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Post-acute sequelae of COVID-19 infection (PASC): Implications for geriatric and neurological care

Edited by
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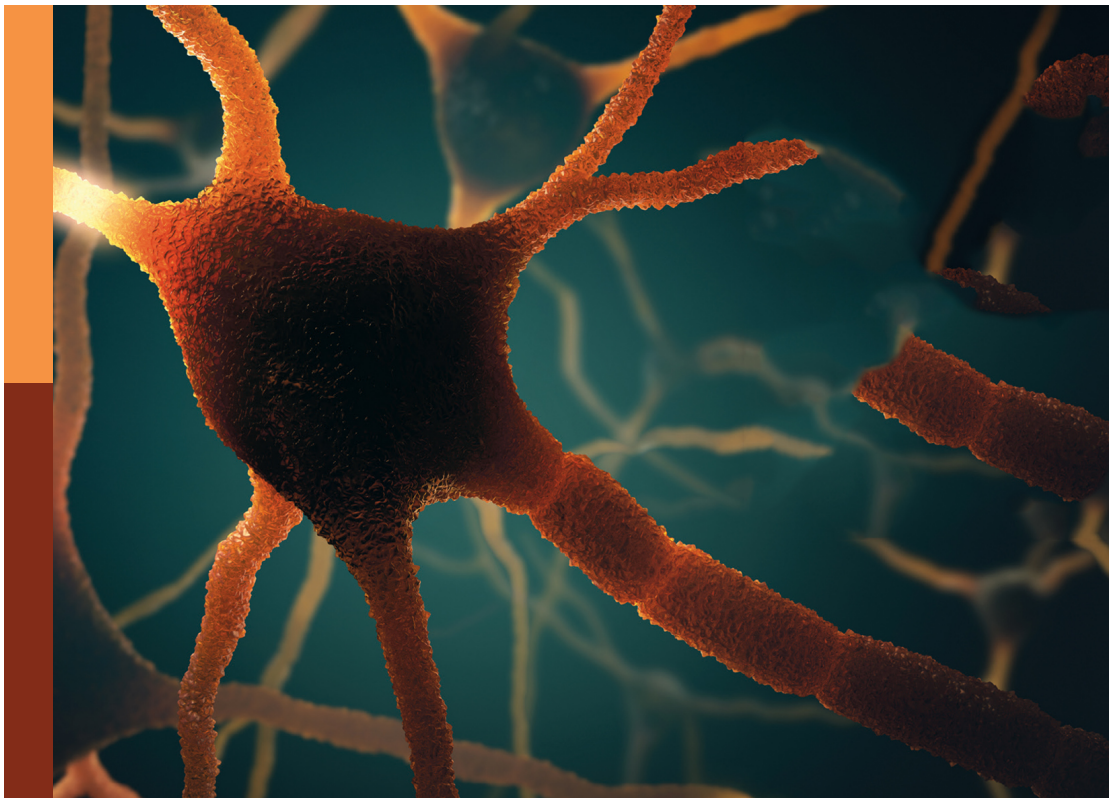

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Post-acute sequelae of COVID-19 infection (PASC): Implications for geriatric and neurological care

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Editorial: Post-Acute Sequelae of COVID-19 infection (PASC): Implications for geriatric and neurological care

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KEYWORDS

Post-Acute Sequelae of COVID-19 infection (PASC), long COVID, cognitive impairment, rehabilitation, Alzhaimer's disease (AD)

Editorial on the Research Topic
Post-Acute Sequelae of COVID-19 infection (PASC): Implications for geriatric and neurological care

1. Introduction

Emerging evidence indicates that many people infected with COVID-19 experience symptoms long after the acute illness phase, characterizing the syndrome Post-Acute Sequelae of SARS-CoV-2 infection (PASC), commonly known as long COVID. Although COVID-19 is primarily a respiratory disease, there are multiple impacts on other systems, including the brain, resulting in cognitive, neuropsychological and neurological impairments. Rehabilitation is thus of paramount importance.

In view of this issue, the guest editorial team thus proposed this *Frontiers in Aging Neuroscience* Research Topic. This Research Topic included nine articles, with six original research and three scoping or systematic review, covering two main areas: (1) Cognitive impairments and (2) Rehabilitation.

2. Cognitive impairments

Cognitive impairments are some of the most prevalent PASC symptoms, causing significant disabilities and impacting quality of life.

Chang et al.'s observational study found 72.5% of 40 participants had impairments in at least one cognitive domain examined, defined as ≤-1.5 standard deviation below measure-specific age- and sex-adjusted norms. The most prevalent impairments were executive function (64.9%), processing speed/attention (52.5%) and working memory (42.5%). COVID-19 related cognitive changes were found in the subacute phase. Limitations include only including patients referred to a psychiatric clinic and the lack of a control group.

Ariza et al. found that compared to the healthy controls (n = 109), PASC participants (n = 319) scored worse on global cognition, processing speed, language and executive function, learning, and memory tests. The reasonably large sample size represented the full spectrum of COVID-19 severity and excluded participants with comorbidities that could cause cognitive impairment. Limitations include using a less sensitive test to assess visual memory and difficulty finding controls.

Two studies by Guo et al. and Guo et al. analyzed data from the COVID and Cognition Study. In the 2022a paper, to better understand symptom clusters and derive symptom profiles, the characteristics of 181 individuals who had COVID-19 infection were compared to 185 who had not been infected. Principal component analyses (PCA) of 34 initial infection symptoms resulted in a five-factor solution explaining 50.59% of item variance; and PCA of 45 symptoms following initial infection generated a six-factor solution explaining 54.17% of item variance. Initial infection neurological symptoms were found to be significant predictors of self-reported cognitive impairment. As one of the first papers to undertake PASC symptom profiling, strengths included homogeneity of COVID-19 variants with mostly Wild-Type or Alpha-variant SARS-CoV-2. Self-reported symptoms, varied symptoms across time-points, varied response options, lack of vaccination status reporting and laboratory confirmation of infection status, and limited generalizability were limitations.

The 2022b study investigated factors associated with COVID-19 infection that could impact language, executive functions and memory. Cognitive deficits were found to distinguish SARS-CoV-2 patients from non-infected or recovered individuals. Verbal memory deficits and slowness remained even after controlling for demographics and infection severity. Chronic fatigue-like symptoms were predictive of cognitive impairments. Similar limitations to the 2022b study was noted, including relying on online retrospective self-report of symptoms.

Biagianti et al.'s systematic review of neuropsychological assessments for use in people with SARS-CoV-2 found cognitive impairments were prevalent and the likelihood of observing impairments varied depending on the tests used. The MoCA could detect subtle cognitive impairments, while the MMSE could better detect more severe impairments. This finding mirror the finding on higher sensitivity and specificity for detecting mild cognitive impairment using MoCA vs. MMSE (Nasreddine et al., 2005). The 19 studies included had small sample sizes and the tests were unable to identify a specific pattern of impairments related to COVID-19 infection.

3. Rehabilitation

The American Congress of Rehabilitation Medicine COVID-19 Task Force summarized health system and rehabilitation recommendations during the COVID-19 pandemic across the care continuum. Negm et al. presented 141 recommendations grouped by (1) setting e.g., rehabilitation inpatient, discharge process, outpatient, (2) health system elements, e.g., rehabilitation equipment/workplace, human resources, telerehabilitation; and (3) precautions for patients and rehabilitation professionals.

Negm et al. described 154 recommendations focusing on acute and post-acute rehabilitation interventions, including geriatric and neurological rehabilitation. Limitations included a lack of empirically-based papers in both the scoping reviews, with available publications comprised of expert opinion or clinical recommendations.

Faieta et al. reported on a 10-item web-based survey that explored the perceptions of 84 caregivers of persons living with dementia. Eighty percent of caregivers reported being isolated from their institutionalized or hospitalized care recipient because of the pandemic, 71.4% were concerned about their care recipient's medical or support care, and 87.2% reported experiencing negative health outcomes. Open-ended comments included mental health concerns i.e., stress, anxiety, depression, inability to sleep, and concerns and worries about their care recipients. Over two-thirds (67.9%) indicated the need for an app to use during COVID-19. The survey was not pilot-tested nor tested for validity; and the use of a web-based platform introduced selection bias and limited generalizability.

Ciro et al.'s study aimed to identify post-hospitalization needs over 30 days using weekly, virtually administered interdisciplinary rehabilitation tools and measures with a convenience sample of 19 people with COVID-19, who hadn't required mechanical ventilation and were discharged from a Level 1 Trauma hospital to home. Initially, participants reported dyspnea were at an increased risk of falls, had difficulties with activities of daily living (ADL) and instrumental activities of daily living (IADL), and had test scores indicative of mild cognitive impairment. At the 30-day follow-up, most participants were independent in mobility and ADLs but had continued IADL needs and cognitive impairments. Limitations include limited generalizability, small sample size, and the missing data.

4. Conclusion

Several existing screening and cognitive tests are sensitive to detect cognitive impairments, especially attention, memory and executive function, experienced by people with PASC. Nevertheless, it is unclear to what extent these tests have the specificity to distinguish PASC-related cognitive impairments from other cognitive impairments caused by neurological conditions. Improvements in assessment could facilitate more timely and effective rehabilitation. Since PASC has been shown to be associated with an increased risk of Alzheimer's Disease and Related Dementias (Golzari-Sorkheh et al., 2022), early detection and rehabilitation of PASC-related cognitive impairments are needed to mitigate this emerging public health issue.

Author contributions

TN: conceptualized and led the writing of this this editorial. PH: conceptualized, recruited associate guest editors, and led the Research Topic. All authors listed were involved in drafting the

editorial and made intellectual contribution to the work and approved it for publication.

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Kristy A. Nielson served as the editor of the Faieta et al. paper.

Conflict of interest

AN is lead author and VD, PH, EP, and FS are co-authors on two papers in this Research Topics collection.

The remaining 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.

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REVIEW
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Rehabilitation Care at the Time of Coronavirus Disease-19 (COVID-19) Pandemic: A Scoping Review of Health System Recommendations

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Purpose: The coronavirus disease-19 (COVID-19) was declared a pandemic by the World Health Organization in March 2020. COVID-19, caused by SARS-CoV-2 has imposed a significant burden on health care systems, economies, and social systems in many countries around the world. The provision of rehabilitation services for persons with active COVID-19 infection poses challenges to maintaining a safe environment for patients and treating providers.

Materials and Methods: Established frameworks were used to guide the scoping review methodology. Medline, Embase, Pubmed, CINAHL databases from inception to August 1, 2020, and prominent rehabilitation organizations' websites were searched.

Study Selection: We included articles and reports if they were focused on rehabilitation related recommendations for COVID-19 patients, treating providers, or the general population.

Data Extraction: Pairs of team members used a pre-tested data abstraction form to extract data from included full-text articles. The strength and the quality of the extracted recommendations were evaluated by two reviewers using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Results: We retrieved 6,468 citations, of which 2,086 were eligible for review, after duplicates were removed. We excluded 1,980 citations based on title and abstract screening. Of the screened full-text articles, we included all 106 studies. A summary of recommendations is presented. We assessed the overall evidence to be strong and of fair quality.

Conclusion: The rehabilitation setting, and processes, logistics, and patient and healthcare provider precaution recommendations identified aim to reduce the spread of SARS-CoV-2 infection and ensure adequate and safe rehabilitation services, whether face-to-face or through teleservices. The COVID-19 pandemic is rapidly changing. Further updates will be needed over time in order to incorporate emerging best evidence into rehabilitation guidelines.

Keywords: COVID-19, pandemic, rehabilitation, health system, GRADE, SARS-CoV-2, scoping review

INTRODUCTION

The coronavirus disease-19 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in March 2020 (WHO, 2021). As of May 27, 2021, 169,615,273 cumulative cases and 3,524,490 deaths (Ritchie et al., 2020) were reported globally. The United States, with a population of 331.4 million people, continued to have the highest burden of COVID-19 on this date, with 33,999,680 cases and 607,726 deaths (Centers for Disease Control and Prevention, 2020). India, the second-most populous country in the world with 1.4 billion people, had 27,547,705 cases and 318,821 deaths (Ministry of Health and Family Welfare, 2020).

The COVID-19 pandemic caused by SARS-CoV-2 has created a significant burden on healthcare systems, economies, and social systems around the world (WHO, 2021). An ongoing concern with the COVID-19 pandemic is the unknown rate of transmission amongst asymptomatic carriers (Zhao H. et al., 2020). Infected individuals are contagious up to 48 h prior to the development of symptoms (Huff and Singh, 2020). As a result, many countries implemented significant public health requirements that changed the daily practices of their citizens.

Local policies on social distancing, closure of non-essential services, and stay-at-home orders have impacted outpatient medical and rehabilitation access to care. In a survey of individuals with chronic neurologic disorders at a center in Italy, nearly one-third of individuals experienced a delay in medical or rehabilitative care, with 19% of individuals reporting a subjective worsening of symptoms (Piano et al., 2020). Loss of rehabilitation services can lead to a decline in physical function and increased symptoms (Manto et al., 2020; Naser Moghadasi et al., 2020).

The provision of rehabilitation services for persons with active COVID-19 infection poses many challenges to maintaining a safe environment for both patients and treating providers. For example, the required use of immunosuppressant agents in individuals with conditions such as multiple sclerosis and some types of cerebellar ataxias increases susceptibility to severe complications from COVID-19 infections. In certain cases, it may be more judicious to delay rehabilitation admission until patients are no longer at risk of spreading COVID-19 infection to uninfected individuals. The recommended time period for an individual to be considered "no longer at risk" is at least 10 days following symptoms onset and 2–3 days symptom-free after discontinuation of antipyretic medications (Faux et al., 2020; Miles et al., 2021). Based on local health department and hospital protocols, recommendations may also include two separate negative COVID-19 test results on subsequent days (Faux et al., 2020; Miles et al., 2021).

While awaiting resolution of SARS CoV-2 in infected patients, infectivity prevents the timely transfer of patients from the acute care or hospital setting, which then delays rehabilitation care and results in bed shortages in the acute care setting. However, specialized rehabilitation units can meet the needs of those who are currently SARS CoV-2 positive. Prior to admission to these specialized units, patients should be screened to assess whether their physical and medical needs can be met at the rehabilitation facility. Dedicated staff should be allocated to the facility and enhanced personal protective equipment (PPE) such as N95 respirators, face shields for eye protection, gloves and a full-body suit or gown to prevent particle deposition on clothing should be utilized (Levi et al., 2020).

A significant challenge for inpatient rehabilitation facilities has been SARS CoV-2 infection prevention in units that provide care for non-infected individuals. It has been reported that in skilled nursing facilities the risk for infection outbreaks is high due to the large number and variety of individuals who need to be in close contact with patients in order to provide adequate care (Appeadu et al., 2020). Furthermore, persons admitted to rehabilitation facilities often have physical impairments that require caregivers to be educated on how to provide physical assistance at home (Gimm et al., 2017; Appeadu et al., 2020).

The COVID-19 pandemic has also accelerated the need for telehealth strategies such as video calls and applications to facilitate access to medical and rehabilitation care. While these strategies have multiple advantages, several limitations exist. First, patients utilizing telehealth need a prior understanding of how to utilize the technology, making access difficult for cognitively impaired individuals and older adults who may not

be technologically savvy (Levi et al., 2020; Sahu and Rathod, 2020). Second, data safety and privacy are of concern with the use of telehealth services (Cottrell and Russell, 2020; Scherrenberg et al., 2020), and can impose barriers for utilization by both the patient and the practitioner when adequate training has not been provided (Deverell et al., 2020). These necessitate the use of unfamiliar applications to facilitate the secure exchange of medical information. Third, costs, including the initial infrastructure to support telehealth services and decreased or absent reimbursement (Besnier et al., 2020; Cottrell and Russell, 2020), are a frequent barrier to delivering telehealth services. Additionally, affordability of devices to access telehealth can be a concern for patients residing in poorer regions (Deverell et al., 2020). Fourth, internet accessibility and connectivity can limit usability (Caze Ii et al., 2020; Polgar et al., 2020; Sahu and Rathod, 2020; Salawu et al., 2020), particularly in less populated areas. Fifth, there is a lack of scientific evidence demonstrating the efficacy of telehealth strategies for rehabilitation treatment (Salawu et al., 2020; Miles et al., 2021). While patients have reported high levels of satisfaction when utilizing telehealth for musculoskeletal physiotherapy (Cottrell and Russell, 2020), there is a need for further research into the use of telehealth strategies. The development of a successful telehealth program requires extensive work at both the early development stage (determining materials, assessments, communication functions) and the transition to a format suitable for telehealth (Caze Ii et al., 2020; Cottrell and Russell, 2020). Finally, few telehealth guidelines for rehabilitation professionals exist.

Due to the rapidly changing impact of the COVID-19 pandemic on healthcare systems globally, and the significant necessity for timely and accessible rehabilitation services, there is a critical need for wide-scale and generalizable rehabilitation-related recommendations. In response to the global pandemic, we launched a COVID-19 task force in the American Congress of Rehabilitation Medicine (ACRM) to help address the lack of contemporary research assessing the impact of COVID-19 on rehabilitation. The task force is a cross-national and multidisciplinary team of clinicians and researchers with diverse rehabilitation and health services expertise across care settings. This report presents system-related rehabilitation recommendations to address the current COVID-19 pandemic and future outbreaks that may affect the delivery of rehabilitation services. More specifically, these recommendations were formulated to support rehabilitation care for individuals with complex healthcare needs and functional limitations who are at higher risk for contracting COVID-19, as well as COVID-19 survivors. We include infection prevention and PPE recommendations, while acknowledging facility-specific and local health policies for mitigating COVID-19 spread (Gimm et al., 2017; Levi et al., 2020; Miles et al., 2020; Salawu et al., 2020).

MATERIALS AND METHODS

We utilized the framework proposed by Arksey and O'Malley (2005) and Levac et al. (2010) to guide our scoping review methodology. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) guidelines were followed to ensure consistency and high quality of research reporting (Tricco et al., 2018).

Development of Research Questions

Our main concept of interest was rehabilitation care (including physiotherapy, occupational therapy, speech-language pathology, physiatry, psychology and other rehabilitation professions) during the COVID-19 pandemic. Our outcomes of interest were rehabilitation related recommendations from health systems, without restriction to country, based on expert opinion, consensus, or research data.

Identifying Relevant Studies

A health science librarian conducted a comprehensive literature search using the Medline, Embase, Pubmed, CINAHL databases (from inception to August 1, 2020), and identified though rehabilitation organizations' websites. Study team members conceptualized the search strategy based on the COVID-19 pandemic and rehabilitation concepts, with multiple text words and subject headings (e.g., MeSH) describing each concept. The search strategy was limited to full-text articles in English (see **Supplementary Material**).

Selection Criteria

Manuscripts/reports were included if they focused on rehabilitation recommendations for addressing COVID-19, COVID-19 survivors, or the general population at the time of the COVID-19 pandemic.

Screening and Study Selection

Search results were uploaded to the Covidence platform (Covidence, 2014). After removing duplicates, four team members (MZ, AS, VM, AN) were paired and independently reviewed the titles and abstracts using the inclusion criteria. If there were insufficient details to make an informed decision on an article, the article was retrieved for review. To confirm eligibility, two team members (MZ, AS, VM, AN) independently assessed the full-text articles using the same inclusion criteria. Any disagreement was resolved through consensus or third-party adjudication (AN).

Data Extraction

A standardized data abstraction form was created and pre-tested. Team members in pairs (MZ, AS, VM, AN) then used the pre-tested data abstraction form to abstract data from included full-text articles.

Quality Assessment

The strength and the quality of the extracted recommendations were evaluated by two reviewers (MZ, VM) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (Andrews et al., 2013; Neumann et al., 2014). The strength of the recommendation evidence included four possible categories: (1) Strong recommendation for, (2)

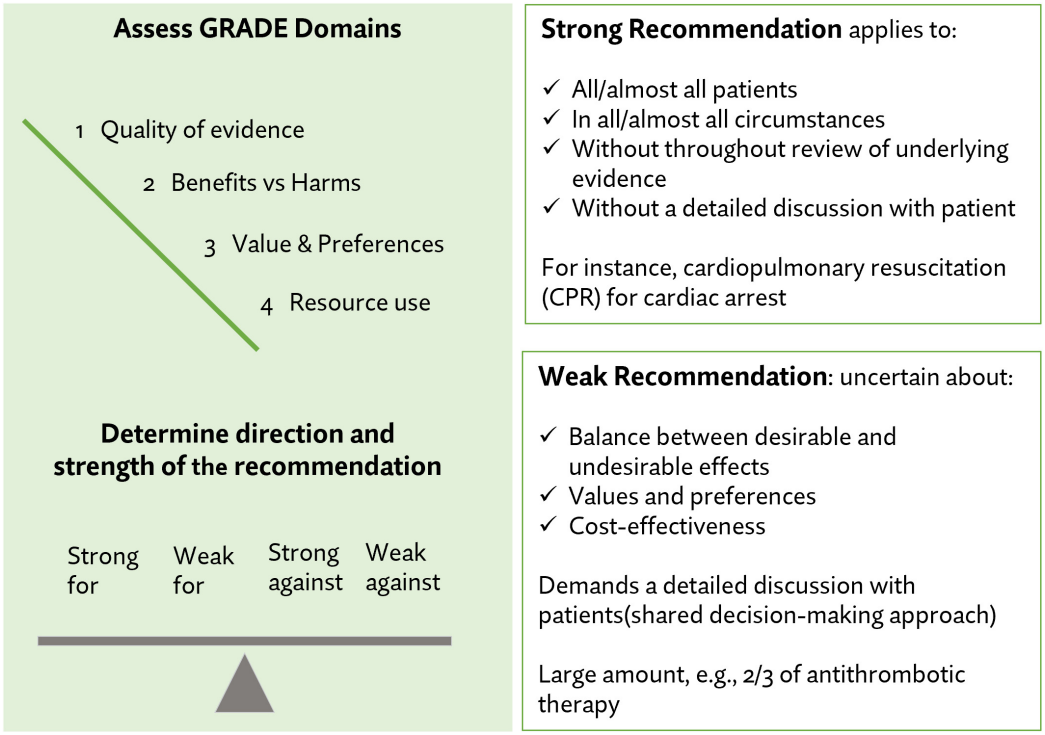

FIGURE 1 | Strength and quality assessments for individual recommendations.

weak recommendation for, (3) weak recommendation against, or (4) strong recommendation against. **Figure 1** shows the GRADE strength categories and outlines the clinical application of recommendations based on level of strength. Three categories were used to assess the quality of recommendation: (1) Good, (2) fair, and (3) poor. The quality and strength of the extracted recommendations are presented in the results.

Summarizing and Reporting the Findings

We organized the extracted recommendations into several sections. For each section, a summary of contributing studies, along with the strength and the quality of recommendations are reported.

RESULTS

We retrieved 6,468 citations, of which 2,086 were eligible after duplicates were removed. Of those, 1,980 citations were excluded based on the title and the abstract screening. Of the screened full-text articles, 106 studies from 22 countries (including low-income, middle-income and high-income) reported COVID-19 related recommendation (**Figure 2**). Of these articles, 69 articles reported health system-related recommendations.

The Extracted Recommendations

A set of health system focused recommendations related to the COVID-19 pandemic is presented. The recommendations were grouped as follows: (1) recommendations for the rehabilitation inpatient facility setting, the discharge process and the outpatient setting; (2) recommendations related to health system elements e.g., rehabilitation equipment/workplace, human resources and telerehabilitation; and (3) precautions for patients and rehabilitation professionals (see **Figure 3**).

Quality and Strength of the Recommendations

Based on the GRADE approach for evidence quality assessment, we have determined the overall evidence for the recommendations included in our report to be strong and of fair quality (**Table 1**). The strength of each recommendation is reported in **Supplementary Table 1**.

Rehabilitation Inpatient Facility

Ten articles that addressed recommendations for rehabilitation inpatient facility, published from April 13, 2020, to August 6, 2020 (Bartolo et al., 2020; Boldrini et al., 2020; Grabowski and Joynt Maddox, 2020; Juárez-Belaúnde et al., 2020; Mammi et al., 2020; Pedersini et al., 2020; Qu et al., 2020; Sheehy, 2020; Simpson and Robinson, 2020; Sonel Tur and Evcik, 2020; Tur and Evcik, 2020), were identified. Six countries—Spain (n = 1), Italy (n = 4), China (n = 1), Turkey (n = 1), Canada (n = 2), US (n = 1), and 10 different institutions, including hospitals, scientific societies, and universities were represented (see **Supplementary Table 1**).

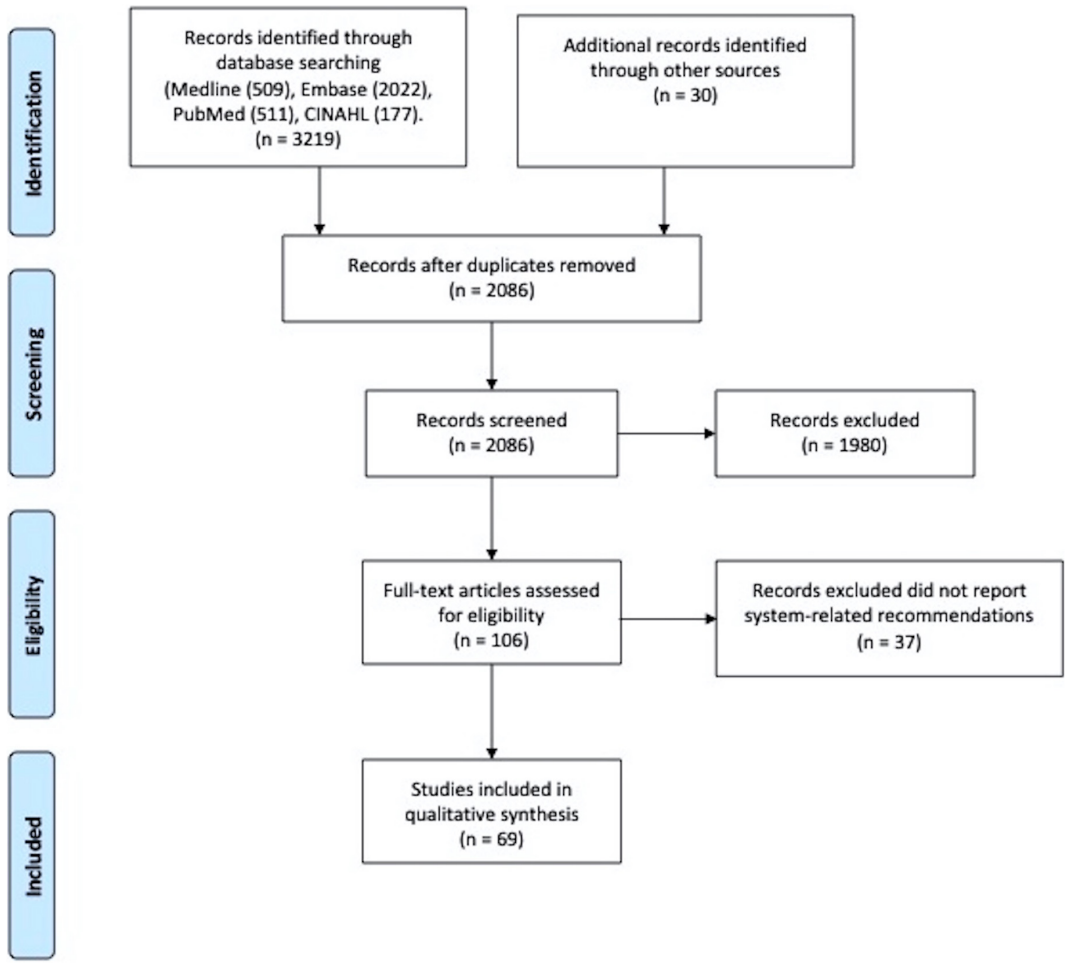

FIGURE 2 | PRISMA flow diagram.

