the risk of exacerbation caused by COVID-19 accumulates in this particular patient group. For example, patients with motor neuron disease and dystrophinopathies often have ventilatory muscle weakness or cardiomyopathy, which may increase the risk of severe COVID-19 infection. Thus, the COVID-19 pandemic may severely affect NMD patients. Several neurological associations and neuromuscular networks have recently guided the impact of COVID-19 on patients with NMD, especially in managing cardiopulmonary involvements. It is recommended that patients with moderate- to high-risk NMD be sophisticatedly monitored to reduce the risk of rapid decline in cardiopulmonary function or potential deterioration of the underlying NMD. However, limited neuromuscular-specific recommendations for NMD patients who contract COVID-19 and outcome data are lacking. There is an urgent need to properly modify the respiratory care method for NMD patients, especially during the COVID-19 pandemic. Conclusively, COVID-19 is a rapidly evolving field, and the practical guidelines for the management of NMD patients are frequently revised. There must be a close collaboration in a multidisciplinary care team that should support their hospital to define a standardized care method for NMD patients during the COVID pandemic. This article reviews evidence-based practical guidelines regarding care delivery, modification, and education, highlighting the need for team-based and interspecialty collaboration.

Keywords: neuromuscular disorder, multidisciplinary care, respiratory care, COVID- 19, telemedicine

OPEN ACCESS

Edited by:
Cheng-Yang Hsieh,
Sin-Lau Christian Hospital, Taiwan

Reviewed by:
Sonu Bhaskar,
Liverpool Hospital & South West Sydney Local Health District (SWSLHD), Australia
Li-Kai Tsai,
National Taiwan University Hospital, Taiwan

****Correspondence:***
Tai-Heng Chen
taihen@kmu.edu.tw

Specialty section:
This article was submitted to Neuromuscular Disorders and Peripheral Neuropathies, a section of the journal Frontiers in Neurology

Received: *18 September 2020*
Accepted: *16 February 2021*
Published: *24 March 2021*

Citation:
Tseng Y-H and Chen T-H (2021) Care for Patients With Neuromuscular Disorders in the COVID-19 Pandemic Era. Front. Neurol. 12:607790. doi: 10.3389/fneur.2021.607790

INTRODUCTION

In December 2019, a severe pneumonia outbreak related to a novel coronavirus disease 2019 (COVID-19) began in Wuhan, China, and soon spread across the world. Compared with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that caused a SARS epidemic in 2003, COVID-19 has a more robust transmission capacity, making prevention and control more complex. As of September 14, 2020, COVID-19 has caused more than 28 million infections, including more than 900,000 deaths worldwide (1). In a short period, the pandemic has greatly changed the current guidelines for managing patients with chronic neurological diseases, leading to a significant impact on the field. This pandemic urges a rapid and unprecedented readjustment of medical services, especially in patients with neuromuscular disease (NMD) known to have an increased risk of severe COVID-19 disease course. Overall, NMD constitutes a group of heterogeneous diseases, most of which are of genetic or autoimmune origins that affect individuals of all ages. The categories of NMD usually, but not exclusively, include muscle disorders (e.g., congenital muscular dystrophies, myopathies, and muscle channelopathies), motor neuron disorders [e.g., spinal muscular atrophy, spinal muscular atrophy (SMA), and amyotrophic lateral sclerosis (ALS)], diseases of the neuromuscular junction [e.g., myasthenia gravis (MG) and Lambert–Eaton myasthenic syndrome], and peripheral nerve disorders (e.g., inflammatory demyelinating polyneuropathy and hereditary motor and sensory neuropathy). Many patients with NMD exhibit multiple disabilities and usually have cardiopulmonary complications. However, since most NMD categories cover various diagnoses and degrees of severity, it is difficult to make specific recommendations that are generally applicable even among patients with the same diagnosis.

So far, there is no evidence that hereditary NMD will increase the risk of SARS-CoV-2 infection; however, comorbidities associated with NMD and its treatment may affect patients' ability to cope with COVID-19 (2–4). Therefore, risk identification and stratification are essential to assess NMD patients' susceptibility to developing a serious course of COVID-19. Following the guidance of the Britain National Neurological Associations and neuromuscular networks, the World Muscle Society announced its position and recommendations regarding the influence of COVID-19 on NMD and associated management (2). These guidances recognize the risk of severe COVID-19 disease course as high or moderately high in all but the mildest forms of NMD. The risk is significantly increased in NMD patients associated with certain comorbidities (**Table 1**). For example, factors that may confer increased risks of severe prognosis in NMD patients should they be infected with COVID-19 include respiratory compromises, myocardial impairment, or using immunosuppressive medications. Moreover, several additional risk factors might further exacerbate the pre-existing debilitation and increase infectious risk in susceptible patients with NMD (5, 6).

PRACTICAL GUIDANCE FOR NMD PATIENTS IN THE COVID-19 PANDEMIC

The COVID-19 pandemic has prompted the rapid reorganization of hospital settings and patient service provision to cope with emerging but unmet medical needs. In particular, the prevention strategies produce impacts on the management for patients with NMD (4, 6). Patients should ensure that they have sufficient medication (at least 1 month) and ventilatory support equipment (2). Switching to patient appointments for telephone interviews helps eliminate the risk of contracting COVID-19. Patients and caregivers should know how to utilize online and telephone-based pharmacies, equipment ordering, and delivery services (7). Nevertheless, social distancing remains the most important intervention to limit the spread of COVID-19, and if possible, all NMD patients should wear masks upon their arrival at the hospital (8).

Management of Immunomodulatory Therapies in Patients With NMD

Some types of NMD are associated with immune-mediated pathogenesis. Patients with NMD who receive immunomodulatory therapy (IMT) are likely at increased risk of having more severe COVID-19 infections (5). Recently, a consensus statement on IMT management during the COVID-19 pandemic is emerging to guide patients and clinicians (5, 6). Based on the pandemic burden of the region, patient compliance and caregiver support, dose reduction of certain IMTs, or switching to alternative agents for high-risk NMD patients can be considered. The decision to temporarily suspend, reduce, or change IMT should be discussed with NMD experts, and patients should not proceed without consultation (9).

Notably, sudden discontinuation of corticosteroids may induce a flare-up of the underlying disease, requiring a higher stress dose and increasing hospitalization risk. Especially during acute illness or hospitalization related to COVID-19, it may be necessary to increase the steroid dose (amount or frequency) and follow the recommended dose in the infection/stress guidance to avoid hyposurrenalism (10, 11). Otherwise, there is no evidence suggesting that intravenous immunoglobulin (IVIG), therapeutic plasmapheresis, or complement inhibitor (Fc receptor antagonists, e.g., efgatirgimod) can increase the risk of COVID-19 infection or aggravate the disease severity (2, 6).

Some cases with severe COVID-19 infection may be related to a cascade of immune dysregulation and overreaction of inflammatory pathways (12). Therefore, certain immunomodulatory drugs used in the treatment of NMD may help resist SARS-CoV-2 infection or ameliorate severe complications. For instance, hydrocortisone and dexamethasone are reported to potentially benefit treating COVID-19 patients with severe cardiopulmonary complications (13). Eculizumab, a monoclonal antibody against complement, has recently been investigated as a potential treatment in autoimmune MG (14). Moreover, the treatment of severe COVID-19 with eculizumab is currently undergoing a clinical trial (NCT04288713) (15).

TABLE 1 | Features of NMD patients conferring higher risk of severe COVID-19 infection.

Affected aspect	Associated features	Susceptible NMD types
Respiratory system	• Weakness of respiratory muscles or diaphragm, resulting in respiratory volumes <60% predicted (FVC<60%) • Use of ventilation *via* mask or tracheotomy • Weak cough and weak airway clearance due to oropharyngeal weakness (bulbar involvement) • Presence of tracheostoma	Any kinds of NMD with respiratory muscle involvement, especially severe -to-moderate types of SMA, ALS, end-stage DMD, severe congenital myopathies, and congenital muscular dystrophies
Cardiac system	NMD-related cardiomyopathy, conductive arrhythmias, and/or on medications for cardiac involvement	DMD/BMD, Emery-Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy (especially infantile form)
Systemic involvement	Risk of deterioration with fever, fasting or infection	Mitochondrial myopathies, metabolic myopathies, SMA
	Risk of rhabdomyolysis with fever, fasting or infection	Mitochondrial myopathies, metabolic myopathies
	Concomitant diabetes and obesity	NMD with inborn metabolic disorders
Medication History	Patients taking steroids and undergoing immunosuppressant treatment	Inflammatory myopathies (e.g., polymyositis, dermatomyositis), DMD/BMD, myasthenia gravis, congenital myasthenic syndrome
Additional risk factors	• Kyphoscoliosis • Highly-active immune-mediated NMD • Older age • Pregnancy (possible) • Concomitant additional neurologic diseases • Dependence from caregivers in hygiene, mobilization and feeding	Any kinds of NMD with associated risk factors

NMD, neuromuscular disorder; FVC, forced vital capacity; SMA, spinal muscular atrophy; ALS, amyotrophic lateral sclerosis; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy.

Adjustment of Disease-Modifying Therapies in Patients With NMD

Hospitalization should be reserved for emergencies. However, preventive strategy with the requirement of isolation may affect treatment options requiring in-hospital setting for administration, such as infusion of nusinersen (Spinraza®), glucosidase alfa (Myozyme®), rituximab, and IVIG. These treatments should not be discontinued arbitrarily, but consideration should be given to shifting treatment to a nonhospital setting (home-visiting or outreach nurse), and collaboration with the pharmaceutical company can be negotiated.

It is recommended to continue intrathecal injections as much as possible for infants with type 1 SMA and children with type 2 SMA. As per the manufacturer's recommendation, the half-life of nusinersen is more than 100 days, affecting alternative splicing for several months (16). Therefore, if these SMA patients miss the planned dose after 4 months, they should be given a subsequent dose of nusinersen on the date minus the number of missed days originally scheduled to ensure a sufficient restoration of SMN protein (17). However, for adolescents and adults, injections could be delayed by 1–4 months, depending on the clinical progression (8). Inspiringly, the U.S. Food and Drug Administration (FDA) has recently approved risdiplam (Evrysdi®) as the first oral and at-home treatment for patients with all types of SMA (18). This therapeutic agent may provide a flexible alternative to SMA-modifying therapy, especially during the pandemic.

Suspending enzyme replacement therapy for 1–3 months is unlikely to cause serious deterioration of the disease. However, there is limited evidence to accurately estimate the risk after a relatively short interruption of treatment (19). It is recommended that patients with Duchenne muscular dystrophy (DMD) continue to use drugs to prevent or treat cardiomyopathy, such as angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (10). IVIG can be changed to subcutaneous immunoglobulin whenever possible (2). The benefits of transitioning from a hospital-based center to at-home infusion should be weighed and may depend on the patient's overall COVID-19 risk, transportation requirement, geographic resources, and insurance coverage. The treatment efficacies between hospital and home facilities are still being studied. Besides, trial centers should be consulted for advice on clinical trials.

Modification of Providing Physiotherapy for Patients With NMD

The pandemic has also prompted the reallocation of rehabilitation services. For many patients with NMD, it is crucial to maintain joint flexibility, muscle strength, and endurance even during a pandemic; therefore, rehabilitation advice should be obtained through alternative strategies, including telemedicine (8). Considering telerehabilitation for NMD patients, the evidence-based database of Cochrane review lacks a comprehensive analysis for these patients. Nevertheless, a retrospective study reported that providing rehabilitation for 26 patients with mixed NMD through telemedicine improved their cognition, self-care, quality of life, and motor function (20). Since most NMD referral hospitals and treatment centers have kept essential telehealth activities, patients and their families are encouraged to contact these departments to obtain personalized support (telerehabilitation) (2, 6). Self-rehabilitation and exercises can be set up according to age, current motor function, and personal goals. As telemedicine's

most encountered limitation is the knowledge gap between the professional providers and home-based caregivers, these programs should be deliberately simple and guided to be delivered by caregivers who are not health professionals. Importantly, effective telemedicine services rather than physical contact services can significantly reduce the risk of infection and spread of COVID-19. Telemedicine approaches can include but are not limited to applying novel technologies such as e-mail, instant messaging applications, and hands-free telephone or webcam interviews. Other innovative communication platforms are emerging and quickly spread to the medical field (21).

MANAGEMENT OF NMD PATIENTS WITH COVID-19 INFECTION

Respiratory Support for NMD Patients With COVID-19 Pneumonia

As respiratory involvements lead to the most deaths and morbidities of patients with NMD, recent evidence indicates accumulating exacerbation risks caused by COVID-19 in NMD patient group (2, 6). Especially in some types of NMD, patients who have respiratory muscle involvement and/or cardiomyopathy are likely at greater risk of contracting a severe COVID-19-related complication.

At this time, respiratory care in NMD patients requires a deliberate revision during the COVID-19 pandemic (22). The WHO recommends that all COVID-19 patients with respiratory distress or hypoxemia be supported immediately with oxygen supplement at 5 L/min and that flow rates are titrated to attain $SpO_2 \geq 90\%$ in nonpregnant adults and $SpO_2 \geq 92–95\%$ in pregnant patients (23). Otherwise, hypercapnia is not a typical feature of SARS-CoV-2 pneumonia, and its presence may implicate the deterioration of respiratory pump weakness (24), which may progress more rapidly in NMD patients. Thus, NMD patients with COVID-19 pneumonia should be closely monitored, such as increased oxygen demand, progressive CO_2 retention, and acidosis. NMD patients presenting with interstitial pneumonia should consider early ventilation support. It should be kept in mind that hypoxemia complicated by COVID-19 pneumonia may even rapidly cause pump failure in previously compensated patients, while hypercapnia can further aggravate the disease process (6).

It has been proposed that COVID-19-related acute respiratory distress syndrome (CARDS) is distinct from the typical form of acute respiratory distress syndrome (ARDS) (25). ARDS usually does not respond to solitary oxygen therapy because hypoxemic persistence is typically the result of intrapulmonary ventilation-perfusion mismatch or shunt. In contrast, CARDS is characterized by relatively high lung compliance in the intermediate stage of COVID-19 pneumonia but significantly reduced in the later stage (25). Therefore, the treatment strategy initiated in CARDS has now shifted to the early support of noninvasive ventilation (NIV) instead of intubation and mechanical ventilation (26). However, data on patients with Middle East respiratory syndrome (MERS) indicate a high failure rate of management with NIV (27), whether a similar outcome in patients with SARS-CoV-2 infection is still unclear. In several large cohorts of COVID-19 patients admitted to the ICU due to acute respiratory failure (ARF), NIV was used in 11–62% of patients, compared with 30–88% of endotracheal intubation with invasive mechanical ventilation (6). Especially in NMD patients, applying NIV as a first-line intervention for ARF has been widely advocated for its potential benefits such as shorter ICU stays and improved overall survival and to avoid intubation and facilitate extubation (28, 29). In addition to respiratory support, the purpose of restoring the pulmonary function should also include treatment strategies for COVID-19-related cytokine storms (30).

However, emerging studies have limited NIV use in severe cases of COVID-19 pneumonia due to a concern that NIV may bring the risk of widespread exhaled airborne virus (31). It may be explained that a single circuit with only one hose is always equipped in an NIV set; therefore, the exhaled gas is not filtered through a valve. Thus, NIV with high airflow may result in more aerosolized COVID-19 virus spreading than conventional ventilators. Recent reports show that modified systems with appropriate interface fitting might reduce viral contamination in the healthcare environment (32). These modified strategies may include the following: (1) before starting or stopping NIV, the patient's mask must be worn tightly, and caregivers must wear personal protective equipment; and (2) a full-face mask for NIV is preferred and should be sealed as tightly as possible. An antiviral filter should be used at the ventilator outlet of the inhalation circuit and after the mask (8). Several innovative NIV interface designs have been applied clinically, providing a more closed ventilation system (22, 26, 33). It should be addressed that patients undergoing NIV should remain under close monitoring and shift to a conventional ventilator if showing rapid deterioration or lack of improvement (6). Intubation may be necessary upon progressive deterioration during COVID-19 infection. However, patients with end-stage NMD, such as ALS and DMD, may request conservative approaches without aggressive management. In this case, an in-depth discussion of palliative care can begin.

In addition, the risk of anesthesia in patients with NMD varies greatly because it depends mainly on baseline lung function and the presence of comorbidities (34). In some NMD cases, masticatory muscle atrophy and limited cervical spine mobility may complicate the intubation process. Therefore, intubation in NMD patients should always follow the guidelines for difficult airway management (34). Besides, patients with NMD should be cautious about the side effects of neuromuscular blockers and anesthetics. Succinylcholine, a depolarizing muscle relaxant, should be avoided in patients with muscular dystrophies, motor neuron diseases, and intrinsic muscle disease because of the risk of malignant hyperthermia, fatal hyperkalemia, and rhabdomyolysis (35–37). Nondepolarizing muscle relaxants should be reduced dosage and titrated carefully in some categories of NMD, including myotonic muscular dystrophy, MG, congenital myasthenic syndrome, SMA, polymyositis, and dysimmune neuropathies (36, 37). In addition, due to the advantages of easy controlled dosage and shorter onset time, intravenous

TABLE 2 | COVID-19 therapeutic agents with potential NMD complications.

Therapeutic agents	Potential NMD-relevant side effects	NMD patients with particular caution in use
Hydroxychloroquine	• QTc interval prolongation may lead to cardiac arrest secondary to cardiac arrhythmia, especially when combined with other QTc-prolonging drugs • Newly onset or exacerbation of MG • Risk of toxic neuropathy and myopathy • Cardiotoxicity and cardiomyopathy • Elevated serum CK level	• Autoimmune and congenital MG • NMD with myocardial involvement, i.e. DMD/BMD • Andersen-Tawil syndrome (a rare form of periodic paralysis) • Myotonic dystrophy
Azithromycin	• QTc interval prolongation • Risk of worsening MG	NMD patients who have similar susceptibility to hydroxychloroquine
Lopinavir/Ritonavir	• QTc interval prolongation may lead to cardiac arrest secondary to cardiac arrhythmia, especially when combined with other QTc-prolonging drugs • Risk of toxic myopathy with rhabdomyolysis, especially in combination with a statin	Careful monitoring of serum CK levels when treating in myopathic patients
Remdesivir	• Myalgias in healthy controls • Elevation in liver enzymes	All kinds of susceptible NMD patients should be monitor serum liver enzymes and CK level
Eculizumab	• Myalgias and arthralgias • Elevation in liver enzymes	All kinds of susceptible NMD patients should be monitor serum liver enzymes and CK level

NMD, neuromuscular disorder; CK, creatinine kinase; MG, myasthenia gravis; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy.

anesthetics are preferable to volatile agents in most patients of NMD (37).