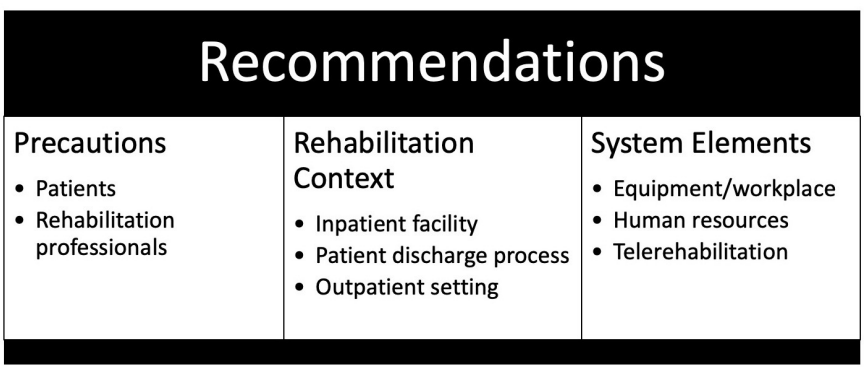

FIGURE 3 | Structure of health system recommendations.

The recommendations found in these 10 articles were based on expert opinion and/or clinical experience. Expertise included the following: researchers (n = 3), rehabilitation and medical professionals (n = 5), and unknown (n = 2, did not report the group involved in developing the recommendations).

Summary of Key Recommendations

- Control the entrance of patients to rehabilitation institutions.
- Standardize pre-examination triage points at outpatient and emergency departments.

TABLE 1 | Recommendations quality.

Standard	Rating
Establishing transparency	Fair
Management of COI* in the guideline development group	Fair
Recommendation development group composition	Good
Recommendation development (evidence-based)	Fair
Establishing evidence foundations and rating strength for each of the recommendations	Fair
Articulation of recommendations	Fair
External review	Not reported
Updating	Fair
Implementation issues	Not reported

**COI, Conflict of interest.*

- Formulate institutional screening procedures for patient admission during the pandemic in accordance with the risk level of the country and region.
- Expedite screening and diagnosis of patients with suspected infection, implement isolation measures quickly, and shorten the time between diagnosis and hospitalization.
- Post notices of behavioral rules at the entrances of, and within all departments.
- Post recommendations for hand hygiene near hand-sanitizing gel dispensers.
- Limit admissions to rehabilitation wards to essential admissions, provide oversight to ensure essential admissions only, and prepare personnel with protective equipment. Close access to all other rehabilitation wards.
- Treat patients in individual rooms before SARS-CoV-2 infection is ruled out. Transfer patients to a conventional ward for further hospitalization after ruling out SARS-CoV-2 infection.
- Proactively monitor nosocomial infections in hospitalized patients to establish health monitoring and a mandatory reporting system for all hospital personnel, including all medical, nursing, management, logistics, cleaning, security, delivery, and other staff.
- Caregiver visits to hospitalized patients to be authorized by clinicians according to the rules of health management. Staff to manage access to avoid any physical contact, even for a limited time.
- Screen and manage escorts and visitors as necessary. Monitor body temperature for all health personnel and visitors with permission. Body temperature should be $\leq 37.5°C$.
- Prohibit access and provide indication for home isolation for individuals with higher temperature.
- Offer virtual visits.
- Suspend all in-person meeting activities and replace them with telephone, email, or other virtual meeting tools.
- Suspend all rehabilitation activities that require internal flow (movement between floors or between floors and gym) for patients with COVID-19.
- Transition all non-essential treatments to a telerehabilitation/virtual reality modality. Manage clinical cases through telephone or webcam counseling to supervise exercise sessions that can be temporarily self-managed by the patient or caregiver.
- When viral variants of COVID-19 are present, evaluate the reintroduction of certain contact situations with appropriate PPE and devices for circumstances that require urgent hands-on treatment to protect the patient from harmful consequences (e.g., hypo-mobility, respiratory dysfunction, or contextual factors).

Patient Discharge Process

Recommendations related to patient discharge were based on six articles, all of which were clinical experience or opinion articles (Alberta Health Services, and Scientific Advisory Group Representative, 2020; Grabowski and Joynt Maddox, 2020; Kemps et al., 2020; Pinto and Carvalho, 2020; Qu et al., 2020; Sheehy, 2020). These articles were published from April 27, 2020, to July 16, 2020, and represented six institutions, including hospitals, scientific societies, and universities from five countries—United States (n = 1), Netherlands (n = 1), Canada (n = 2), Brazil (n = 1), China (n = 1) (see **Supplementary Table 1**). Of the six articles, two were published by researchers, and three were published by rehabilitation and medical professionals. The remaining article did not report the group involved in developing the recommendations.

Summary of Key Recommendations

- Avoid transferring patients with COVID-19 into the mainstream skilled nursing facility population, as patients may still be able to transmit the disease.
- Provide discharged patients who are released from isolation to the community setting with various comprehensive rehabilitation treatment options as appropriate based on the type of dysfunction experienced by the patient.
- With regard to occupational therapists or health professionals with similar training in discharge planning:
    - Prepare and plan for discharge, including home safety and caregiver supports.
    - Consider social determinants of health when discharge planning (e.g., income).
- For patients discharged to home or to other facilities in the community, provide guidance on ways to manage and closely monitor physical activity.
- Develop a template for patients discharged from acute care that addresses immediate needs and rehabilitation considerations using available tools such as the Patient-Oriented Discharge Summary or Rehabilitation Prescription.

Outpatient Rehabilitation Setting

Seven articles that addressed the outpatient rehabilitation setting (Azhari and Parsa, 2020; Boldrini et al., 2020; Ismail, 2020; Koumpouras and Helfgott, 2020; Phillips et al., 2020; Piepoli, 2020; Polastri et al., 2020) were identified. These articles, all

expert opinion articles, were published from April 1, 2020, to June 5, 2020, representing five countries—Iran (n = 1), Italy (n = 3), Egypt (n = 1), Canada (n = 1), United States (n = 1) and seven institutions including hospitals, scientific societies, and universities (see **Supplementary Table 1**). Of the seven articles, three were developed by researchers, and the remaining four articles were developed by rehabilitation and medical professionals.

Summary of Key Recommendations

- Provide instructions about social distancing and hand hygiene for both patients and staff at entrance.
- Disinfect all devices and equipment after each session.
- If there is insufficient PPE, consider cancelation of a patient appointment in the case of suspected or confirmed COVID-19.
- Introduce home and community-based physical therapy care via mobile applications to patients who would be most impacted by canceled rehabilitation or exercise sessions at outpatient clinics.

Rehabilitation Equipment/Workplace

Four expert opinion articles addressing rehabilitation equipment and workplace (Grabowski and Joynt Maddox, 2020; Mammi et al., 2020; Sheehy, 2020; Thomas et al., 2020) were identified. Article publication dates ranged from March 30, 2020, to May 26, 2020. Five countries—[Italy (n = 1), Australia (n = 1), Belgium (n = 1), Canada (n = 2), and United States (n = 1)] and four institutions including hospitals, scientific societies, and universities were represented (see **Supplementary Table 1**). Of the four articles, two were developed by rehabilitation and medical professionals, and one was developed by researchers. The remaining article did not report the group involved in developing the recommendation.

Summary of Key Recommendations

- Create separate working spaces e.g., separate therapy spaces, offices, gym(s), a front office, and a visitor waiting room.
- Decontaminate shared equipment between patients. Use single use equipment, when possible, e.g., Thera Bands rather than hand weights. Pay particular attention to decontaminating electrode sponges, hydrocollator heat packs, gels, topical lotions, and items for training manual dexterity.
- Identify additional physical resources required for physiotherapy interventions. Disinfect equipment to minimize the risk of cross-infection e.g., respiratory equipment; mobilization, exercise and rehabilitation equipment; and equipment storage containers.
- Identify and develop a facility inventory of respiratory, mobilization, exercise and rehabilitation equipment and determine the process of equipment allocation as pandemic levels increase (i.e., to prevent movement of equipment between infectious and non-infectious areas).

Human Resources

Four expert opinion articles that addressed human resources in rehabilitation (Bartolo et al., 2020; Grabowski and Joynt Maddox, 2020; Sheehy, 2020; Thomas et al., 2020) were identified. These articles were published from April 30, 2020, to May 26, 2020, representing five countries [Canada (n = 2), Italy (n = 1), Australia (n = 1), Belgium (n = 1), and the United States (n = 1)] and four institutions including hospitals, scientific societies and universities (see **Supplementary Table 1**). Of the four articles, one was developed by researchers, and two were developed by rehabilitation and medical professionals. The remaining article did not report the group involved in developing the recommendations.

Summary of Key Recommendations

- Recruit additional staff to perform tasks with attainable skills and that can be acquired relatively quickly.
- Plan for an increase in the required physiotherapy workforce. For example:
    - Allow additional shifts for part-time staff.
    - Offer staff the ability to electively cancel leave.
    - Recruit a pool of staff available to work on an *ad hoc* basis.
    - Recruit academic and research staff, and staff who have recently retired or are currently working in non-clinical roles.
    - Allow for work in different shift patterns (e.g., 12-h shifts, extended evening shifts, etc.).
- Require physiotherapists to have specialized knowledge, skills and decision-making ability to work within the intensive care unit (ICU) setting. Have hospitals identify physiotherapists with previous ICU experience and ask them to return to the ICU setting.
- Have hospitals identify physiotherapists without recent cardiorespiratory physiotherapy experience and have them support additional hospital services. For example, physiotherapists without acute care or ICU training could be trained for non-clinical duties e.g., facilitate rehabilitation and discharge pathways.
- Identify existing learning resources for staff who could be deployed to the ICU setting. For example:
    - eLearning packages (e.g., Clinical Skills Development Service for Physiotherapy and Critical Care Management).
    - Local physiotherapy staff assistance with ICU orientation.
    - PPE training.
- Ensure staff at high risk do not enter the COVID-19 isolation area. When planning for staffing and developing rosters, staff at higher risk of developing serious illness from COVID-19 should not be scheduled to work with or be exposed to infected patients; this includes staff who
    - Are pregnant
    - Have significant chronic respiratory illnesses

- Are immunosuppressed
- Are > 60 years of age
- Have severe chronic health conditions such as heart disease, lung disease, and diabetes.
- Have immune deficiencies, such as neutropenia, disseminated malignancy, and conditions or treatments that produce immunodeficiency.

- Include considerations for workforce planning for pandemic-specific requirements such as donning and doffing PPE and for non-clinical duties such as enforcing infection control procedures.
- Recognize that staff will likely have an increased workload and a risk of heightened anxiety at work and home. Support staff during and beyond the active treatment phases e.g., via access to employee assistance programs, counseling, and facilitated debriefing sessions.

Telerehabilitation

Eighteen articles that addressed telerehabilitation (Besnier et al., 2020; Chang and Boudier-Revéret, 2020; D Leochico, 2020; Grabowski and Joynt Maddox, 2020; Hosey and Needham, 2020; Ismail, 2020; Juárez-Belaúnde et al., 2020; Kemps et al., 2020; Maggio et al., 2020; Pedersini et al., 2020; Piepoli, 2020; Rehabilitative Care Alliance, 2020; Tenforde et al., 2020; Verduzco-Gutierrez et al., 2020; Viswanath and Monga, 2020; Yeo et al., 2020; Zhao H. M. et al., 2020; Handu et al., 2021) were identified. Of the 18 articles, 17 were developed based on expert opinion and/or clinical experience, and one was developed using a combination of expert and/or clinical experience and evidence-based methods, including systematic review, survey, and observational studies. The articles were published from April 1 to July 16, 2020, representing 11 countries [Netherlands (n = 1), United States (n = 5), China (n = 1), Italy (n = 3), Philippines (n = 1), United Kingdom (n = 1), Canada (n = 2), Singapore (n = 1), South Korea (n = 1), Egypt (n = 1)]—and eighteen institutions including hospitals, scientific societies, and universities (**Supplementary Table 1**). Of the 18 articles, ten were developed by researchers and seven were developed by rehabilitation and medical professionals. The remaining article did not report the group involved in developing the recommendations.

Summary of Key Recommendations

- Replace face-to-face sessions with remote assessment and monitoring/guidance, use telephone, text messaging, emails, video consultations, web-based platforms and applications, based on availability of local equipment and expertise.
- Use telemedicine to provide interventions typically facilitated by rehabilitation professionals e.g., physiotherapy, speech therapy, occupational therapy, patient telemonitoring, and teleconsultation, and assisting home-bound patients.
- Utilize telemedicine to provide emotional support to patients, ensure appropriate home adaptation, and prepare family members prior to discharge.
- Use telemedicine platforms supported by smartphones to increase access.
- Advise patients to complete the encounter in a location that provides privacy.
- Account for factors that impact patient comfort when performing telehealth visits. These considerations include assessment of prolonged sitting and assessing the safety of the surrounding environment to perform balance testing.
- Give healthcare providers access to relevant patient medical records before patient visits, including prior patient visit records and diagnostic testing and imaging.
- Document the visit when the clinician connects with the patient. Ensure patient identification is checked prior to the start of the visit for a new patient or for a patient without scanned identification in the medical record or patient file. In addition, obtain verbal consent from patients for telemedicine and provide a brief orientation to telemedicine at the start of the patient encounter.
- Record the patient's location at the time of visit and gather emergency contact information. Document the chief complaint and reason for the visit and demographics (e.g., age, sex, gender, race/ethnicity).
- Encourage patients to have their medications on hand for documentation of medication reconciliation.
- Provide each patient with instructions prior to the visit on how to access the software platform. Programs can perform a "test call" with support staff to ensure the device runs the software correctly and has sufficient digital connection, ideally in the planned location for a telemedicine visit.
- Provide patient access for the visit through a secure URL link, or existing smartphone apps with a "virtual waiting room."
- Follow a sequence mirroring an in-person visit, including identifying the chief complaint and purpose for the visit, along with relevant history.
- Use instant messaging software or apps for coordination between providers and office staff during and after the visit.
- Document the telemedicine visit similar to how an in-person visit is documented.
- Advise virtual visits during the COVID-19 pandemic to facilitate appropriate physician compensation for the visit.
- Record history of present illness, relevant past medical, surgical, family and social history; review of systems; functional status, and drug allergies.
- For physical examination, optimize observations through a video platform. Document patient instructions in narrative and descriptive format.
- Considerations when contemplating virtual care delivery of rehabilitation interventions:
  - Older adult's access to technology, internet and other limitations e.g., communication abilities.
  - Potential safety issues. Engage informal caregivers to provide assistance for safety and/or for technical support.
  - Type of older adult's disability e.g., hearing or vision and its impact on their ability to participate.

- Older adult's cognitive ability, and subsequent implications for safety, ability to complete a self-directed program and receipt of any information or instructions.
- Awareness of confidentiality issues if the older adult is living in a multi-person household. Offer to provide additional sessions via phone call or private in-person visits for sensitive issues.
- Accept digital consents or signatures for paperwork where originals are required to avoid delays because of mailing time.
- Accommodate the needs of older adults and their caregivers by being flexible.
- Allow for extra time to build rapport and trust.
- Anticipate potential technical issues.
- Provide virtual care options for psychosocial support during the in-hospital stay as a mode to enable social engagement and caregiver involvement.

Rehabilitation Patient Precautions

Seven articles that addressed rehabilitation patients' precautions (Bartolo et al., 2020; Mammi et al., 2020; Reuter-Oppermann et al., 2020; Romano-Bertrand et al., 2020; Sheehy, 2020; Thomas et al., 2020) were identified. These articles, all expert opinion articles, were published from March 30, 2020, to August 1, 2020, representing eight countries [Italy (n = 3), Germany (n = 1), Austria (n = 1), Switzerland (n = 1), France (n = 1), Australia (n = 1), Belgium (n = 1), Canada (n = 2)] and seven institutions including hospitals, scientific societies and universities (**Supplementary Table 1**). Of the seven articles, two were developed by researchers, four were developed by rehabilitation and medical professionals. The remaining publication did not report the group involved in developing the recommendations.

Summary of Key Recommendations

- For patients using rehabilitation facility tools/gym/pool, ensure, and encourage:
  - Hygiene and behavioral rules before entrance into pools.
  - Use of individual dressing rooms. Use of individual dedicated compartments to hang clothes.
  - Use of soap and water for showers and use booth bath when possible.
  - Swim cap and swimming goggles in pools.
  - Avoidance of bathers suspected of/infected with COVID-19 or with respiratory and/or digestive symptoms.
  - Use of hand sanitizers at the entrance to the facility.
  - Use of surgical masks until reaching the dressing room and when dressed post bathing.
  - Posting of signs for a 2-m circumference physical distancing rule.
  - If patients need to sneeze and/or cough, they should do so directly into their hands, then immediately wash hands with soap and water.
  - Avoid touching face, nose, mouth, and eyes.

Rehabilitation Professionals Precautions

Thirteen articles that addressed precautions for health professionals (Bartolo et al., 2020; Grabowski and Joynt Maddox, 2020; Japan ECMOnet for Covid-19, 2020; Kleinpell et al., 2020; Pandian and Sebastian, 2020; Pedersini et al., 2020; Qu et al., 2020; Reuter-Oppermann et al., 2020; Romano-Bertrand et al., 2020; Sheehy, 2020; Thomas et al., 2020; Zeng et al., 2020; Handu et al., 2021) were identified. These articles were published from March 30 to August 1, 2020 representing 11 countries [Australia (n = 1), Belgium (n = 1), Canada (n = 2), Germany (n = 1), Austria (n = 1), Switzerland (n = 1), Italy (n = 2), China (n = 2), France (n = 1), India (n = 1), and the United States (n = 4)] and 13 institutions including hospitals, scientific societies and universities (**Supplementary Table 1**). Twelve articles were developed based on expert opinion and/or clinical experience, and one was developed using evidence-based methods, including systematic review, survey and observational studies. Of the 13 publications, five were developed by rehabilitation and medical professionals, six were developed by researchers. The remaining two articles did not report the group involved in developing the recommendations.

Summary of Key Recommendations

- Plan therapeutic activities to minimize the number of personnel involved, when possible, e.g., one therapist with a gait aid rather than a therapist and an assistant.
- Minimize the number of personnel entering a patient's room. Have a single staff member perform most (if not all) of the care and duties for a particular patient e.g., delivery of food trays, making the bed, giving medications, and helping with morning care.
- Educate and empower all healthcare professionals involved in rehabilitation teams.
- Train all staff in correct donning and doffing of PPE, including N95 "fit-checking." Maintain a registry of staff who have completed PPE education and fit checking.
- For healthcare workers:
  - Ensure strict adherence to mitigating measures in order to prevent cross-transmission outside of pools/gyms.
  - Wear a surgical mask or goggles or face shield when in close contact with patients.
  - Maintain physical distancing of at least a 2-m circumference.
  - Practice regular hand hygiene and avoid touching face and eyes.
- Include additional PPE precautions for staff caring for COVID-19 infected patients and/or those with significant respiratory illness, e.g., in situations when aerosol-generating procedures and/or prolonged or very close contact with the patient are likely. For all confirmed or suspected cases, implement droplet precautions at a minimum. Have staff adhere to following:

  - Surgical mask, FFP2 or FFP3 mask.
  - Fluid-resistant long-sleeved gown.
  - Goggles or face shield.
  - Gloves.

- Additional considerations for Staff:

  - Hair cover for aerosol-generating procedures.
  - Shoes impermeable to liquids that can be wiped down. The use of recurrent shoe covers is not recommended as repeated removal is likely to increase the risk of staff contamination.

- In dedicated units caring for a patient with confirmed or suspected COVID-19, implement patient and staff supervision of all donning and doffing by an additional appropriately trained staff member.
- Preferably only use single-use equipment and avoid sharing equipment.
- Have staff wear an additional plastic apron if a large volume of fluid exposure is expected.
- Have staff clean and disinfect any PPE items that are to be reused, e.g., goggles.
- Have staff wear scrubs and a T-shirt at work; have them shower and change into street clothes before going home.
- Have staff adhere to the following guidelines:

  - Change clothes before and after work
  - Shower before rejoining family.
  - Limit or avoid physical contact until after showering
  - Use alcohol-based hand sanitizer before entering the home.
  - Shower and wash clothes away from family.
  - Isolate from family members and wear a mask while at home.

DISCUSSION

A comprehensive summary of healthcare system related recommendations for rehabilitation services and settings (inpatient, discharge process, outpatient), logistical considerations (equipment, human resources and telerehabilitation), and precautions for both patients and rehabilitation professionals has been developed through this scoping review. The majority of the recommendations were based on expert opinions and/or consensus. The overall quality of the recommendations was determined to be fair, and most of the individual recommendations were graded as strong.

We anticipate the COVID-19 pandemic and subsequent generation of evidence will continue to evolve. Planning is underway to update the recommendations presented in this review in the near future, incorporating the most recent evidence. As COVID-19 vaccinations become more available and vaccine uptake increases across the globe, the impact of COVID-19 may lessen, and as a result the need for, and type of recommendations may change.

The impact of the COVID-19 pandemic extends beyond the number of individuals who have contracted the virus. Secondary negative effects of social isolation resulting from the required implementation of health policies for mitigating COVID-19 spread and the challenges in accessing health services are evident (Lebrasseur et al., 2021). Implementation of evidence-based and clinically relevant strategies to ensure the provision of health services for those impacted by COVID-19 is essential.

The strengths of our scoping review include pre-specified eligibility inclusion criteria, a comprehensive and up-to-date search strategy, and the inclusion of relevant articles from low-income, middle income, and high-income countries. Our review utilized duplicate assessments for eligibility determination, data extraction, evidence synthesis, and application of the GRADE method (Andrews et al., 2013; Neumann et al., 2014) in rating the strength and quality of the recommendations. Additionally, both published literature and the experiences of a multidisciplinary author team were used to develop the summary.

While this review synthesized and summarized the best available recommendations published to date, there are several limitations. We acknowledge that included recommendations were largely from expert opinion and clinical experience-based articles rather than higher-level primary studies, e.g., randomized controlled trials (RCTs). Although systematic reviews, meta-analyses, RCTs, and observational studies provide a higher level of evidence, primary studies or systematic reviews related to COVID-19 rehabilitation recommendations were not found. This is not entirely surprising considering the rapid onset and the "newness" of having to manage healthcare within the context of the COVID-19 pandemic.

In conclusion, the comprehensive summary of health-system-related rehabilitation recommendations for the global COVID-19 pandemic focuses on reducing the spread of SARS-CoV-2 infection and ensuring adequate and safe rehabilitation services, whether face-to-face or through teleservices, as appropriate. As the COVID-19 pandemic is rapidly changing, further updates are warranted in order to incorporate emerging evidence into rehabilitation guidelines.

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

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SUPPLEMENTARY MATERIAL

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Can Technology Abate the Experience of Social Isolation for Those Affected by Dementia?

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Background: The widespread social isolation measures recently utilized to mitigate the spread of COVID-19 to older adults may have exuded unexpected consequences. Social isolation among older adults is a risk factor for poor health outcomes. Innovative solutions to balancing public safety and health maintenance for those with dementia and their caregivers are needed.

Methods: A sample of *N* = 82 dementia caregivers participated in a web-based survey to investigate their perceptions on (1) changes in personal mental health due to isolation from their loved one, and (2) the perceived need for use of smart mobile device app use in these situations.

Results: The majority of our sample (87%) reported experiencing negative mental health outcomes beyond those experienced in typical situations. Furthermore, over 70% of caregivers were concerned with the care their loved on received during social isolation. Finally, 67% reported perceived need to use SMD apps in these times of social isolation.

Conclusion: Our findings provide preliminary insight into troubling consequences occurring when individuals with dementia are socially isolated from their caregivers. An inverse relationship between SMD app use and poor mental health points to the potential for communication technology to lessen the negative impacts of social isolation, when it becomes necessary to public safety.

Keywords: dementia, caregiver, mobile device, applications, isolation

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INTRODUCTION

The need for research specifically on social isolation measures between an individual with Alzheimer's disease and related dementias (ADRD) and their informal caregiver is supported by an understanding of the way in which various forms of isolation, and the experience of loneliness that can result, negatively impact health outcomes. Research has shown that isolation and loneliness are positively associated with cardiovascular disease, diabetes, risky health behaviors, and poorer cognition (Shankar et al., 2013). Recent evidence has pointed to social isolation, in the more general sense, as one of 12 modifiable risk factors (lower education, hypertension, obesity, hearing loss, smoking, depression, low physical activity, social isolation, and diabetes)

that contribute to approximately 35% of dementia cases (Livingston et al., 2017). Therefore, social distancing measures should be considered in light of both the health risks avoided *and* created by social isolation.

Social Isolation and Dementia in the COVID-19 Pandemic

Social isolation has taken on a new meaning with the COVID-19 pandemic and the subsequent quarantine and social distancing public health measures implemented in both community and institutional settings across the globe. While initiated to lessen the spread of COVID-19, quarantine and social isolation procedures have in many cases led to the seclusion of vulnerable individuals, such as individuals with ADRD. Within this article, the term social isolation is primarily focusing on public health measures restricting hospital and extended care-facility visitation for extended periods, separating those with ADRD from their family members or informal caregivers. This drastic change in access to meaningful interpersonal relationships and social support cannot be overlooked. Furthermore, the social isolation measures designed to support safety, and reduce risk for the aging population, must be weighed against the potential negative impact that social isolation may have on quality of life.

The measurable impacts of social isolation in those with dementia should be further elucidated through improved understanding of the caregivers' perspectives, as informal caregiver roles are commonly assumed by family members who advocate for the health and well-being of their loved one. The health of caregivers is measurably impacted (e.g., incidence of caregiver burden and negative mental health outcomes) by their role as a care provider (Brodaty et al., 2014; Park et al., 2015; Coffman et al., 2017; Liu et al., 2017). The unique context of strict social isolation with the onset of COVID-19 has the potential to impact both those with ADRD and caregivers in negatively. One might posit that separation from a care recipient could lessen burden of care and ongoing responsibilities for a caregiver. However, the negative outcomes of social isolation that result in separation of an informal caregiver (often a family member) from their loved one may instead produce worry and anxiety in the caregiver with regard to the well-being of their loved one. To improve the quality of life and care provision in conditions of social isolation, it is necessary to understand the perceptions of caregivers regarding the impact of social isolation from their loved ones, and the value of potential technology mediated solutions.

Technology use among older adults is increasingly prevalent (Anderson and Rainie, 2015; Pew Research Center, 2018, 2021). Therefore, it is an optimal point in time to increase research into the potential for technology mediated solutions for socially isolated older adults, to include those affected by dementia. van Boekel et al. (2019) carried out a systematic review of the available literature to investigate dementia stakeholder perspectives on technology use. Authors reported that technology use among those with dementia is facilitated by the potential for technology to prolong autonomy in the community setting (van Boekel et al., 2019). They also reported that technology use among dementia caregivers can help to alleviate stress and worry about their loved on with dementia (van Boekel et al., 2019). Both of these indicating the potential usefulness of technology mediated interventions to support both members of the ADRD dyad (caregiver and care recipient). Of interest, the authors note that the perspectives of community dwelling older adults with dementia aligned with the perspectives of healthy aging populations (van Boekel et al., 2019). Therefore, technology mediated communication to combat social isolation should be investigated in healthy aging, dementia, and caregiver populations.

The present study focuses on the impact of social isolation as perceived by ADRD caregivers. With increased use of smart mobile devices (SMD) across both age and socioeconomic demographics (Anderson and Rainie, 2015; Pew Research Center, 2018; Vogels, 2020), we will also investigate the use and perceptions of SMD apps as a possible solution to help compensate for physical separation through distance care and communication functions.

OBJECTIVE

The objectives of this study were to determine whether COVID-19 related social isolation between an individual with ADRD and a caregiver. . .

(1) Impacted caregiver mental health beyond what would be expected with caregiving in a typical context.
(2) Facilitated perceived need for use of smart mobile device (SMD) apps (e.g., video conference apps, messaging apps, browsers, etc.).

Our *a priori* hypotheses were (1) that social isolation related to the COVID-19 pandemic will be reported to increase poor mental health outcomes in caregivers beyond what is experienced in a typical context (e.g., non-COVID-19 isolation), and (2) that caregivers will report a perceived need for SMD app use during periods of social isolation. For the purpose of this study SMD refers to hardware that can house software (apps); the investigation is assessing use of apps, but inclusive of various types of SMDs such as smart phones or tablets pending participant preference.

MATERIALS AND METHODS

Design

This study adheres to a cross-sectional design *via* a single time point web-based survey.

Participants and Recruitment

Inclusion criteria included ≥18 years of age and the ability to read English or French (the survey was available in English and French) and providing informal care to an individual with ADRD. The definition of caregiver included spouses of individuals with dementia, adult children and other familial relations of individuals with dementia, and friends or other

community care providers of individuals with dementia. In order to capture broad experiences of ADRD caregivers the COVID-19 pandemic, both caregivers who experienced social isolation from their loved ones and those who had not, or had not *yet* experienced social isolation from their loved one could respond. The prompt indicated that if they had not been socially isolated from their loved one, they could respond based on expected experiences. This approach allows recruitment of a broader sample of caregivers that is not contingent on current means, access, or inclination to place their loved one with ADRD in a care-facility–a choice that could be influenced by socioeconomic status, context, or cultural values.

An *a priori* power analysis was complete on G*Power 3.1.9.3 software considering $f^2 = 0.15$, $p = 0.05$, and Power = 0.80, this yielded $N = 68$. Therefore, the target sample size was $N = 82$ participants to account for 20% attrition (attrition was anticipated to occur in this survey-based study when potential participants initiated the survey, but then discontinued due to inapplicability or lack of interest).

Email and social media were used for recruitment. Potential participants previously known to research personnel through existing networks and through rehabilitation and medical organization [i.e., AGE-WELL (a Canadian National Centre of Excellence on Technology and Aging Research), American Congress of Rehabilitation Medicine, and Quebec Health Research Network on Aging] list serves were contacted *via* email. Social media-based recruitment included posting to platforms such as LinkedIn, Twitter, and Facebook. Study methods were approved by the Centre Intégré Universitaire de Santé et de Services Sociaux de la Capitale-National Ethics Board (Ethics Approval No. CER 2020-1984).

Procedures

The survey created for the purpose of this study included 10 items designed to investigate the relationship between the caregiver and care recipient, disease severity of the individual with dementia (i.e., mild, moderate, severe), the incidence of care recipient isolation due to COVID-19, need for app use (as perceived by caregiver), type of apps used by caregivers, and caregiver mental health outcomes (see **Supplementary Appendix A**). Multiple choice or Likert scale response options were provided to assess both person factors and experiential variables. The survey also allotted space for open comments for participants to share additional thoughts and experiences. The survey was managed using Lime Survey Software version 2.05+ (Limesurvey GmbH, 2020) and released online from May to September 2020. Participants completed the survey based on their experiences and perceptions as to how hospitalization of the person they care for during COVID-19 did *or* could have impacted them (as a caregiver) and the care recipient. All surveys were completed anonymously.

Analyses

Survey results were analyzed using descriptive statistics (mean, standard deviation, frequency, proportion). A Principal Component Analysis (PCA) was used to evaluate the relationship of three independent variables (type of relationship to the individual with dementia, the disease severity of the individual with dementia, number of app types used) to the dependent variable of interest (number of negative mental health outcomes). The associations between these variables were explored using PCA for categorical data (SPSS, 26, proc CATPCA) to determine the most appropriate method of interpreting the data. While the classical PCA outputs loadings at the variable level, the categorical PCA outputs loadings for each category of each variable. Therefore, a graphical examination was then performed to determine whether the intervals between categories were equally spaced along the linear continuum associated to each variable. Further analyses were selected based on groupings of data (i.e., categories) that were closely located on the graph, and the slope of each continuum was considered to determine association (i.e., similar slopes indicative of a strong correlation and orthogonal slopes indicative of independence between variables) (Abdi and Williams, 2010). An ordinal regression model analysis (SPSS, 26, proc PLUM) was then completed to assess the influence of (1) relationship type (between caregiver and care recipient), (2) disease severity, and (3) extent of app use on number of mental health changes reported. Open-ended responses were summarized and documented, but no formal content analysis was conducted for the present report.

RESULTS

A total of 84 participants completed our survey (17 French surveys, 67 English). All participants were self-defined caregivers of an individual with ADRD. Of the 84 participants 54 (64.29%) were adult children providing care, 19 (22.62%) were spouses, 6 (7.14) were grandchildren, and 5 (5.95%) identified as other (to include a significant other, an art therapist, occupational therapist, and lifelong roommate) (see **Table 1**). Within our sample, 48 (57.14%) reported actively providing care to a person with ADRD, ranging from mild AD [9; (10.71%)]; moderate AD [29 (34.52%)]; and severe AD [31 (36.90%)] (see **Supplementary Table 1**).

A total of 67 (79.76%) caregivers reported that their care recipient with ADRD was isolated due to institutionalization or hospitalization, and 60 (71.43%) caregivers were concerned about the care that medical or support personnel were able to provide to their care recipient. Sixty-eight (87.18%) caregivers reported experiencing negative health outcomes beyond what they normally experience during this period of isolation or fear of isolation associated with COVID-19.

The need for SMD app use during COVID-19 was indicated by 57 (67.86%) of respondents (see **Table 2**).

TABLE 1 | Perceived need for smart personal device.

	Frequency	Percent	Cumulative frequency	Cumulative percent
N/A	6	7.14	6	7.14
No	21	25.00	27	32.14
Yes	57	67.86	84	100.00

TABLE 2 | Ordinal regression analysis.

Estimates of parameters

		Estimation	Standard error	Forest	ddl	Sig.	95% confidence interval	
							Lower terminal	Upper terminal
Dependent	No neg. MH outcomes	–3.458	0.913	14.334	1	0.000	–5.248	–1.668
	1 neg. MH outcomes	–2.230	0.873	6.519	1	0.011	–3.942	–0.518
	2 neg. MH outcomes	–0.102	0.837	0.015	1	0.903	–1.742	1.539
Independent	Grandchild or Other relation Caregiver	–0.705	0.721	0.957	1	0.328	–2.117	0.707
	Adult Child Caregiver	–0.056	0.501	0.012	1	0.911	–1.037	0.925
	Spousal Caregiver	0[a]			0			
	Mild Dementia	–0.504	0.827	0.371	1	0.542	–2.126	1.118
	Moderate Dementia	–0.516	0.650	0.629	1	0.428	–1.791	0.759
	Severe Dementia	0.437	0.651	0.451	1	0.502	–0.839	1.713
	Other Dementia	0[a]			0			
	No apps	–2.133	0.618	11.923	1	0.001*	–3.344	–0.922
	1 type of app	–1.448	0.553	6.859	1	0.009*	–2.532	–0.364
	2–5 types of apps used	0[a]			0			

Link function: Logit. [a]*This parameter is set to 0 because it is redundant.*
**Indicates significance.*

The categorical PCA indicated that 67% of the variance of four variables represented two principal components (representing 36 and 31%). Graphical observation suggested that only "number of apps used" was related to mental health outcomes. The number of apps used was the only variable significantly associated to the number of negative health outcomes (Nagelkerke pseudo-$R2$ = 0.216, p = 0.009). Specifically, the likelihood of more negative health outcomes increased if no apps were used (95% CI, –3.344 to –0.922, p = 0.001), or only one app was used (95% CI, –2.532 to –0.364, p = 0.009), but did not increase significantly if 2 or more app types were used (see **Table 2**). It should be noted that model reported a Nagelkerke R squared of only 0.216, indicating that this model explains a small portion of the variance seen in mental health outcomes.

Caregivers who experienced additional anxiety during COVID-19 related isolation described their anxiety and fears about the potential that their loved was not being fed appropriately or that their loved one die could alone. Participants also discussed challenges with distance communication options, noting specific barriers such as inability to read facial expressions of their loved one with dementia, or the need to coordinate or attend to numerous calls (see **Supplementary Appendix B** for full statements).

DISCUSSION

Social isolation is a multi-dimensional experience that has been described according the following attributes: "loneliness, social support, social contact, number of confidants, social connectedness/social connectivity, social networks, and social well-being" (Chen and Schulz, 2016). Health concerns related to isolation among older adults are not novel to the COVID-19 context, as awareness and intervention continue to be of societal and research interests. Crewdson (2016) outlined the multifaceted outcomes related to loneliness among older adult populations to include psychiatric, behavioral, and physical outcomes, which may arguably holistically change one's quality of life.

The sample population of caregivers was primarily comprised of adult children and spousal caregivers, both of whom are likely to have spent a fair portion of life with their loved one now living with ADRD. Most of those care recipients had moderate or severe ADRD and over 75% of those with ADRD were isolated due to institutionalization or hospitalization. It is critically important to highlight over 70% of caregivers reported that the isolation of a loved one with dementia related to COVID-19 both impacted their perceptions of the care their loved one was receiving and affected the caregivers' mental health beyond what they would experience in a normal context. This provides important information about the potential impact of isolation due to COVID-19 for individuals with ADRD and their caregivers.

Our results indicate an inverse relationship between SMD app use and poor mental health. Specifically, *fewer* apps (<2) utilized is associated with a greater number of mental health issues. This is a very preliminary finding and so its definitive indications cannot be determined. However, we will posit and discuss a suspected rationale. Smart personal device apps have been shown to be useful among dementia caregivers (Yousaf et al., 2019; Faieta et al., 2021) and many apps offer features that can be useful for communicating or caring at a distance. Therefore, it is possible that using two or more apps is reflective of a caregiver's technological ability and comfort level with technology. Caregivers who are more comfortable with smart personal technology can utilize numerous distance communication methods–messaging, video chat, social media, email, etc. Many of the qualitative comments indicated that inability to monitor the care of a loved one with dementia was a source of stress and worry. Caregivers who reached out to their loved ones or to care-facility staff *via* SMDs may have experienced

a greater level of control or empowerment when using technology mediated communication, rather than continuing in unremitting isolation from their care recipient. SMD communication apps can be used between caregiver and care recipient and also between caregiver and medical staff. Improving communication through app use might reduce feelings of anxiety and helplessness experienced by caregivers by providing alternative methods of maintaining involvement in provision of care.

The impact of SMD apps as methods of distance communication or caregiver supports is contingent on a number of internal and external factors that affect the human-technology-interface. While information and communication technologies have been found to yield positive outcomes, the ability of communication technologies to mitigate social isolation and support connectedness have not yet been found to *consistently* persist beyond 6 months and that they are not necessarily suitable solutions for every older adult (Chen and Schulz, 2016). Technology evaluation criteria include accessibility factors–for example, is the SMD app visually accessible, does the interface require a certain level of hand dexterity to use? Chen and Schulz (2016) noted that the suitability of information and communication technologies may be impacted by things such as "interest in ICT, motivations for ICT use, cognitive capability, sufficient eyesight, and basic physical ability to use the equipment (e.g., figure or hand movement, skills of using the touch pad)." Other criteria include external and context related factors such affordability, dependability, and learnability (Batavia and Hammer, 1990).

The post-pandemic context is anticipated propel further research into the integration of SMD apps into healthcare and health maintenance. This must be done in light of various usability and accessibility factors as they fluctuate across user groups. Specifically, technology design, research, and implementation should take the unique needs and experiences of older adults into account as well as considerations such as loneliness, economic and environmental factors, and technological ability level (Conroy et al., 2020). Older adults, caregivers, and individuals with dementia in isolated situations may lack informed technology recommendation and adequate support in technology use. Lack of guidance and support can create situations in which apps seem to be hopeful solutions to overcoming communication barriers, but instead prove to be ineffective and lead to further disappointment. Conroy et al. (2020) suggests that technical and scheduling support be offered at the family, care provider, and organizational level to enable older adults to utilize technologies to mitigate the experience of loneliness.

There are numerous factors that can contribute to matches between technology and user, such as the design of the technology, ability to assess the technology, lack of education on technology use–each factor likely impacted by the lack of older adult involvement in the research and design of pervasive technologies such as SMD apps. Sufficient inclusion of older adults as a "target consumer" of general consumer-level, SMDs has yet to be enacted. Mannheim et al. (2019) describes a "gray digital divide" barring older adults from digital technology research and design. Increased education and awareness regarding the equitable inclusion of broad age demographics into the research and design process is needed in order to bridge this divide. This is not to say that research into technology for older adults will not be without challenge–to include methodological barriers like high dropout rates and semantical challenges such as use of a consistent definition of social isolation throughout supporting literature (Chen and Schulz, 2016). Continued interdisciplinary approaches and innovative solutions are needed to overcome these and other barriers to ensure that older adults with ADRD are supported in the pandemic, post-pandemic, and recovery environments.

In sum, there is great potential for SMD apps to influence the quality of life for those impacted by ADRD by facilitating distance communication and care options. SMD apps that can be used by the ADRD or ADRD caregiver populations should be designed with the unique needs and experiences of these groups in mind. The impact of technology on health and quality of life can be influenced by implementation methods, and players–in this case referring to the individual with ADRD, the informal caregiver(s), and staff members at the respective care-facility of residence. Future research should utilize participatory design methods to both (1) develop and identify useful SMD apps to combat social isolation between a caregiver and ADRD care recipient in care-facility settings, and (2) develop end-user sensitive implementation strategies to ensure SMD apps are impactful.

Limitations

The survey used was designed for the purposes of the present study, therefore it is not a validated instrument. Importantly, this study is exploratory in nature and was used to gather as much insight as possible in a critical window, the period of heightened social isolation during the COVID-19 outbreak in 2020. Therefore, the content and language used in the survey prioritized low respondent burden and general applicability (questions would be applicable to as many caregivers as possible). The use of a self-report survey can be viewed as a limitation due to risk of response bias. However, the perceptions of the respondents represent their reality and are likely the driving factors of behavior. Therefore, these perceptions are what we are most interested in finding. In addition, the items in this survey cannot be viewed as holistically reflecting all potential app uses nor all mental health outcome possibilities. Therefore, the findings in this study should be considered against existing literature and augmented with future studies. Finally, the present survey offers preliminary insight into the experiences and perspectives of a limited sample of caregivers. The web-based format of the survey may introduce selection bias toward participants who are more familiar and comfortable with technology. However, due to COVID-19 safety considerations at the time of data collection this was considered the most appropriate method of collection. The anonymity of the survey limited our ability to determine the generalizability of our results. This sample ($N = 82$) cannot be considered generalizable to the general ADRD caregiver population. Future research is needed to investigate (1) the generalizability of our findings, and (2) the experience and perspectives of caregivers that represent specific racial, ethnic, and cultural, and age groups.

CONCLUSION

The present study provides insight into the experiences of caregivers of people with ADRD during period of widespread social isolation. The majority of our sample of caregivers reported that the individual they care for was socially isolated due to institutionalization or hospitalization during COVID-19, and over 87% of caregivers experienced negative mental health outcomes beyond what would have been experienced in typical contexts (e.g., situations unaffected by COVID-19 isolation). The majority of caregivers in our sample perceived the need for SMD app use in their situations. Complementing earlier findings, the present study found that absence or more limited SMD app use was associated with poorer mental health outcomes. Future studies should further investigate the extent and generalizability of app impact in social isolation conditions within the dementia community. Additionally, future research should assess the impact of app evaluation to improve the fit between app and user, thereby potentially improving the usability and usefulness of apps to address distance caregiving and communication.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available, because, requests to access original data will be evaluated on an individual basis. Requests to access the datasets should be directed to corresponding author KB, krista.best@fmed.ulaval.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Centre Intégré Universitaire de Santé et de Services Sociaux de la Capitale-National Ethics Board (Ethics Approval No. CER 2020-1984). The patients/participants provided their informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to this research through conceptualization, data collection or analysis, and to the development of this manuscript.

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SUPPLEMENTARY MATERIAL

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COVCOG 2: Cognitive and Memory Deficits in Long COVID: A Second Publication From the COVID and Cognition Study

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COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been often characterized as a respiratory disease. However, it is increasingly being understood as an infection that impacts multiple systems, and many patients report neurological symptoms. Indeed, there is accumulating evidence for neural damage in some individuals, with recent studies suggesting loss of gray matter in multiple regions, particularly in the left hemisphere. There are several mechanisms by which the COVID-19 infection may lead to neurological symptoms and structural and functional changes in the brain, and cognitive problems are one of the most commonly reported symptoms in those experiencing Long COVID – the chronic illness following the COVID-19 infection that affects between 10 and 25% of patients. However, there is yet little research testing cognition in Long COVID. The COVID and Cognition Study is a cross-sectional/longitudinal study aiming to understand cognitive problems in Long COVID. The first paper from the study explored the characteristics of our sample of 181 individuals who had experienced the COVID-19 infection, and 185 who had not, and the factors that predicted ongoing symptoms and self-reported cognitive deficits. In this second paper from the study, we assess this sample on tests of memory, language, and executive function. We hypothesize that performance on "objective" cognitive tests will reflect self-reported cognitive symptoms. We further hypothesize that some symptom profiles may be more predictive of cognitive performance than others, perhaps giving some information about the mechanism. We found a consistent pattern of memory deficits in those that had experienced the COVID-19 infection, with deficits increasing with the severity of self-reported ongoing symptoms. Fatigue/Mixed symptoms during the initial illness and ongoing neurological symptoms were predictive of cognitive performance.

Keywords: Long COVID, cognition, neurological, memory, executive functions, language, COVID-19, symptoms

INTRODUCTION

Traditionally, COVID-19 has been considered a respiratory disease. However, around 35% of patients – and up to 85% of those who become severely ill – report neurological symptoms including headache, dizziness, myalgia, or loss of taste and smell (e.g., Mao et al., 2020). The most well-known neurological symptom – alteration in taste or smell (anosmia/dysgeusia) – is also one of the most common symptoms of the disease (e.g., Lechien et al., 2020), often the first symptom to manifest (Mao et al., 2020; Romero-Sánchez et al., 2020) and last to abate (Lechien et al., 2020).

There is accumulating evidence that COVID-19 is associated with neural damage, particularly in the presence of neurological symptoms (Helms et al., 2020; Kandemirli et al., 2020). Post-mortem studies of patients who have died of COVID-19 show evidence for ischemic lesions and indications of neuro-inflammation (Matschke et al., 2020). Multiple studies have indicated abnormalities such as hemorrhagic lesions in the orbitofrontal cortex (Le Guennec et al., 2020), the medial temporal lobe, and the hippocampus (Moriguchi et al., 2020; Poyiadji et al., 2020), bilateral thalamic lesions, and sub-insular regions (Poyiadji et al., 2020). The changes may be functional as well as structural, with nearly 90% of electroencephalography (EEG) studies conducted in patients with COVID-19 revealing epileptiform discharges, mostly within the frontal lobes (Galanopoulou et al., 2020). A study using the UK Biobank cohort conducted structural and functional brain scans before and after infection with COVID-19 on 394 patients compared with 388 matched controls who had not experienced the COVID-19 infection (Douaud et al., 2021). Significant loss of gray matter was identified in areas with high connectivity to the olfactory system (the hypothesized route of viral entry into the brain). The parahippocampal gyrus, the lateral orbitofrontal cortex, and the insula were particularly affected, and gray matter reductions were notably concentrated in the left hemisphere. The mechanistic implications of this left hemisphere bias are not clear but may reflect asymmetry in the connectivity of the olfactory system (Royet and Plailly, 2004). An analysis of the small subset of this sample (n = 15) who had been hospitalized indicated more severe gray matter loss in these participants, particularly in the left cingulate cortex, and the right amygdala, and the hippocampus. Bougakov et al. (2021) have argued that depending on the mechanism and location of neural damage, there are several cognitive deficits that might be expected to be detectable in patients with COVID-19. For example, SARS-CoV-2 may be able to attack the brain directly, perhaps *via* the olfactory nerve (Lechien et al., 2020; Politi et al., 2020), causing encephalitis. Besides, severe hypoxia from respiratory issues may induce hypoxic/anoxic encephalopathy (Guo et al., 2020). The unusual clotting seen in patients with COVID-19 may be associated with acute ischemic and hemorrhagic cerebrovascular events (CVAs: Beyrouti et al., 2020; Li et al., 2020; Wang et al., 2020; Kubánková et al., 2021), leading to more lasting brain lesions. Finally, a maladaptive immune response to infection can negatively impact neural systems *via* hemorrhagic encephalopathy (Das et al., 2020; Poyiadji et al., 2020) or peripheral neuropathy (e.g., Guillain-Barre syndrome; Alberti et al., 2020; Whittaker et al., 2020; Zhao et al., 2020).

Much of the evidence suggesting that cognitive dysfunction may occur following the COVID-19 infection comes from those who experience "post-COVID-19 syndrome"/"post-acute sequalae SARS-CoV-2" (PASC)/"Long COVID." The National Institute for Health and Care Excellence (NICE) guidelines describe "post-COVID-19 syndrome" as "*Signs or symptoms that develop during or after infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis*" (National Institute for Health and Care Excellence, 2020). Disagreements exist as to the exact symptoms, longevity, and severity required to qualify for a diagnosis of PASC, making it difficult to ascertain prevalence precisely. However, estimates of patients with COVID-19 having some degree of chronic illness range from 10 to 25% (e.g., Cirulli et al., 2020; Ding et al., 2020; Sudre et al., 2020; Tenforde et al., 2020; Nehme et al., 2021; Office for National Statistics, 2021). The patient-created term "Long COVID" has increasingly been used as an umbrella term to describe this highly heterogeneous condition (Callard and Perego, 2021).

Cognitive dysfunction is one of the most common symptoms reported in research into Long COVID, occurring in around 70% of patients (Cirulli et al., 2020; Bliddal et al., 2021; Davis et al., 2021; Ziauddeen et al., 2021), and in many cases appearing second only to fatigue. In one study, 86% of participants indicated that cognitive dysfunction and/or memory impairment was impacting their ability to work (Davis et al., 2021). In our first paper in the COVID and Cognition study (Guo et al., 2022), we found a similar prevalence of cognitive symptoms to previous studies, with 77.8% reporting difficulty concentrating, 69% reporting brain fog, 67.5% reporting forgetfulness, 59.5% reporting tip-of-the-tongue (ToT) word-finding problems, and 43.7% reporting semantic disfluency (saying or typing the wrong word). In that analysis, we found that the experience of chronic fatigue-like ("Fatigue/Mixed") and neurological symptoms during the first 3 weeks significantly predicted the experience of cognitive symptoms later in the subsequent illness. Those individuals experiencing ongoing "Cardiopulmonary/Fatigue," "Neurological" and "Gastrointestinal/Autoimmune" symptoms were also found to be more likely to be experiencing cognitive symptoms.

It is often difficult to ascertain to what extent quite broadly defined self-reported cognitive deficits such as "difficulty concentrating" and "brain fog" translate into measurable changes in cognitive performance. While there are multiple lines of evidence to suggest that individuals experiencing Long COVID experience cognitive symptoms, there is, to date, little research objectively measuring cognition post-COVID-19.