Intermittent prone positioning during the mechanical ventilation support seems beneficial to improve the oxygenation of patients with COVID-complicated ARDS (38). However, this position might be contraindicated in NMD patients. NMD patients with severe kyphoscoliosis may compress the tracheobronchial tract against the vertebral body on prone positioning (39). NMD patients with complicated deformities in anatomy may affect the choice of pulmonologists for prolonged prone positioning during the ventilator support.

Effects of COVID-19 Therapeutic Agents on Patients With NMD

Emerging therapeutic trials have been initiated in the context of COVID-19 infections. Although several preliminary data of clinical trials appear promising, the evidence on infected NMD patients is limited. Certain investigational treatments for COVID-19 may be prescribed for NMD patients compassionately, as outside trial conditions. Nevertheless, this off-label medication use in NMD patients should only be taken after consultation with NMD specialists (2, 8). **Table 2** summarizes the specific precautions for NMD patients when receiving drugs prescribed to treat COVID-19.

Chloroquine and its less toxic derivative hydroxychloroquine have been indicated for antimalaria and some chronic rheumatic diseases. Recent reports have raised concerns about the possible beneficial effects of hydroxychloroquine on SARS-CoV-2, and it has been tested as a supplementary therapeutic agent in hospitalized COVID-19 patients (40). Nevertheless, the efficacy of hydroxychloroquine against COVID-19 is not yet clear. Some small uncontrolled studies have shown benefits, and at least one controlled research has shown the opposite finding (41–43).

In patients with NMD, particular attention must be paid to hydroxychloroquine treatments for COVID-19 due to possible adverse effects. The most potentially dangerous complication of hydroxychloroquine use is arrhythmias, especially QTc prolongation (44). The risk is increased when hydroxychloroquine is combined with azithromycin. Great attention must be given to certain patients who have NMD-related cardiac involvement (45). Particularly during the long-term hydroxychloroquine use, an increased risk of conductive disorders (QTc prolongation) and myocardial damage can potentially worsen systolic left ventricular dysfunction in patients with certain types of NMD (2, 5, 8). Currently, hydroxychloroquine is suggested contraindicated to patients with DMD or myotonic dystrophy for treatment options of COVID-19 (10). Besides hydroxychloroquine, some drugs now used against COVID, such as lopinavir and ritonavir, also contribute to the QTc prolongation (46).

Notably, hydroxychloroquine, especially in combination with azithromycin, can cause new onset or aggravation of MG (5, 47). Increased creatine kinase (CK), vacuolar myopathy, and toxic neuropathy may occur in some patients with long-term hydroxychloroquine use (6, 48). Complications of toxic myopathy with rhabdomyolysis in patients treated with lopinavir/ritonavir combined with a statin have been reported (49). However, COVID-19 may be complicated with myositis presenting myalgia or fatigue and increased CK in about one-third of admitted patients (50, 51). It is recommended to conduct careful risk/benefit assessment before dosing these agents on patients with myopathy, and regular monitoring of serum CK levels is required when receiving these drugs (5). It is currently not recommended to use these drugs for prophylaxis purposes in NMD patients because their preventive efficacy has not been proven and may cause serious toxicity.

CONCLUSION

COVID-19 is a rapidly evolving field, and the evidence-based best practices in NMD patients are subject to revision frequently. Patients with NMD present unique management challenges in the COVID-19 pandemic. The severity of manifestations and potential complications vary with individual circumstances and patients. Individually designed care plans coordinated among multiple providers are critical to optimizing the treatment effects of these vulnerable patients. Since the possibility of second waves of the pandemic, we will need a robust reorganization of neuromuscular centers, where the role of telehealth providers will be significant. Collaborative efforts among institutions in the NMD community will help provide the data to inform the modified management of NMD patients infected by COVID-19. Importantly, close collaboration must be integrated into a multidisciplinary care team, including but not limited to neuromuscular specialists, intensive care specialists, pulmonologists, rehabilitation therapists, and gastroenterologists. These teams should support their hospital to define standardized and targeted care for NMD patients during the COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

Y-HT and T-HC contributed to the conception and design of the study, acquisition of data, revision of the manuscript critically for relevant intellectual content, and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

FUNDING

This research was funded by Kaohsiung Medical University Hospital in Kaohsiung, Taiwan, grant number KMUH-108-8R47.

REFERENCES

1. World Health Organization. *Coronavirus Disease (COVID-19) Weekly Epidemiological Update*. Available online at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200914-weekly-epi-update-5.pdf?sfvrsn=cf929d04_2 (accessed September 14, 2020).
2. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *N Engl J Med*. (2020) 382:1663–5. doi: 10.1056/NEJMc2005073
3. Angelini C, Siciliano G. Neuromuscular diseases and Covid-19: Advices from scientific societies and early observations in Italy. *Eur J Transl Myol*. (2020) 30:9032. doi: 10.4081/ejtm.2019.9032
4. Bhaskar S, Bradley S, Israeli-Korn S, Menon B, Chattu VK, Thomas P, et al. Chronic neurology in COVID-19 era: clinical considerations and recommendations from the REPROGRAM Consortium. *Front Neurol*. (2020) 11:664. doi: 10.3389/fneur.2020.00664
5. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. (2020) 94:959–69. doi: 10.1212/WNL.0000000000009566
6. Costamagna G, Abati E, Bresolin N, Comi GP, Corti S. Management of patients with neuromuscular disorders at the time of the SARS-CoV-2 pandemic. *J Neurol*. (2020). doi: 10.1007/s00415-020-10149-2. [Epub ahead of print].
7. Howard IM, Kaufman MS. Telehealth applications for outpatients with neuromuscular or musculoskeletal disorders. *Muscle Nerve*. (2018) 58:475–85. doi: 10.1002/mus.26115
8. Sole G, Salort-Campana E, Pereon Y, Stojkovic T, Wahbi K, Cintas P, et al. Guidance for the care of neuromuscular patients during the COVID-19 pandemic outbreak from the French Rare Health Care for Neuromuscular Diseases Network. *Rev Neurol*. (2020) 176:507–15. doi: 10.1016/j.neurol.2020.04.004
9. World Muscle Society. *Covid-19 and People With Neuromuscular Disorders: World Muscle Society Position and Advice*. Available online at: www.worldmusclesociety.org/news/view/150 (accessed September 14, 2020).
10. Veerapandiyan A, Wagner KR, Apkon S, McDonald CM, Mathews KD, Parsons JA, et al. The care of patients with Duchenne, Becker, and other muscular dystrophies in the COVID-19 pandemic. *Muscle Nerve*. (2020) 62:41–5. doi: 10.1002/mus.26902
11. International MGC-WG, Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci*. (2020) 412:116803. doi: 10.1016/j.jns.2020.116803
12. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. (2020) 20:363–74. doi: 10.1038/s41577-020-0311-8
13. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: evidence and hope during the pandemic. *JAMA*. (2020) 324:1292–5. doi: 10.1001/jama.2020.16747
14. Muppidi S, Utsugisawa K, Benatar M, Murai H, Barohn RJ, Illa I, et al. Long-term safety and efficacy of eculizumab in generalized myasthenia gravis. *Muscle Nerve*. (2019) 60:14–24. doi: 10.1002/mus.26447
15. Diurno F, Numis FG, Porta G, Cirillo F, Maddaluno S, Ragozzino A, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur Rev Med Pharmacol Sci*. (2020) 24:4040–7. doi: 10.26355/eurrev_202004_20875
16. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. (2016) 388:3017–26. doi: 10.1016/S0140-6736(16)31408-8
17. Veerapandiyan A, Connolly AM, Finkel RS, Arya K, Mathews KD, Smith EC, et al. Spinal muscular atrophy care in the COVID-19 pandemic era. *Muscle Nerve*. (2020) 62:46–9. doi: 10.1002/mus.26903
18. The U.S. Food and Drug Administration. *FDA Approves Oral Treatment for Spinal Muscular Atrophy*. Available online at: https://www.fda.gov/news-events/press-announcements/fda-approves-oral-treatment-spinal-muscular-atrophy (accessecd September 11, 2020).
19. Scheidegger O, Leupold D, Sauter R, Findling O, Rosler KM, Hundsberger T. 36-Months follow-up assessment after cessation and resuming of enzyme replacement therapy in late onset Pompe disease: data from the Swiss Pompe Registry. *J Neurol*. (2018) 265:2783–8. doi: 10.1007/s00415-018-9065-7
20. Levy CE, Silverman E, Jia H, Geiss M, Omura D. Effects of physical therapy delivery via home video telerehabilitation on functional and health-related quality of life outcomes. *J Rehabil Res Dev*. (2015) 52:361–70. doi: 10.1682/JRRD.2014.10.0239
21. Bhaskar S, Bradley S, Chattu VK, Adisesh A, Nurtazina A, Kyrykbayeva S, et al. Telemedicine Across the Globe-Position Paper From the COVID-19 Pandemic Health System Resilience PROGRAM (REPROGRAM) International Consortium (Part 1). *Front Public Health*. (2020) 8:556720. doi: 10.3389/fpubh.2020.556720
22. Chen TH, Hsu JH. Respiratory management for patients with neuromuscular disorders during the COVID-19 pandemic. *Ther Adv Respir Dis*. (2020) 14:1753466620953789. doi: 10.1177/1753466620953789
23. World Health Organization. *Clinical Management of Severe Acute Respiratory Infection When Novel Coronavirus (2019-nCoV) Infection Is Suspected: Interim*

Guidance. Available online at: https://apps.who.int/iris/handle/10665/330893 (accessecd September 12, 2020).
24. Fan E, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *Lancet Respir Med.* (2020) 8:816–21. doi: 10.1016/S2213-2600(20)30304-0
25. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med.* (2020) 46:1099–102. doi: 10.1007/s00134-020-06033-2
26. Armirfarzan H, Shanahan JL, Schuman R, Leissner KB. Helmet CPAP: how an unfamiliar respiratory tool is moving into treatment options during COVID-19 in the US. *Ther Adv Respir Dis.* (2020) 14:1753466620951032. doi: 10.1177/1753466620951032
27. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med.* (2014) 160:389–97. doi: 10.7326/M13-2486
28. Chen TH, Liang WC, Chen IC, Liu YC, Hsu JH, Jong YJ. Combined noninvasive ventilation and mechanical insufflator-exsufflator for acute respiratory failure in patients with neuromuscular disease: effectiveness and outcome predictors. *Ther Adv Respir Dis.* (2019) 13:1753466619875928. doi: 10.1177/1753466619875928
29. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. *Thorax.* (2012) 67(Suppl. 1):i1–40. doi: 10.1136/thoraxjnl-2012-201964
30. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, et al. Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: The REPROGRAM Consortium Position Paper. *Front Immunol.* (2020) 11:1648. doi: 10.3389/fimmu.2020.01648
31. Namendys-Silva SA. Respiratory support for patients with COVID-19 infection. *Lancet Respir Med.* (2020) 8:e18. doi: 10.1016/S2213-2600(20)30110-7
32. Hui DS, Chow BK, Lo T, Ng SS, Ko FW, Gin T, et al. Exhaled air dispersion during noninvasive ventilation via helmets and a total facemask. *Chest.* (2015) 147:1336–43. doi: 10.1378/chest.14-1934
33. Dellweg D, Haidl P, Kerl J, Koehler D. Noninvasive ventilation masks with viral filters to protect health care workers from SARS-CoV-2 / Coronavirus infections. *Res Square.* (2020). doi: 10.21203/rs.3.rs-21269/v1
34. Racca F, Mongini T, Wolfler A, Vianello A, Cutrera R, Del Sorbo L, et al. Recommendations for anesthesia and perioperative management of patients with neuromuscular disorders. *Minerva Anestesiol.* (2013) 79:419–33.
35. Katz JA, Murphy GS. Anesthetic consideration for neuromuscular diseases. *Curr Opin Anaesthesiol.* (2017) 30:435–40. doi: 10.1097/ACO.0000000000000466
36. Kynes JM, Blakely M, Furman K, Burnette WB, Modes KB. Multidisciplinary perioperative care for children with neuromuscular disorders. *Children.* (2018) 5:126. doi: 10.3390/children5090126
37. Klingler W, Lehmann-Horn F, Jurkat-Rott K. Complications of anaesthesia in neuromuscular disorders. *Neuromuscul Disord.* (2005) 15:195–206. doi: 10.1016/j.nmd.2004.10.017
38. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. *JAMA.* (2020) 323:1499–500. doi: 10.1001/jama.2020.3633
39. Brown J, Rogers J, Soar J. Cardiac arrest during surgery and ventilation in the prone position: a case report and systematic review. *Resuscitation.* (2001) 50:233–8. doi: 10.1016/S0300-9572(01)00362-8
40. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review. *Ann Intern Med.* (2020) 173:287–96. doi: 10.7326/M20-2496
41. Cohen MS. Hydroxychloroquine for the prevention of Covid-19 - searching for evidence. *N Engl J Med.* (2020) 383:585–6. doi: 10.1056/NEJMe2020388
42. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med.* (2020) 383:2041–52.
43. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* (2020) 56:105949. doi: 10.1016/j.ijantimicag.2020.105949
44. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open.* (2020) 3:e208857. doi: 10.1001/jamanetworkopen.2020.8857
45. Park KM, Shin KJ, Kim SE, Park J, Ha SY, Kim BJ. Prolonged corrected QT interval in patients with myotonic dystrophy type 1. *J Clin Neurol.* (2013) 9:186–91. doi: 10.3988/jcn.2013.9.3.186
46. Sapp JL, Alqarawi W, MacIntyre CJ, Tadros R, Steinberg C, Roberts JD, et al. Guidance on minimizing risk of drug-induced ventricular arrhythmia during treatment of COVID-19: A Statement from the Canadian Heart Rhythm Society. *Can J Cardiol.* (2020) 36:948–51. doi: 10.1016/j.cjca.2020.04.003
47. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. *Muscle Nerve.* (2019) 60:693–9. doi: 10.1002/mus.26689
48. Khosa S, Khanlou N, Khosa GS, Mishra SK. Hydroxychloroquine-induced autophagic vacuolar myopathy with mitochondrial abnormalities. *Neuropathology.* (2018) 38:646–52. doi: 10.1111/neup.12520
49. de Kanter CT, Keuter M, van der Lee MJ, Koopmans PP, Burger DM. Rhabdomyolysis in an HIV-infected patient with impaired renal function concomitantly treated with rosuvastatin and lopinavir/ritonavir. *Antivir Ther.* (2011) 16:435–7. doi: 10.3851/IMP1747
50. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* (2020) 395:497–506. doi: 10.1016/S0140-6736(20)30183-5
51. Zhang H, Charmchi Z, Seidman RJ, Anziska Y, Velayudhan V, Perk J. COVID-19-associated myositis with severe proximal and bulbar weakness. *Muscle Nerve.* (2020) 62:E57–60. doi: 10.1002/mus.27003

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CASE REPORT
published: 08 April 2021
doi: 10.3389/fneur.2021.606617

Case Report: Cerebrovascular Events Associated With Bacterial and SARS-CoV-2 Infections in an Adolescent

*Charles de Marcellus[1,2], Laurent Dupic[1,2], Charles-Joris Roux[3], Imane El Aouane El Ghomari[4], Perrine Parize[5], Romain Luscan[2,6], Florence Moulin[1,2] and Manoelle Kossorotoff[7,8]**

[1] Pediatric Intensive Care Unit, APHP University Hospital Necker-Enfants Malades, Paris, France, [2] Université de Paris, Paris, France, [3] Pediatric Radiology Department, APHP University Hospital Necker-Enfants Malades, Paris, France, [4] Pediatric Department, CH André Mignot Versailles, Le Chesnay, France, [5] Department of Infectious Diseases and Tropical Medicine, APHP University Hospital Necker-Enfants Malades, Paris, France, [6] Pediatric Otorhinolaryngology Department, APHP University Hospital Necker-Enfants Malades, Paris, France, [7] French Center for Pediatric Stroke, Pediatric Neurology Department, APHP University Hospital Necker-Enfants Malades, Paris, France, [8] Inserm U1266, Paris, France

OPEN ACCESS

Edited by:
Jesús Porta-Etessam,
Hospital Clínico San Carlos, Spain

Reviewed by:
Lina Palaiodimou,
University General Hospital Attikon, Greece
Kuldeep Dhama,
Indian Veterinary Research Institute (IVRI), India
Ruchi Tiwari,
U.P. Pandit Deen Dayal Upadhyaya Veterinary University, India
Marialuisa Zedde,
Local Health Authority of Reggio Emilia, Italy
Ibrahim C. Haznedaroglu,
Hacettepe University Hospital, Turkey

***Correspondence:**
Manoelle Kossorotoff
manoelle.kossorotoff@aphp.fr

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 20 November 2020
Accepted: 12 March 2021
Published: 08 April 2021

Citation:
de Marcellus C, Dupic L, Roux C-J, El Aouane El Ghomari I, Parize P, Luscan R, Moulin F and Kossorotoff M (2021) Case Report: Cerebrovascular Events Associated With Bacterial and SARS-CoV-2 Infections in an Adolescent. Front. Neurol. 12:606617. doi: 10.3389/fneur.2021.606617

Neurologic manifestations associated with Covid-19 are increasingly reported, especially stroke and acute cerebrovascular events. Beyond cardiovascular risk factors associated with age, some young adults without medical or cardiovascular history had stroke as a presenting feature of Covid-19. Suggested stroke mechanisms in this setting are inflammatory storm, subsequent hypercoagulability, and vasculitis. To date, a handful of pediatric stroke cases associated with Covid-19 have been reported, either with a cardioembolic mechanism or a focal cerebral arteriopathy. We report the case of an adolescent who presented with febrile meningism and stupor. Clinical, biological, and radiological features favored the diagnosis of Lemierre syndrome (LS), with *Fusobacterium necrophorum* infection (sphenoid sinusitis and meningitis) and intracranial vasculitis. The patient had concurrent SARS-CoV-2 infection. Despite medical and surgical antimicrobial treatment, stroke prevention, and venous thrombosis prevention, he presented with severe cerebrovascular complications. Venous thrombosis and stroke were observed, with an extension of intracranial vasculitis, and lead to death. As both *F. necrophorum* and SARS-CoV-2 enhance inflammation, coagulation, and activate endothelial cells, we discuss how this coinfection may have potentiated and aggravated the usual course of LS. The potentiation by SARS-CoV-2 of vascular and thrombotic effects of a bacterial infection may represent an underreported cerebrovascular injury mechanism in Covid-19 patients. These findings emphasize the variety of mechanisms underlying stroke in this disease. Moreover, in the setting of SARS-CoV-2 pandemic, we discuss in what extent sanitary measures, namely, lockdown and fear to attend medical facilities, may have delayed diagnosis and influenced outcomes. This case also emphasizes the role of clinical assessment and the limits of telemedicine for acute neurological condition diagnosis.