The study of Alemanno et al. (2021) investigated cognitive function in the post-acute phase (1 month after discharge) in patients with COVID-19 that had experienced severe illness. Using the Montreal Cognitive Assessment (MoCA) score, they showed that 80% of patients showed indications of cognitive deficit, particularly in memory, executive function, and language. Similarly, Helms et al. (2020) found that, at discharge from

the intensive care unit (ICU), 33% of patients showed evidence of dysexecutive syndrome, with symptoms such as inattention, disorientation, or poorly organized movements in response to the command. In their study of 29 patients (average age 65) presenting at least one new neurological symptom since COVID-19 infection, Hosp et al. (2021) found that cognitive performance may be linked to neurological abnormalities and symptoms. A positron emission tomography (PET) analysis revealed predominant frontoparietal hypometabolism, correlating to lower MoCA scores and extended neuropsychological testing. In particular, patients with COVID-19 showed deficits in tests of verbal memory and executive functions. One issue with all of these studies' data is limited to severely ill patients, mostly of older age (65+). It is thus difficult to determine whether these deficits are specific to COVID-19 or a more general response to acute respiratory distress (ARD) and ventilation. It is known, for example, that survivors of critical illness are known to experience long-term cognitive impairment (Hopkins et al., 1999; Jackson et al., 2003; Ehlenbach et al., 2010; Iwashyna et al., 2010; Pandharipande et al., 2013), particularly if they experience delirium (e.g., Girard et al., 2010; Pandharipande et al., 2013). Thus, it is important to establish to what extent cognitive dysfunction is a feature of post-COVID-19 pathology, or merely reflective of the large number of patients with COVID-19 that experience ARD. Furthermore, it must be investigated whether these deficits extend to younger populations. In an early indication that this might be the case, Almeria et al. (2020) assessed younger (aged 24–60) patients 10–40 days post-discharge, of which only 20% had been in intensive care, but 60% required oxygen. They found that those reporting neurological symptoms had lower performance on attention, memory, and executive function, once again suggesting a degree of association between symptomatology and degree of cognitive deficit.

In a very large study using 81,337 participants in the Great British Intelligence Test (GBIT; mean age 46.75), Hampshire et al. (2021) compared participants who reported having had the COVID-19 infection to concurrently tested control participants. The authors conducted an analysis of the association between symptom severity and cognitive performance controlled for age, gender, education level, income, racial-ethnic group, and pre-existing medical disorders. Among 12,689 participants that suspected that they had had COVID-19, 326 had a positive test, and 192 were hospitalized. Participants who had received a positive test had a lower global score and this deficit scaled with the severity of initial respiratory illness: There was not only a substantial effect size for people who had been hospitalized but also a clear effect for mild but biologically confirmed cases who reported no breathing difficulties. The largest effect sizes were seen in tests of verbal reasoning, multi-stage planning, and spatial attention. Most participants had fully recovered at the time they took the test; however, 24% of those with test-confirmed COVID-19 reported residual symptoms. Controlling for residual symptoms, respiratory severity during the initial illness remained a strong predictor of global cognitive performance, while the presence of ongoing symptoms did not predict significant variance. There was no significant association between time since illness and cognitive performance; however, this analysis excluded those with ongoing symptoms.

The study conducted by Graham et al. (2021) investigated cognition and quality of life measures in 100 non-hospitalized patients (mean age 43) presenting to a neuro-COVID clinic with neurological symptoms persisting for at least 6 weeks from symptom onset. These patients reported a median of five neurologic symptoms and over 80% reported having experienced brain fog. Some, but not all, of these symptoms, had resolved at the time of cognitive assessment. A subset of participants was assessed with the National Institutes of Health (NIH) Toolbox covering processing speed, attention and executive memory, executive function, and working memory, and these scores were compared to established baselines. The authors reported 53% of participants as having abnormal findings, with short-term memory and attention being most commonly impaired. Participants also had significantly reduced cognition- and fatigue-related quality of life indices. However, given that performance in this study was compared to established baselines rather than a control group, it is difficult to be confident of the proportion of the seen deficit that is attributable to COVID-19 rather than the general stress and disruption caused by the pandemic.

Despite being probable that there is a relationship between the COVID-19 infection, neurological symptoms, and cognitive dysfunction, many questions remain about the specific nature of the cognitive impairment in Long COVID. We distinguish three main ones that drive our research program and which it attempts to answer: First, what are the associations between reported symptoms and cognitive outcomes? Second, given the heterogeneous nature of Long COVID, is diversity reflected in a diversity of cognitive issues, or is there a specific sub-phenotype of Long COVID that is associated with cognitive deficits? Finally, are those that report "subjective" cognition and memory complaints more likely to demonstrate impairments in "objective" cognitive assessments of the same functions?

In this study, we reported on the first stage of a mixed cross-sectional/longitudinal study, the COVID and Cognition Study (COVCOG), aimed at understanding cognition following the COVID-19 infection relative to that of concurrently tested controls. Using the online assessment platform Gorilla[1], we set out to bring together information about symptom profiles both during and following initial infection and detailed analysis of cognitive performance across a range of domains including memory, language, and executive function. The aims of this study do not include identifying a specific mechanism of cognitive deficit (as that requires types of tests and analysis not feasible in an online study) but rather to "map the terrain," providing sufficient breadth and detail of mechanism-relevant information to facilitate and inform the future mechanistic investigation.

The first aim of this investigation was to ascertain whether differences could be found in cognitive performance between those that had and those that had not experienced the COVID-19 infection. Problems with memory and with speech and language are the most commonly reported cognitive symptoms (after

[1]www.gorilla.sc; Cauldron Science, Cambridge, United Kingdom.

"brain fog") in Long COVID, affecting around 70 and 40% of patients, respectively (Davis et al., 2021). Given this, we hypothesize that where cognitive differences exist, these will be larger, or more likely, in tests assessing memory or language relative to those assessing (for example) executive function.

A second hypothesis, following previous findings (e.g., Hampshire et al., 2021; Hosp et al., 2021) is that the degree of cognitive deficit will relate to the severity and nature of the initial illness. In particular, it seems likely that the number and severity of neurological symptoms during the initial illness may be indicative of the degree of impact of the disease on neural function (whether that be *via* direct infection, inflammation or CVA, or another route), which would be most likely to result in subsequent cognitive deficits. Our previous publication on this study (Guo et al., 2022) found that ongoing cognitive symptoms were predicted by Fatigue/Mixed, Neurological/Psychiatric, and Respiratory/Infectious (e.g., cough, fever, loss of taste and smell) symptoms experienced during the initial illness. We predict that similar associations will be found between symptom factors during the initial illness and performance on cognitive tasks and that these may be most pronounced for neurological symptoms.

We further hypothesize that not just the presence but the nature of ongoing illness will be associated with cognitive deficits. We predict that those with severe ongoing symptoms will be more likely to show concomitantly more severe deficits in cognitive tasks. Our first paper from this study found that ongoing Cardiopulmonary/Fatigue, Neurological and Gastrointestinal/Autoimmune symptoms were associated with greater cognitive symptoms. We hypothesize that these symptom factors will be similarly associated with performance on cognitive tests.

Finally, we predict that any deficits will be greatest in those individuals experiencing ongoing cognitive symptoms. Indeed, we might expect those reporting specific cognitive symptoms (e.g., "forgetfulness") to be particularly impaired on tests of cognition that assess the associated skill (e.g., memory).

MATERIALS AND METHODS

Participants

A total of 421 participants aged 18 and over were recruited through word of mouth, student societies, and online/social media platforms such as the Facebook *Long COVID Support Group* and the *Prolific* recruitment site. They were recruited from the majority English-speaking countries (the United Kingdom, Ireland, United States, Canada, Australia, New Zealand, or South Africa) and were English speakers. Of these, 181 (130 women) had experienced the COVID-19 infection (65 test-confirmed, 96 suspected) and 185 (118 women) had not. A further 55 had "unknown" infection status (did not think they had had COVID-19 but had had an illness that could potentially have been). Among those that had had COVID-19, 42 (29 women) had recovered by the time of test ("Recovered group," *R*), 53 (36 women) continued to experience mild or moderate ongoing symptoms ("Ongoing (Mild/Moderate) group," *C*+), and 66 (54 women) experienced severe ongoing symptoms ("Ongoing (Severe) group," *C*++). The other 20 participants were too early in the illness to indicate ongoing symptoms. Comorbidity was not an exclusion criterion. Full details of our sample, including demographic and medical history characterizations, are provided in our previous publication on this study (Guo et al., 2022).

Procedure

The study was reviewed by the University of Cambridge Psychology Ethics Committee (PRE.2020.106, September 8, 2020). This is a mixed cross-sectional/longitudinal online study conducted using Gorilla (Anwyl-Irvine et al., 2020; see text footnote 1). The results reported here are for the baseline session of the study only. The baseline session consisted of a questionnaire covering demographics, previous health, and experience of COVID-19, followed by a series of cognitive tests.

Participants answered questions relating to their age, sex, education level, country of permanent residence, ethnicity, and profession. They were then asked a series of questions relating to their medical history and health-related behaviors (such as smoking and exercise). Next, they were asked for details of their experience of COVID-19. The COVID-status was established based on their response to a series of questions (starting with "Have you had COVID-19?") and their response to a series of questions regarding the presence and severity of ongoing symptoms. Full details of the questionnaires and grouping dynamics are provided in our previous publication on this study (Guo et al., 2022). Finally, participants were asked to give details on a large number of individual symptoms during three time periods: the initial 3 weeks, "in the time since then," and the past 1–2 days. Participants were also asked to report a 5-point Likert scale, from very bad (1) to very good (5) on how current symptom severity was on the day of the test.

Cognitive Tests

Figures 1A–D,F shows the 6 cognitive tasks that were presented. All participants completed tasks, while only the "No COVID" group completed task e.

Word List Recognition Memory Test (Figure 1D)

Participants were shown a list of 16 words one by one with the instruction to memorize as many as possible. They were then shown 32 (16 old and 16 new) words and asked to report which had been on the original list (**Figure 1D**). Target and distractor words were scored and matched for imagery and concreteness. The dependent variables on this task were % correct, d′, and reaction time (RT).

Pictorial Associative Memory Test (Figure 1B)

Participants were required to memorize a series of 17 stationery and food-item pairs each displayed on the screen for 3 s. The recall phase took place immediately thereafter and involved 15 trials, each of which presented an item of stationery and asked participants to select the associated food item from 9 options (**Figure 1B**). The dependant variables were % correct and reaction time.

Category Fluency Test (Figure 1C)

Participants were presented with the category word "Animals" and had 1 min to type every example of that category they could

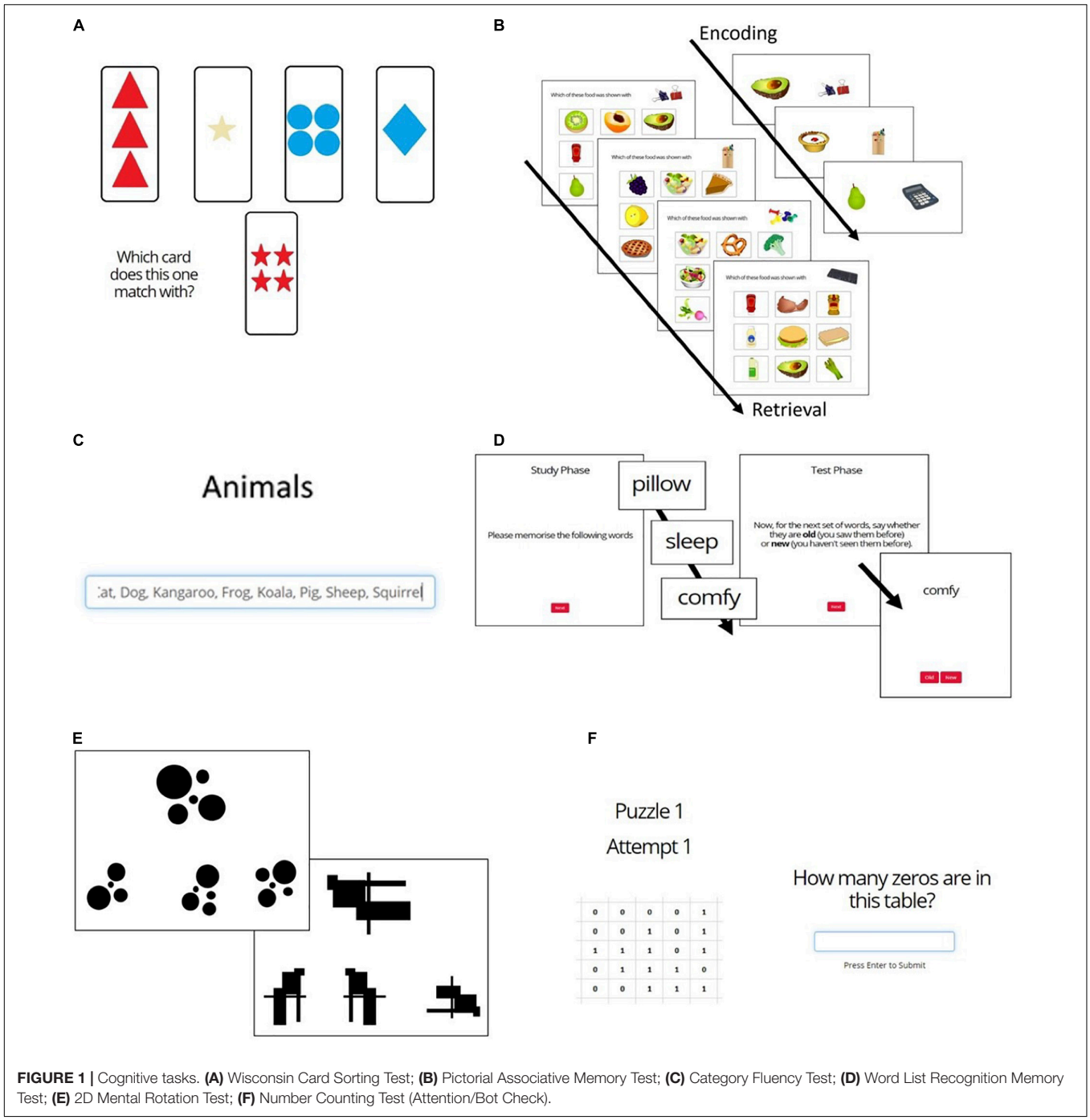

FIGURE 1 | Cognitive tasks. **(A)** Wisconsin Card Sorting Test; **(B)** Pictorial Associative Memory Test; **(C)** Category Fluency Test; **(D)** Word List Recognition Memory Test; **(E)** 2D Mental Rotation Test; **(F)** Number Counting Test (Attention/Bot Check).

think of. The words were entered into a scrolling text box such that, after around 6 words, earlier words started to move out of view (**Figure 1C**). Dependent variables were number of correct words, % produced words that were correct, number of incorrect (unrelated) words (e.g., "table"), number of incorrect (related) words (e.g., "fur"), and number of repetitions.

Mental Rotation Test (Figure 1E)

Participants were presented with 16 trials in which they saw an abstract image and had to select which of three possible options represented that image rotated (**Figure 1E**). This is a test of visual working memory. Outcome variables were % correct and reaction time.

Wisconsin Card Sorting Test (Figure 1A)

This executive function (EF) task assesses task switching and inhibition. Across 64 trials, participants were required to match a given card to one of the four cards based on either color, shape, or number (**Figure 1A**). They were not explicitly told the matching rule but must infer this from the feedback on their choices. Every

few trials the rule changed, and participants must find and follow the new rule based on feedback.

Number Counting Test (Figure 1F)

This task was included in the baseline as an attention/"bot" control for data quality. It presented a grid of 1s and 0s and asked the participants to count the 0s (**Figure 1F**). This is not cognitively difficult but requires concentration. Because the grid is an image, this is also difficult for most AIs. Participants were given 3 attempts at this task. The numbers given by participants giving 3 incorrect answers were manually checked. If the numbers appeared to be genuine attempts (i.e., close but incorrect), then the participant was considered genuine and was included in the dataset. No participants were removed due to failing this task.

Relational Reasoning Test

Across 35 trials, participants were shown a 3 × 3 matrix of images with one missing and were asked to select from 4 options which image should fill the gap. This task was given only to the No COVID group and was intended as a means by which to IQ-match control participants for potential pre-post infection longitudinal explorations. Data from this task are not reported in this paper.

Data Processing and Analysis

Analyses were conducted using IBM SPSS Statistics for Windows, version 23[2]. We describe quantitative variables using means and *standard deviations*, and numbers and percentages for qualitative variables. Sidak's correction for multiple comparisons was employed where appropriate, and both corrected and uncorrected analyses are shown.

As there were a large number of cognitive test variables, we reduced these *via* factor analysis to produce 4 factors representing Executive Functions (Performance), Executive Functions (Reaction Time), Memory, and Category Fluency. Analyses were conducted first on these factors to give an overview of the pattern of cognitive performance and then on the individual variables to give a more detailed picture.

We investigated differences in cognitive performance, first, by dividing the sample into two groups (COVID/No COVID), and, second, by subdividing the COVID group by symptom longevity and severity (Recovered, Ongoing Mild/Moderate infection, and Ongoing Severe infection). Where parametric analysis was not appropriate, we employed the Pearson's chi-square (χ^2) for categorical variables and the Mann–Whitney test and the Kruskal–Wallis test for continuous variables depending on the number of COVID groups. To explore what variables were associated with infection or ongoing symptoms, we employed various independent multinomial logistic regression models (backward elimination method). To investigate differences between groups (COVID/No COVID; Recovered, Ongoing Mild/Moderate, Ongoing Severe) and the outcome of the cognitive tasks, we employed independent *t*-test/Mann–Whitney and ANOVA/Kruskal-Wallis tests. We also performed general linear models (GLM) controlling for sex, age, country, and education level. We also examined whether any total score from the cognitive tasks could be associated with variance in initial illness severity (Asymptomatic/Very mild, Mild, and Moderate/Severe) using independent simple regression models.

As reviewed in detail in our previous publication (Guo et al., 2022), we used exploratory principal component analysis to cluster the symptoms experienced during the initial infection, and the symptoms subsequently experienced since that time. We identified 5 factors for symptoms experienced during the first 3 weeks of illness. These included a "Neurological/Psychiatric" factor characterized by disorientation, delirium, and visual disturbances; a "Fatigue/Mixed" factor characterized by fatigue, chest pain/tightness, and muscle/body pains; a "Gastrointestinal" factor characterized by diarrhea, nausea, and vomiting; a "Respiratory/Infectious" factor characterized by fever, cough, and breathing issues; and a "Dermatological" factor characterized by rash, itchy welts, and foot sores. For symptoms experienced in the time since the initial illness, 6 factors were identified: A "Neurological" factor characterized by disorientation, confusion, and delirium; a "Gastrointestinal/Autoimmune" factor characterized by hot flushes, nausea, and diarrhea; a "Cardiopulmonary/Fatigue" factor characterized by breathing issues, chest pain/tightness, and fatigue; a "Dermatological/Fever" factor characterized by face/lips swelling, foot sores, and itchy welts; an "Appetite Loss" factor characterized by weight loss and loss of appetite, and finally, a "Mood" factor characterized by depression, anxiety, and vivid dreams. To assess currently experienced symptom factors, we employed the *sum scores by factor* method using the "since then" symptom factors as a base. We used linear multiple regression models (backward elimination method) to test whether ongoing factors predicted performance on cognitive tests.

RESULTS

Factor Analysis of Cognitive Variables

The cognitive task variables were *a priori* divided into two groups: language and memory (incorporating all Word List, Associative Memory, and Category Fluency variables), and executive functions (including all WCST and 2D Mental Rotation variables), and factor analyses were conducted on these separately. Each exploratory factor analysis (EFA) was limited to two factors. Two items (one in each analysis: WCST perseverative error reaction time and Category Fluency repetitions) that did not load into any factor were removed. The re-run analyses explained 48.9% and 58.9% of the variance, respectively. We thus ended with four performance factors: Executive Functions Performance (including score and errors for WCST and performance on 2D Mental Rotation), Executive Functions Reaction Times (including all reaction times from both EF tasks), Memory (including all variables from both Word List and Associative Memory), and Category Fluency (including all Category Fluency variables). See **Supplementary Table 1** for rotated component matrix.

Ten extreme outliers (identified by Q plot) were removed from each of the Category Fluency and EF Reaction Time factors to

[2]IBM, Armonk, New York, NY, United States.

bring skewness and kurtosis within acceptable bounds [Category: skew = –0.623 (0.139); kurtosis = –0.181 (0.276); EF RT: skew = –0.508 (0.138); kurtosis = –0.153 (0.274)]. Similarly, 9 extreme outliers (identified by Q plot) were removed from the Memory factor [skew = –0.623 (0.139); kurtosis = –0.181 (0.276)].

COVID-19 and Cognition

Memory and Word Finding

A first analysis was run using the task factors comparing the "COVID" and "No COVID" groups. There was a significant negative influence of the COVID-19 infection on memory performance, even when controlling for age, sex, country, and education level [$F(1,304) = 10.903$, $p = 0.001$].

There was also a significant difference between groups on the Category Fluency factor [$F(1,307) = 6.297$, $p = 0.013$, $\eta_p'^2 = 0.02$], but this disappeared when controlling for demographic variables (see **Figure 2** and **Table 1**).

For individual variables, primary analysis suggested that individuals who had experienced the COVID-19 infection had significantly lower performance ($U = 3.29$, $p < 0.001$) and slower reaction time ($U = 3.53$, $p < 0.001$) than the No COVID group on the Word List Recognition Memory Test (**Table 2**). After controlling for age, sex, country, and education level, these effects were maintained [% correct: $F(1,315) = 6.77$, $p = 0.01$; RT: $F(1,315) = 12.66$, $p < 0.001$)], with d′ becoming significant [$F(1,315) = 5.78$, $p = 0.017$]. A much weaker trend was seen in the Pictorial Associative Memory Test, suggesting a reduced performance in the COVID group ($t = 1.91$, $p = 0.056$) and no impact on reaction time ($p = 0.671$). When controlling for age, sex, country and education level, the significance of this group effect strengthened, suggesting that those who had experienced the COVID-19 infection scored lower than the No COVID group [$F(1,319) = 4.01$, $p = 0.046$]. Considering only analyses controlling for demographic factors, only reaction time on the Word List Recognition survived conservative correction for multiple comparisons (Sidak $\alpha = 0.0028$).

For Category Fluency, uncorrected analysis found that, although the COVID group repeated more words ($U = 2.35$, $p = 0.019$), they gave fewer incorrect (related) words ($U = 2.23$, $p = 0.026$) than the No COVID group. However, these effects disappeared after factoring out age, sex, country, and education level.

Other Tasks

There were no significant differences between the groups on the Executive Function Performance factor, but there was a significant group difference in Executive Function Reaction Time [$t(311) = 2.610$, $p = 0.009$], but this dropped below significance once age, sex, country, and education were accounted for (see **Figure 2** and **Table 1**).

In terms of individual variables, there were no group differences in performance on the WCST; however, the COVID-group had significantly slower reaction time on trials with both correct responses ($U = 3.03$, $p = 0.002$; see **Table 2**) and non-perseverative errors ($U = 2.86$, $p = 0.004$). No significant difference was found after controlling for age, sex, country, and education level. There were no significant differences between groups on performance on the 2D Mental Rotation Test.

Ongoing Symptom Severity and Cognition

Memory and Word Finding

There was a significant difference between ongoing symptom severity groups in the Memory factor [$F(2,150) = 5.724$, $p = 0.004$], which was weakened but still significant when demographic factors were accounted for [$F(2,136) = 3.653$, $p = 0.028$]. Pairwise analysis controlling for demographic variables showed a significant difference between the Recovered and Ongoing (Severe) groups [$F(1,88) = 6.414$, $p = 0.013$]. There

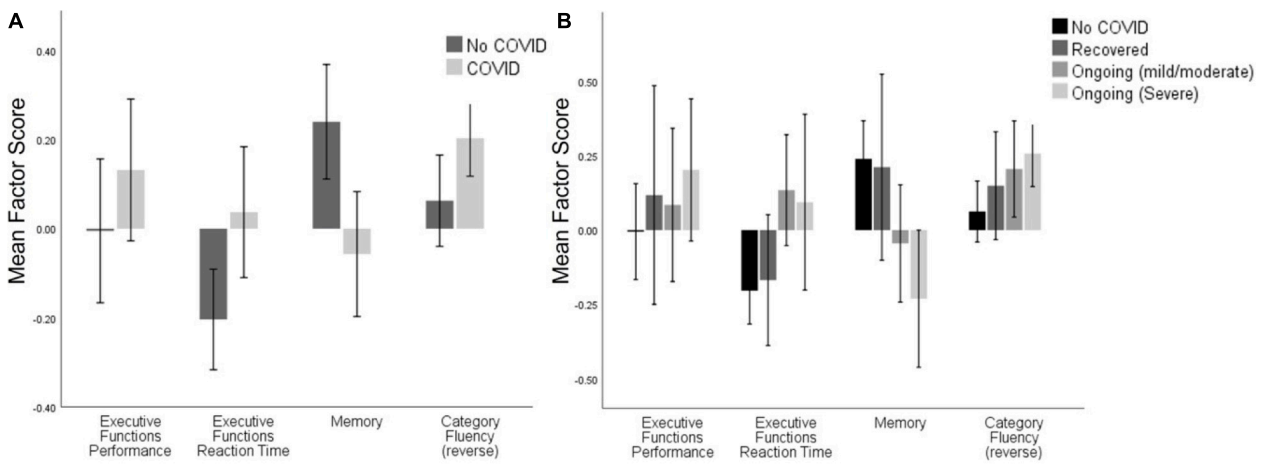

FIGURE 2 | Cognitive task factor scores across **(A)** the No COVID group and the COVID group, and **(B)** the No COVID group and the three ongoing severity groups. Significant differences were seen between the No COVID group and Ongoing (Mild/Moderate) on Memory [$t(87.6) = 2.4$, $p = 0.018$], and between No COVID and Ongoing (Severe) on Memory [$t(99.8) = 3.9$, $p < 0.001$] and Category Fluency [$t(152) = 3.05$, $p < 0.003$]. After controlling for demographic variables, only the differences in Memory maintained significance (see **Supplementary Table 2**). Error bars: ± 2 SE.

TABLE 1 | Cognitive performance factors across COVID and No COVID groups (top) and symptom severity levels (bottom).

	Comparing No COVID and COVID			
	Primary (uncontrolled) comparison		Comparison controlling for age, sex, country and education level (GLM)	
	T/*F* (df)	*p*	*F* (df)	*p*
Factor 1: EF Performance	1.729 (321)	0.085	0.888 (1,307)	0.347
Factor 2: EF Reaction Time	2.610 (311)	0.009*	2.991 (1,297)	0.085
Factor 3: Memory	3.157 (309)	0.002*	10.903 (1,304)	0.001*
Factor 4: Category Fluency	6.297 (307)	0.013	1.523 (1,293)	0.218
Within the COVID group comparing *R*, *C* +, *C* + +				
Factor 1: EF Performance	0.384 (2,149)	0.682	0.236 (2,135)	0.790
Factor 2: EF Reaction Time	2.077 (2,145)	0.129	0.343 (2,131)	0.710
Factor 3: Memory	4.821 (2,145)	0.009*	4.205 (2,131)	0.017
Factor 4: Category Fluency	0.561 (2,144)	0.191	0.065 (2, 130)	0.937

**denotes p-Values below Sidak-correct alpha at 0.0028.*

TABLE 2 | Cognitive task results between No COVID and COVID groups.