Keywords: Covid-19, SARS-CoV-2, stroke, cerebral venous thrombosis, Lemierre syndrome, cerebral vasculitis

INTRODUCTION

Neurologic complications of Covid-19 are increasingly reported, especially stroke and acute cerebrovascular events. In large series, SARS-CoV-2 infection appears to be associated with an increased risk of ischemic stroke, up to 4.5%, and this complication may be associated with an increased mortality risk (1, 2). Beyond cardiovascular risk factors associated with age, some young adults without medical or cardiovascular history had stroke as a presenting feature of Covid-19 (3). Suggested stroke mechanisms in this setting are notably inflammatory storm, subsequent hypercoagulability, and vasculitis (4). Children are less frequently infected by SARS-CoV-2 and usually have less severe forms of Covid-19 than adults (5–7). Regarding pediatric stroke occurrence, a handful of pediatric stroke cases associated with Covid-19 have been reported so far, with stroke attributed to embolic or hemodynamic mechanism (8, 9), focal cerebral arteriopathy (FCA) (10, 11), or bilateral vasculitis (12).

We report the case of an adolescent with bacterial meningitis, Lemierre syndrome (LS), and concurrent SARS-CoV-2 infection, with fatal cerebrovascular complications. This case suggests other stroke mechanisms that are scarcely described and presented in the pediatric population, such as a potential direct aggravating role of SARS-Cov-2 in the setting of a severe bacterial infection, and an indirect aggravating role of sanitary measures in the occurrence and severity of these cerebrovascular events.

CASE DESCRIPTION

A 16-year-old male of Caribbean descent without medical history presented with febrile neck stiffness, stupor, brisk reflexes, and no respiratory symptom, after 8 days of fever. Serum inflammatory studies showed elevated white blood cell count (12.6 G/L), elevated C-reactive protein (250 mg/L), procalcitonin (86 μg/L), and interleukin-6 (15.6 pg/mL, normal < 8.5 pg/mL) levels. Hematology data showed initial thrombopenia (76 G/L), elevated fibrinogen (4.8 g/l), and D-dimer (1,357 ng/mL) levels. CSF analysis after receiving one cefotaxime injection favored bacterial meningitis with purulent fluid (1,566 cells/μl, 76% neutrophils), low glucose level (27 mg/dL), and elevated protein level (500 mg/dL). CSF Gram staining revealed both Gram-positive cocci and Gram-negative bacilli, without possible further identification; culture was sterile. CSF meningitis/encephalitis PCR panel and SARS-CoV-2 PCR were negative. Nasopharyngeal PCR was positive for SARS-CoV-2. Blood culture was positive for *F. necrophorum* and *Streptococcus constellatus*. Brain MRI revealed vasculitis of the Circle of Willis, with vessel wall enhancement and stenosis of the left internal carotid artery, middle cerebral artery (MCA), and anterior cerebral artery, associated with sphenoid sinusitis (**Figure 1**). The association of a sphenoid sinusitis with anaerobic germ and an intracranial arteritis, but without initial cervical or cerebral vein involvement, oriented toward a diagnosis of atypical LS, prompting antimicrobial treatment, stroke prevention, and venous thrombosis prevention. Antimicrobial management associated an intravenous combined antibiotic drug course adapted to microbiological findings and meningeal and bone diffusion (cefotaxime, metronidazole, and levofloxacin) with endoscopic sphenoidotomy achieving good drainage. Stroke prevention combined anti-inflammatory (dexamethasone pulse course) and antithrombotic (aspirin) treatments, associated with careful maintenance of hemodynamic homeostasis. The patient had daily echocardiography and transcranial Doppler assessments to adjust blood volume and blood pressure, in order to maintain adequate cerebral perfusion. Venous thrombosis prevention relied on prophylactic dose enoxaparin treatment. While still in the pediatric intensive care unit, the patient presented with sudden right hemiplegia and aphasia 9 days after admission. MRI confirmed recent arterial ischemic stroke in the left MCA territory, severe and bilateral vasculitis, and left ophthalmic vein thrombosis (**Figure 1**). Despite anti-inflammatory and antithrombotic treatment intensification with high-dose methylprednisolone pulse course, tocilizumab (anti-IL-6 receptor), remdesivir, and full-dose enoxaparin, clinical situation deteriorated, and the patient became comatose with severe brainstem dysfunction. While intubated, the patient had systematic standard chest X-Rays and arterial blood gases; all were normal. Intracranial pressure monitoring revealed intractable intracranial hypertension and the patient died 17 days after admission.

Abbreviations: CSF, cerebro-spinal fluid; LS, Lemierre syndrome; MCA, middle cerebral artery; MRI magnetic resonance imaging; PCR, polymerase chain reaction.

DISCUSSION

This adolescent presented a dramatic LS associating progressive intracranial vasculitis, subsequent arterial stroke, and venous thrombosis, leading to death despite maximal treatment. LS complicates an acute cervical or oropharyngeal bacterial infection. Its extended definition comprises head/neck venous thrombosis but also cervical and/or intracranial arterial vasculitis, potentially leading to stroke, especially in younger children and adolescents (13, 14). Septic embolism is also reported. In immunocompetent children, *F. necrophorum* is classically associated with head and neck infection-related LS. LS is a potentially severe condition. In a recent literature analysis at individual patient level including 712 patients with LS, global mortality reached 4% for the 2000-2017 period. It decreased to 2.3% for the 2012-2016 period, probably because of earlier diagnosis and better management, usually associating medical (antibiotic, anti-inflammatory, and antithrombotic treatments) and surgical therapies (14, 15). Among reported patients with LS, cerebrovascular complications (stroke, brain ischemia, brain edema, or herniation) occurred in 18/712 patients (2.5%). The majority (12/18) were children, adolescents, or young adults. Stroke was most often associated with systemic spread of the infection, especially pulmonary injury (11/14). Mortality related to cerebrovascular complications concerned only 0.8% (6/712) of patients with LS but 33% of patients with cerebrovascular complications. Death occurred early in the disease course (median 3 days after LS diagnosis) (14). Our patient, an

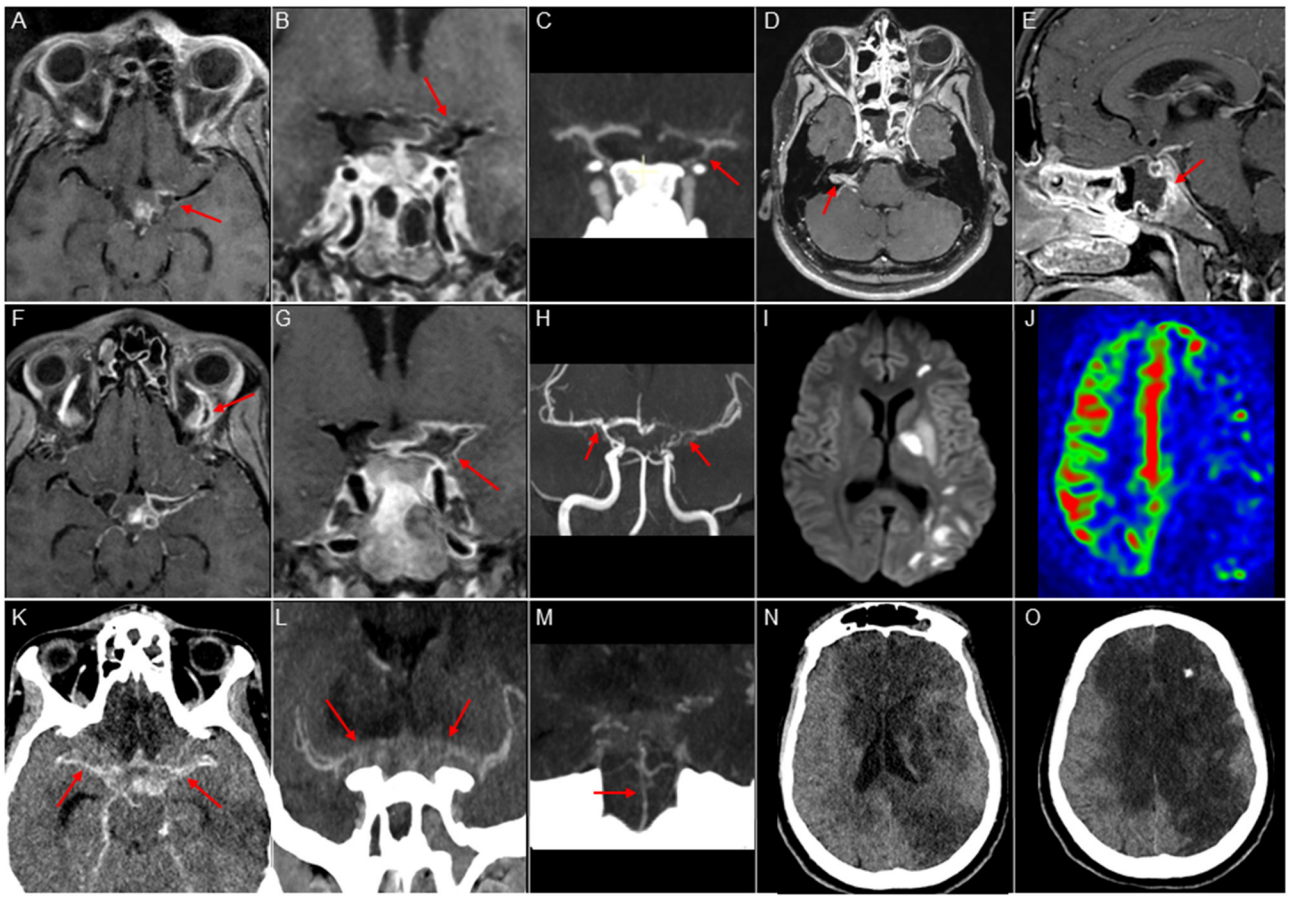


FIGURE 1 | Imaging features. Upper panel: MRI and CT scan at admission. **(A,B,D,E)**: Cube T1 FatSat post Gadolinium contrast, axial **(A,D)**, coronal **(B)**, and sagittal **(E)** views. **(C)**: Contrast-enhanced CT with arterial phase, coronal view. Vasculitis of the Circle of Willis: stenosis of the left internal carotid artery, middle cerebral artery, and anterior cerebral artery **(A-C)**, with vessel wall enhancement **(A,B)**. Right acoustic-facial neuritis (**D**, arrow), sphenoid sinusitis with adjacent osteitis (**E**, arrow). Medium panel: MRI after sudden right hemiplegia and aphasia. **(F,G)** Cube T1 FatSat post Gadolinium contrast, axial view; **(H)** 3D Time-of-Flight angio-MR coronal view; **(I)** DWI sequence, axial view; **(J)** Arterial Spin Labeling perfusion sequence, axial view. Recent arterial ischemic stroke in the left middle cerebral territory **(I)** with extended hypoperfusion **(J)**, worsening of severe and bilateral vasculitis **(F-H)**, and left ophthalmic vein thrombosis (**F**, arrow). Lower panel: CT scan at day 14. **(K)**: post-contrast axial view; **(L,M)** angio-CT coronal view; **(N,O)**: axial view. Worsening of the intracranial vasculitis **(K-M)**, with basilar artery involvement **(M)**. Large bilateral infarcts in anterior and middle cerebral artery territories **(N,O)**.

immunocompetent adolescent, had a similar devastating disease course despite maximal treatment. Nevertheless, he presented atypical features, with slower disease progression and prominent vasculitis, which has been scarcely reported. We suggest that the coinfection with SARS-CoV-2 may have played a direct and indirect role in this evolution.

First, concurrent bacterial and viral infections may have synergistic effects. This process is well-described when pathogens may target the same organ(s). In the setting of Covid-19, coinfection with a viral or bacterial (*Mycoplasma pneumoniae)* respiratory pathogen is frequently found in children (16), and may represent a risk factor of severe disease or poor outcome (17, 18). Our patient had no respiratory involvement and synergistic effects through mutual potentiation of common pathophysiological processes may also be hypothesized. Beyond *F. necrophorum*'s reported affinity to endothelial cells and effects on coagulation (19, 20), well-described SARS-Cov-2 direct pro-inflammatory and pro-coagulant effects may represent additional risk factors for cerebrovascular events in the setting of LS. In patients with Covid-19, marked inflammatory status has been associated with stroke (3), and vasculitis related to endothelial cell infection *via* ACE2 receptors has been observed, with endothelial damage and increased subintimal inflammation, followed by hemorrhage or thrombosis (4, 21). Diffuse endothelial inflammation leading to ischemia was demonstrated in several organs including kidney, small bowel, and lung (22). Hyperinflammation can also lead to hypercoagulability, immunothrombosis through the upregulation of neutrophil extracellular traps, and formation of immune complexes. Patients with Covid-19 frequently display hypercoagulability (23) and an increased rate of thrombus, especially pulmonary embolism, encouraging antithrombotic prophylactic treatment

(24). Cerebral venous thrombosis or stroke with large artery thrombus were also reported (3). In line with these findings, we hypothesize a synergistic effect of *F. necrophorum* and SARS-CoV-2 infections in stroke and venous thrombosis occurrence, and in the severity of the intracranial vasculitis observed in our case.

This coinfection potentiation suggests a different stroke mechanism from those hypothesized in the previously reported pediatric stroke cases associated with SARS-CoV-2. Two children had a FCA presumably associated with SARS-CoV-2 (10, 11), including one with vessel wall enhancement. FCA is a pediatric entity frequently observed during or after viral infection, in which the infection is supposed to act as a trigger of a localized self-limited inflammatory course, usually without notable systemic inflammation. Therefore, one should not be surprised to observe FCA with SARS-CoV-2, as it is observed with varicella, herpesviruses, viral respiratory pathogens, etc. (25). Two children had stroke complicating pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C), a pediatric condition related to uncontrolled inflammatory response and cytokine storm during or following infection with SARS-CoV-2 (8). One had refractory shock and extracorporeal membrane oxygenation (ECMO) support; stroke occurence in the anterior and middle cerebral arteries was probably related to thromboembolic disorders related to ECMO (8). One recent report of a 9-year-old patient with PIMS-TS with aseptic meningitis, stroke, and bilateral internal carotid arteries stenosis suggested SARS-CoV-2 associated vasculitis (12). Our case goes beyond, rather suggesting a runaway of inflammation and hypercoagulation, leading to diffuse and progressive vasculitis, multiple strokes, but also cerebral venous thrombosis. Interestingly, another case may suggest the same mechanism, reporting a 2 year 7-month-old girl with tuberculosis meningitis and Covid-19, complicated by arterial ischemic stroke and cerebral venous thrombosis (26). Tuberculosis meningitis is known to predispose to arterial vasculitis and stroke, but this particularly severe evolution seems similar to our case. These findings emphasize the severity of SARS-CoV-2 coinfection, with a possible mechanism of "super-infection" (27), especially in the setting of a bacterial infection predisposing to cerebrovascular events. Of note, discrimination between causal relationship and incidental comorbidity remains difficult and it is currently unclear whether the infection *per se* represents an independent stroke risk factor (28).

Second, an indirect aggravating role of SARS-Cov-2 might be discussed, related to diagnostic delay. Appropriate therapy, but also timely diagnosis, is crucial in the management of LS (14). In our patient, the ongoing epidemic situation might have played an aggravating role. Retrospectively, at symptom onset the patient was in quarantine at home with his family, as his mother had proven Covid-19 infection. The first probabilistic diagnosis issued by his general practitioner after phone assessment because of headaches and fever was Covid-19; maintaining quarantine was recommended. This might have delayed adapted management and influenced outcome. Facing the pandemic, several countries, notably in Europe and North America, implemented sanitary measures to limit epidemic spreading, including quarantine for patients with Covid-19 and contacts, and temporary lockdown. Although important at a collective level, these measures may hamper adequate individual management. Fear of nosocomial SARS-CoV-2 infection may limit medical facilities attendance. Delayed diagnoses and increased disease severity have already been reported in an adult with LS (29) and in children with various conditions (30). This underlines a specificity of pediatric neurology, in which clinical examination of children with acute symptoms remains of utmost importance, and reminds us about the limits of telemedicine in acute settings.

This case of an adolescent with dramatic LS and concurrent SARS-CoV-2 infection suggests synergistic effects of viral and bacterial infections on inflammation and coagulation activation. It also highlights the limits of collective sanitary measures and their potential influence on individual health. Ongoing studies will help increasing knowledge about SARS-CoV-2 infection pathophysiology and improving patients' management and outcome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MK, FM, C-JR, LD, and CM designed and conceptualized the report, acquired and interpreted patient data, drafted the manuscript for intellectual content, reviewed, and revised the manuscript. IE, PP, and RL acquired and interpreted patient data, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

We thank the patient's parents, the physicians, and nurses involved in the care of this patient. We thank Mrs. Kim Tran Dong for providing editorial assistance.

REFERENCES

1. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* (2020) 77:683–90. doi: 10.1001/jamaneurol.2020.1127
2. Katsanos AH, Palaiodimou L, Zand R, Yaghi S, Kamel H, Navi BB, et al. The impact of SARS-CoV-2 on stroke epidemiology and care: a meta-analysis. *Ann Neurol.* (2021) 89:380–8. doi: 10.1002/ana.25967
3. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med.* (2020) 382:e60. doi: 10.1056/NEJMc2009787
4. Lou M, Yuan D, Liao S, Tong L, Li J. Potential mechanisms of cerebrovascular diseases in COVID-19 patients. *J Neurovirol.* (2021) 27:35-51. doi: 10.1007/s13365-021-00948-2
5. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. *Pediatrics.* (2020) 145:e20200702. doi: 10.1542/peds.2020-0702
6. Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics.* (2020) 145:e20200834. doi: 10.1542/peds.2020-0834
7. Oualha M, Bendavid M, Berteloot L, Corsia A, Lesage F, Vedrenne M, et al. Severe and fatal forms of COVID-19 in children. *Arch Pédiatrie.* (2020) 27:235–8. doi: 10.1016/j.arcped.2020.05.010
8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* (2020) 395:1607–8. doi: 10.1016/S0140-6736(20)31094-1
9. Kaushik S, Ahluwalia N, Gangadharan S, Esperenza M, Murthy R, Ofori-Amanfo G, et al. ECMO support in SARS-CoV2 multisystem inflammatory syndrome in children in a child. *Perfusion.* (2020). doi: 10.1177/0267659120954386. [Epub ahead of print].
10. Mirzaee SMM, Gonçalves FG, Mohammadifard M, Tavakoli SM, Vossough A. Focal cerebral arteriopathy in a pediatric patient with COVID-19. *Radiology.* (2020) 297:E274-5. doi: 10.1148/radiol.2020202197
11. Gulko E, Overby P, Ali S, Mehta H, Al-Mufti F, Gomes W. Vessel wall enhancement and focal cerebral arteriopathy in a pediatric patient with acute infarct and COVID-19 infection. *AJNR Am J Neuroradiol.* (2020) 41:2348-50. doi: 10.3174/ajnr.A6778
12. Tiwari L, Shekhar S, Bansal A, Kumar S. COVID-19 associated arterial ischaemic stroke and multisystem inflammatory syndrome in children: a case report. *Lancet Child Adolesc Health.* (2020) 5:88-90. doi: 10.1016/S2352-4642(20)30314-X
13. Le Monnier A, Jamet A, Carbonnelle E, Barthod G, Moumile K, Lesage F, et al. *Fusobacterium necrophorum* middle ear infections in children and related complications: report of 25 cases and literature review. *Pediatr Infect Dis J.* (2008) 27:613–7. doi: 10.1097/INF.0b013e318169035e
14. Valerio L, Zane F, Sacco C, Granziera S, Nicoletti T, Russo M, et al. Patients with Lemierre syndrome have a high risk of new thromboembolic complications, clinical sequelae and death: an analysis of 712 cases. *J Intern Med.* (2021) 289:325-39. doi: 10.1111/joim.13114
15. Shamriz O, Engelhard D, Temper V, Revel-Vilk S, Benenson S, Brooks R, et al. Infections caused by *Fusobacterium* in children: a 14-year single-center experience. *Infection.* (2015) 43:663–70. doi: 10.1007/s15010-015-0782-x
16. Wu Q, Xing Y, Shi L, Li W, Gao Y, Pan S, et al. Coinfection and other clinical characteristics of COVID-19 in children. *Pediatrics.* (2020) 146:e20200961. doi: 10.1542/peds.2020-0961
17. Mannheim J, Gretsch S, Layden JE, Fricchione MJ. Characteristics of hospitalized pediatric coronavirus disease 2019 cases in Chicago, Illinois, March–April 2020. *J Pediatr Infect Dis Soc.* (2020) 9:519-22. doi: 10.1093/jpids/piaa070
18. Mirzaei R, Goodarzi P, Asadi M, Soltani A, Aljanabi H ali abraham, Jeda AS, et al. Bacterial co-infections with SARS-CoV-2. *Iubmb Life.* (2020) 72:2097-111. doi: 10.1002/iub.2356
19. Kumar A, Menon S, Nagaraja TG, Narayanan S. Identification of an outer membrane protein of *Fusobacterium necrophorum* subsp. necrophorum that binds with high affinity to bovine endothelial cells. *Vet Microbiol.* (2015) 176:196–201. doi: 10.1016/j.vetmic.2014.12.015
20. Forrester LJ, Campbell BJ, Berg JN, Barrett JT. Aggregation of platelets by *Fusobacterium necrophorum*. *J Clin Microbiol.* (1985) 22:245–9. doi: 10.1128/JCM.22.2.245-249.1985
21. Kakarla V, Kaneko N, Nour M, Khatibi K, Elahi F, Liebeskind DS, et al. Pathophysiologic mechanisms of cerebral endotheliopathy and stroke due to SARS-CoV-2. *J Cereb Blood Flow Metab.* (2021). doi: 10.1177/0271678X20985666. [Epub ahead of print].
22. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* (2020) 395:1417–8. doi: 10.1016/S0140-6736(20)30937-5
23. Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. *Thromb Haemost.* (2020) 120:998–1000. doi: 10.1055/s-0040-1710018
24. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood.* (2020) 135:2033–40. doi: 10.1182/blood.2020006000
25. Fullerton HJ, Hills NK, Elkind MSV, Dowling MM, Wintermark M, Glaser CA, et al. Infection, vaccination, and childhood arterial ischemic stroke. *Neurology.* (2015) 85:1459–66. doi: 10.1212/WNL.0000000000002065
26. Essajee F, Solomons R, Goussard P, Van Toorn R. Child with tuberculous meningitis and COVID-19 coinfection complicated by extensive cerebral sinus venous thrombosis. *BMJ Case Rep.* (2020) 13:e238597. doi: 10.1136/bcr-2020-238597
27. Bengoechea JA, Bamford CGG. SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19? *EMBO Mol Med.* (2020) 12: e12560. doi: 10.15252/emmm.202012560
28. Tsivgoulis G, Palaiodimou L, Zand R, Lioutas VA, Krogias C, Katsanos AH, et al. COVID-19 and cerebrovascular diseases: a comprehensive overview. *Ther Adv Neurol Disord.* (2020) 13. doi: 10.1177/1756286420978004. [Epub ahead of print].
29. Howley F, O'Doherty L, McEniff N, O'Riordan R. Late presentation of 'Lemierre's syndrome': how a delay in seeking healthcare and reduced access to routine services resulted in widely disseminated *Fusobacterium necrophorum* infection during the global COVID-19 pandemic. *BMJ Case Rep.* (2020) 13:e239269. doi: 10.1136/bcr-2020-239269
30. Lazzerini M, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision of care in Italy resulting from fear of COVID-19. *Lancet Child Adolesc Health.* (2020) 4:e10–1. doi: 10.1016/S2352-4642(20)30108-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 09 April 2021
doi: 10.3389/fneur.2021.642912

Prolonged Intubation in Patients With Prior Cerebrovascular Disease and COVID-19

Shibani S. Mukerji[1,2†], Sudeshna Das[1,2†], Haitham Alabsi[1,2,3†], Laura N. Brenner[2,4], Aayushee Jain[1,5], Colin Magdamo[1], Sarah I. Collens[1], Elissa Ye[5], Kiana Keller[1], Christine L. Boutros[1], Michael J. Leone[5], Amy Newhouse[2,6,7], Brody Foy[8,9], Matthew D. Li[10,11], Min Lang[10], Melis N. Anahtar[8], Yu-Ping Shao[5], Wendong Ge[5], Haoqi Sun[1,2,5], Virginia A. Triant[2,6,12,13], Jayashree Kalpathy-Cramer[10,11], John Higgins[8,9], Jonathan Rosand[1,2,3], Gregory K. Robbins[2,12‡] and M. Brandon Westover[1,2,3,5‡]*

[1] Department of Neurology, Massachusetts General Hospital, Boston, MA, United States, [2] Harvard Medical School, Boston, MA, United States, [3] Henry and Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston, MA, United States, [4] Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, MA, United States, [5] Clinical Data A.I. Center (CDAC), Massachusetts General Hospital, Boston, MA, United States, [6] Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, United States, [7] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, United States, [8] Department of Pathology, Massachusetts General Hospital, Boston, MA, United States, [9] Department of Systems Biology, Harvard Medical School, Boston, MA, United States, [10] Department of Radiology, Massachusetts General Hospital, Boston, MA, United States, [11] Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA, United States, [12] Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, United States, [13] The Mongan Institute, Massachusetts General Hospital, Boston, MA, United States

Objectives: Patients with comorbidities are at increased risk for poor outcomes in COVID-19, yet data on patients with prior neurological disease remains limited. Our objective was to determine the odds of critical illness and duration of mechanical ventilation in patients with prior cerebrovascular disease and COVID-19.

Methods: A observational study of 1,128 consecutive adult patients admitted to an academic center in Boston, Massachusetts, and diagnosed with laboratory-confirmed COVID-19. We tested the association between prior cerebrovascular disease and critical illness, defined as mechanical ventilation (MV) or death by day 28, using logistic regression with inverse probability weighting of the propensity score. Among intubated patients, we estimated the cumulative incidence of successful extubation without death over 45 days using competing risk analysis.

Results: Of the 1,128 adults with COVID-19, 350 (36%) were critically ill by day 28. The median age of patients was 59 years (SD: 18 years) and 640 (57%) were men. As of June 2nd, 2020, 127 (11%) patients had died. A total of 177 patients (16%) had a prior cerebrovascular disease. Prior cerebrovascular disease was significantly associated with critical illness (OR = 1.54, 95% CI = 1.14–2.07), lower rate of successful extubation (cause-specific HR = 0.57, 95% CI = 0.33–0.98), and increased duration of intubation (restricted mean time difference = 4.02 days, 95% CI = 0.34–10.92) compared to patients without cerebrovascular disease.

OPEN ACCESS

Edited by:
Giovanni Assenza,
Campus Bio-Medico University, Italy

Reviewed by:
Minjee Kim,
Northwestern University, United States
Jacopo Lanzone,
Policlinico Universitario Campus Bio-Medico, Italy
Francesco Motolese,
Campus Bio-Medico University, Italy

***Correspondence:**
M. Brandon Westover
mwestover@mgh.harvard.edu

† These authors have contributed equally to this work and share first authorship

‡ These authors have contributed equally to this work and share last authorship

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care,
a section of the journal Frontiers in Neurology

Received: 17 December 2020
Accepted: 05 March 2021
Published: 09 April 2021

Citation:
Mukerji SS, Das S, Alabsi H, Brenner LN, Jain A, Magdamo C, Collens SI, Ye E, Keller K, Boutros CL, Leone MJ, Newhouse A, Foy B, Li MD, Lang M, Anahtar MN, Shao Y-P, Ge W, Sun H, Triant VA, Kalpathy-Cramer J, Higgins J, Rosand J, Robbins GK and Westover MB (2021) Prolonged Intubation in Patients With Prior Cerebrovascular Disease and COVID-19. Front. Neurol. 12:642912. doi: 10.3389/fneur.2021.642912

Interpretation: Prior cerebrovascular disease adversely affects COVID-19 outcomes in hospitalized patients. Further study is required to determine if this subpopulation requires closer monitoring for disease progression during COVID-19.

Keywords: cerebrovascular disease, COVID-19, respiratory failure, stroke, history of neurological disease, intubation, critical illness, outcomes

INTRODUCTION

Disease outcomes associated with the novel coronavirus 2019 (COVID-19) are heterogeneous and include asymptomatic disease, mild respiratory tract illness, severe pneumonia with respiratory failure and acute respiratory distress syndrome, and death (1). It is estimated that one in four patients infected with SARS-CoV-2 requires supplemental oxygen or invasive mechanical ventilation (1–5). To date, survival has been correlated with multiple factors including age, medical comorbidities, and host response to the virus that may lead to multiorgan dysfunction, coagulopathy, and elevated inflammatory markers (1, 4–7).

The prevalence of hospitalized patients with neurological comorbidities COVID-19 widely varies between 1 and 12% depending on the cohort and comorbidities studied (8–15). Our understanding of the risk of COVID-19 critical illness due to chronic neurological conditions remains limited, with cohorts from Asia and Europe suggesting a history of ischemic or hemorrhagic stroke as risk factors for severe events such as mechanical ventilation (MV) (8) and death (8, 10). Recently, two meta-analyses reviewed the relationship between the prior cerebrovascular disease and in-hospital outcomes in COVID-19, using data derived from Chinese and European cohorts, and suggested an increase in risk for critical illness (16) and mortality (17) among patients with prior cerebrovascular disease.

Studies prior to the pandemic suggest that patients with neurological comorbidities are at increased risk for critical illness compared to similarly matched older patients (18, 19). Cerebrovascular comorbidities are common among older adults in the United States (U.S.) where an estimated 3% of adults have had a prior ischemic stroke (7.8 million) (20). A recent study from a U.S. cohort of 3,248 patients suggested an increased odds of in-hospital death among individuals with stroke and COVID-19, however, detailed data on other in-hospital adverse outcomes is largely unknown (21). Given that prior cerebrovascular disease is one of the most common neurological comorbidities in hospitalized patients with COVID-19, information regarding severe outcomes in this population would be valuable for prioritizing prevention strategies in the outpatient neurology setting, providing prognostic information for patients and families, and assisting hospital projections as countries experience increasing numbers of SARS-CoV-2 infections.

In this study, we examined the relationship between prior cerebrovascular diseases and critical illness in the first 28 days of admission and determined the likelihood of successful extubation over a 45-day in-hospital follow-up among adults with positive SARS-CoV-2 RNA admitted to an academic hospital in Boston, Massachusetts, during the first 2 months of the city's outbreak. We hypothesized that prior cerebrovascular disease was a risk factor for critical illness in COVID-19 and a comorbidity associated with increased duration of mechanical ventilation (MV).

METHODS

Study Setting and Population

This is an observational study of 1,128 consecutive patients with laboratory-confirmed SARS-CoV-2 infection hospitalized at Massachusetts General Hospital (MGH), a single-center tertiary care facility in Boston, MA. Laboratory confirmation of SARS-CoV-2 infection was obtained using real-time reverse transcription-polymerase chain reaction assays with Food and Drug Administration emergency use authorization. We identified 1,216 patients seen in the Emergency Department (ED) or hospitalized between March 1st and May 5th, 2020, given that the first reported case of SARS-CoV-2 infection in Boston was March 2nd, 2020 (**Figure 1**). Patients < 18 years old and patients classified as being seen in the ED using electronic data collection but were seen in outpatient clinics after manual review of cases were excluded from analyses. The institutional review board approved this study (Protocol #: 2013P001024) with a waiver of consent for retrospective analyses.

Data Collection

Engineers from the MGH Clinical Data AI Center extracted COVID-19-related data from the Partners Healthcare Systems Enterprise Data Warehouse, which comprises electronic medical record data from the Mass General Brigham network (formerly Partners Healthcare). Data queried for this study included demographics, admission, discharge, intubation and extubation events, diagnosis and International Classification of Diseases, Tenth Revision, Clinical Modification codes (ICD-10-CM), vital signs, laboratory values within 48 h of admission, and other data. Diagnostic categories were created by grouping ICD-10-CM diagnosis codes using a combination of groupings by SNOMED CT, an ontology-based terminology owned and maintained by the standards development organization SNOMED International and licensed through the National Library of Medicine. Four clinicians performed a manual chart review of identified cases of prior cerebrovascular disease up to 7 days before COVID-19 hospital admission (HA, SM, LB, and AN); a new diagnosis of cerebrovascular disease was recorded if the event occurred within 7 days prior to or after a positive SARS-CoV-2 PCR result.

Of the patients with COVID-19 included in this study, 289 underwent diagnostic neuroimaging after admission (computed tomography or magnetic resonance imaging of the brain), with 484 unique studies performed during the study period. Two radiologists (MDL and MLa) identified evidence of prior

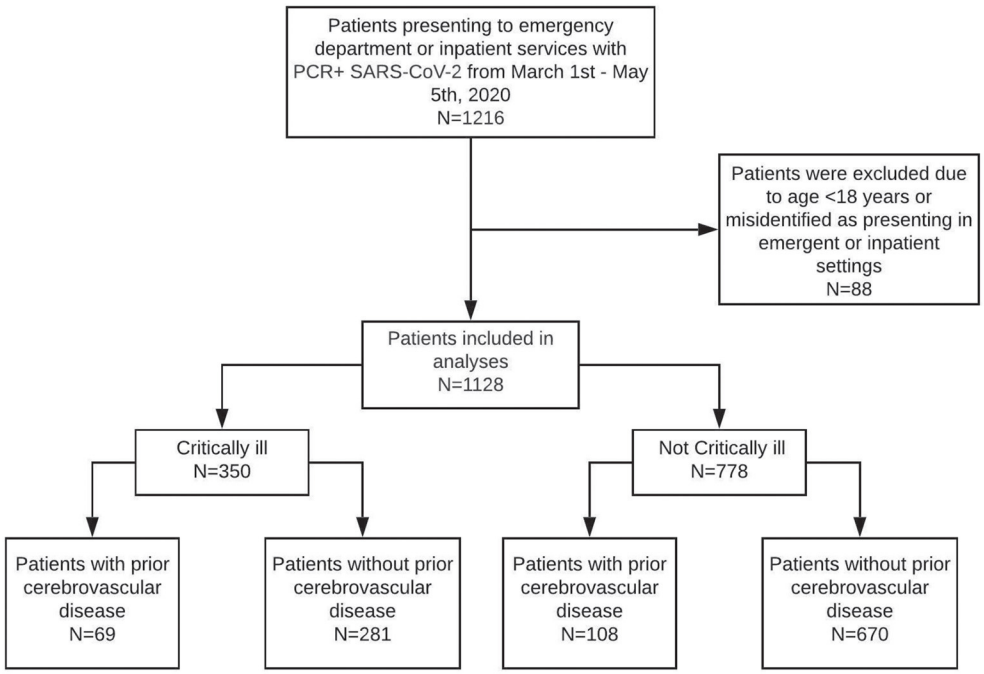


FIGURE 1 | Cohort diagram.

intracerebral pathology by reviewing neuroradiographic reports and categorizing intracranial pathology into seven clinical findings: acute or subacute ischemic infarct, chronic ischemic infarct, acute or subacute intracranial hemorrhage, chronic intracranial hemorrhage, post-surgical change (limited to any intracranial surgery), intracranial mass (metastases or primary malignancies), and traumatic brain injury. These measures were used to provide ancillary information on cerebrovascular disease history in addition to ICD-10-CM codes; all positive imaging data not identified using ICD-10-CM codes were manually reviewed to confirm the clinical suspicion of diagnosis (HA and SM), and added 14/289 additional cases.

The date of intubation was obtained using ventilator flowsheets, marking positive end-expiratory pressure (PEEP), and FiO2. Date of extubation was flagged if there were no PEEP and FiO2 readings after 48 h of continuous intubation markings on ventilator flowsheets. Two critical care physicians (HA and LB) manually confirmed intubation in all cases and extubation status and date in 83% of cases ($n = 243/294$). Death and death date was extracted from the EHR. All patients with a date of death were manually reviewed by study team members (AN, LB, SC, and KK) to determine if they transitioned to comfort-measures-only (CMO) and if so, date of transition was recorded.