	No COVID (*n* = 185)	COVID (*n* = 181)	Primary (uncontrolled) comparison		Comparison controlling for age, sex, country and education level	
	Mean (*SD*)		*T*/*U*	*p*	*F* (GLM)	*p*
Word List Recognition						
d'	2.97(1.62)	2.68 (1.54)	–1.93	0.054	5.78	0.017
% Correct	0.85 (0.15)	0.82 (0.14)	–3.29	0.001*	6.77	0.01
RT	1250.54 (248.47)	1381.77 (350.88)	3.53	<0.001*	12.66	<0.001*
Category Fluency						
Correct	15.18 (6.09)	15.13 (5.58)	–0.087	0.931	2.3	0.13
Repetitions	0.07 (0.25)	0.19 (0.53)	2.35	0.019	2.19	0.14
Related	0.83 (0.94)	0.65 (1.03)	–2.23	0.026	0.04	0.852
Incorrect	0.04 (0.23)	0.11 (0.78)	0.54	0.592	3.11	0.079
% Correct	0.92 (0.16)	0.94 (0.10)	1.25	0.210	0.04	0.844
Associative Memory						
% Correct	0.63 (0.25)	0.58 (0.23)	–1.91	0.056	4.01	0.046
RT	5250.25 (2164.04)	5262.40 (1899.87)	0.43	0.671	0.74	0.39
WCST						
Correct	38.54 (10.21)	40.55 (9.38)	1.86	0.063	1.31	0.253
Persev Error	11.46 (9.53)	9.58 (8.80)	–1.59	0.113	1.43	0.232
Non-persev Error	6.43 (2.78)	5.94 (2.83)	–1.89	0.059	2.14	0.145
RT (Correct)	2135.24 (940.77)	2255.93 (764.40)	3.03	0.002*	0.02	0.891
RT (P Error)	2712.45 (1295.11)	10181.33 (82716.56)	1.90	0.057	0.19	0.663
RT (NP Error)	2928.04 (3447.46)	2999.21 (1339.14)	2.86	0.004	0.30	0.583
2D Mental Rotation						
% Correct	0.68 (0.21)	0.72 (0.19)	1.62	0.106	0.86	0.356
RT	9746.80 (6008.79)	10640.36 (7541.73)	1.66	0.097	0.01	0.923

**denotes p-Values below Sidak-correct alpha at 0.0028.*

was no association between symptom severity and the Category Fluency factor (see **Table 1**).

In terms of individual variables (see **Table 3**), significant differences between ongoing symptom sub-groups were found on Word List % correct [$H(3) = 22.51$, $p < 0.001$; **Figure 3**] and reaction time [$H(3) = 24.07$, $p < 0.001$]. Pairwise tests with Sidak $\alpha = 0.008$ revealed that those with severe ongoing symptoms had lower % correct than the No COVID group ($p < 0.001$) and those that had recovered ($p < 0.001$) and had slower reaction time than the No COVID group ($p < 0.001$). Those with mild/moderate ongoing symptoms also had slower reaction time than the No COVID group ($p < 0.001$) and the Recovered group ($p = 0.004$). When age, sex, country and education level were factored out by GLM, d′ [$F(3,310) = 2.90$, $p = 0.035$], % correct [$F(3,310) = 4.99$, $p = 0.002$], and reaction time [$F(3,310) = 6.88$, $p < 0.001$] differences were all significant, but only % correct and reaction time survived correction for multiple comparisons (Sidak $\alpha = 0.0028$). Pairwise tests suggested that those with

TABLE 3 | Cognitive task results among Recovered, Ongoing (Mild/Moderate), and Ongoing (Severe) groups.

	Recovered (*n* = 42)	Ongoing (Mild/Moderate) (*n* = 52)	Ongoing (Severe) (*n* = 65)	Primary (uncontr.) comparison		Controlling for age, sex, country, and education level	
	Mean (*SD*)			*F/H*	*p*	*F*	*p*
Word List Recognition							
d'	2.94 (1.41)	2.76 (1.44)	2.48 (1.70)	6.92	0.074	2.90	0.035
% Correct	0.86 (0.02)	0.84 (0.12)	0.79 (0.15)	22.51	<0.001*	4.99	0.002*
RT	1264.65 (244.69)	1425.98 (357.92)	1436.25 (383.57)	24.07	<0.001*	6.88	<0.001*
Category Fluency							
Correct	16.60 (6.79)	14.98 (5.05)	14.67 (4.83)	1.07	0.363	3.11	0.027
Repetitions	0.03 (0.16)	0.22 (0.51)	0.28 (0.68)	14.81	0.002*	2.98	0.032
Related	0.90 (1.55)	0.64 (0.80)	0.50 (0.76)	7.55	0.056	0.24	0.872
Incorrect	0.28 (1.09)	0.00 (0.00)	0.11 (0.88)	4.89	0.18	2.18	0.09
% Correct	0.93 (0.13)	0.94 (0.07)	0.94 (0.09)	1.85	0.603	0.41	0.747
Associative Memory							
% Correct	0.59 (0.26)	0.61 (0.23)	0.54 (0.21)	2.04	0.109	2.94	0.034
RT	4623.61 (1638.63)	5492.73 (1808.11)	5547.68 (2068.46)	7.18	0.066	0.54	0.656
WCST							
Correct	39.89 (9.41)	37.93 (8.54)	40.08 (8.90)	1.62	0.184	0.76	0.517
Pers. Error	10.34 (8.37)	11.78 (8.19)	9.54 (8.90)	4.51	0.212	0.86	0.461
Non-pers. Error	6.00 (2.92)	6.43 (2.71)	6.37 (2.60)	5.17	0.16	0.64	0.592
RT (Correct)	1897.28 (429.13)	2354.45 (805.85)	2467.67 (871.57)	21.46	<0.001*	1.07	0.363
RT (P Error)	2449.46 (1430.98)	24575.75 (146119.13)	4075.03 (7750.17)	16.15	0.001*	1.48	0.221
RT (NP Error)	2849.75 (1681.02)	2968.08 (1225.25)	3030.36 (1188.10)	11.48	0.009	1.27	0.286
2D Mental Rotation							
% Correct	0.74 (0.19)	0.73 (0.19)	0.70 (0.18)	3.44	0.329	0.73	0.538
RT	10394.03 (5249.34)	11004.28 (6140.60)	10674.06 (9717.56)	4.38	0.224	0.04	0.991

** denotes p-Values below Sidak-correct alpha at 0.0028.*

severe ongoing symptoms had significant lower d′ ($p = 0.004$), lower % correct ($p < 0.001$), and slower reaction time than the No COVID group ($p < 0.001$). Those with mild/moderate ongoing symptoms still had slower reaction time than the No COVID group ($p < 0.001$). In contrast to these findings with Word List Recognition Memory, primary analysis did not find significant group differences on Pictorial Associative Memory on either performance or reaction time. However, after controlling age, sex, country and education level, a main effect emerged for % correct [$F(3,314) = 2.94$, $p = 0.034$]; however, this did not survive correction for multiple comparisons (Sidak $\alpha = 0.0028$). Nonetheless, pairwise comparisons suggested that those with severe ongoing symptoms scored lower than the No COVID group ($p = 0.005$, Sidak $\alpha = 0.008$).

For Category Fluency, primary analysis showed a significant group effect in repetitions [$H(3) = 14.81$, $p = 0.002$; **Figure 3**]. Pairwise comparison with Sidak $\alpha = 0.008$ found that those with severe ongoing symptoms had more repeated words than both the No COVID ($p = 0.002$) and Recovered groups ($p = 0.004$). When GLM controlling for age, sex, country, and education level was conducted, there were significant main effects on the number of correct words [$F(3,301) = 3.11$, $p = 0.027$] and repetitions [$F(3,301) = 2.98$, $p = 0.032$], but neither of these survived correction for multiple comparisons (Sidak $\alpha = 0.0028$). Pairwise tests showed that those with severe ongoing symptoms had fewer correct words than the Recovered group ($p = 0.008$), but no pairwise comparisons were significant for repetitions.

Other Tasks

There was no effect of symptom severity group on either of the Executive Function factors (see **Table 1**).

There were significant group effects for the WCST in reaction time for trials with correct responses [$H(3) = 21.46$, $p < 0.001$], perseverative terrorism [$H(3) = 16.15$, $p = 0.001$], and non-perseverative errors [$H(3) = 11.48$, $p = 0.009$]. Pairwise tests with Sidak $\alpha = 0.008$ showed that those with mild/moderate ongoing symptoms had a slower reaction time for trials with correct responses than the No COVID group ($p = 0.005$) and the Recovered groups ($p = 0.008$). Similarly, those with severe ongoing symptoms were slower for correct responses than the Recovered ($p < 0.001$) and the No COVID groups ($p < 0.001$). For trials containing perseverative errors, both those with mild/moderate ($p = 0.002$) and severe ($p = 0.002$) ongoing symptoms have slower reaction times than those who recovered. Those with mild/moderate ongoing symptoms were also slower than the No COVID group for trials containing non-perseverative errors ($p = 0.005$). However, after controlling for age, sex, country, and education level, all these significances disappeared. There were no significant effects in 2D Mental Rotation.

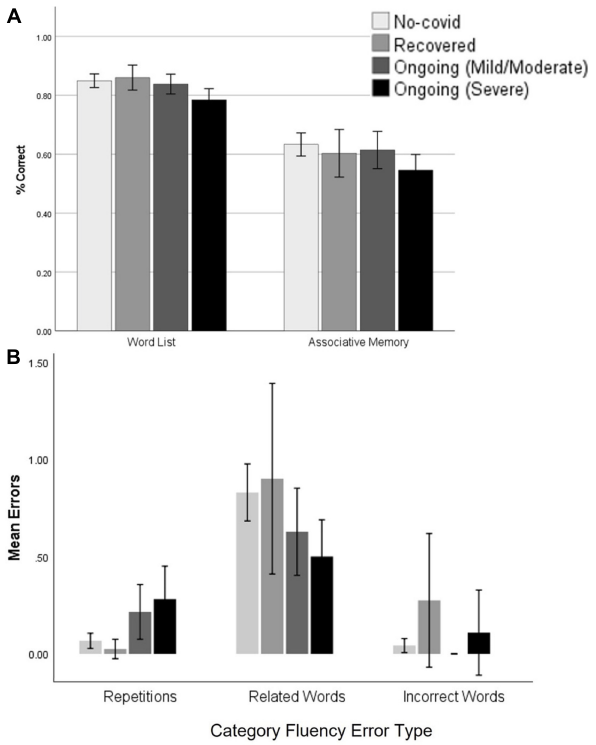

FIGURE 3 | Word List and Associative Memory performance across ongoing symptom groups **(A)**; Category Fluency errors across groups on ongoing symptom severity **(B)**. Error bars: ±2 SE.

Initial Illness and Subsequent Cognitive Performance

The Severity of Initial Illness

We assessed whether more severe initial illness [grouped into three: Asymptomatic/Very mild; Mild (bed-bound); Moderate/Severe (very ill or hospitalized)] was associated with cognitive performance at the time of test (often weeks or months later). First, we examined this in terms of the cognitive task factors. There was no effect of initial symptom severity on any of the cognitive task factor scores (EF Performance: $F(2,149) = 0.479$, $p = 0.620$; EF RT: $F(2,146) = 0.019$, $p = 0.982$; Memory: $F(2,146) = 1.087$, $p = 0.340$; Category Fluency: $F(1,145) = 1.171$, $p = 0.313$).

Next, we examined which (if any) individual cognitive task variables could be associated with variance in initial illness severity (Asymptomatic/Very mild, Mild, Moderate/Severe) using independent simple regression models with COVID-19 illness severity as the dependent variable and all cognitive task variable as predictors. There was a significant association for Word List Recognition [$F(1,142) = 6.369$, $p = 0.013$, standardized $B = -0.207$, $R^2_{adj} = 0.036$], but no other cognitive task was associated with initial illness severity. These associations did not survive correction for multiple comparisons (Sidak $\alpha = 0.0028$).

We also examined whether any particular diagnoses during the initial illness were related to subsequent cognitive performance. After removing diagnoses with very low prevalence (< 4%), none of the remaining diagnoses (hypoxia, blood clots, and Inflammatory syndrome) presented any significant association with cognitive performance.

Nature of Initial Illness and Cognitive Performance

Individual Neurological Symptoms

To test whether any of the specific neurological symptoms experienced during the first 3 weeks of illness (initial symptoms) were related to subsequent cognitive performance, we carried out multiple linear regressions with cognitive performance factors as the dependent variable and the neurological symptoms as possible predictors. Almost no participants showed hallucination or delirium (< 10% of participants), so these were removed from the analysis.

A single early neurological symptom emerged as predicting variance in cognitive task factors. Both Executive Function Performance ($\eta_p'^2 = 0.03$) and Memory ($\eta_p'^2 = 0.038$) were predicted by initial disorientation (EF Performance: $R_{adj}^2 = 0.024$, $p = 0.032$; Memory: $R_{adj}^2 = 0.031$, $p = 0.017$). Variance in Executive Function RT and Category Fluency factors were not predicted by early neurological symptoms. With individual cognitive tests as the dependent variable, several models emerged; however, none of the models survived correction for multiple comparisons (Sidak $\alpha = 0.0028$; **Supplementary Table 3**). Headache severity was associated with slower reaction time of the Word List Recognition Test ($p = 0.005$) and fewer correct answers on the Category Fluency ($p = 0.003$) and Pictorial Associative Memory ($p = 0.036$) Tests. Confusion predicted the percentage of correct answers of the Category Fluency ($p = 0.047$) and the Word List Recognition Tests ($p = 0.006$). Altered consciousness predicted Word List Recognition d′ ($p = 0.003$), and dizziness predicted perseverative errors in the WCST ($p = 0.035$). Disorientation predicted WCST correct answers ($p = 0.019$), and numbness predicted WCST reaction time for trials with correct answers ($p = 0.003$). Speech difficulty, disturbed vision, and loss of smell/taste did not predict any cognitive outcome.

Initial Symptom Factors

As reported in our previous publication with this sample (Guo et al., 2022), we used exploratory factor analysis to reduce reported symptoms into related factors. For initial symptoms, 5 factors were identified: "Neurological/Psychiatric" (characterized by disorientation, delirium, and visual disturbances); "Fatigue/Mixed" (characterized by fatigue, chest pain/tightness, and muscle/body pains); "Gastrointestinal" (characterized by diarrhea, vomiting, and nausea); "Respiratory/Infectious" (characterized by fever, cough, and breathing issues); and "Dermatological" (characterized by itchy welts, rash and foot sores). To assess whether any of the symptom-factors predicted any aspect of the different cognitive tasks, we conducted various multiple linear regression models (backward elimination method) with the symptom factors as predictors and cognitive task as the dependent variables.

No model significantly predicted variation in the EF Performance or Category Fluency factors. Individual differences

in EF Reaction Time were significantly predicted by a model which contained only the Dermatological factor ($\eta'_p{}^2$ = 0.079) and predicted over 8% of variance ($R_{adj}{}^2$ = 0.081, $p < 0.001$; see **Figure 4**). Individual differences on the Memory factor were significantly predicted by a model containing the Fatigue/Mixed factor ($\eta'_p{}^2$ = 0.061) and predicted 5.4% of variance ($R_{adj}{}^2$ = 0.054, p = 0.002).

The initial-symptom factors predicted aspects of all the individual cognitive tasks (**Table 4**). The Fatigue/Mixed factor predicted d′ (p = 0.008) and reaction time (p = 0.003) within the Word List Recognition Test, as well as Category Fluency correct answers (p = 0.014). The Fatigue/Mixed factor also predicted WCST reaction time (for correct answers, p = 0.002) in combination with the Dermatological factor. When the Fatigue/Mixed factor was combined with the Respiratory/Infectious factor, the significant variance was predicted in Word List % correct (p = 0.003), and the Respiratory/Infectious factor independently predicted correct choices on the WCST (p = 0.042). Finally, the Dermatological factor independently predicted reaction time in the 2D Mental Rotation Test (p = 0.001) and the Pictorial Associative Memory Test (p = 0.048). Compared against a corrected alpha (Sidak α = 0.0028), the models predicting WCST reaction time and 2D Mental Rotation maintained significance (see **Table 4**).

Nature of Ongoing Illness and Cognitive Performance

Ongoing Symptoms and Cognitive Performance

As reported in our previous publication with this sample (Guo et al., 2022), 6 factors were identified within the ongoing symptoms: "Neurological" (characterized by disorientation, confusion, and delirium); "Gastrointestinal/Autoimmune" (characterized by diarrhea, hot flushes, and nausea); "Cardiopulmonary/Fatigue" (characterized by breathing issues, chest pain/tightness, and fatigue); "Dermatological/Fever" (characterized by face/lips swelling, foot sores, and itchy welts); "Appetite Loss" (characterized by weight loss and loss of appetite); and "Mood" (characterized by depression, anxiety, and vivid dreams). To assess whether symptoms experienced in the time since the initial infection predicted any aspect of the different cognitive tasks, we entered the ongoing symptom factors into a series of regressions with the cognitive task variables as dependents.

For these ongoing symptoms, no model significantly predicted variance in the EF Reaction Time, Memory, or Category Fluency factors. The Neurological factor alone predicted variance in EF Performance ($\eta'_p{}^2$ = 0.031; $R_{adj}{}^2$ = 0.024, p = 0.037). Different symptom factors were able to explain variance in different individual cognitive tasks (**Table 5**). The Cardiopulmonary/Fatigue factor predicted a significant amount of variance in Word List % correct (p = 0.03) and reaction time in WCST trials containing correct answers (p = 0.01). The Neurological factor predicted variance in WCST correct answers (p = 0.046), and in combination with the Dermatological/Fever factor predicted performance on the WCST (p = 0.013). The Neurological factor and Mood factors together predicted % of words produced that were correct in the Category Fluency Test (p = 0.004) Finally, the Gastrointestinal/Autoimmune factor predicted variation in Word List reaction time (p = 0.046). None of these associations survived correction for multiple comparisons (Sidak α = 0.0028).

Nature of Current Illness and Cognitive Performance

The Severity of Current Illness

Given the often-cyclical nature of symptoms, participants were asked to report to what degree they were experiencing a "bad day" in terms of symptoms on the day of testing. To address the question of whether group differences in performance were due to severity of illness on the day of testing, we first assessed whether completing the test on a "bad day" impacted cognitive performance. No cognitive task factor showed any significant associations with current symptom severity. In terms of individual cognitive task variables, there were group effects in Category Fluency repetitions [$F(4,117) = 5.809$, $p < 0.001$] and 2D Mental Rotation reaction time [$F(4,118) = 5.371$, p = 0.001], both of which survived correction for multiple comparisons (Sidak α = 0.0028). However, no effect was directional [with the only significant correlation being with 2D Mental Rotation performance (r = –0.184, p = 0.042, which did not survive correction for multiple comparisons (Sidak α = 0.0028)].

To test whether associations between ongoing symptoms and cognitive performance were not better explained by the symptoms' severity on the day of testing, rather than the presence of ongoing symptoms *per se*, we performed stepwise regressions with the cognitive task factors as the dependent, current symptom severity (good/bad day) as the first step and the ongoing symptom subgroup ($R/C+/C++$) as the second step. Current symptom severity was not a significant predictor of any cognitive outcome.

Current Symptom Factors

As reported in our previous publication (Guo et al., 2022), factor scores for current symptoms were calculated from the 6 ongoing symptom factors. No current symptom factors significantly predicted individual differences in either Executive Function factors or the Category Fluency factor. A model containing the Neurological factor ($\eta'_p{}^2$ = 0.041) predicted variance in the Memory factor ($R_{adj}{}^2$ = 0.034, p = 0.018).

In terms of individual task variables, the degree to which current symptoms aligned with the Mood factor ($\eta'_p{}^2$ = 0.043) predicted the percentage of correct words in the Category Fluency Test ($R_{adj}{}^2$ = 0.037, p = 0.013), while alignment with the Dermatological/Fever factor ($\eta'_p{}^2$ = 0.029) predicted variance in the number of repetitions ($R_{adj}{}^2$ = 0.022, p = 0.043). The extent to which current symptoms aligned with the Neurological factor ($\eta'_p{}^2$ = 0.028) predicted the number of WCST perseveration errors ($R_{adj}{}^2$ = 0.021, p = 0.047). Alignment with the Cardiopulmonary/Fatigue factor ($\eta'_p{}^2$ = 0.035) predicted WCST reaction time of correct answers ($R_{adj}{}^2$ = 0.028 p = 0.025).

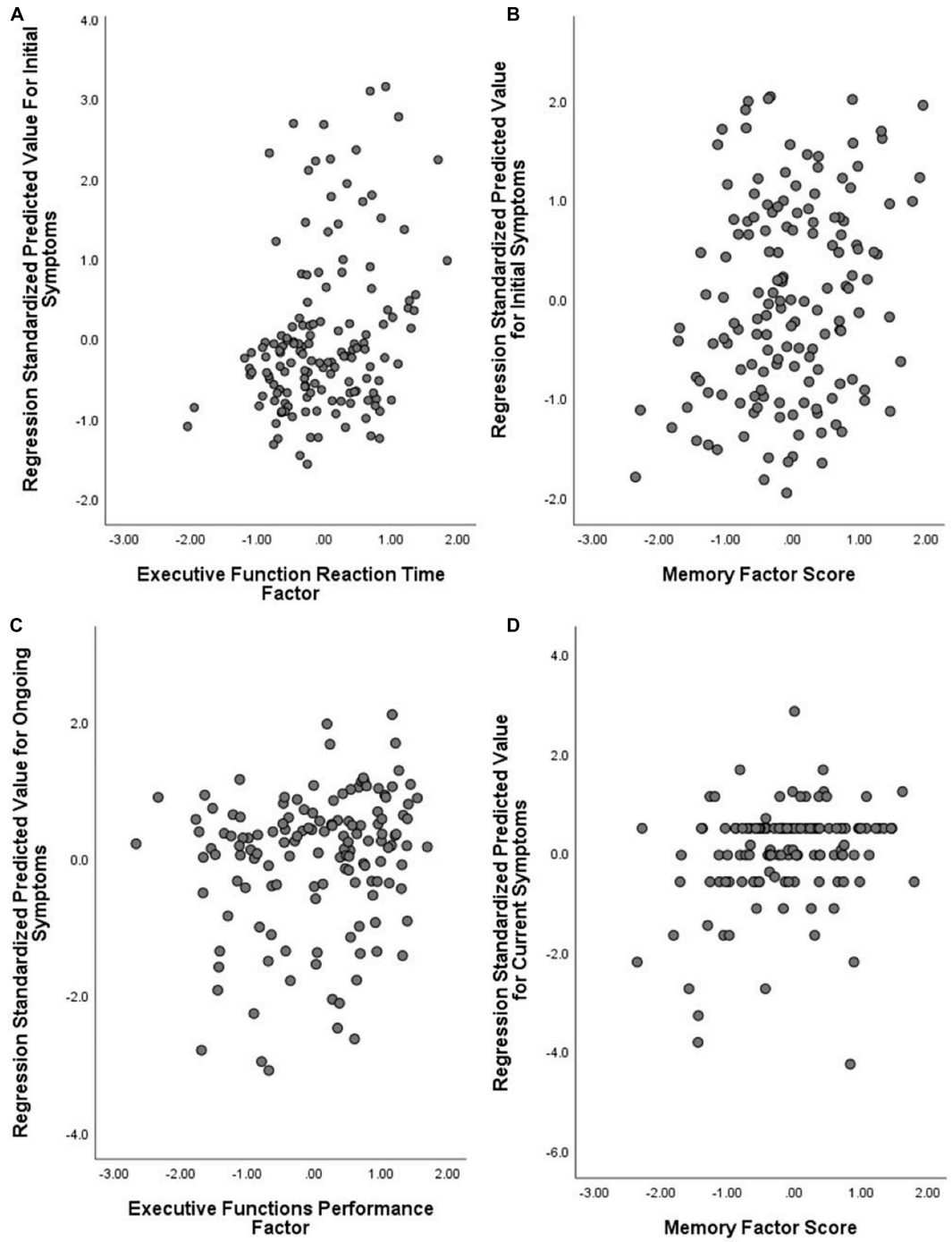

FIGURE 4 | Symptom factors predicting cognitive task factors. **(A)** Initial symptoms model (Dermatological) predicting Executive Function Reaction Time; **(B)** Initial symptoms model (Fatigue/Mixed) predicting Memory; **(C)** Ongoing symptoms model (Neurological) predicting Executive Function Performance; and **(D)** Current symptoms model (Neurological) predicting Memory. Note that symptom factors are reversely coded (lower numbers translate to more severe symptoms).

None of the factors were associated with any variables within the Associative Memory or Word List tests. After correcting for multiple comparison (Sidak $\alpha = 0.0028$), no associations were significant.

Cognitive Symptoms and Cognitive Performance

As reported in our previous publication with this sample (Guo et al., 2022), cognitive symptoms were highly prevalent.

TABLE 4 | Initial symptom factors and subsequent cognitive performance.

Symptom Factor (Predictor)	Cognitive Outcome (dependent variable)	*F*	*p*	$\eta'_p{}^2$	Adjusted R^2
Fatigue/Mixed	Word List d'	(1,158) = 7.28	0.008	0.044	0.038
	Word List (RT)	(1,158) = 9.27	0.003	0.055	0.049
	Category Fluency (Correct)	(1,156) = 6.17	0.014	0.038	0.032
	WCST RT (Correct)	(1,156) = 10.26	0.002*	0.062	0.056
Fatigue/Mixed + Respiratory/Infectious	Word List (% Correct)	(1,157) = 5.88	0.003	0.039 0.022	0.058
Respiratory/Infectious	WCST (Correct)	(1,156) = 4.19	0.042	0.026	0.020
Dermatological	Associative Memory (RT)	(1,159) = 7.95	0.005	0.048	0.042
	2D Mental Rotation Test (RT)	(1,158) = 10.70	0.001*	0.063	0.058

** denotes p-Values below Sidak-correct alpha at 0.0028.*

TABLE 5 | Ongoing symptom factors and subsequent cognitive performance.

Symptom Factor (Predictor)	Cognitive Outcome (dependent variable)	*F*	*p*	$\eta'_p{}^2$	Adjusted R^2
Cardiopulmonary/Fatigue	Word List (% correct)	(1,143) = 4.77	0.030	0.032	0.026
	WCST (RT Correct)	(1,141) = 6.79	0.010	0.046	0.039
Neurological	WCST (Correct)	(1,141) = 4.04	0.046	0.028	0.021
Neurological + Dermatological/Fever	WCST (Perseverative errors)	(2,140) = 4.51	0.013	0.031 0.030	0.047
Neurological + Mood	Category Fluency (% correct)	(2,139) = 5.66	0.004	0.052 0.030	0.062
Gastrointestinal/Autoimmune	Word List (RT)	(1,143) = 4.06	0.046	0.028	0.021

** denotes p-Values below Sidak-correct alpha at 0.0028.*

Within those currently experiencing symptoms (n = 126), 77.8% reported difficulty concentrating, 69% reported brain fog, 67.5% reported forgetfulness, 59.5% reported ToT problems and 43.7% reported semantic disfluency (saying or typing the wrong word).