Exposure and Outcome Measures

The binary variable for cerebrovascular history included at least one diagnosis of ischemic stroke, intracerebral hemorrhage (ICH), venous sinus thrombosis (VST), subarachnoid hemorrhage (SAH), or subdural hemorrhage (SDH) recorded at least 7 days prior to admission. A composite outcome, critical illness (not to be confused with critical illness myopathy), was defined as invasive MV or death within 28 days of admission (4), and used for the primary analysis. A secondary outcome was the probability of successful extubation, defined as liberation from mechanical ventilation irrespective of the mode of ventilation delivery (i.e., endotracheal or tracheostomy tube). Follow-up time was right-censored on June 20th, 2020, to allow 45 days of observation for intubated patients given long-durations of intubation in COVID-19 patients. All positive prior neurological diagnoses and outcomes were confirmed manually by chart review (HB, SM, AN, LB, SC, and KK).

Statistical Analysis

Continuous and categorical variables were presented as median [interquartile range, (IQR)] and n (%), respectively. Mann-Whitney U tests, χ^2 tests, or Fisher's exact tests were used to compare differences between critical and non-critical patients where appropriate.

The control for confounding was done using inverse probability weighting (IPW) method. The propensity scores for cerebrovascular disease were estimated with a multivariable logistic regression model that included age, sex, Latinx ethnicity, and Black or African American race. The predicted probabilities from this propensity-score model were used to calculate the stabilized IPW scores (22). Logistic regression models using IPW are reported, and models estimated odds ratios (OR) [95% confidence intervals (CI)] for the association between history of cerebrovascular disease and critical illness by day 28. In sensitivity analyses, a matching strategy was used to match patients with and without cerebrovascular disease in a 1:2 ratio by age, sex, Latinx, and Black or African American race. The smallest average absolute distance was used to match across all pairs (R 4.0.0 MatchIt package).

We examined the effect of cerebrovascular disease history on the duration of intubation, with death as a competing event. Time was measured in days from intubation to successful extubation or death (two mutually exclusive events) and censored at 45 days if no event was observed. If a patient was extubated and died during the observation period, the event recorded was death. We estimated the cause-specific hazard of transitioning from intubation to successful extubation and calculated the hazard ratio (HR) for patients with cerebrovascular history compared to those without using a propensity score weighted Cox proportional hazards model. The cumulative incidence curves (CICs) for extubation and death were computed using the R package *causalCmprsk* with both Cox PH and Aalen-Johansen's non-parametric estimators (23, 24). Propensity score weights were used for generating the CIC curves to account for confounding by age and sex. We estimated exposure effect as the restricted mean time difference, which is the area under the CIC curve and provides a more clinically meaningful measure than HR (25).

RESULTS

Clinical Characteristics of Patients Admitted With COVID-19

A total of 1,128 adult patients were seen in the emergency department or admitted between March 10th and May 5th, 2020, with laboratory-confirmed SARS-CoV-2 RNA infection (**Figure 1**). The median age of patients was 59 years old (IQR 45–73; range 18–103), 640 (57%) were men, and 401 (36%) were Latinx ethnicity. Chronic medical illnesses were common with 362 (32%) diagnosed with hypertension, 208 (18%) with diabetes, 113 (10%) with renal disease, and 115 (10%) with heart failure (**Table 1**).

By day 28 of admission, 350 patients (31%) became critically ill, including 127 (11%) who died (**Table 1**). Most patients were intubated within 24 h of admission (median 0 days, IQR 0–3 days). The median time to death among those hospitalized was 9.5 days (IQR 4–17), and most deaths occurred in patients over 70 years old, and 28% (35/127) were transitioned to comfort measures only (CMO) within 48 h of admission (**Figure 2A**). Mortality among those intubated was 24% (70/293). Across ethnic and racial groups, critical illness occurred in 44 of 137 (32%) Black or African American patients, 147 of 467 (31%) white patients, and 110 of 401 (27%) patients of Latinx ethnicity.

Odds of Critical Illness in Patients With Prior Cerebrovascular Disease

A history of ischemic stroke ($n = 112$; 9.9%), ICH ($n = 22$; 2.0%), or SDH ($n = 60$; 5.3%) was frequent among COVID-19 patients with a total of 177 (16%) patients having at least one prior cerebrovascular disease diagnosis. Patients with a prior cerebrovascular disease were more likely to be critically ill compared to non-critically ill individuals [69/350 (20%) vs. 108/778 (14%), $p = 0.02$].

Compared to patients without a cerebrovascular history, individuals with a prior cerebrovascular were older [median 74 [63, 82] vs. 56 [43, 69], $p < 0.001$], more likely to have a history of current use tobacco [71/177 (40%) vs. 243/951 (26%), $p < 0.001$], and more likely to have a higher burden of medical comorbidities as measured by Charlson Comorbidity Index ≥ 3 [87/177 (49%) vs. 172/951 (18%), $p < 0.001$]. A high proportion of patients with cerebrovascular disease ages 50–69 years old died (**Figures 2B,C**), and across all ages, in-hospital 28-day mortality was higher between patients with vs. without cerebrovascular disease [37/177 (20.9%) vs. 90/951 (9.5%), $p < 0.001$]. The proportion of patients mechanically ventilated or who died, stratified by history of cerebrovascular disease subtype, are detailed in **Supplementary Table 1**. A total of 39/1,128 (3.5%) patients had a new cerebrovascular event after their COVID-19 diagnosis (7 patients had two or more events), of which 22/39 (56%) had a past history of cerebrovascular disease.

Given prior reports of abnormal inflammatory and thromboembolic indices in patients with a history of ischemic stroke (8), common laboratory markers tested in COVID-19 were assessed on admission. Patients with cerebrovascular disease had higher admission median levels of D-dimer, troponin ($p < 0.001$ for both) and prothrombin time ($p < 0.01$), but minimally lower levels of inflammatory markers such as CRP [63.90 [23.50, 133.30] vs. 75.15 [36.2, 146.1], $p < 0.01$] and ferritin [442 [193.0, 872.0] vs. 547 [286.3, 1051.3], $p < 0.01$] compared to patients without cerebrovascular disease (**Table 2**). While there were no statistical differences in absolute lymphocyte counts ($p = 0.3$) or platelet levels ($p = 0.06$), patients with cerebrovascular disease had slightly higher red cell distribution widths (RDW) [14.10 [13.00, 15.33] vs. 13.20 [12.60, 14.10], $p < 0.001$], a measure associated with all-cause mortality (26, 27).

In unadjusted analyses, the odds of critical illness were higher in patients with cardiovascular disease compared to patients without cerebrovascular disease [OR 1.5; 95% CI [1.09–2.12]]. In multivariable analyses with IPW according to the propensity score, cerebrovascular disease remained independently associated with critical illness [adjusted OR 1.54, 95% CI [1.14–2.07]] (**Table 3**). A subsequent sensitivity analysis that used a 2:1 matching ratio (no cerebrovascular disease: cerebrovascular disease) yielded similar results [OR 1.58, 95% CI [1.08–2.36]].

Cumulative Incidence of Successful Extubation in Patients With Cerebrovascular Disease

To further understand the relationship between prior cerebrovascular disease and COVID19 severe outcomes, we used a competing risk analysis framework to determine the relationship between cerebrovascular disease and duration of intubation without subsequent death. The cumulative incidence of successful extubation without death in patients with cerebrovascular disease was lower compared to those without cerebrovascular history (**Figure 3**), and there was a significant association between prior cerebrovascular disease and likelihood of successful extubation (adjusted cause-specific HR, 0.57; 95% CI, 0.33–0.98). Over a 45-day observation window, patients with cerebrovascular disease had a longer intubation time with a restricted mean time difference of

TABLE 1 | Baseline characteristics of patients hospitalized with COVID-19.

	Overall (n = 1,128)	Critically Ill (n = 350)	Not Critically Ill (n = 778)	*P*-value, Critically ill vs. Not Critically Ill
DEMOGRAPHICS, *N (%)*				
Age, median [IQR]	59 [45, 73]	65.00 [53, 77]	56.00 [42, 70]	<0.001*
18–29	59 (5.2)	7 (2.0)	52 (6.7)	
30–39	125 (11.1)	22 (6.3)	103 (13.2)	
40–49	168 (14.9)	42 (12.0)	126 (16.2)	
50–59	227 (20.1)	63 (8/0)	164 (21.1)	
60–69	207 (18.4)	76 (21.7)	131 (16.8)	
70–79	177 (15.7)	72 (20.6)	105 (13.5)	
80–89	129 (11.4)	55 (15.7)	74 (9.5)	
≥ 90	36 (3.2)	13 (3.7)	23 (3.0)	
Sex				0.003*
Female	488 (43.3)	128 (36.6)	360 (46.3)	
Male	640 (56.7)	222 (63.4)	418 (53.7)	
Race				
African American or Black	137 (12.1)	44 (12.6)	93 (12.0)	0.845
Asian	41 (3.6)	13 (3.7)	28 (3.6)	1.000
White	467 (41.4)	147 (42.0)	320 (41.1)	0.835
Latinx Ethnicity	401 (35.5)	110 (31.4)	291 (37.4)	0.008*
Tobacco Use				<0.001*
Never	645 (57.2)	168 (48.0)	477 (61.3)	
Former	218 (19.3)	81 (23.1)	137 (17.6)	
Present	96 (8.5)	25 (7.1)	71 (9.1)	
Not asked	45 (4.0)	10 (2.9)	35 (4.5)	
MEDICAL COMORBIDITIES, *N (%)*				
Charlson Comorbidity Index Score, mean (SD)	1.53 (2.24)	1.83 (2.47)	1.39 (2.12)	0.002*
0 comorbidities	562 (49.8)	157 (44.9)	405 (52.1)	
1–2 comorbidities	307 (27.2)	93 (26.6)	214 (27.5)	
≥ 3 comorbidities	259 (23.0)	100 (28.6)	159 (20.4)	0.008*
Hypertension	362 (32.1)	121 (34.6)	241 (31.0)	0.260
Diabetes	204 (18.1)	72 (20.6)	132 (17.0)	0.170
Myocardial infarction	33 (2.9)	14 (4.0)	19 (2.4)	0.213
Congestive heart failure	115 (10.2)	46 (13.1)	69 (8.9)	0.037*
Chronic obstructive pulmonary disease	154 (13.7)	49 (14.0)	103 (13.5)	0.893
Renal disease	113 (10.0)	52 (14.9)	61 (7.8)	<0.001*
Peripheral vascular disease	87 (7.7)	41 (11.7)	46 (5.9)	0.001*
Body Mass Index, median [IQR]	28.8 [25.3, 33.3]	28.9 [25.3, 34.1]	28.8 [25.2, 32.9]	0.450
NEUROLOGIC COMORBIDITIES, *N (%)*				
Cerebrovascular comorbidities	177 (15.7)	69 (19.7)	108 (13.9)	0.016*
Acute Ischemic Stroke	112 (9.9)	49 (14.0)	63 (8.1)	0.016*
Venous Sinus Thrombosis	4 (0.4)	3 (0.9)	1 (0.1)	0.173
Subarachnoid Hemorrhage	5 (0.4)	3 (0.9)	2 (0.3)	0.358
Subdural Hemorrhage	60 (5.3)	18 (5.1)	42 (5.4)	0.973
Intracerebral Hemorrhage	22 (2.0)	11 (3.1)	11 (1.4)	0.087
Other neurological comorbidities				
Dementia	39 (3.5)	15 (4.3)	24 (3.1)	0.398
Movement disorder	28 (2.5)	10 (2.9)	18 (2.3)	0.737
Neuromuscular disorder	56 (5.0)	22 (6.3)	34 (4.4)	0.222
Seizure history	25 (2.2)	6 (1.7)	19 (2.4)	0.583
Brain tumor	8 (0.7)	1 (0.3)	7 (0.9)	0.451

**indicates a $p < 0.05$. Charlson Comorbidity Index Score includes acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatoid disease, peptic ulcer disease, liver disease, diabetes with and without complications, hemiplegia or paraplegia, renal disease, cancer, metastatic solid tumor, and HIV/AIDS.*

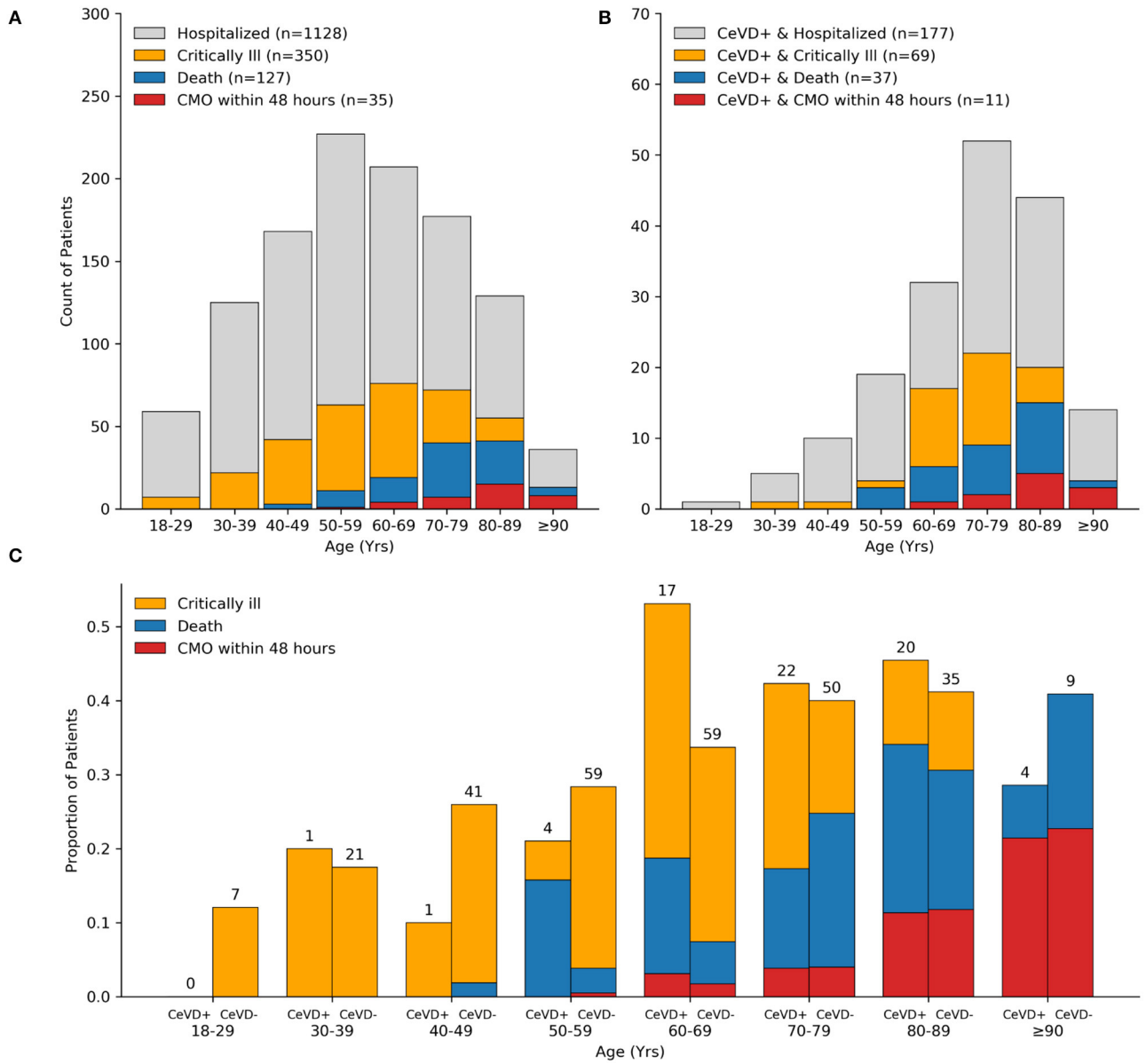


FIGURE 2 | Distribution of COVID-19 severe outcomes by cerebrovascular disease history. Bar plots showing counts of all hospitalized patients **(A)** and cerebrovascular disease subset **(B)** with the indicated COVID-19 outcome stratified by decade of life. The majority of critically ill patients over age 70 years and 100% of patients age 90 years old or older died within 28 days of admission. Age distribution of patients with cerebrovascular disease and COVID-19 was left-skewed compared to the total cohort. Bar plots showing the proportion of critically ill patients who died stratified by cerebrovascular disease status and decade of life. Counts (top of bars) show the number of critically ill patients in respective age groups and cerebrovascular disease status **(C)**. CeVD, cerebrovascular disease; CMO, comfort measures only.

4.02 days [0.34, 9.32] added time on mechanical ventilation compared to patients without cerebrovascular disease using a Cox-PH model. The time difference was modeled using non-parametric cumulative incidence functions in sensitivity analyses and showed an additional 5.65 days [2.40, 10.85] of intubation time in patients with cerebrovascular disease. There were no differences in cause-specific HR for death between patients with and without cerebrovascular history after adjustments.

DISCUSSION

In this observational study, we present one of the largest analyses with extended follow-up among US hospitalized patients with prior cerebrovascular disease and COVID-19. Of the 1,128 hospitalized patients, 16% (177/1,128) had at least one diagnosis of cerebrovascular disease prior to COVID-19, and odds of critical illness in this subpopulation were 1.5-times higher compared to those without cerebrovascular disease. Additionally,

TABLE 2 | Lab values of patients with COVID-19 stratified by cerebrovascular disease.

Lab values [median [IQR]]	Cerebrovascular History (n = 177)	No Cerebrovascular History (n = 951)	P-value
CBC			
WBC	6.64 [4.95, 9.04]	6.50 [5.05, 8.65]	0.856
ALYMPH	0.96 [0.67, 1.41]	1.00 [0.69, 1.39]	0.310
ANEUT	4.67 [2.98, 6.65]	4.87 [3.45, 6.79]	0.458
HGB	12.45 [10.90, 13.70]	13.40 [12.20, 14.60]	<0.001*
RDW	14.10 [13.00, 15.33]	13.20 [12.60, 14.10]	<0.001*
PLT	189.50 [148.75, 252.25]	204.00 [158.00, 259.75]	0.063
INFLAMMATORY			
D-DIMER	1292.00 [773.00, 2243.50]	968.00 [619.50, 1635.00]	<0.001*
FERRITIN	442.00 [193.00, 872.00]	547.00 [286.25, 1051.25]	0.008*
IL-6	18.40 [7.80, 55.50]	21.00 [10.50, 40.15]	0.633
CRP	63.90 [23.50, 133.30]	75.15 [36.20, 146.10]	0.005*
ESR	39.00 [22.00, 67.00]	39.00 [23.00, 60.00]	0.484
LDH	284.00 [226.00, 373.00]	318.00 [245.00, 424.00]	0.002*
COAGULATION FACTORS			
PT	14.30 [13.50, 15.50]	13.70 [13.20, 14.53]	<0.001*
PT.INR	1.10 [1.00, 1.20]	1.10 [1.00, 1.20]	<0.001*
PTT	35.90 [32.25, 40.70]	34.10 [31.00, 38.80]	0.008*
CHEMISTRY			
AST	37.00 [23.75, 51.25]	39.00 [27.00, 59.00]	<0.001*
ALT	22.00 [15.00, 36.00]	30.00 [19.00, 51.00]	<0.001*
BILI, TOTAL	0.40 [0.30, 0.62]	0.45 [0.30, 0.60]	0.040*
CREATININE	1.06 [0.83, 1.71]	0.89 [0.74, 1.10]	<0.001*
eGFR	59.00 [32.00, 81.00]	85.00 [61.25, 101.00]	<0.001*
LDH	284.00 [226.00, 373.00]	318.00 [245.00, 424.00]	0.002*
METABOLIC			
TOTAL CHOL	130.00 [106.00, 159.00]	131.00 [109.00, 151.00]	0.682
HBA1C	6.50 [6.00, 8.00]	6.50 [5.90, 8.20]	0.731

**indicates a $p < 0.05$. WBC, White Blood Cell; Alymph, Lymphocyte count; ANEUT, Neutrophil count; HGB, Hemoglobin; RDW, Red blood cell distribution; PLT, Platelet; IL-6, Interleukin-6; C.P.R., C-reactive protein; ESR, Erythrocyte sedimentation rate; LSH, Lactic acid dehydrogenase; PT, Prothrombin Time; INR, International normalized ratio; PTT, Partial thromboplastin time; AST, Aspartate transaminase; ALT, Alanine Transaminase; BILI, Bilirubin; eGFR, eGFR glomerular filtration rate; HBA1C, Hemoglobin A1c.*

these data show that patients with cerebrovascular disease were less likely to achieve successful extubation and estimated to be ventilated for 4–5 days longer than patients without a prior cerebrovascular disease. Given that available data on cerebrovascular disease comorbidity and in-hospital outcomes are limited, we anticipate these findings to be relevant for outpatient prevention strategies and prognostic discussions with patients and families, especially as countries experience resurges of SARS-CoV-2 infections.

In this cohort, the majority of patients with a prior cerebrovascular disease had a prior acute ischemic stroke (9.9%; 11/1,128), a prevalence which was higher than expected from U.S. 2013–2016 stroke estimates of 2.5% for adults ages > 20 years old (14). These results are consistent with published cohorts suggesting a greater number of hospitalized COVID-19 patients with cerebrovascular disease than prevalence estimates and increased likelihood of negative outcomes (4, 8, 10–13, 16, 17, 21, 28–31). The findings presented here extends our understanding of comorbidities that may contribute to increased risk of critical illness in COVID-19, and additionally suggests that critically ill COVID-19 patients with cerebrovascular disease may be prone to longer mechanical ventilation time than patients of similar ages and demographics without cerebrovascular disease. It is possible that patients with prior history of cerebrovascular disease are vulnerable to prolonged ventilation in COVID-19 given a propensity for lower levels of premorbid function, increased probability of cerebrovascular events after diagnosis or increased risk of frailty, a clinical state which is a strong predictor of adverse health effects including hospitalization, disability, and mortality (32). Recent data also suggests that COVID-19 patients with delirium are more likely to have longer duration of intubation (33). Given that predictors of delirium include medical comorbidities such as cerebrovascular disease, it may be challenging to distinguish which factors predominate in conferring risk of longer intubation times and requires large scale studies. Irrespective of cause, the impact of longer duration of intubation can be extrapolated

TABLE 3 | Associations between cerebrovascular disease history and critical illness.

Number of events/number of patients at risk (%)	
Prior cerebrovascular disease	69/177 (39.9%)
No prior cerebrovascular disease	281/951 (29.5%)
	Odds of critical illness: OR [95% CI], *P*-value
Unadjusted	1.52 [1.09–2.12], 0.01
IPW adjusted[α]	1.54 [1.14–2.07], < 0.01
2:1 PS matched[β]	1.58 [1.08–2.36], 0.02

[α]*the odds ratio was calculated for age, sex, Latinx ethnicity, and Black or White race using an inverse propensity-score weighted IPW logistic regression analysis. The analysis included all 1,128 patients.*

[β]*sensitivity analyses calculating the odds ratio from 2:1 propensity score (PS) matched cohort. Analyses include 531 cases without cerebrovascular disease history and 177 cases with cerebrovascular disease.*

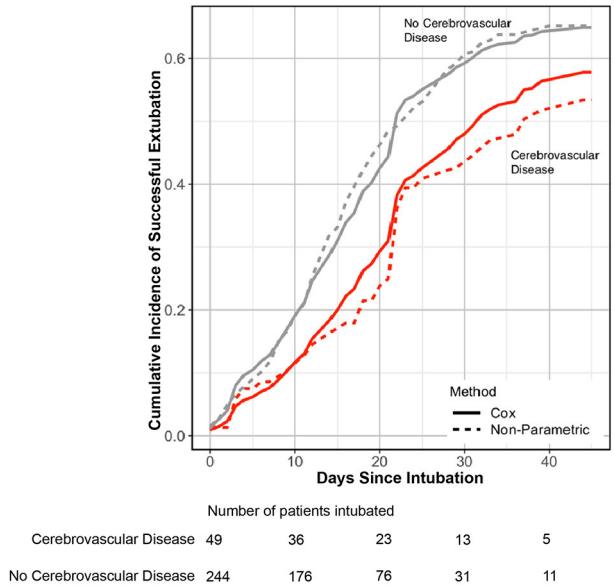


FIGURE 3 | Incidence of successful extubation over 45-days of in-hospital observation. Cox proportional (line) and non-parametric (dashed line) estimation of cumulative incidence of transitioning from intubation to extubation without death in patients with cerebrovascular disease (red) and no cerebrovascular disease history (gray). Patients with cerebrovascular disease had lower cumulative incidence of successful extubation without death over a 45-day observation window [adjusted cause-specific HR 0.57 [95% CI 0.33–0.98]]. The number of patients intubated is shown on the bottom stratified by presence or absence of cerebrovascular disease. CI, Confidence interval; HR, Hazard ratio.

from other critical care studies prior to the COVID-19 pandemic, which show that increased ventilation times are associated with a greater need for sedation and analgesics and higher rates of ventilator-associated pneumonia, line infections, urinary tract infections, delirium, ileus, and decubitus ulcers (34–36). Further, additional days on ventilators are likely to lead to greater rehabilitation needs, reduced cognitive function, and could be uniquely detrimental for patients with prior neurological deficits and their family members (37, 38).

A prior study suggested that patients with cerebrovascular disease may have more aggressive inflammatory responses on admission for COVID-19 (8). While our data did not show increases in CRP or ferritin or evidence of lymphopenia among patients with a prior cerebrovascular disease, they had higher levels of D-dimer and troponin levels, consistent with a prior study of stroke patients (8). Additionally, admission RDW was elevated in patients with cerebrovascular disease in this study. Elevated RDW has been shown to be a marker of all-cause mortality, a predictor of complicated hospitalizations that included the need for MV from infectious causes such as influenza (26, 39). and recent data suggests an association with increased mortality risk in COVID-19 (40). Given that COVID-19 is associated with diffuse coagulopathy and thrombotic events (41–43). further study is required to determine if COVID-19 infection exacerbates vascular pathology present in patients with cerebrovascular disease and if this subpopulation requires closer diagnostic monitoring for coagulopathy and disease progression during COVID-19.

Our work has several limitations worth noting. It is a single-center observational study and relies on the EHR, which may not capture full medical histories; thus, some misclassification of prior medical diagnosis is possible. To minimize misclassification bias, our group manually validated data relying on expertise from clinicians in multiple disciplines. We allowed for ancillary data regarding history of cerebrovascular disease based on radiographic imaging data to be introduced, and while we added only a small fraction of patients to the overall cohort with history of cerebrovascular disease (14 patients), this may have led to residual confounding. Data on premorbid level of functioning and details of prior lung function were unavailable and could impact the likelihood of successful extubation; neither could be adjusted for in our analyses. Long-term follow-up that includes cognitive assessments for patients with prior cerebrovascular disease will be critical to understand the longitudinal impact of COVID-19 in this subgroup. Finally, we used SARS-CoV-2 RT-PCR positive results as an indicator of COVID-19 disease, however, PCR results may be an incidental finding in some cases. At the time of admission for this cohort, asymptomatic patients were not routinely tested using SARS-COV-2 RT-PCR, and the majority of cases presented were clinically considered as having COVID-19.

In summary, our findings show that patients with cerebrovascular disease and COVID-19 have higher odds of critical illness, and a lower incidence of successful extubations. This subpopulation is estimated to have longer mechanical ventilation times compared to patients of similar ages without cerebrovascular disease. In aggregate, these data suggest there are important opportunities for proactive outpatient neurological care and open discussion regarding vaccine allocation priorities and

for the management and expectations of duration of mechanical ventilation and critical disease in patients with cerebrovascular disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Mass General Brigham (MGB) institutional review board (IRB). Written informed consent for participation was not required for this study in accordance with the IRB for retrospective analyses.

AUTHOR CONTRIBUTIONS

SM, SD, HA, GR, and MW: had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SM, SD, HA, JR, GR, and MW: concept and design. SM, SD, HA, LB, SC, EY, KK, and CB: drafting of the manuscript. SM, SD, HA, LB, BF, JH, MDL, ML, VT, JR, GR, and MW: critical revision of the manuscript for important intellectual content. SM, SD, CM, HS, MJL, AJ, WG, Y-PS, EY, and MW: statistical analysis. SM, SD, HA, GR, and MW: supervision. All authors: acquisition, analysis, or interpretation of data.

FUNDING

SM was supported by the National Institute of Mental Health at the National Institutes of Health (Grant no. K23MH115812), the Harvard University Eleanor and Miles Shore Fellowship Program and James S. McDonnell Foundation. HS and MJL were supported by a Developmental Award from the Harvard University Center for AIDS Research (HU CFAR NIH/NIAID fund 5P30AI060354-16). SD and CM were supported by the National Institute on Aging (P30AG062421). VT was supported by NIH R01HL132786 and NIH R01AG062393. MW was supported by the Glenn Foundation for Medical Research and American Federation for Aging Research (Breakthroughs in Gerontology Grant); American Academy of Sleep Medicine (AASM Foundation Strategic Research Award); Football Players Health Study (FPHS) at Harvard University; Department of Defense through a subcontract from Moberg I.C.U. Solutions, Inc; by the N.I.H. (1R01NS102190, 1R01NS102574, 1R01NS107291, and 1RF1AG064312).

ACKNOWLEDGMENTS

We would like to acknowledge all front-line healthcare workers taking care of patients during the COVID-19 pandemic.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.642912/full#supplementary-material

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* (2020) 395:1054–62. doi: 10.1016/S0140-6736(20)30566-3
2. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep.* (2020) 69:343–6. doi: 10.15585/mmwr.mm6912e2
3. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med.* (2020) 382:2372–4. doi: 10.1056/NEJMc2010419
4. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet.* (2020) 395:1763–70. doi: 10.1101/2020.04.15.20067157
5. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA.* (2020) 323:1574–81. doi: 10.1001/jama.2020.5394
6. Wu C, Chen X, Cai Y, Xia JA, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med.* (2020) 180:934–43. doi: 10.1001/jamainternmed.2020.0994
7. Sun H, Jain A, Leone MJ, Alabsi HS, Brenner LN, Ye E, et al. CoVA: an acuity score for outpatient screening that predicts COVID-19 Prognosis. *J Infect Dis.* (2020) 223:38–46. doi: 10.1093/infdis/jiaa663
8. Qin C, Zhou L, Hu Z, Yang S, Zhang S, Chen M, Yet al. Clinical Characteristics and Outcomes of COVID-19 Patients With a History of Stroke in Wuhan, China. *Stroke.* (2020) 51:2219–23. doi: 10.1161/STROKEAHA.120.030365
9. Trejo-Gabriel-Galán JM. Ictus como complicación y como factor pronóstico de COVID-19. *Neurología.* (2020) 35:318–22. doi: 10.1016/j.nrl.2020.04.015
10. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for, clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20.
11. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ.* (2020) 368:m1091. doi: 10.1136/bmj.m1091
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA.* (2020) 323:1061–69. doi: 10.1001/jama.2020.1585
13. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology.* (2020) 95:e1060–70. doi: 10.1212/WNL.0000000000009937
14. Frontera JA, Sabadia S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, et al. A prospective study of neurologic disorders in hospitalized COVID-19 patients in New York City. *Neurology.* (2020) 96:e575–86. doi: 10.1212/WNL.0000000000010979
15. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Transl Neurol.* (2020) 7:2221–30. doi: 10.1002/acn3.51210
16. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with Coronavirus Disease 2019

(COVID-19): a pooled analysis of published literature. *Int J. Stroke.* (2020) 15:385–9. doi: 10.1177/1747493020921664
17. Florez-Perdomo WA, Serrato-Vargas SA, Bosque-Varela P, Moscote-Salazar LR, Joaquim AF, Agrawal A, et al. Relationship between the history of cerebrovascular disease and mortality in COVID-19 patients: a systematic review and meta-analysis. *Clin Neurol Neurosurg.* (2020) 197:106183. doi: 10.1016/j.clineuro.2020.106183
18. Teeters DA, Moua T, Li G, Kashyap R, Biehl M, Kaur R, et al. Mild cognitive impairment and risk of critical illness. *Crit Care Med.* (2016) 44:2045–51. doi: 10.1097/CCM.0000000000001842
19. Phelan EA, Borson S, Grothaus L, Balch S, and Larson EB. Association of incident dementia with hospitalizations. *JAMA.* (2012) 307:165–172. doi: 10.1001/jama.2011.1964
20. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation.* (2019) 139:e56–528. doi: 10.1161/CIR.0000000000000659
21. Kummer BR, Klang E, Stein LK, Dhamoon MS, Jetté N. History of stroke is independently associated with in-hospital death in patients with COVID-19. *Stroke.* (2020) 51:3112–4. doi: 10.1161/STROKEAHA.120.030685
22. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health.* (2010) 13:273–7. doi: 10.1111/j.1524-4733.2009.00671.x
23. Allignol A, Schumacher M, Beyersmann J. Empirical transition matrix of multi-state models: the etm package. *J Stat Softw.* (2011) 38:1–15. doi: 10.18637/jss.v038.i04
24. Bella Vakulenko-Lagun CM, Charpignon ML, Zheng B, Albers M, Das S. *causalCmprsk: Nonparametric and Cox-based Estimation of Average Treatment Effects in Competing Risks. R Package Version 1.0.0.* Available online at: https://github.com/Bella2001/causalCmprsk, 2020
25. Zhao L, Tian L, Claggett B, Pfeffer M, Kim DH, Solomon S, et al. Estimating treatment effect with clinical interpretation from a comparative clinical trial with an end point subject to competing risks. *JAMA Cardiol.* (2018) 3:357–8. doi: 10.1001/jamacardio.2018.0127
26. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med.* (2009) 169:515–23. doi: 10.1001/archinternmed.2009.11
27. Ayubi E, Safiri S. The association between red cell distribution width and poor outcomes in hospitalized patients with influenza: methodological issues. *J Crit Care.* (2017) 41:324. doi: 10.1016/j.jcrc.2017.07.016
28. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ.* (2020) 369:m1985. doi: 10.1136/bmj.m1985
29. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* (2020) 46: 846–8. doi: 10.1007/s00134-020-05991-x
30. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region—case series. *N Engl Med J.* (2020) 382:2012–2. doi: 10.1056/NEJMoa2004500
31. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* (2020) 395:507–13. doi: 10.1016/S0140-6736(20)30211-7
32. Evans NR, Wall J, To B, Wallis SJ, Romero-Ortuno R, Warburton EA. Clinical frailty independently predicts early mortality after ischaemic stroke. *Age Ageing.* (2020) 49:588–91. doi: 10.1093/ageing/afaa004
33. Helms J, Kremer S, Merdji H, Schenck M, Severac F, Clere-Jehl R, et al. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Crit Care.* (2020) 24:491. doi: 10.1186/s13054-020-03200-1
34. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman M, S.Webb AR, et al. Royal Perth Hospital, Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients. *Br J Anaesth.* (2010) 104:459–64. doi: 10.1093/bja/aeq025
35. Moitra VK, Guerra C, Linde-Zwirble WT, Wunsch H. Relationship Between ICU length of stay and long-term mortality for elderly ICU survivors. *Crit Care Med.* (2016) 44:655–62. doi: 10.1097/CCM.0000000000001480
36. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med.* (2014) 371:287–8. doi: 10.1056/NEJMc1406274
37. Wilcox ME, Brummel NE, Archer K, Ely EW, Jackson JC, Hopkins RO. Cognitive dysfunction in ICU patients: risk factors, predictors, and rehabilitation interventions. *Crit Care Med.* (2013) 41:S81–98. doi: 10.1097/CCM.0b013e3182a16946
38. Meyers EE, Presciutti A, Shaffer KM, Gates M, Lin A, Rosand J, et al. The impact of resilience factors and anxiety during hospital admission on longitudinal anxiety among dyads of neurocritical care patients without major cognitive impairment and their family caregivers. *Neurocrit Care.* (2020) 33:468–78. doi: 10.1007/s12028-020-00913-7
39. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M, et al. Recurrent events trial, relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation.* (2008) 117:163–8. doi: 10.1161/CIRCULATIONAHA.107.727545
40. Foy BH, Carlson CT, Reinertsen E, Valls PI, Lopez RP, Palanques-Tost E, et al. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 infection. *JAMA Network Open.* (2020) 3:e2022058. doi: 10.1001/jamanetworkopen.2020.22058
41. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med.* (2020) 383:120–8. doi: 10.1056/NEJMoa2015432
42. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis.* (2020) 20:1365–6. doi: 10.1016/S1473-3099(20)30367-4
43. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al.. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol.* (2020) 75:2950–73. doi: 10.1016/j.jacc.2020.04.031

Conflict of Interest: JR is supported by OneMind and the American Heart Association and has consulted for Boehringer Ingelheim, outside the scope of this work. MA is co-founder, equity holder, and has consulted for Day 0 Diagnostics, outside the scope of this work. LB has research funding from Apple Inc., outside the scope of this work. JK-C has research funding from General Electric, outside the scope of this work. GR reports grants paid to MGH from Pfizer, Gilead, Citius Pharm, Emergent Biosolutions, Leonard Meron Bioscience, for clinical trial support outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 03 September 2021
doi: 10.3389/fneur.2021.613838

Changes in the Care of Neurological Diseases During the First Wave of the COVID-19 Pandemic: A Single Private Center Study in Argentina

Ismael L. Calandri[1], Maximiliano A. Hawkes[2]*, Mariano Marrodan[1], Sebastián F. Ameriso[1], Jorge Correale[1] and Ricardo F. Allegri[1]*

[1] Departamento de Neurología, Fleni, Buenos Aires, Argentina, [2] Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE, United States

OPEN ACCESS

Edited by:
Vijay Sharma,
National University of Singapore, Singapore

Reviewed by:
Minjee Kim,
Northwestern University, United States
Selami Aykut Temiz,
Necmettin Erbakan University, Turkey
Daniel Bereczki,
Semmelweis University, Hungary

***Correspondence:**
Ismael L. Calandri
icalandri@fleni.org.ar
Maximiliano A. Hawkes
maximilianohawkes@gmail.com

Specialty section:
This article was submitted to Neurocritical and Neurohospitalist Care,
a section of the journal Frontiers in Neurology

Received: 03 October 2020
Accepted: 21 July 2021
Published: 03 September 2021

Citation:
Calandri IL, Hawkes MA, Marrodan M, Ameriso SF, Correale J and Allegri RF (2021) Changes in the Care of Neurological Diseases During the First Wave of the COVID-19 Pandemic: A Single Private Center Study in Argentina. Front. Neurol. 12:613838. doi: 10.3389/fneur.2021.613838

Introduction: Healthcare systems are struggling to cope with the rapid evolution of the COVID-19 pandemic. In Argentina, the pandemic is advancing despite prolonged lockdown measures. We aim to analyze the impact of the easing of lockdown measures in the number of visits to the emergency department (ED), and outpatient consultations (OC) to a tertiary neurological center.