A cognitive symptom factor was created separately to the non-cognitive symptoms (see Guo et al., 2022) for both ongoing and current symptoms. There was no association between the ongoing cognitive symptom factor and any cognitive task factor. In terms of individual cognitive task variables, the ongoing cognitive symptom factor significantly predicted variance in the Word List Recognition Memory Test, with more severe reported cognitive symptoms associated with lower % correct ($\eta'_p{}^2 = 0.038$; $R_{adj}{}^2 = 0.031$, $p = 0.02$) and slower reaction times ($\eta'_p{}^2 = 0.039$; $R_{adj}{}^2 = 0.032$, $p = 0.018$). Ongoing cognitive symptoms were also associated with a number of repetitions in the Category Fluency Test ($\eta'_p{}^2 = 0.032$; $R_{adj}{}^2 = 0.025$, $p = 0.032$) and reaction time in the 2D Mental Rotation ($\eta'_p{}^2 = 0.029$; $R_{adj}{}^2 = 0.022$, $p = 0.042$). However, none of these associations survived correction for multiple comparisons (Sidak $\alpha = 0.0028$).

Current cognitive symptoms significantly predicted variance in the Memory factor ($\eta'_p{}^2 = 0.046$; $R_{adj}{}^2 = 0.039$, $p = 0.012$) only. In terms of individual variables, current cognitive symptoms significantly predicted variance in Word List performance (but not RT) metrics (d′: $\eta'_p{}^2 = 0.03$; $R_{adj}{}^2 = 0.024$, $p = 0.036$; % correct: $\eta'_p{}^2 = 0.06$; $R_{adj}{}^2 = 0.053$, $p = 0.003$), Category Fluency repetitions ($\eta'_p{}^2 = 0.048$; $R_{adj}{}^2 = 0.041$, $p = 0.009$), and 2D Mental Rotation reaction time ($\eta'_p{}^2 = 0.041$; $R_{adj}{}^2 = 0.034$, $p = 0.015$). However, none of these associations survived correction for multiple comparisons (Sidak $\alpha = 0.0028$).

Some specific cognitive symptoms can be related directly to tests of the associated ability. Participants that reported currently experiencing forgetfulness were compared to those not reporting this symptom on measures of memory. Forgetfulness was associated with a reduced score on the overall Memory factor [$t(134) = 2.111$, $p = 0.037$; **Figure 5**], even when demographic variables were accounted for [$F(1,120) = 8.840$, $p = 0.03$]. For individual memory variables, those reporting forgetfulness scored significantly lower on the Word List Recognition Memory Test ($U = 2.48$, $p = 0.013$) but no difference was found for Associative Memory. After controlling for age, sex, country, and education level, no differences were significant among the individual variables.

Participants reporting linguistic problems (two cognitive symptoms: ToT, semantic disfluency; one neurological symptom: speech difficulty, e.g., slurring) were compared to those not reporting these symptoms on measures of involving verbal/linguistic challenge. For the Category Fluency factor, there was no effect of ToT [$t(135) = 0.414$, $p = 0.680$], semantic disfluency [$t(135) = 0.671$, $p = 0.503$], or speech difficulty [$t(16.4) = 0.039$, $p = 0.969$]. In terms of individual linguistic (Word list and Category Fluency) variables, those reporting ToT problems trended toward lower % correct of Word List Recognition ($U = 1.91$, $P = 0.057$) and repeated significantly more words on the Category Fluency factor ($U = 2.22$, $p = 0.026$) than those without this symptom. Those reporting semantic disfluency had significant lower % correct ($U = 2.49$, $p = 0.013$) and d′ ($U = 1.99$, $p = 0.047$) on Word List Recognition than those without this symptom. Finally, those reporting speech difficulty had significantly lower % correct on Word List Recognition ($U = 2.15$, $p = 0.031$) and more repetitions on Category Fluency ($U = 2.37$, $p = 0.018$) than those not reporting this symptom.

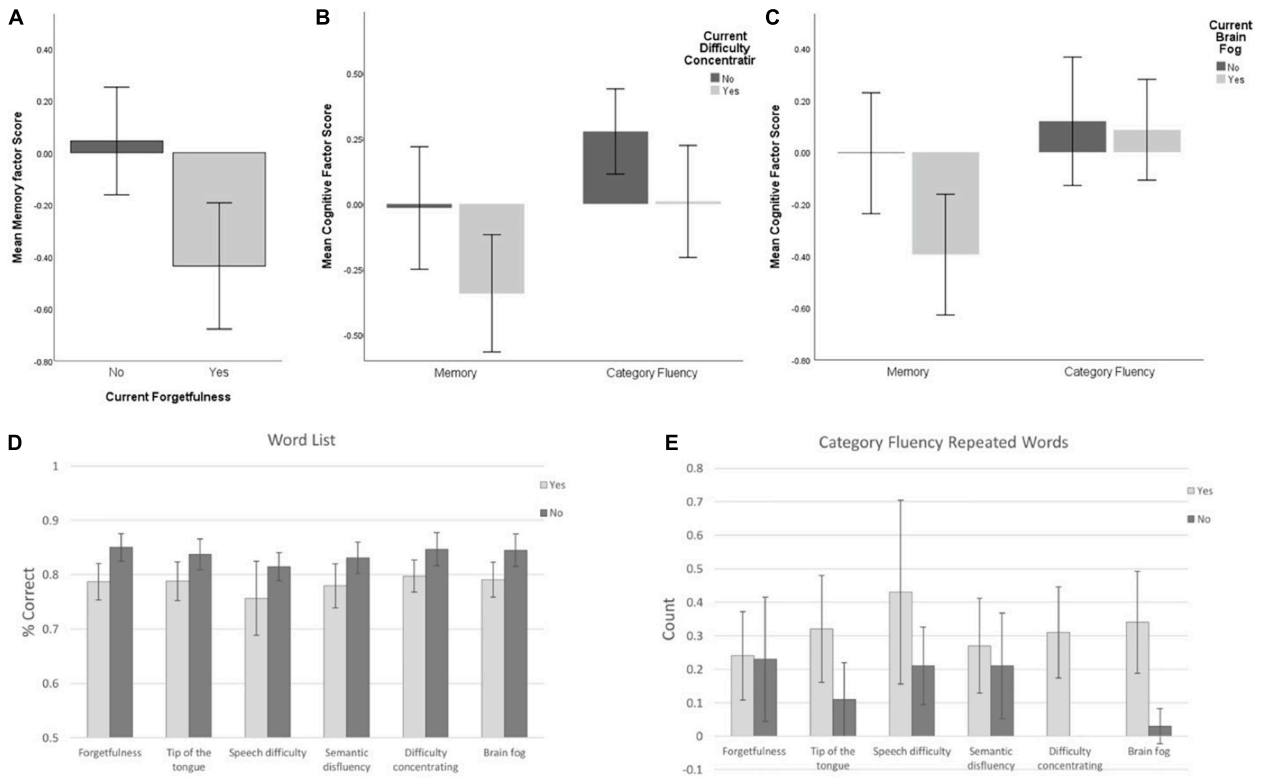

FIGURE 5 | (A) Memory factor score for those reporting (or not) current forgetfulness. **(B)** Memory and Category Fluency factor scores for those reporting (or not) current difficulty concentrating or **(C)** brain fog. **(D)** Word List % correct among groups with/without current cognitive symptoms; **(E)** Category Fluency repetitions among groups with/without current cognitive symptoms. Error bars: ± 2 SE.

Again, after controlling for age, sex, country and education level, no differences were significant.

Finally, to establish whether any cognitive performance differences were due to "general" issues with cognition, we compared individuals experiencing "general" cognitive issues (difficulty concentrating and brain fog) to those not reporting these symptoms across all cognitive tests.

Difficulty concentrating was not associated with variance in any cognitive task factor. However, controlling for demographic variables revealed an association between reporting difficulty concentrating and lower scores on the Category Fluency factor [$F(1,121) = 4.199$, $p = 0.043$]. Brain fog was associated with significantly reduced performance on the Memory factor only [$t(134) = 2.151$, $p = 0.033$], which dropped below significance ($p = 0.054$) when demographic variables were accounted for. Neither Executive Function factors showed any significant association with these symptoms.

In terms of individual variables, those reporting difficulty concentrating had fewer correct words ($U = 2.11$, $p = 0.034$) and more repetitions ($U = 2.74$, $p = 0.006$) on Category Fluency but had faster reaction time on 2D Mental Rotation ($U = 2.26$, $p = 0.024$) than those not reporting this symptom. After controlling for age, sex, country and education level, these differences remained significant: Those reporting difficulty concentrating produced fewer correct words [$F(1,106) = 8.19$, $p = 0.005$] and more repetitions [$F(1,106) = 4.28$, $p = 0.04$] on Category Fluency, and reacted faster on the 2D Mental Rotation Test [$F(1,107) = 5.68$, $p = 0.019$]. However, none of these survived correction for multiple comparisons (Sidak $\alpha = 0.0028$).

Those reporting brain fog had lower performance on Word List Recognition ($U = 2.35$, $p = 0.019$) and produced more repetitions in Category Fluency ($U = 3.04$, $p = 0.002$) than those not reporting this symptom. After controlling for age, sex, country and education level, the difference on Word List Recognition disappeared but those reporting brain fog still had more repetitions on Category Fluency [$F(1,106) = 6.9$, $p = 0.01$]. However, this did not survive correction for multiple comparisons (Sidak $\alpha = 0.0028$).

DISCUSSION

In this study, we present that the second subset of initial findings from a cross-sectional/longitudinal study investigating cognition post-COVID-19: The COVID and Cognition Study (COVCOG). In the first paper (Guo et al., 2022), we described the characteristics of the sample of 181 (130 women) individuals who had experienced the COVID-19 infection (74% of which self-identified as experiencing "Long COVID") and 185 (118 women) who had not. Those who had had COVID-19 had a relatively even spread of those that had fully recovered at the time of test

(n = 42) or had mild/moderate (n = 53) or severe (n = 66) ongoing symptoms. The majority of the sample fell between ages 18–60, were of White Northern European ethnicity, had attended college/university, and lived in the United Kingdom. In this second investigation, we explored how factors associated with COVID-19 infection may impact the performance on cognitive tests.

Participants were assessed on a range of cognitive tasks intended to cover different aspects of memory (verbal memory and associative memory), language (word finding), and executive functions (task switching and visual working memory). Our first hypothesis was that those who had experienced the COVID-19 infection would be likely to show deficits in tasks challenging memory and language, given the prevalence of self-reported cognitive symptoms in these areas.

We found that the fact of the COVID-19 infection (irrespective of ongoing symptoms) was associated with reduced performance on a factor created from memory task variables, but not other cognitive task factors (once demographic variables were accounted for). Detailed analysis of individual variables showed an increased reaction time when performing a verbal memory task (alongside several other Word List and Associative Memory variables, which did not survive correction for multiple comparisons). When considering the severity of ongoing symptoms, once again memory emerged as a significant factor, with those with severe ongoing symptoms performing significantly worse than those that had recovered. Looking at individual variables, the impact on verbal memory specifically became clear, with both performance (% correct) and reaction time being significantly affected by the severity of ongoing illness in a dose-dependent manner (those with severe symptoms were worse than those with mild symptoms who were worse than those that had recovered). The picture was less clear for non-verbal associative memory, which did not show the main effect (after correcting for multiple comparisons) but pairwise analyses did demonstrate a clear performance advantage in those who had not experienced the COVID-19 infection relative to those with severe ongoing symptoms. The Category Fluency word-finding task showed a similar pattern, with main effects falling below the threshold for significance once multiple comparisons were accounted for, but pairwise analysis revealing a strong negative impact of severe ongoing illness on the ability to produce category words. Looking at executive functions, similar to Hampshire et al. (2021), we found little to no effect of the COVID-19 infection on 2D Mental Rotation, which is thought to assess visuospatial working memory (Hyun and Luck, 2007). While some group differences emerged in reaction times during the WCST, these disappeared after controlling for demographic factors, suggesting that they may have been an artifact of the slightly older age of those with ongoing COVID-19 symptoms.

Long COVID is often reported to be a cyclical illness, with symptoms changing in severity over time. As such, it was important to establish whether the severity of symptoms on the day of the test (rather than in general) might account for significant variance in cognitive performance. We found that the extent to which participants reported that they were having a "bad day" in terms of symptoms on the day of the test was not directionally associated with performance on any task and did not contribute to models predicting cognitive performance from the severity of ongoing symptoms. This suggests that it was the general severity of the ongoing illness, rather than feeling ill on that day in particular, that was driving alterations in cognitive performance.

Given these findings, we suggest that, as others have found (e.g., Hampshire et al., 2021), "objective" cognitive differences do exist between those that have and have not experienced the COVID-19 infection. In particular, we found that these are related to the severity of ongoing illness (with those who report having fully recovered being, in our sample, indistinguishable from those who have not had the infection) and that they may be most pronounced in tests of verbal memory. Particular difficulties with language and verbal memory align with the frequency of self-reported deficits in these areas in other studies of Long COVID (e.g., Davis et al., 2021; Ziauddeen et al., 2021) as well as evidence for the concentration of gray matter loss in the left hemisphere (Douaud et al., 2021).

In our previous publication on the COVCOG sample (Guo et al., 2022), we reported that differences in long-term severity of Long COVID symptoms could be partially predicted by the severity and nature of the initial illness. In this study, we found that the reported severity of initial illness did not influence later performance on cognitive tasks taken. However, there was an influence on the *nature* of the initial illness. Using the symptom factors we introduced previously (Guo et al., 2022), we found that individual differences in the initial Dermatological symptom factor predicted around 8% of the variance in Executive Functions Reaction Times, while around 5% of the variance in Memory was predicted by individual differences in the Fatigue/Mixed initial symptom factor. These results were reflected in the individual cognitive variables, where the Fatigue/Mixed symptom factor predicted multiple memory variables (e.g., word list d′, % correct, and reaction time), while the Dermatological factor predicted Associative Memory and 2D Mental Rotation reaction time. Interestingly, the initial symptom factors predicting cognitive performance were not quite the same as those that were found to predict cognitive symptoms in our previous analysis. In our previous publication (Guo et al., 2022), we showed that a model containing all factors except the Dermatological symptom factor predicted around 20% of the variance in ongoing cognitive symptoms and that a similar model (omitting Respiratory symptoms) predicted around 14% of the variance in current cognitive symptoms. One explanation for the differential findings in this study may be that measures of reaction time may not align so closely to individuals' perceived cognitive issues.

One hypothesis was that neurological symptoms during the acute phase may signal an increased likelihood of subsequent cognitive issues. While we found no clear association between the initial Neurological factor and cognitive function, one specific symptom, disorientation, experienced during this period predicted variance in both Executive Functions and Memory. There were also several associations between neurological symptoms experienced in the first 3 weeks and individual cognitive task variables (notably headache, altered consciousness,

and numbness); however, these did not survive correction for multiple comparisons. As discussed in our previous report (Guo et al., 2022), the Fatigue/Mixed factor, while not labeled "Neurological" contains a large number of neurological symptoms, including confusion, numbness, headache, and dizziness, the latter two of which loaded more highly on the Fatigue/Mixed factor than on the Neurological/Psychiatric factor (which was more characterized by disorientation, visual disturbances, delirium, and altered consciousness). The fact that it was this factor, rather than the Neurological/Psychiatric factor, that predicted later cognitive task performance may be informative as to the mechanism of action. The Fatigue/Mixed factor might be considered to incorporate many of the expected features of systemic inflammation, in contrast to the Neurological/Psychiatric factor that is more closely linked to the neurological system only. This account accords with the other factors that emerged as predictors. While named for the fact that they affect the skin, the symptoms in the "Dermatological" factor are also linked with systemic inflammation, incorporating cross-loading symptoms such as limb weakness. These findings suggested that systemic inflammation associated with acute COVID-19 infection may have contributed to cognitive deficits across different domains up to 6 months later.

Links between systemic inflammation and cognitive functions have been previously reported in experimental (Harrison et al., 2009) and population-level studies (Gimeno et al., 2009). For example, Typhoid-vaccine-induced inflammation can lead to poorer performance in a reaction time task that was associated with systemic IL-6 levels and substantia nigra activation (Brydon et al., 2008). In an epidemiological study, higher levels of the inflammation marker, IL-6, were associated with reduced hippocampal volumes in middle-aged healthy volunteers (Marsland et al., 2008). Certain brain circuits involving the amygdala, the hippocampus, and the striatum have been particularly noted to be more sensitive to the impact of peripheral inflammation (Kraynak et al., 2018). The role of such limbic circuits in autonomic and visceromotor regulation suggests a link between peripheral inflammation physiology and implicated brain circuits. On the other hand, some studies proposed a role of the dorsolateral prefrontal cortex on peripheral inflammation *via* projections on the adrenal medulla that can affect attentional control (Miller et al., 2013). As such, there is a good reason to implicate systemic inflammation as a candidate causal mechanism for cognitive impacts.

In terms of ongoing symptoms, the main finding to emerge was that the Neurological factor predicted variance in Executive Function Performance, perhaps driven by an influence of this cluster of symptoms on the WCST (though no individual task variable survived correction for multiple comparisons). The Neurological factor also emerged as a significant predictor of cognitive performance among the current symptoms, this time significantly predicting variance in Memory. These associations align to some degree with the previous finding that the current cognitive symptoms were well predicted by models containing ongoing Neurological, Gastrointestinal, and Cardiopulmonary/Fatigue symptoms, and current Neurological and Cardiopulmonary/Fatigue symptoms (Guo et al., 2022). The shift in predictive power from predominantly inflammatory variables during the acute phase, to more classic neurological symptoms during the ongoing illness, raises the possibility that damages or processes instigated by an excessive immune response to infection may lead to disruption of neural function with neurological and cognitive consequences that linger independently. Such a mechanistic hypothesis would require targeted investigation of inflammatory markers, as well as functional and structural imaging.

As has been noted, the symptom factors that predicted performance on cognitive tasks were not always the same as those that predicted individual differences in cognitive symptoms. Indeed, individual differences in ongoing cognitive symptoms did not predict variance in any cognitive task performance factor. *Currently* experienced cognitive symptoms were, however, associated with reduced memory performance, driven by differences in multiple verbal memory tasks (particularly Word List and repetitions within the Category Fluency Test). When investigating specific cognitive symptoms, those who reported currently experiencing forgetfulness showed significantly lower Memory factor score, while those reporting linguistic issues did not score differently on the Category Fluency factor (although there were some associations with individual Category Fluency and Word List task variables that did not withstand controlling for demographic factors). The finding that those currently reporting cognitive issues-particularly memory problems—scored significantly lower on objective cognitive tasks than those experiencing ongoing symptoms but *not* reporting such symptoms, and that both are linked with ongoing neurological symptoms is important. It suggests that subjective experience of cognitive deficits in this population may be considered predictive of the need for neurological assessment and treatment.

In this study, one of the symptom factors included mood symptoms. Although we did not specifically examine the interplay between mood symptoms and inflammation, it is an area that warrants attention. There is substantial literature highlighting the crucial link between depression and low-grade inflammation (Dantzer et al., 2008). The extent to which COVID19-induced mood symptoms and inflammation interact—together leading to poorer cognitive performance—is an important clinical aspect for future investigation. A recent study with depressed patients showed that reaction time and processing speed were more sensitive to peripheral inflammation whereas executive functions were relatively spared (Kaser et al., 2021). Longitudinal results from our study can help understand the longstanding impact of COVID-19 induced inflammation on mood as well as cognition, and the interaction between the two.

Limitations

Many of the limitations of this study have been reviewed in our previous report (Guo et al., 2022). One major limitation of this study is that, due to the novelty of the topic, it was not designed with clear, specific hypotheses, and as such, much of the analysis was necessarily exploratory, resulting in a large number of analyses and comparisons. To account for these, Sidak alpha adjustments were used, with the result that only the very strongest effects survived at conventional

statistical thresholds. We consider this conservative approach appropriate but note that it is likely to be associated with a high type 2 error rate and, thus, that some associations that did not reach these thresholds may yet be upheld upon further investigation/replication. A stated aim of this study was to generate hypotheses that could be tested in later, more targeted research, and thus while only the strongest statistical outputs should be treated as concrete findings, those that do not reach this threshold are also reported, such that they can inform and motivate future research. Of particular note is that, while rarely surviving corrections for multiple comparisons, variables associated with the Word List Recognition Memory Test repeatedly emerged as being modulated by facets of Long COVID. This is particularly relevant since it was predominantly this task that was influenced by the severity of ongoing symptoms. All elements of this task (performance and reaction time) were predicted by Fatigue/Mixed symptoms during the initial illness, and performance was related to ongoing Cardiopulmonary/Fatigue symptoms and current Neurological symptoms and Appetite Loss. Word List performance was also linked with the severity of cognitive symptoms, both ongoing and current. The consistent implication of verbal memory as vulnerable to factors associated with the COVID-19 infection should certainly warrant, further, more targeted investigation.

Another potentially notable finding that may be somewhat obscured by alpha corrections is the consistency in the association between neurological symptoms and executive function, particularly within the WCST. While the more "encephalitis-like" Neurological/Psychiatric initial symptom factor did not show associations with later WCST performance, individual elements of it (dizziness, disorientation, numbness) did. As already stated, during the ongoing illness, the Neurological factor strongly predicted the number of perseveration errors but was also associated with reduced correct responses and slower reaction times. This pattern was carried over into currently experienced symptoms, with neurological symptoms once again predicting perseveration errors. Taken as a pattern, these findings (though not all individually strong) may suggest that more severe neurological symptoms may be indicative of alterations in the frontal lobe function, evidenced by problems with response inhibition. This, again, should be investigated in more targeted future studies.

An additional limitation of this study was that the data was collected online. While online assessment facilitated cognitive testing during lockdown, and with patients from around the world, it meant that we were less able to guarantee high-quality data by ensuring that participants were in a suitable environment or concentrating properly on the task. This was mitigated to some degree by the use of the "concentration/bot check" task, which did not highlight a problem with lack of concentration. It is also increasingly becoming accepted that online cognitive testing can produce highly robust and reliable results and that Gorilla.sc is a reliable platform on which to conduct this type of research (e.g., Hilbig, 2016; Anwyl-Irvine et al., 2020). Nonetheless, future research should confirm these findings using full lab-based cognitive testing batteries.

Our study contained very few individuals who fell at either end of the severity spectrum (e.g., were asymptomatic or required ventilation). The deficits identified in the study of Hampshire et al. (2021) were substantial and related to severity, with ventilated participants showing performance reductions larger than those seen (using the same tasks) following a stroke and greater than the average 10-year decline. They also found that detectable deficits were also present in those that experienced no respiratory symptoms at all and those that did not have ongoing symptoms. In contrast, our present results suggest that those who report being completely recovered from COVID-19 were indistinguishable from those that had not experienced infection at all. This difference may be due to the relative power of the two studies (with Hampshire and colleagues having a large sample). It may also be related to differences in how symptomatology was recorded. Hampshire and colleagues only asked about "breathing difficulties" in the initial illness, and their assessment of ongoing symptoms was a sub-choice within "have you had, or suspect you have had symptoms of COVID-19 " ("No"/"Yes but the symptoms passed"/"Yes currently experiencing symptoms"). Given that people's experience of symptoms during the long-term sequelae of COVID-19 can be very different from the "Classic" COVID-19 symptoms of breathing difficulties, cough, and loss of sense of taste and smell, many individuals who were experiencing, for example, ongoing cognitive or neurological symptoms may not have considered these to qualify in this context. Further research will be necessary to clarify these discrepancies.

Long Term Risks

The accumulating neural and cognitive findings in Long COVID patient groups present a concerning picture when considering long-term cognitive health. In particular, loss of gray matter within the temporal lobe in COVID-19 (Douaud et al., 2021), along with the evidence for reduced memory performance presented here, supports the suggestion that those who have experienced the COVID-19 infection may be at increased risk for later neurodegeneration and dementia (de Erausquin et al., 2021).

While some authors have particularly highlighted the neurodegenerative risks posed *via* viral invasion of the central nervous system (CNS) (Douaud et al., 2021), in fact, almost all candidate mechanisms of neural impact raise the possibility of increased vulnerability to dementia. SARS-CoV-2 is increasingly being recognized as an inflammatory disease (Pearce et al., 2020; Sims et al., 2021). In addition to having major physical impacts, excessive and chronic inflammation is also associated with considerable damage in the brain. Chronic neuroinflammation is heavily implicated in the pathophysiology of neurodegenerative diseases (Chen et al., 2016), with evidence of inflammation commonly being found in the brains of patients with Alzheimer's disease (AD) (McGeer and McGeer, 2010; Zotova et al., 2010). The dramatic impact of infections, such as *Escherichia coli* on survival and proliferation of hippocampal neurons (Ekdahl et al., 2003; Monje et al., 2003), has previously indicated that this region may be vulnerable to deleterious effects of inflammatory viral infection, and development of dementia following viral infections such as influenza have been previously noted (e.g., Honjo et al., 2009). COVID-19 has also been linked to abnormal blood clotting, which again has been linked to disease severity

and death (Xiang-Hua et al., 2010; Tang et al., 2020; Wang et al., 2020; Wichmann et al., 2020), with microthrombi in multiple organs, including the brain (Zhang et al., 2020). Clotting is a significant factor when considering the risk for neurological damage and cognitive impairment because of the risk of CVAs and stroke (e.g., Klok et al., 2020). Indeed, an increased incidence of stroke has been reported in hospitalized patients with COVID-19 (Li et al., 2020; Oxley et al., 2020). A large proportion of stroke survivors experience cognitive impairment, and, unlike physical impairments, these tend to worsen rather than improve over time, leading to the description of "post-stroke dementia" (Mijajlović et al., 2017). Many small stroke events ["transient ischemic attacks" (TIAs)] go unnoticed at the time but may cause cumulative damage, leading to cognitive decline and dementia vulnerability. Indeed, recent studies have indicated that the proportion of dementia that is caused by small vessel ischemia may be as high as 36–67% (e.g., Seshadri and Wolf, 2007; Grau-Olivares and Arboix, 2009).