Methods: We compared the number of ED visits with the social mobility overtime. We also compared the number of OC, and the geographic distribution of patients' addresses between 2019 and 2020.

Results: ED visits decreased 48.33% ($n = 14{,}697$ in 2019 vs. $n = 7{,}595$ in 2020). At the beginning of the lockdown, the social mobility decreased in pharmacies/groceries, and workplaces, along with a reduction in the number of ED visits. With the easing of lockdown restrictions, the social mobility decreased in residential places, slightly increased in workplaces and almost return to normal in pharmacies/groceries. Variations in ED visits correlate better with social mobility in workplaces (coef. =0.75, $p < 0.001$) than in groceries/pharmacies (coef. =0.68, $p < 0.001$). OC decreased 43%. Fourteen percent of OC were tele consults. This was associated with an increase of the geographical area of influence of our center (standard distance of 109 km in 2019 and 127 km in 2020).

Conclusions: Despite an increase in social mobility, the number of ED visits and OC to an Argentinian tertiary neurological center remain worrisomely low. The pandemic catalyzed the introduction of telemedicine in our country. This has also allowed patients from distant zones to gain access to specialized neurological care.

Keywords: neurology, COVID-19, Latin America, neurological care, telemedicine, lockdown

INTRODUCTION

The COVID-19 pandemic has challenged healthcare systems worldwide (1). Social distancing, frequent hand sanitation, contact tracing, widespread testing, and the use of face masks are generally accepted strategies to stop the spread of the disease (2). Yet, the implementation of lockdowns, particularly their extent and duration, is still a matter of debate (3). This is particularly relevant in low- and middle-income countries where the negative impact on the economy may carry worse consequences than the pandemic itself (4). Additionally, strict lockdown measures may have unfavorable consequences for the mental health of the population and treatment of chronic diseases.

Argentina implemented a strict nationwide lockdown on March 20, 2020, with only 128 COVID-19 cases and 3 COVID-19-related deaths reported (5). Mass media, health authorities, and the medical community strongly recommended avoiding "non-urgent" contacts with the healthcare system in anticipation of a surge in COVID-19-related consults (5). Then, we reported a dramatic decline in the number of consults to the emergency department (ED) and outpatients clinics (OCs) of a tertiary neurological center (5). We emphasized the importance of tailoring the lockdown measures to particular epidemiological situations and providing appropriate medical care for non-COVID-19 medical conditions (5). Lockdown measures were partially relaxed on April 27, 2020. Some commercial and outdoor activities were allowed, while public or private events with more than 10 people, public transportation for non-essential workers, touristic activities, and attendance to cinemas, theaters, clubs, and cultural centers remained prohibited, despite distressing social and economic situations (6).

In this article, we aim to analyze the impact of easing lockdown measures on the number of visits for acute neurological conditions during the first wave of the pandemic. We also explored the impact of the first wave of the COVID-19 pandemic in the number and modality of neurological outpatient visits.

METHODS

Study Design

We compared the number of visits to the ED of a tertiary neurological center with the mobility of the population from March 1 to August 31, 2020.

The number of visits was evaluated by reviewing the institutional electronic administrative records. A process of consolidation and data wrangling ensures data reliability. Administrative data of a medical consultation, the department where it was performed, and clinical data from the EMR are automatically integrated to avoid redundancies. Lastly, data are reviewed by a medical audit team.

We used the Google Mobility Index to evaluate the mobility of the population in the Buenos Aires Metropolitan Area. We analyzed three areas: pharmacies/groceries, residential places, and workplaces (7). The Buenos Aires Metropolitan Area (3,830 km^2, 13,641,973 inhabitants) includes the Autonomous City of Buenos Aires and 24 adjacent districts of the Province of Buenos Aires (8).

The Google Mobility Index collects data from cell phones with Android operating systems or Google applications (e.g., Google Maps) to generate georeferenced information about people's movement trends over time by geography. The data are anonymized, aggregated by specific regions, and open access. The Google Mobility Index may be particularly useful in Argentina since 92% of cell phone devices use Android software (9). Furthermore, it has been successfully used to study the excess of cerebrovascular mortality during the COVID-19 pandemic (10).

We present the changes in social mobility and ED visits as the percentage reduction of the Google Mobility Index and the number of visits to the ED from 2019 to 2020, respectively. To avoid inaccuracies in the number of visits to the ED, as well as social mobility caused by weekends and holidays, we matched weekdays in 2019 and 2020. We also compared the number of outpatient visits, and the geographic distribution of patient's addresses between March 1, 2020, and August 31, 2020, with the same period in 2019. The geographical distribution of patient's addresses is shown on a map as points and point densities. To graphically emphasize possible changes in the number of outpatient visits of patients who live outside the Buenos Aires Metropolitan Area, we used a natural break classifier to determine the most appropriate scale. The borders of all Argentinian provinces have remained closed since the beginning of lockdown. Hence, all outpatient visits with an address outside the Great Buenos Aires Metropolitan Area were done with telemedicine.

This research was approved by the Institutional Ethics Committee.

Statistical Analysis

A Pearson correlation was used to assess the synchrony of the mobility of the population and the number of ED consults overtime. The results are presented as correlation coefficients. A p-value < 0.01 was considered significant.

We also calculated the standard distance between our center and the addresses of patients who consulted in 2019 and compared it with 2020. Data analysis was performed with Python Software, version 3.8. Data wrangling was performed with Pandas (11) and NumPy (12) packages. The statistical analysis was performed with SciPy (13) and charts were made with Matplotlib package (14). The geographical analysis was performed with ArcGIS Desktop 10.8 (ESRI) software (15). For graphical representation and analysis, we used WGS 1984 Web Mercator (Auxiliary Sphere) spatial reference.

RESULTS

Our institution is a 113-bed tertiary academic center located in Buenos Aires City, Argentina (16). It is exclusively committed to the attention of neurological and neurosurgical diseases. Although our center is a national and regional referral center, its main influence is the Buenos Aires Metropolitan Area.

The healthcare system in Argentina is segmented and heterogeneous. It is based on the public provision of healthcare

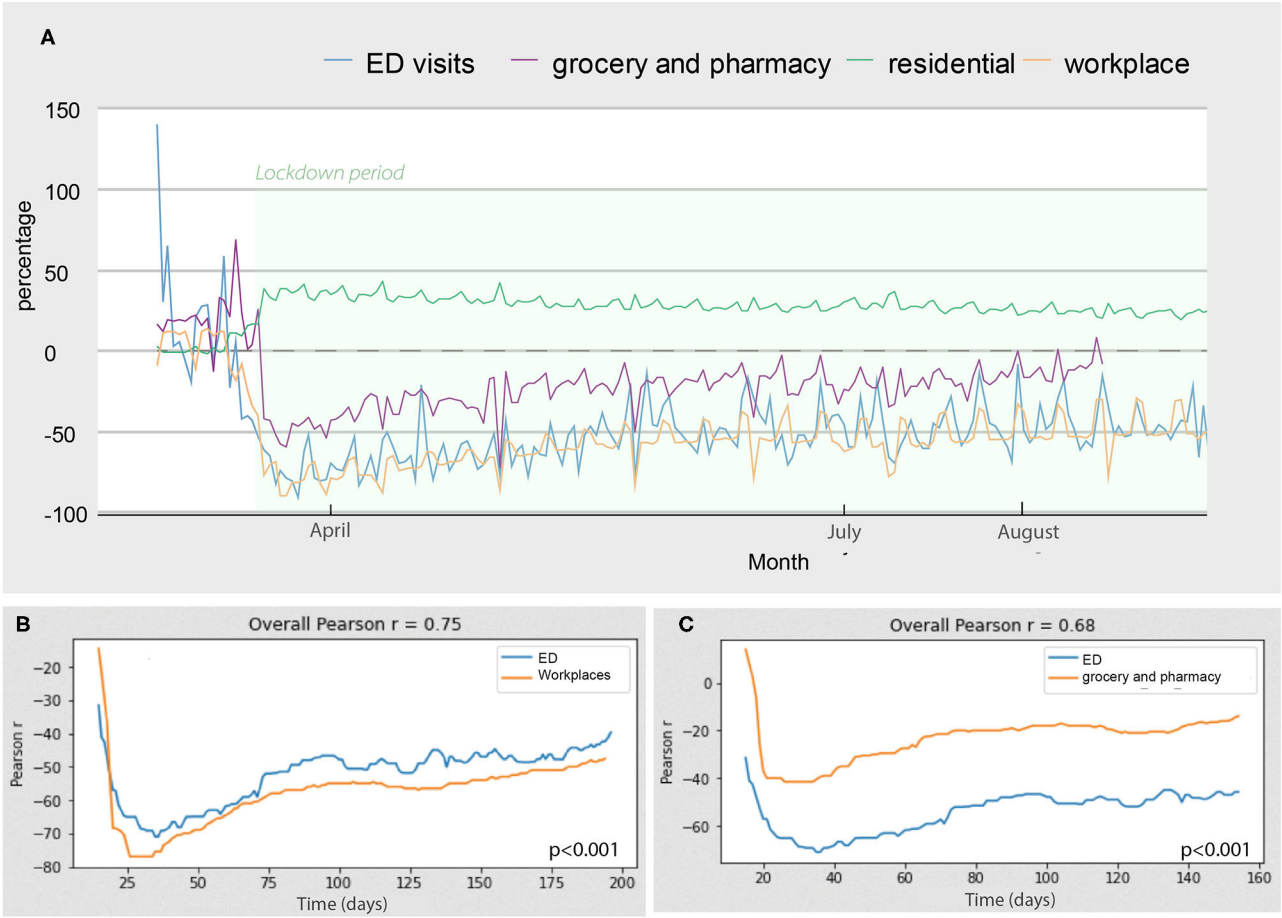


FIGURE 1 | Evolution of the number of ED consults and social mobility. Changes in social mobility and number of ED visits over time. **(A)** The lines represent the percentage of change compared to the same period of 2019. The correlation plots show the correlation between the number of ED consults and social mobility in workplaces **(B)** and between the number of ED consults and social mobility in groceries and pharmacies **(C)**.

for every habitant. Additionally, 52% of people are covered by worker's organizations, 9% by private health insurances, and 8.3% by government-funded social insurance for the retired population "PAMI" (17). The majority of our patients have private or worker's organizations health insurance. Before the beginning of the pandemic, no health insurance covered telemedicine consults. Hence, while there was an operational telemedicine service, only sporadic consults were performed.

Impact of Lockdown Measures Easing in the Number of Visits to the ED

We analyzed $n = 92{,}534$ administrative records from the ED, $n = 71{,}917$ from 2019, and $n = 20{,}617$ from 2020. Compared with the same period of 2019, the number of visits to the ED during March–August 2020 decreased 48.33% ($n = 14{,}697$ in 2019 vs. $n = 7{,}595$ in 2020).The most frequent reason for ED consultation was headache (2019 = 53% and 2020 = 57%) and the most frequent reason for hospital admission was ischemic stroke (2019 = 28%, 2020 = 33%). There were no significant differences in the reason for ED consultation between 2019 and 2020 ($p = 0.17$).

Figure 1 shows the comparison between the number of visits to the ED and social mobility over time. At the beginning of the lockdown, social mobility increased in residential areas and decreased in pharmacies/groceries and workplaces. This correlates with a sharp reduction in the number of visits to the ED (**Figure 1A**). As lockdown measures relaxed, we observed the opposite. A correlation analysis showed that the number of ED visits had a small increase, similar to the increased social mobility in workplaces (correlation coefficient 0.75, $p < 0.001$, **Figure 1B**). However, the social mobility in groceries/pharmacies increased significantly more than the number of ED visits (correlation coefficient 0.68 $p < 0.001$, **Figure 1C**).

Impact of the Pandemic on In-hospital Mortality

Our center recorded 21 deaths and 1,712 admissions in 2019, and 30 deaths in 1,278 admissions during 2020. The median monthly mortality was 2.5 in 2019 compared to 5.5 in 2020. Although numerically higher, the difference is not statistically significant ($p = 0.058$). In 2020, the causes of death were stroke ($n = 4$),

TABLE 1 | Percentage reduction in outpatient visits according to month and neurological subspecialty.

Department	March		April		May		June		July		August	
	2019 (*n*)	2020 (%)	2019 (*n*)	2020 (%)	2019 (*n*)	2020 (%)	2019 (*n*)	2020 (%)	2019 (*n*)	2020 (%)	2019 (*n*)	2020 (%)
Endovascular Neurosurgery	72	−15.3%	91	−85.7%	76	−38.2%	82	−47.6%	95	−44.2%	92	−40.2%
Cardiology	846	−24.5%	919	−89.8%	997	−54.1%	863	−26.7%	912	−21.1%	1,027	−31.5%
Headache and Pain	1,016	−42.9%	1,048	−88.4%	1,270	−59.7%	983	−24.6%	1,079	−25.2%	1,197	−30.6%
Internal Medicine	357	−33.3%	405	−88.1%	384	−56.5%	368	−35.3%	451	−36.1%	402	−28.4%
Electrophysiology	16	−12.5%	33	−78.8%	25	−36.0%	21	−61.9%	25	−84.0%	32	−65.6%
Neuromuscular Disorders	222	17.1%	218	−61.9%	252	−21.4%	252	6.7%	303	−2.0%	261	18.0%
Epilepsy	249	−19.7%	284	−89.8%	312	−51.6%	262	−20.2%	302	−30.5%	301	−35.2%
EEG* Video-Telemetry	172	−23.3%	166	−88.6%	168	−38.1%	151	−30.5%	199	−39.7%	210	−41.9%
Multiple Sclerosis	411	−21.4%	444	−86.0%	424	−24.8%	407	2.7%	531	−20.2%	417	−4.1%
Sleep medicine	216	−91.7%	206	−100%	204	−100%	145	−78.0%	158	−38.7%	212	−15.8%
Movement Disorders	478	−30.1%	528	−94.3%	541	−50.3%	387	−11.1%	484	−36.4%	565	−34.9%
Neuro-Ophtalmology	240	−37.9%	282	−92.2%	319	−65.8%	174	16.7%	309	−44.0%	263	−19.4%
Neurosurgery (adults)	600	−26.2%	607	−85.0%	731	−64.6%	636	−36.2%	572	−28.7%	728	−39.7%
Pediatric Neurosurgery	189	−16.4%	188	−94.1%	228	−71.1%	201	−54.7%	218	−52.3%	238	−43.7%
Neuroendocrinology	163	20.2%	264	−92.8%	311	−45.3%	269	−21.6%	307	−28.7%	327	−42.5%
Neurophysiology	18	−66.7%	23	−30.4%	28	−85.7%	16	−68.8%	25	−96.0%	22	−72.7%
Stroke	612	−33.5%	674	−90.2%	697	−52.8%	738	−33.5%	838	−46.9%	796	−38.8%
General Neurology	1,607	−35.7%	1,518	−92.0%	1,673	−52.4%	1,530	−40.3%	1,769	−47.9%	1,860	−45.3%
Cognitive Neurology	754	−32.5%	671	−90.8%	754	−59.5%	583	−11.8%	741	−40.2%	809	−31.8%
Pediatric Neurology	739	−42.5%	878	−92.3%	916	−45.2%	886	−22.5%	1,117	−30.9%	1,004	−21.9%
Neuro-Oncology	415	−12.9%	492	−31.5%	473	−18.2%	438	−4.6%	523	−24.9%	481	−10.0%
Neuro-Orthopedic	510	−34.7%	438	−94.5%	524	−70.6%	442	−50.2%	478	−61.1%	475	−42.3%
Neuro-Otology	360	−42.8%	458	−91.9%	432	−59.7%	378	−23.5%	433	−25.6%	516	−31.6%
Psychiatry	546	−49.3%	472	−96.0%	535	−63.7%	495	−34.1%	513	−37.4%	612	−39.5%
Total	10,808	−30.85%	11,307	−87.69%	12,274	−52.52%	10,707	−25.37%	12,382	−34.24%	12,847	−31.46%
											70,325	−42.67%