Summary

In this second investigation of the first baseline session of the COVID and Cognition study, we explored whether those who had experienced the COVID-19 infection showed measurable differences in assessments of cognitive performance. We found a consistent association between the COVID-19 infection and reduced memory performance, with those with ongoing symptoms being less accurate and slower in a test of verbal memory, but (once demographics and multiple comparisons were accounted for) there were no significant group effects in any other cognitive domain. When considering the nature of symptoms experienced, Fatigue/Mixed and Dermatological symptoms during the initial 3 weeks of illness were associated with reduced memory performance and slower reaction times on Executive Function Performance and Reaction Time tasks, respectively. Neurological symptoms during the ongoing illness were associated with performance in the Executive Function tasks, while the same symptoms experienced at the time of test predicted variance in memory. These were the most robust findings, with a conservative correction for multiple comparisons, suggesting that other identified associations may be worthy of further investigation.

In combination with previous evidence for cognitive dysfunction (e.g., Hampshire et al., 2021) and neural damage following the COVID-19 infection (Douaud et al., 2021), these findings are concerning and suggest that COVID-19 is an illness that may be associated with considerable cognitive and neurological sequelae of unknown longevity. This is particularly concerning given the potential for these changes to translate into greater vulnerability to neurodegeneration. These findings should be of note to policymakers, both in the context of post-COVID support provision and in the nature of the response to the ongoing pandemic. It is yet to be seen whether the proportion of infections that translate into Long COVID remains similar in the face of changes in both population immunity (*via* both vaccination and previous infection) and disease variants. However, if the current patterns persist, the long-term societal impacts of unmitigated spread may be considerable. In terms of follow-up support for patients, we reported in our previous publication (Guo et al., 2022) that a large proportion of our sample reported difficulty in getting support from medical professionals, and one reason for this may be a reluctance to consider self-reported cognitive deficits as a concrete indicator (rather than, for example, a component of general fatigue). It is thus notable that, in this study, self-reported memory issues were associated with measurable reductions in memory ability and that these are linked with other neurological symptoms. This suggests that neurological and neuropsychological assessment should be made more widely available to patients with Long COVID reporting cognitive deficits.

The COVID and Cognition participants were followed up multiple times following this assessment, and future publications with this cohort will prove informative as to the likely progression in symptoms and cognitive performance over time. However, given the associations shown in our previous publication with the number of weeks since infection (Guo et al., 2022), it seems likely that a considerable proportion of individuals may show stable cognitive symptoms over many months.

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 Psychology Research Ethics Committee, University of Cambridge. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LGC and PG designed the study. PG, SY, AB, RL, AS, LC, and LGC recruited and collected the data. PG, AB, SY, and LC analyzed the data. LGC, PG, AB, and SY wrote the manuscript. MH provided statistical advice. MK provided medical advice and oversight. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.804937/full#supplementary-material

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COVCOG 1: Factors Predicting Physical, Neurological and Cognitive Symptoms in Long COVID in a Community Sample. A First Publication From the COVID and Cognition Study

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Since its first emergence in December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has evolved into a global pandemic. Whilst often considered a respiratory disease, a large proportion of COVID-19 patients report neurological symptoms, and there is accumulating evidence for neural damage in some individuals, with recent studies suggesting loss of gray matter in multiple regions, particularly in the left hemisphere. There are a number of mechanisms by which COVID-19 infection may lead to neurological symptoms and structural and functional changes in the brain, and it is reasonable to expect that many of these may translate into cognitive problems. Indeed, cognitive problems are one of the most commonly reported symptoms in those experiencing "Long COVID"—the chronic illness following COVID-19 infection that affects between 10 and 25% of patients. The COVID and Cognition Study is a part cross-sectional, part longitudinal, study documenting and aiming to understand the cognitive problems in Long COVID. In this first paper from the study, we document the characteristics of our sample of 181 individuals who had experienced COVID-19 infection, and 185 who had not. We explore which factors may be predictive of ongoing symptoms and their severity, as well as conducting an in-depth analysis of symptom profiles. Finally, we explore which factors predict the presence and severity of cognitive symptoms, both throughout the ongoing illness and at the time of testing. The main finding from this first analysis is that that severity of initial illness is a significant predictor of the presence and severity of ongoing symptoms, and that some symptoms during the initial illness—particularly limb weakness—may be more common in those that have more severe ongoing symptoms. Symptom profiles can be well described in terms of 5 or 6 factors, reflecting the variety of

this highly heterogenous condition experienced by the individual. Specifically, we found that neurological/psychiatric and fatigue/mixed symptoms during the initial illness, and that neurological, gastrointestinal, and cardiopulmonary/fatigue symptoms during the ongoing illness, predicted experience of cognitive symptoms.

Keywords: Long COVID, cognition, neurological, memory, executive functions, language, COVID-19, symptoms

INTRODUCTION

Manifestations of coronavirus 2 (SARS-CoV-2) infection vary in severity ranging from asymptomatic to fatal. In the acute stage, symptomatic patients—at least in the early variants—typically experience respiratory difficulties that can result in hospitalization and require assisted ventilation (Baj et al., 2020; Heneka et al., 2020; Jain, 2020). While COVID-19 is primarily associated with respiratory and pulmonary challenge, 35% of patients report neurological symptoms including headache and dizziness (e.g., Mao et al., 2020). In severe illness, neurological symptoms can be seen in 50–85% of patients (e.g., Pryce-Roberts et al., 2020; Romero-Sánchez et al., 2020). Indeed, alteration in taste or smell (anosmia/dysgeusia) is reported in over 80% of cases (e.g., Lechien et al., 2020), is often the first clinical symptom (Mao et al., 2020; Romero-Sánchez et al., 2020) and regularly persists beyond resolution of respiratory illness (Lechien et al., 2020).

Accumulating evidence suggests that many COVID-19 patients experiencing severe illness show evidence of neural damage (Helms et al., 2020; Kandemirli et al., 2020) and unusual neural activity (Galanopoulou et al., 2020). There are a number of postulated mechanisms linking COVID-19 infection with neurological problems (Bougakov et al., 2021). For example, based on the behavior of previous SARS viruses, SARS-CoV-2 may attack the brain directly perhaps via the olfactory nerve (Lechien et al., 2020; Politi et al., 2020) causing encephalitis. Severe hypoxia from respiratory failure or distress can also induce hypoxic/anoxic-related encephalopathy (Guo et al., 2020). There is considerable evidence that COVID-19 is associated with abnormal blood coagulation, which can increase risk of acute ischemic and hemorrhagic cerebrovascular events (CVAs) (Beyrouti et al., 2020; Li et al., 2020; Wang et al., 2020; Kubánková et al., 2021) leading to more lasting brain lesions. Indeed, ischemic or hemorrhagic lesions have been found in COVID-19 patients in multiple studies (Le Guennec et al., 2020; Matschke et al., 2020; Moriguchi et al., 2020; Poyiadji et al., 2020). A recent study using the United Kingdom Biobank cohort comparing structural and functional brain scans before and after infection with COVID-19 identified significant loss of gray matter in the parahippocampal gyrus, lateral orbitofrontal cortex and insula, notably concentrated in the left hemisphere in patients relative to controls (Douaud et al., 2021).

A key candidate mechanism is dysfunctional or excessive immune response to infection. For example, excessive cytokine release ("cytokine storm") and immune-mediated peripheral neuropathy (e.g., Guillain-Barre syndrome) are both linked with neurological and sensory-motor issues (Alberti et al., 2020; Das et al., 2020; Poyiadji et al., 2020; Whittaker et al., 2020; Zhao et al., 2020). In addition to acute effects, chronic inflammation has also been associated with neural and cognitive dysfunction, particularly in the hippocampus—a key area responsible for memory (Ekdahl et al., 2003; Monje et al., 2003; Jakubs et al., 2008; Belarbi et al., 2012). Considerable rodent evidence links inflammatory cytokines with cognitive impairments (e.g., IL-1β: Thirumangalakudi et al., 2008; Beilharz et al., 2014, 2018; Che et al., 2018; Mirzaei et al., 2018; TNF-α: Thirumangalakudi et al., 2008; Beilharz et al., 2014; Almeida-Suhett et al., 2017). These findings are broadly reflected in human studies, wherein circulating cytokines have been associated with reduced episodic memory (e.g., Kheirouri and Alizadeh, 2019) and chronic neuroinflammation has been heavily implicated in the pathophysiology of neurodegenerative diseases (McGeer and McGeer, 2010; Zotova et al., 2010; Chen et al., 2016; Bossù et al., 2020). Given the volume of reports of excessive immune response to COVID-19 infection (Mehta et al., 2020; Tay et al., 2020), and evidence for neuroinflammation from postmortem reports (Matschke et al., 2020) research into cognitive sequalae is highly implicated.

Given the evidence for widespread neural symptoms and demonstrable neural damage, it could be expected that COVID-19 infection would be associated with cognitive deficits. Indeed, there is some early evidence linking neural changes following COVID-19 and cognitive deficits. Hosp et al. (2021) found that evidence of frontoparietal hypometabolism in older patients presenting with post-COVID-19 neurological symptoms via positron emission tomography (PET) was associated with lower neuropsychological scores, particularly in tests of verbal memory and executive functions.

Many forms of neuropathology would be unlikely to be present uniquely as cognitive deficits, but would be associated with a range of related symptoms. Some of these symptoms may be neurological (e.g., disorientation, headache, numbness) while others may reflect systemic/multisystem involvement (e.g., reflecting the symptom profile of chronic inflammatory or autoimmune diseases). It may therefore be possible to gain information as to the mechanism of neurological involvement via investigation of symptomatology. If it is possible to identify groups of symptoms (such as neurological, respiratory, systemic) during either the acute or post-acute phase of illness that predict cognitive problems, this may aid in the identification of patients that are at risk of developing cognitive deficits. In a highly heterogenous condition, in which up to 200 symptoms have been suggested (Davis et al., 2021), reduction of dimensionality is essential to allow meaningful associations to be drawn between experienced symptoms and relevant outcomes.

The United Kingdom Office for National Statistics [ONS] (2021) has estimated that around 21% of those experiencing COVID-19 infection still have symptoms at 5 weeks, and that 10% still have these symptoms at 12 weeks from onset. These figures may not tell the full story, being based on a list of 12 physical symptoms which does not include neurological or cognitive manifestations (e.g., Alwan and Johnson, 2021; Ziauddeen et al., 2021). Other calculations suggest that around 1 in 3 non-hospitalized COVID-19 patients have physical or neurological symptoms after 2–6 weeks from disease onset (Sudre et al., 2020; Tenforde et al., 2020; Nehme et al., 2021) and that 11–24% still have persisting physical, neurological or cognitive symptoms 3 months after disease onset (Cirulli et al., 2020; Ding et al., 2020). A community-based study reported that around 38% symptomatic people experienced at least one physical or neurological symptom lasting 12 weeks or more from onset and around 15% experienced three or more of these symptoms (Whitaker et al., 2021). Ongoing symptoms seem to occur regardless of the severity of the initial infection, with even asymptomatic patients sometimes going on to develop secondary illness (FAIR Health, 2021; Nehme et al., 2021), however, initial severity may impact severity of ongoing issues (e.g., Whitaker et al., 2021).

The National Institute for Health and Care Excellence (NICE) guidelines describe "post-COVID-19 syndrome" as "*Signs or symptoms that develop during or after infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis*" (National Institute for Health and Care Excellence [NICE], 2020). One difficulty with this definition is that the "signs or symptoms" that qualify for the diagnosis are not specified (e.g., Alwan and Johnson, 2021; Ziauddeen et al., 2021) thus many patients could go uncounted and unrecognized clinically, or conversely over-liberal inclusion may lead to overcounting. The patient-created term "Long COVID" has increasingly been used as an umbrella term to describe the highly heterogenous condition experienced by many people following COVID-19 infection (Callard and Perego, 2021).

Emerging evidence suggests that Long COVID is a debilitating multisystem illness that affects multiple organ systems and there have been some attempts to characterize "phenotypes." An online survey involved in 2,550 non-hospitalized participants detected two clusters within both initial and ongoing symptoms. Initial symptoms showed a majority cluster with cardiopulmonary symptoms predominant, and a minority cluster with multisystem symptoms that did not align specifically with any one organ system. Similarly, ongoing symptoms were clustered into a majority cluster with cardiopulmonary, cognitive symptoms and exhaustion, and a minority cluster with multisystem symptoms. Those with more related symptoms in the initial major cluster were more likely to move into ongoing multisystem cluster, and this movement can be predicted by gender and age, with higher risk in women, those younger than 60, and those that took less rest during the initial illness (Ziauddeen et al., 2021).

"Long COVID" research has repeatedly identified cognitive dysfunction as one of the most common persistent symptoms (after fatigue), occurring in around 70% of patients (Cirulli et al., 2020; Bliddal et al., 2021; Davis et al., 2021; Ziauddeen et al., 2021). Indeed, brain fog and difficulty concentrating are more common than cough is at many points in the Long COVID time course (Assaf et al., 2020). Ziauddeen et al. (2021) report nearly 40% of participants endorsing at least one cognitive symptom during the initial 2 weeks of illness, with this persisting in the long term. However around 30% of participants also reported developing cognitive symptoms—particularly brain fog and memory problems—later. Indeed, Davis et al. (2021) demonstrate that brain fog, memory problems and speech and language problems were more commonly reported at week 8 and beyond than they were during initial infection. Furthermore, strenuous cognitive activity was found to be one of the most common triggers leading to relapse/exacerbation of existing symptoms (Davis et al., 2021; Ziauddeen et al., 2021). Crucially, 86% of participants indicated that cognitive dysfunction and/or memory impairment was impacting their ability to work, with nearly 30% reporting being "severely unable to work" and only 27% working as many hours as they had pre-COVID-19 (Davis et al., 2021). These figures suggest that the cognitive sequelae of COVID-19 have the potential for long-term consequences not just for individuals but also—given the prevalence of Long COVID—for the economy and wider society.

Here we report on the first stage of a mixed cross-sectional/longitudinal investigation—The COVID and Cognition Study (COVCOG)—aimed at understanding cognition in post-acute COVID-19. The aims of this current paper are threefold: First, to provide a detailed demographic profile of our sample, comparing those who had experienced COVID-19 infection to those who had not, and those who recovered to those who continued to experience COVID-19 symptoms after acute phase of illness. Second, we aim to contribute to the understanding of phenotypes of Long COVID by using a rigorous factor analytic approach to identify groups of symptoms that tend to co-occur. We investigate symptom profiles both during and following initial infection in those that had experienced COVID-19. This allows investigation of symptoms during initial illness that may be predictive of ongoing symptoms, as well as exploring the nature of those ongoing symptoms themselves. These phenotypes may, through future studies, be directly linked to disease profiles and mechanisms. In an application of this second aim, a third objective is to use the symptom factors extracted (such as those incorporating neurological symptoms) to investigate predictors of self-reported cognitive deficits. Due to the novel character of both the virus and the subsequent ongoing illness at the time of study creation, this study was designed not to test specific hypotheses but to map the terrain, generating hypotheses for future, more targeted investigation.

MATERIALS AND METHODS

Participants

A total of 421 participants aged 18 and over were recruited through word of mouth, student societies and online/social media platforms such as the Facebook *Long COVID Support Group* (over 40K members). Of these, 163 participants were recruited through the *Prolific* recruitment site,

targeting participants with demographic profiles otherwise underrepresented in our sample. Specifically, recruitment through *Prolific* was limited to those with low socioeconomic status and levels of education below a bachelor's degree. As the study was conducted in English, participants were recruited from majority English speaking countries (the United Kingdom, Ireland, United States, Canada, Australia, New Zealand, or South Africa). Informed consent to use of anonymized data was obtained prior to starting.

Data collection for this stage of the study took place between October 2020 and March 2021, and recorded data on infections that occurred between March 2020 and February 2021. As such, all participants with experience of COVID-19 infection were likely to have been infected with either Wild-Type or Alpha-variant SARS-CoV-2, as the later-emerging variants (e.g., Delta, Omicron) were not common in the study countries at that time. Study recruitment started before the roll out of vaccinations, thus we do not have confirmed vaccination status for all participants. Once vaccination became available, the questionnaire was revised to ask about vaccination status. Of the 33 participants who were tested after this point, 11 (2 in the No COVID group, 9 in the COVID group) reported being vaccinated. Among them, 8 had received the first dose and 3 had had two doses. The majority (over 80%) had the vaccine within the last 7 days to last month. All received Pfizer (BNT162b2) except 1 (COVID group) who received AstraZeneca (AZD1222).

Procedure

The study was reviewed by University of Cambridge Department of Psychology ethics committee (PRE.2020.106, 8/9/2020). The current paper is part of a larger, mixed cross-sectional/longitudinal online study ("COVCOG") conducted using the online assessment platform Gorilla.[1] The COVCOG study consists of a baseline assessment of characteristics and cognition in samples of individuals who had or had not experienced COVID-19 infection. Both groups completed questionnaire and a range of cognitive tasks and were then followed up at regular intervals. The results reported here are for the questionnaire section of the baseline session only. The questionnaire covered demographics, previous health and experience of COVID-19.

Participants answered questions relating to their age, sex, education level, country of permanent residence, ethnicity, and profession. They were then asked a series of questions relating to their medical history and health-related behaviors. These included self-reporting their height and weight—which were used to calculate body mass index (BMI), and their usual diet intake, use of tobacco and alcohol, and physical activity (before the illness if infected) on a 6-point frequency scale from "Never" to "Several times daily." Following this, they were asked for details of their experience of COVID-19. Because many of the participants in this study contracted COVID-19 before confirmatory testing of infection state was widely available, both those with ("Confirmed") and without test confirmation ("Unconfirmed") were included in the "COVID" group. Those that didn't think they had had COVID-19 but had experienced an illness that *could* have been COVID-19 were assigned an "Unknown" infection status. Those that confirmed that they had not had COVID-19, nor any illness that might have been COVID-19, were included in the "No COVID" group. The procedure for grouping and progression through the baseline session is detailed in **Figure 1**.

Participants in the "COVID" group indicated the number of weeks since infection on a drop-down menu. Those that reported being within the first 3 weeks of infection proceeded straight to debriefing and were followed up 2 weeks later, once the initial infection was passed. Apart from this delay, they proceeded with the experiment in the same way as the rest of the COVID group. Participants then answered questions on the severity of the initial illness and whether they were experiencing ongoing symptoms. Finally, participants were asked to give details on a large number of individual symptoms during three time periods: initial illness (first 3 weeks), ongoing illness ("since then," i.e., the time since initial infection), and currently (past 1–2 days). When reporting on initial symptoms, participants gave an indication of severity on a scale of 1–3 from "Not at all" to "Very severe." When reporting symptoms over the period "since then" they reported on both severity and regularity of symptoms on a scale of 1–5 from "Not at all" to "Very severe and often." When reporting on symptoms in the past 1–2 days, they reported the presence or absence of the symptoms dichotomously (i.e., check the box of the symptom if present). These symptom lists were developed based on currently available medical literature reporting symptoms experienced by COVID-19 patients and through consulting medical doctors and COVID-19 patients from the *Long COVID Support Group*. Participants in the "No COVID" Group were not asked their experience of COVID-19.

Data Processing and Analysis

Analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0. We describe quantitative variables using means and standard deviations, and numbers and percentages for qualitative variables. Sidak's correction for multiple comparisons was employed. All *p*-values are reported uncorrected, and the Sidak-corrected alpha is quoted where appropriate.

We investigated differences in the first group of variables: sociodemographic, medical history, and health behaviors, concerning two COVID group classifications. First dividing the sample into two groups (COVID/No COVID), second subdividing the COVID group by symptom longevity and severity (Recovered, Ongoing mild infection, and Ongoing severe infection). Where parametric analysis was not appropriate, we employed the Pearson's chi-square (χ^2) test for categorical variables and the Mann-Whitney and Kruskal-Wallis test for continuous variables depending on the number of COVID groups. To investigate differences between groups (COVID/No COVID; Recovered/Ongoing mild/Ongoing severe), we employed Mann-Whitney and ANOVA/Kruskal-Wallis. To examine whether these variables and initial symptoms predicted degrees of ongoing illness, we ran independent multinomial logistic regression, using forward stepwise method to identify what items within these variables were significant predictors

[1] www.gorilla.sc

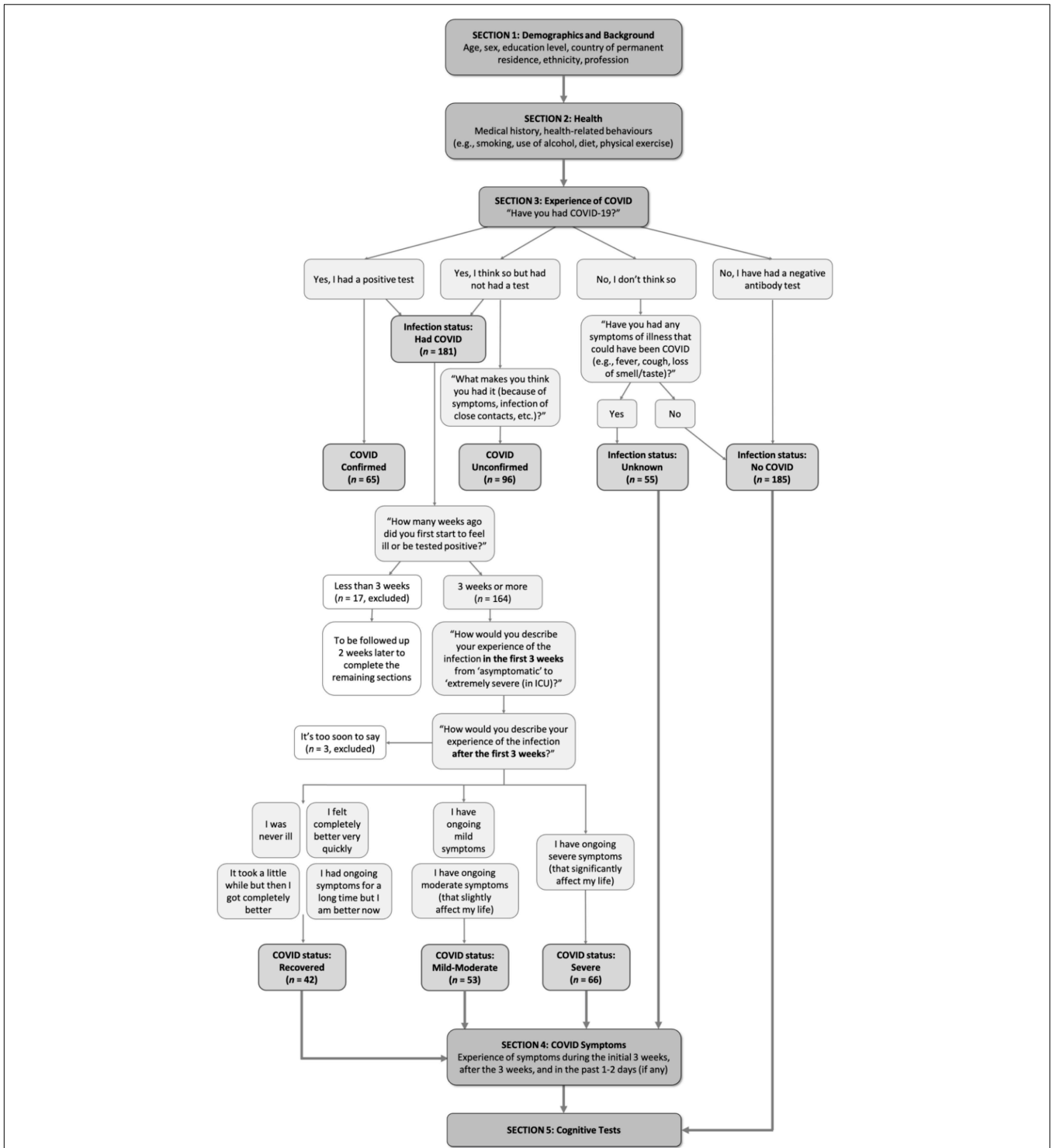

FIGURE 1 | Study procedural flow.

while controlling for demographics including sex, age, education, and country of residence. Next, to determine suitable groups of symptoms, we employed exploratory principal component analysis (PCA) with varimax rotation. Based on our high number of items (Nunnally, 1978) and the novelty of the subject (Henson and Roberts, 2006), we performed two PCAs, one for the initial symptoms and another one symptoms experienced since the initial phase. We then used the high-loading items

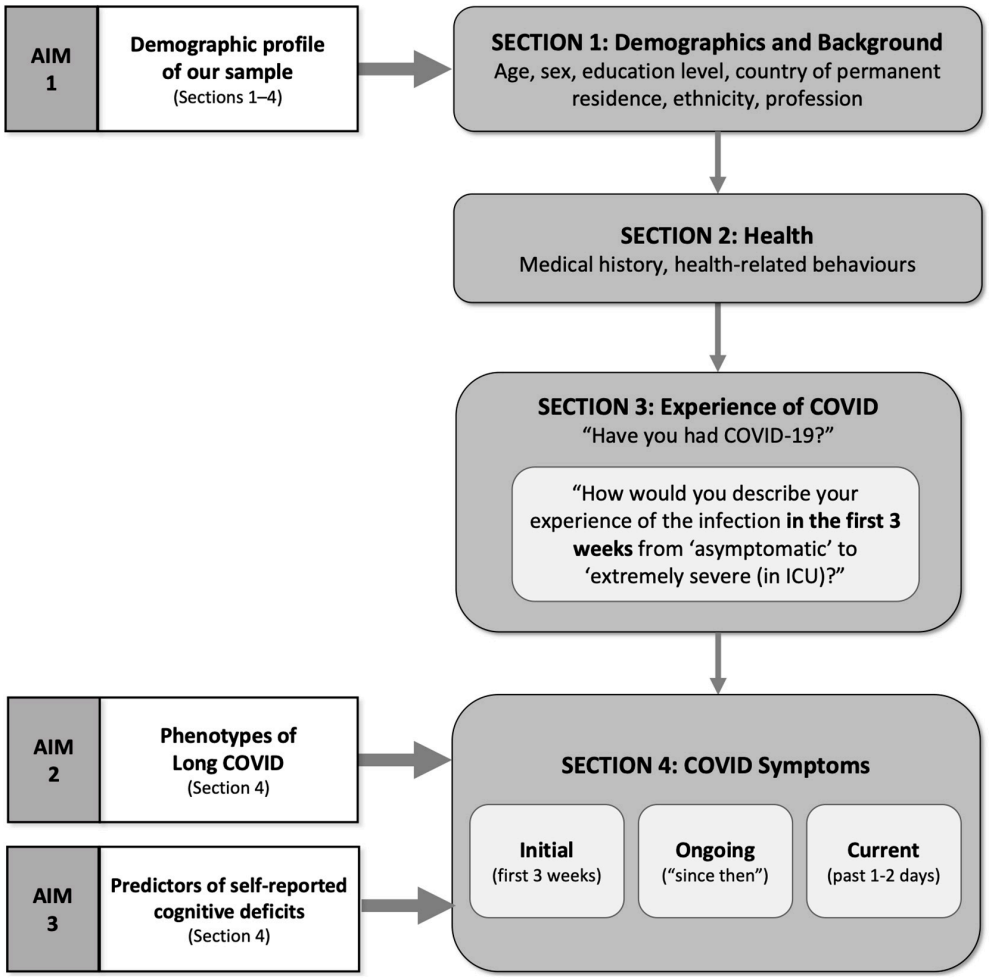

FIGURE 2 | Data analyzed in relation to our study aims.

on the "since then" symptom factors to calculate profiles for currently experienced symptoms. To explore what symptom factors were associated with infection or ongoing symptoms, we employed various independent multinomial logistic regression with backward elimination of variables $p > 0.05$ to identify the best fitted models. Data analyzed in relation to our study aims are depicted in **Figure 2**.

RESULTS

Sample Characteristics

No COVID (*NC*: *n* = 185) vs. COVID (*C*: *n* = 181)

Distributions of demographics including sex, age, education level, country, and ethnicity of the two groups (*NC*/*C*) are shown in **Table 1**. The majority of participants were from the United Kingdom and were of White (Northern European) ethnicity (over 70% in both groups). Pearson's chi-square tests showed that the groups did not significantly differ in sex, but differed in age [$\chi^2(5) = 19.08$, $p = 0.002$, $V = 0.228$] and level of education [$\chi^2(5) = 56.86$, $p < 0.001$, $V = 0.394$], with the COVID group tending to fall into the older age ranges and higher education level more than the No COVID group.

Employment

Supplementary Table 1 shows the distributions of pre-pandemic profession and employment status. To adjust for multiple comparisons, Sidak corrections were applied and alpha levels were adjusted to 0.003 for profession and 0.007 for employment status. The COVID group had significantly more people working in healthcare [$\chi^2(1) = 12.77$, $p < 0.001$, $V = 0.187$] and engaging in full-time work before the pandemic [$\chi^2(1) = 21.19$, $p < 0.001$, $V = 0.241$]. In contrast, the No COVID group were more likely not to be in paid work [Profession "Not in paid work" $\chi^2(1) = 27.72$, $p < 0.001$, $V = 0.275$; Employment status "Not Working" $\chi^2(1) = 13.18$, $p < 0.001$, $V = 0.190$], and they were more likely to be students [$\chi^2(1) = 8.91$, $p = 0.003$, $V = 0.156$].

Health and Medical History

Supplementary Table 2 compares medical history and health behaviors across the COVID and No COVID groups, which may

TABLE 1 | Distribution of demographics in No COVID and COVID groups.

	No COVID (n = 185)	COVID (n = 181)	Chi-square tests
Sex			n.s.
Man	63 (34.1%)	48 (26.5%)	
Woman	118 (63.8%)	130 (71.8%)	
Other	4 (2.2%)	3 (1.7%)	
Age			$\chi^2(5) = 19.08$, $p = 0.002$, $V = 0.228$
18–20	42 (22.7%)	17 (9.4%)	
21–30	45 (24.3%)	33 (18.2%)	
31–40	37 (20%)	38 (21%)	
41–50	23 (12.4%)	35 (19.3%)	
51–60	25 (13.5%)	39 (21.5%)	
61 or above	13 (7%)	19 (10.5%)	
Education			$\chi^2(5) = 56.86$, $p < 0.001$, $V = 0.394$
GCSE or below	20 (10.8%)	14 (7.7%)	
A level	55 (29.7%)	18 (9.9%)	
Attended college without obtaining degree/Technical training/Associate degree	58 (31.4%)	35 (19.3%)	
Bachelor's degree	21 (11.4%)	55 (30.4%)	
Master's/Professional degree	17 (9.2%)	49 (27.1%)	
Doctorate degree	14 (7.6%)	10 (5.5%)	
Country			n.s.
United Kingdom	137 (74.1%)	130 (71.8%)	
North America	24 (13%)	33 (18.2%)	
Other	24 (13%)	18 (9.9%)	
Ethnicity			$\chi^2(1) = 11.77$, $p = 0.001$, $V = 0.179$
Northern European	131 (70.8%)	155 (85.6%)	
Southern European/Latinx	13 (7%)	19 (10.5%)	n.s.
African/Afro-Caribbean	10 (5.5%)	7 (3.9%)	n.s.
Asian	29 (15.6%)	8 (4.5%)	$\chi^2(1) = 12.76$, $p < 0.001$, $V = 0.187$
Other/Prefer not to say	9 (4.8%)	6 (3.4%)	n.s.

be informative as to vulnerabilities. Sidak correction adjusted the alpha level to 0.003 for medical history and 0.008 for health behaviors. Pearson's chi-square tests showed that inflammatory or autoimmune diseases [$\chi^2(1) = 9.81$, $p = 0.002$, $V = 0.164$] were found more commonly in the COVID group than the No COVID group. Mann-Whitney U-tests showed that the COVID group consumed more fruit and vegetables ($U = 13{,}525$, $p = 0.001$) and had higher level of physical activity ($U = 13{,}752$, $p = 0.002$) than the No COVID group, while the No COVID group consumed sugary ($U = 14168.5$, $p = 0.008$) food more than the COVID group. ANOVA showed that the COVID group ($M = 26.71$, $SD = 7.26$) had higher BMI than the No COVID group ($M = 25.15$, $SD = 5.64$), [$F_{(1,\ 361)} = 5.24$, $p = 0.023$]. However this effect was not significant after controlling for sex, age, education and country [$F_{(1,\ 357)} = 1.57$, $p = 0.211$].

Characteristics of Those Experiencing Ongoing Symptoms

To understand the potential association between the progression of COVID-19 and various potential risk factors at baseline, including demographics, medical history and health behaviors, and the severity of initial illness and initial symptoms, we further divided the COVID group into three duration subgroups: (i) those who, at the time of test, had recovered from COVID-19 ("Recovered group," R; $n = 42$), (ii) those who continued to experience mild or moderate ongoing symptoms ["Ongoing (Mild/Moderate) group," $C+$; $n = 53$], and (iii) those who experienced severe ongoing symptoms ["Ongoing (Severe) group," $C++$; $n = 66$]. Those who were still at their first 3 weeks of COVID-19 infection ($n = 17$) or those who reported "it is too soon" to comment on their ongoing symptoms ($n = 3$) were not included in the following analyses. Participants in all groups ranged between 3 and 31 + weeks since symptom-onset, and a majority (81.5%) of those with ongoing symptoms reporting after more than 6 months since infection.

Figure 3 shows the distribution of demographic variables across the COVID-19 duration subgroups (further details available in **Supplementary Table 3**). In each, more than half of the participants were from the United Kingdom (54.8–92.4%) and were of White (Northern European) ethnicity (69–93.9%). Pearson's chi-square tests suggested that age [$\chi^2(10) = 53.41$, $p < 0.001$, $V = 0.407$] and education level [$\chi^2(10) = 20.03$, $p = 0.029$, $V = 0.249$], but not sex, significantly differed between subgroups. In terms of age, the R subgroup tended to fall more in the younger age ranges (see **Figure 3A**). In terms of education level, the R subgroup tended to have lower education level (GCSE or below and A level), but the $C++$ (Severe) subgroup clustered more in higher education level (bachelor's degree) (see **Figure 3B**). The subgroups also differed in the time elapsed since infection at the time of completing the study [$\chi^2(6) = 19.64$, $p = 0.003$, $V = 0.247$]. The R subgroup were more likely to be in their first 10 weeks of infection, while the $C++$ (Severe) subgroup were more likely to be at their 31 weeks or above (**Figure 3C**).

A multinomial logistic regression indicated that only age, but not sex or education, was significantly associated with COVID-19 progression [$\chi^2(10) = 43.6$, $p < 0.001$]. People in the age ranges of 18–20 and 21–30 years were more likely to recover from COVID-19 than to progress into mild/moderate (ps = 0.02–0.03) or severe ($p = 0.002$) ongoing symptoms.

We examined whether medical history and health behaviors were different between COVID-19 duration subgroups. **Table 2** shows the descriptive statistics of these factors in R, $C+$, and $C++$ subgroups for medical history and pre-pandemic health behaviors. None of the listed health conditions significantly differed between subgroups (against Sidak $\alpha = 0.003$). There were, however, significant group differences (Sidak $\alpha = 0.008$) in fruit and vegetables consumption [$H(2) = 15.92$, $p < 0.001$] and fatty food consumption [$H(2) = 36.54$, $p < 0.001$]. Both ongoing

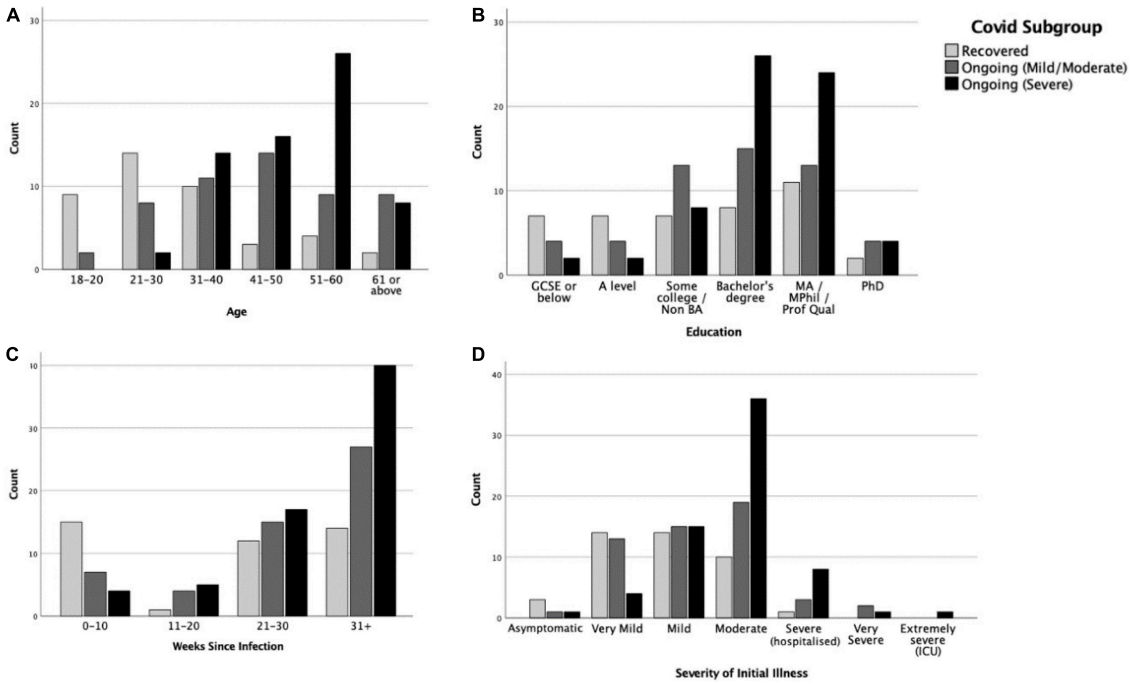

FIGURE 3 | Distributions of **(A)** age, **(B)** education level, **(C)** weeks since infection, and **(D)** severity of initial illness in Recovered, Ongoing (Mild/Moderate) and Ongoing (Severe) subgroups.

symptom subgroups ate more fruit and vegetables ($C++$: $U = 810$, $p < 0.001$; $C+$: $U = 808$, $p = 0.016$) and less fatty food ($C+$: $U = 773.5$, $p = 0.005$; $C++$: $U = 552.5$, $p < 0.001$) than the R subgroup. The $C+$ (Mild/Moderate) subgroup also consumed more fatty food than the $C++$ (Severe) subgroup ($U = 1142$, $p < 0.001$). The subgroups did not significantly differ in BMI [$F_{(2, 157)} = 0.085$, $p = 0.919$].

After controlling for sex, age, education, and country, a forward stepwise multinomial logistic regression indicated that no medical history variables were associated with COVID-19 progression, however, health behaviors including fatty food consumption [$\chi^2(2) = 23.25$, $p < 0.001$], physical activity [$\chi^2(2) = 10.31$, $p = 0.006$], and alcohol consumption [$\chi^2(2) = 8.18$, $p = 0.017$] were all significantly associated with COVID-19 progression. In our sample, people consuming more fatty food had a higher chance of having recovered from COVID-19 ($p < 0.001$) or having developed mild/moderate ongoing symptoms ($p < 0.001$) than progressing into severe ongoing symptoms. Higher levels of physical activity were associated with reduced chance of recovery relative to progression onto mild/moderate ($p = 0.002$) or severe ongoing symptoms ($p = 0.034$). Those drinking alcohol more frequently were more likely to recover from COVID-19 than to develop severe ongoing symptoms ($p = 0.007$).

Severity of Initial Illness

The severity of illness in the first 3 weeks of infection was associated with subsequent symptom longevity. Multinomial logistic regression showed that severity of initial illness was significantly associated with COVID-19 progression [$\chi^2(2) = 24.44$, $p < 0.001$], with higher initial severity associated with more severe subsequent ongoing symptoms (ps < 0.001–0.02). This effect was maintained after controlling for sex, age, education, and country [$\chi^2(2) = 12.28$, $p = 0.002$; $C++ > C+$: $p = 0.048$; $C++ > R$: $p = 0.001$]. Those with severe ongoing symptoms experienced more severe initial illness than those whose ongoing symptoms were mild/moderate ($U = 1{,}258$, $p = 0.005$, **Figure 3D**) and those who were fully recovered ($U = 658.5$, $p < 0.001$). The severity difference between the $C+$ (Mild/Moderate) subgroup and the R subgroup was also significant ($U = 842$, $p = 0.034$).

Supplementary Table 4 shows the relative frequencies of particular diagnoses received during the initial illness. Of the 109 participants who sought medical assistance, the most common diagnoses received were hypoxia (14.7%), blood clots (5.5%), and inflammation (4.6%).

Symptoms During Initial Illness

Symptoms that appeared in less than 10% of participants were excluded. Kruskal-Wallis H-tests (Sidak $\alpha = 0.001$) showed significant duration-group differences in 11/33 symptoms in terms of the severity experienced (see **Figure 4**, more information in **Supplementary Table 5**). In *post hoc* analysis (Sidak $\alpha = 0.017$), muscle/body pains, breathing issues and limb weakness showed gradation, with the $C++$ (Severe) subgroup having experienced the most severe symptoms, followed by the $C+$ (Mild/Moderate) subgroup, and the R subgroup experiencing the least (p ranges < 0.001–0.012). Some symptoms

TABLE 2 | Distribution of medical history and health behaviors (1 = Never–6 = Several times daily; higher scores indicating higher frequency) in COVID subgroups: Recovered (R), Ongoing (Mild/Moderate) (C+) and Ongoing (Severe) (C++).

	Recovered (*R*) (*n* = 42)	**Ongoing (Mild/Moderate) (*C* +) (*n* = 53)**	**Ongoing (Severe) (*C* + +) (*n* = 66)**	
Medical history: Frequency (%)				**Chi-square tests**
Asthma	6 (14.3%)	10 (18.9%)	21 (31.8%)	n.s.
Depression	9 (21.4%)	12 (22.6%)	9 (13.6%)	n.s.
Other mental health disorder	12 (28.6%)	9 (17%)	4 (6.1%)	$\chi^2(2) = 10.04$, $p = 0.007$, $V = 0.250$
Obesity	6 (14.3%)	8 (15.1%)	6 (9.1%)	n.s.
High blood pressure	3 (7.1%)	10 (18.9%)	6 (9.1%)	n.s.
History of migraines	4 (9.5%)	6 (11.3%)	7 (10.6%)	n.s.
Inflammatory/Autoimmune	4 (9.5%)	6 (11.3%)	8 (12.1%)	n.s.
Chronic fatigue syndrome/Myalgic encephalomyelitis (ME)	–	2 (3.8%)	5 (7.6%)	n.s.
Psychiatric/Neurodevelopmental disorder	2 (4.8%)	2 (3.8%)	3 (4.5%)	n.s.
Cardiovascular disease/Angina	–	3 (5.7%)	3 (4.5%)	n.s.
Diabetes (Type 2)	–	1 (1.9%)	1 (1.5%)	n.s.
Diabetes (Type 1)	–	–	–	n.s.
Cancer	–	–	2 (3%)	n.s.
A clotting disorder	1 (2.4%)	–	1 (1.5%)	n.s.
None of the above	15 (35.7%)	14 (26.4%)	24 (36.4%)	n.s.
Health Behaviors: *Mean (SD)*				**Kruskal-Wallis *H*-tests/ Mann-Whitney *U*-tests**
Diet: Fruit and vegetables	4.52 (1.29)	5.15 (0.95)	5.41 (0.93)	$H(2) = 15.92$, $p < 0.001$* $C++ > R$: $U = 810$, $p < 0.001$* $C+ > R$: $U = 808$, $p = 0.016$*
Diet: Sugary food	3.71 (1.2)	3.34 (0.9)	3.24 (1.05)	n.s.
Diet: Fatty food	3.6 (0.94)	3.11 (0.8)	2.58 (0.63)	$H(2) = 36.54$, $p < 0.001$* $R > C+$: $U = 773.5$, $p = 0.005$* $R > C++$: $U = 552.5$, $p < 0.001$* $C+ > C++$: $U = 1{,}142$, $p < 0.001$*
Physical activity	3.31 (1.18)	4.04 (1.16)	3.85 (1.51)	$H(2) = 9.03$, $p = 0.011$ $C++ > R$: $U = 1{,}027$, $p = 0.02$ $C+ > R$: $U = 722.5$, $p = 0.003$
Alcohol	2.81 (0.97)	2.68 (1.11)	2.47 (1.01)	n.s.
Smoking	1.48 (1.17)	1.57 (1.47)	1.15 (0.86)	$H(2) = 8.42$, $p = 0.015$ $C+ > C++$: $U = 1{,}542$, $p = 0.021$

** denotes p-values below Sidak-correct alpha (i.e., non-null).*

did not show gradation with severity of ongoing symptoms, but were reliably higher in those with ongoing symptoms. Both the ongoing symptoms subgroups reported more severe symptoms of fatigue, brain fog and chest pain/tightness during the initial illness than those that recovered ($ps < / = 0.001$) but did not differ from one another. Those with severe ongoing symptoms experienced more severe nausea and blurred vision than those with mild/moderate or who recovered (p ranges < 0.001–0.009). Finally, the $C++$ (Severe) subgroup experienced more abdominal pain, altered consciousness and confusion during the initial illness than the *R* subgroup ($ps < / = 0.001$).

After controlling for sex, age, education, and country, a forward stepwise multinomial logistic regression suggested that six initial symptoms were significantly associated with COVID-19 progression. These were: limb weakness [$\chi^2(2) = 25.92$, $p < 0.001$], brain fog [$\chi^2(2) = 13.82$, $p = 0.001$], chest pain or tightness [$\chi^2(2) = 10.81$, $p = 0.005$], dizziness [$\chi^2(2) = 7.82$, $p = 0.02$], cough [$\chi^2(2) = 7.74$, $p = 0.021$], and breathing difficulties [$\chi^2(2) = 6.98$, $p = 0.031$]. People initially experiencing more severe limb weakness were more likely to experience severe ongoing symptoms than to recover ($p < 0.001$) or develop mild/moderate ongoing symptoms ($p < 0.001$). More severe initial breathing issues ($p = 0.014$) and dizziness ($p = 0.037$) were associated with greater likelihood of severe than mild/moderate ongoing symptoms, but people with more severe initial dizziness ($p = 0.02$) and cough ($p = 0.009$) were more likely to recover rather than to develop mild/moderate ongoing symptoms. More severe initial brain fog and chest pain/tightness were associated with more progression into mild/moderate than either severe ongoing symptoms (brain fog: $p = 0.029$; chest pain: $p = 0.026$) or recovery (brain fog: $p = 0.001$; chest pain: $p = 0.007$).

Symptoms During Ongoing Illness

Excluding those who reported being totally asymptomatic throughout or feeling completely better very quickly after initial illness (who did not report on ongoing symptoms, $n = 15$), the COVID subgroups were asked to report on their ongoing experience of a list of 52 symptoms. Symptoms that appeared

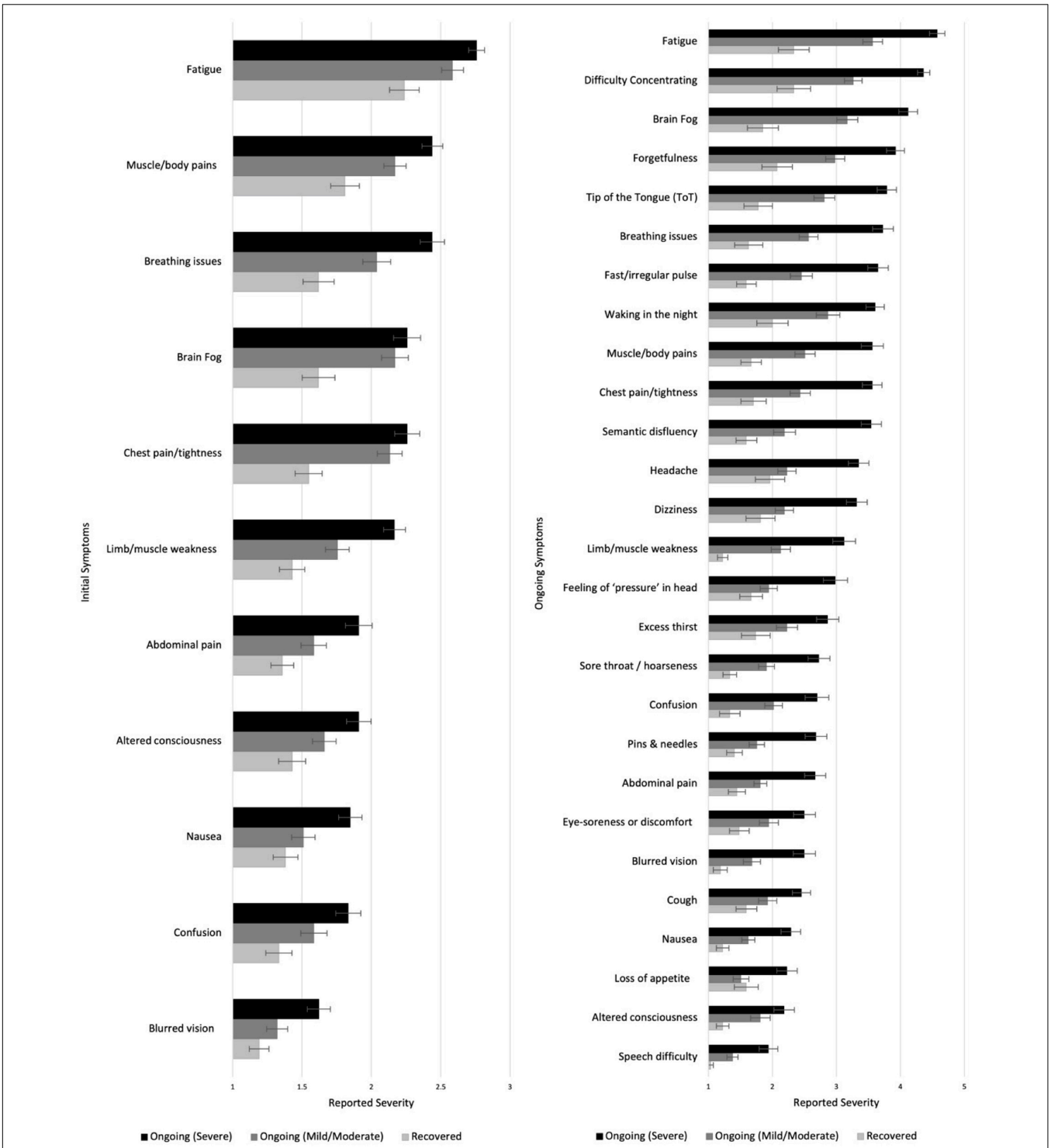

FIGURE 4 | Severity of different symptoms during the initial **(left)** and ongoing **(right)** illness among those who recovered or had ongoing mild or severe illness. Higher scores indicate higher severity.

in less than 10% of participants were excluded. The duration-groups differed significantly in 27/47 symptoms (Sidak $\alpha = 0.001$; see **Figure 4** and **Supplementary Table 6**). *Post hoc* tests (Sidak $\alpha = 0.017$) showed that the $C++$ (Severe) subgroup reported higher levels of severity than the R subgroup in all 27 symptoms ($ps < 0.001$–0.017) and then the $C+$ (Mild/Moderate) subgroup

in all except two (altered consciousness and eye-soreness; *p*s < 0.001–0.017). The *C* + (Mild/Moderate) subgroup also reported experiencing higher severity in 16 symptoms (including fatigue, difficulty concentrating, brain fog, and forgetfulness) than the *R* subgroup (*p*s < 0.001–0.016; see **Figure 4** and **Supplementary Table 6**; see also **Supplementary Table 7** for similar analysis of current symptoms).

Symptoms in Those With Confirmed or Suspected COVID-19 vs. "Other" Illnesses

As much of our sample experienced infection early in the pandemic before widespread testing was available, not all cases included in our COVID group were confirmed by a polymerase chain reaction (PCR) test (infection statuses: "Confirmed" COVID, "Unconfirmed" COVID). Meanwhile, a significant minority of participants had an illness during the pandemic period that they did *not* think was COVID-19 (infection status: "Unknown") (see **Figure 1**). We compared symptom prevalence across these three groups (Unknown, n = 55; Unconfirmed, n = 96; Confirmed, n = 65) for both the initial 3 weeks of illness, and the time since then. Those who were still at their first 3 weeks of COVID-19 infection (n = 17) and who reported "it is too soon" to comment on their ongoing symptoms (n = 3) were not included in this analysis.

The groups significantly differed in 14 out of 31 symptoms during the initial illness (Sidak α = 0.0016; **Supplementary Table 8**). Both Confirmed and Unconfirmed groups reported higher severity than the Unknown group on 13 symptoms (including fatigue, muscle/body pains and loss of smell/taste; *p* ranges < 0.001–0.014; Sidak α = 0.017). Additionally, the Unconfirmed group reported more severe blurred vision than the Unknown group ($p < 0.001$), and the Unknown group reported more severe sore throat/hoarseness than the Confirmed group ($p < 0.001$). As for the differences within those with COVID-19, the Confirmed group experienced greater loss of smell/taste than the Unconfirmed group ($p = 0.002$), while the