**Electroencephalogram.*

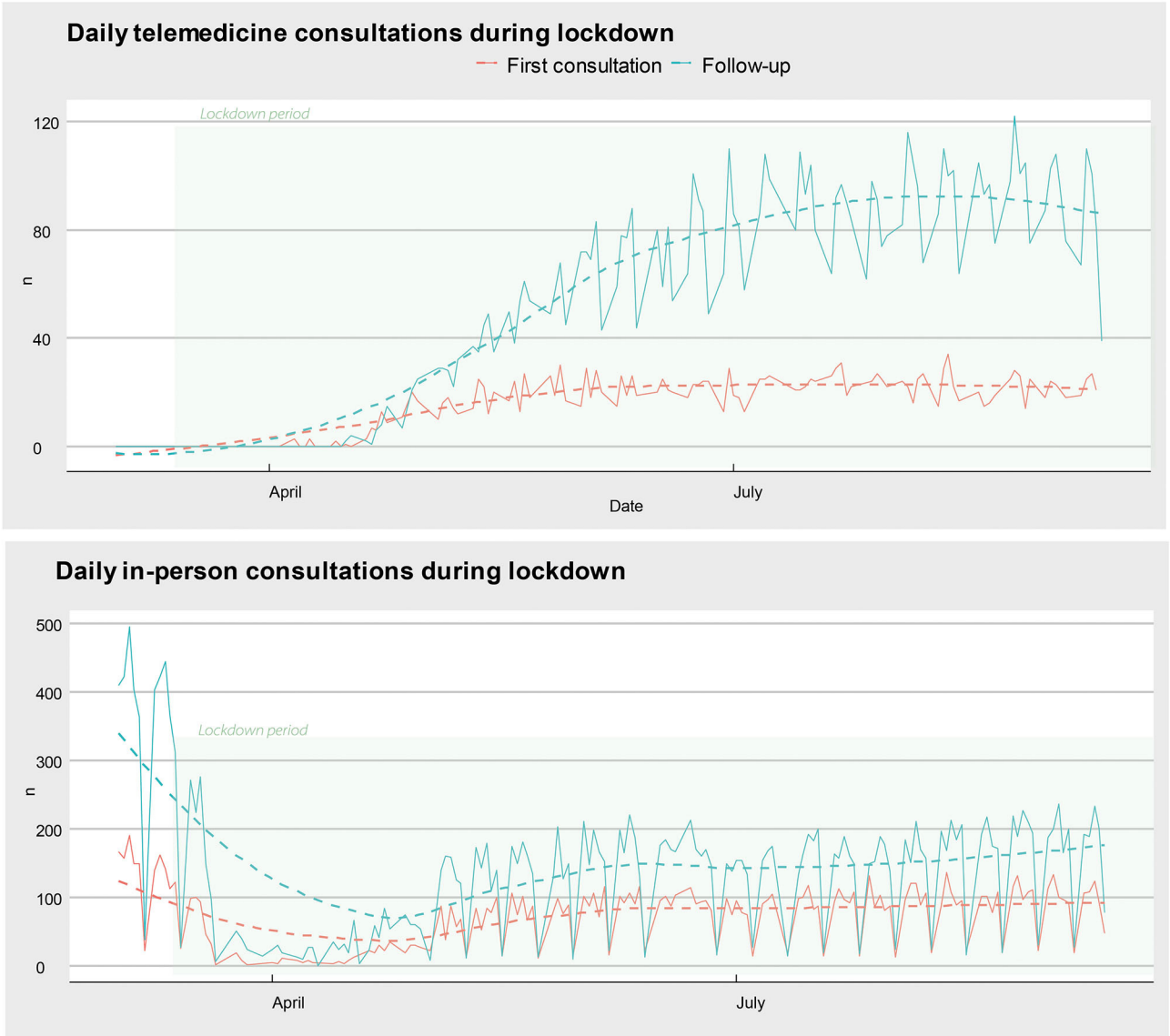


FIGURE 2 | Evolution of telemedicine and in-person consults during the lockdown. The number of first-time (red) and follow-up (blue) visits over time. The dashed lines represent the time trend in a general linear model. Of note, telemedicine visits increase in early April, shortly after the beginning of the lockdown mandate (March 20).

status epilepticus ($n = 2$), complications of chronic neurological diseases ($n = 11$), rupture of abdominal aortic aneurysm ($n = 1$), and complications of brain tumors ($n = 12$). In 2019, the causes of death were stroke ($n = 3$), complications of chronic neurological diseases ($n = 4$), status epilepticus ($n = 1$), and complications of cancer/brain tumors ($n = 12$).

Impact of the Pandemic in the Number and Modality of Outpatient Visits

A total of 141,772 outpatients visits were registered during March–August 2019. This number decreased to 64,343 in 2020 (43% decrease). The reduction in the number of consults peaked in April (almost 90%), in hand with the beginning of strict lockdown measures. **Table 1** shows the monthly percentage reduction in outpatient visits according to neurological subspecialty. A total of 9,014 outpatient visits were teleconsults. This represents 14% of all outpatient consultations performed during the same period of time. Most teleconsults were follow-up visits for chronic neurological diseases (78%), and the remainder were first-time evaluations (22%) (**Figure 3**). The geographical analysis of the outpatient's addresses reveals a significant increase in the area of influence of our center (**Figure 3**). The standard distance of patient's addresses to our medical center increased from 109 km in 2019 to 127 km in 2020 (**Figure 3**).

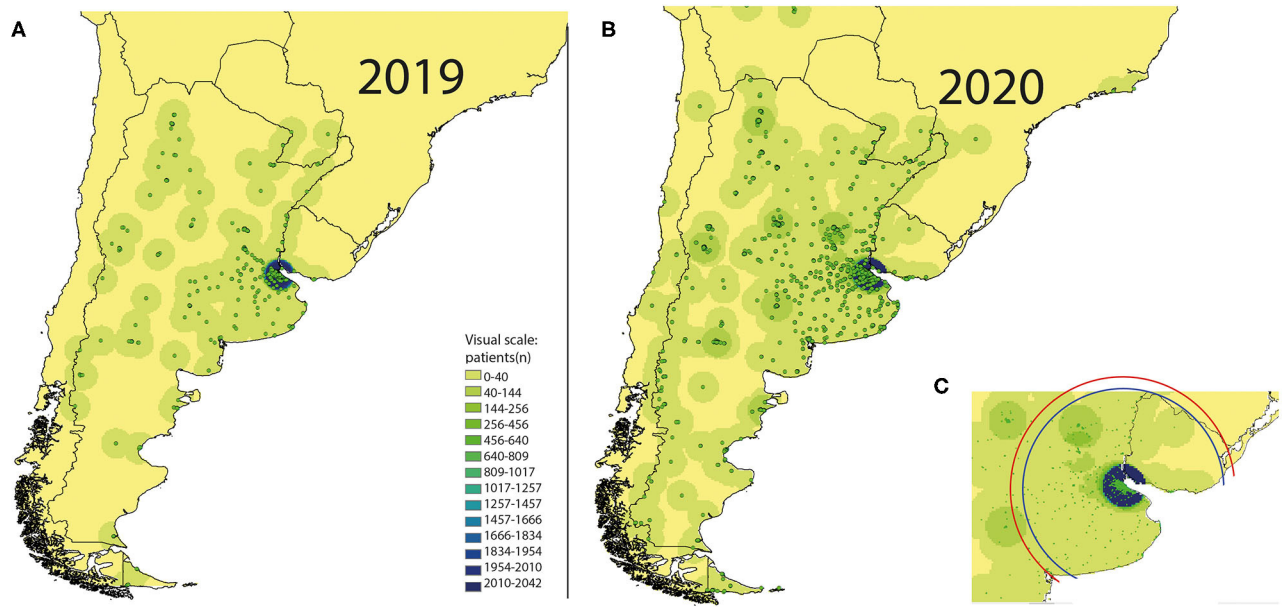


FIGURE 3 | Changes in the geographical area of influence of our center due to the introduction of telemedicine. The points and point densities represent the number of patients according to the geographical location of their addresses. Compared to 2019 **(A)**, in 2020 **(B)**, more patients from distant areas of Argentina and bordering countries had access to our center. During the study time frame, all the national and international borders remain closed. Thus, the observed changes can be attributed to the introduction of telemedicine. **(C)** shows the standard distance measured from the patient's addresses to our center in 2019 (blue circle = 109 km) and 2020 (red circle = 127 km).

DISCUSSION

The consequences of the COVID-19 pandemic exceed the COVID-19 disease itself (18). During the peak of the first wave of the pandemic, Europe and had an increase in non-COVID-19-related deaths of 14 and 25%, respectively (19). There are several potential explanations for this: (1) a proportion of COVID-19-related deaths have not been counted as such, (2) avoidable non-COVID-19-related diseases that could not be properly treated because of the saturation of healthcare systems, (3) decompensation of chronic medical conditions due to in adequate medical care, (4) late or no consultation to the ED due to fear of contracting COVID-19 and/or wrong messages from mass media, healthcare authorities, and medical community (5, 19, 20).

Several studies have reported a dramatic drop in the number of visits to the ED for serious and urgent medical conditions such as heart attack and stroke (20). During the beginning of the lockdown, we reported that the number of admissions for acute ischemic stroke and transient ischemic attacks decreased 50 and 80%, respectively. Also, the number of patients who consulted the ED or OC with MS relapses and seizures decreased 50 and 83%, respectively (5).

The findings of the present study show that, 5 months after the beginning of pandemic, and despite partial relaxation of lockdown measures, the number of emergent and outpatient visits to a tertiary neurological Argentinian center remained low in comparison to the increase in social mobility in areas such as pharmacies and groceries. Whether our results can be extrapolated to the entire Argentinian healthcare system is difficult to ascertain due to the paucity of published data, lack of specific public statistics, and the single-center design of our study. However, as all medical centers were requested to remain fully available for a potential surge in COVID-19 cases, most outpatient visits were not allowed, and the message to the population was to avoid "unnecessary" or "non-urgent" medical consultations; we believe that our data may reflect the trend in a significant proportion of the Argentinian healthcare facilities.

Social mobility in pharmacies/groceries is common in nearby shops. Hence, this was unlikely affected by the unavailability of public transportation. The decreased mobility in residential places also means that social mobility increased (**Figure 1**).The social mobility in workplaces marginally increased compared to the strict lockdown period but remained low compared to the increased social mobility in pharmacies and groceries. This can be explained by the fact that most non-essential activities were prohibited by law during the study time frame. Also, public transportation was available only for essential workers, limiting the mobility of the majority of workers and patients. Altogether, our data suggest that continuous efforts are still needed to improve and refine the communication to the population concerning the importance of continuing regular medical check-ups and visiting the ED when acute symptoms develop. Non-COVID-19 diseases still occur, matter, and many can be properly prevented and treated, avoiding irreversible neurological sequelae in many cases. This issue must be clearly explained to people. Patients who need regular infusions for chronic diseases, such as immunosuppressive

treatments for MS, should be particularly counseled about the dangers of discontinuation of their treatments. Although, at the beginning of the pandemic, it was suggested to defer the time of administration of some immunosuppressive drugs, now with the evidence that the COVID-19 pandemic will most likely remain for a long period, these considerations are under review (21).

We also found that despite a dramatic drop in the total number of outpatient visits, the use of telemedicine increased substantially, particularly for follow-up visits (**Figure 2**). Remarkably, the pandemic catalyzed the introduction of telemedicine in our country, mainly because of improvements in the coverage of healthcare insurances. These advances may be due to a combination of increased social demand and public health needs. In this context, teleconsults are particularly useful to facilitate the access of patients with chronic neurological conditions at high risk of developing severe COVID-19 disease (e.g., patients with MS on chronic immunosuppressants) to regular medical follow-up visits (22). The descriptive analysis of the maps in **Figure 3** suggests that the introduction of telemedicine for outpatient visits has expanded the area of influence of our center, allowing patients from distant areas of the country and bordering countries to gain access to specialized neurological care. This is particularly important in Latin America because the number of neurologists per 100,000 inhabitants is low in many regions and they tend to concentrate in big cities (23, 24).

Developing efficient technologic tools and providing massive access to telemedicine has been challenging worldwide. While in some countries telemedicine could be implemented efficiently without delays, significant difficulties and disparities persist in several areas (25–28). This reinforces the importance and continues the need for multidisciplinary work to develop more efficient communication tools for patients and healthcare providers and to generalize access to the internet, particularly in underserved areas.

The main strength of this investigation is the detailed comparison of neurological service use during the first wave of the pandemic period to a control period for all types of neurological disorders, and comparisons of service use to the changes in social mobility. This study also has limitations worth mentioning. First, we report data from a single tertiary center, limiting its generalization. Second, it contemplates the effects of the lockdown measures in Argentina. Hence, data cannot be extrapolated to other countries with different social, demographic, economic, and healthcare structures. Third, we report data of a private hospital: the majority of patients serviced had extra insurance in addition to the public provision of healthcare. Thus, the results may not be representative of the total healthcare service use of the country due to a selection bias. Fourth, we only evaluated the first wave of the pandemic. Fifth, our data set does not allow us to evaluate potential morbidity and mortality of patients who did not seek medical attention or consulted to another center. A population-based registry and publicly available official data are needed to further explore this issue.

CONCLUSIONS

In Argentina, 5 months after the beginning of the pandemic, and despite an increase in social mobility, the number of visits to the ED and OC of a tertiary neurological center remains worrisomely low. The pandemic catalyzed the introduction of telemedicine in our country. This has also allowed patients from distant zones to gain access to specialized neurological care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

IC and MH contributed equally to the manuscript. IC, MH, and MM recolect data, interpret results, and write the manuscript. IC perfomed the statistical analysis. JC, SA, and RA provided original ideas, review manuscript, and add interpretation. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Blumenthal D, Fowler EJ, Abrams M, Collins SR. Covid-19 - implications for the health care system. *N Engl J Med*. (2020) 383:1483–8.
2. Centers for Disease Control and Prevention (CDC). *Identify Strategies to Reduce Spread of COVID-19*. (2020). Available online at: https://www.cdc.gov/coronavirus/2019-ncov/php/contact-tracing/strategies-to-reduce-spread.html (accessed February 10, 2020).
3. Dickens BL, Koo JR, Lim JT, Park M, Quaye S, Sun H, et al. Modelling lockdown and exit strategies for COVID-19 in Singapore. *Lancet Reg Heal West Pacific*. (2020) 1:100004. doi: 10.1016/j.lanwpc.2020.100004
4. Chowdhury R, Luhar S, Khan N, Choudhury SR, Matin I, Franco OH. Long-term strategies to control COVID-19 in low and middle-income countries: an options overview of community-based, non-pharmacological interventions. *Eur J Epidemiol*. (2020) 35:743–8. doi: 10.1007/s10654-020-00660-1
5. Calandri IL, Hawkes MA, Marrodan M, Ameriso SF, Correale J, Allegri RF. The impact of an early strict nationwide lockdown on the pattern of consultation for neurological diseases. *J Neurol Sci*. (2020) 418:117084. doi: 10.1016/j.jns.2020.117084
6. Worldometer. *Coronavirus Cases/Argentina*. Available onlinne at: https://www.worldometers.info/coronavirus/country/argentina/ (accessed February 10, 2020).
7. Google. *COVID-19 Community Monility Reports*. (2020).
8. *Censos IN de Ey. Censo*. (2010). Available online at: https://www.indec.gob.ar/indec/web/Nivel4-Tema-2-41-135 (accessed February 10, 2020).
9. *Stat Counter*. (2020). Available online at: https://statcounter.com/ (accessed September 15, 2020).
10. Jasne AS, Chojecka P, Maran I, Mageid R, Eldokmak M, Zhang Q, et al. Stroke code presentations, interventions, and outcomes before and during the COVID-19 pandemic. *Stroke*. (2020) 51:2664–73. doi: 10.1161/STR.0000000000000347
11. McKinney W. Data structures for statistical computing in python. In: van der Walt S, Millman J, editors. *Proceedings of the 9th Python in Science Conference*, Vol. 445, San Francisco (2010), 51–6.

12. Harris CR, Millman KJ, van der Walt SJ, Gommers R, Virtanen P, Cournapeau D, et al. Array programming with NumPy. *Nature.* (2020) 585:357–62. doi: 10.1038/s41586-020-2649-2
13. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in python. *Nat Meth.* (2020) 17:261–72. doi: 10.1038/s41592-019-0686-2
14. Hunter JD. Matplotlib: A 2D graphics environment. *Comput Sci Eng.* (2007) 9:90–5. doi: 10.1109/MCSE.2007.55
15. *QGIS*. Available online at: https://qgis.org/en/site/ (accessed September 15, 2020).
16. FLENI. Available online at: https://www.fleni.org.ar (accessed September 15, 2020).
17. Hawkes MA, Farez MF, Calandri IL, Ameriso SF. Perception of stroke symptoms and utilization of emergency medical services. *Arq Neuropsiquiatr.* (2016) 74:869–74. doi: 10.1590/0004-282x20160142
18. Horton R. Offline: COVID-19 is not a pandemic. *Lancet*. (2020) 396:874. doi: 10.1016/S0140-6736(20)32000-6
19. Viglione G. How many people has the coronavirus killed? *Nature*. (2020) 585:22–4. doi: 10.1038/d41586-020-02497-w
20. Lange SJ, Ritchey MD, Goodman AB, Dias T, Twentyman E, Fuld J, et al. Potential indirect effects of the COVID-19 pandemic on use of emergency departments for acute life-threatening conditions — United States, January–May 2020. *Am J Transplant.* (2020) 20:2612–7. doi: 10.1111/ajt.16239
21. Multiple Sclerosis International Federation. *Global COVID-19 advice for people with MS*. (2020).
22. Bloem BR, Dorsey ER, Okun MS. The coronavirus disease 2019 crisis as catalyst for telemedicine for chronic neurological disorders. *JAMA Neurol.* (2020) 77:927–8. doi: 10.1001/jamaneurol.2020.1452
23. Somoza MJ, Melcon MO. Número de neurólogos y carga de enfermedades neurológicas en Argentina. *Neurol Argentina.* (2015) 7:89–94. doi: 10.1016/j.neuarg.2014.12.001
24. Site. *WHOW, World Health Organization Web Site*. The Atlas of Heart Disease and Stroke. Brighton, UK (2004), p. 26–31.
25. Temiz SA, Dursun R, Daye M, Ataseven A. Evaluation of dermatology consultations in the era of COVID-19. *Dermatol Ther.* (2020) 33:e13642. doi: 10.1111/dth.13642
26. Saleem SM, Pasquale LR, Sidoti PA, Tsai JC. Virtual ophthalmology: telemedicine in a COVID-19 Era. *Am J Ophthalmol.* (2020) 216:237–42. doi: 10.1016/j.ajo.2020.04.029
27. Ganapathy K. Telemedicine and neurological practice in the COVID-19 Era. *Neurol India.* (2020) 68:555–9. doi: 10.4103/0028-3886.288994
28. Omboni S. Telemedicine during the COVID-19 in Italy: a missed opportunity? *Telemed J E Health.* (2020) 26:973–5. doi: 10.1089/tmj.2020.0106

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership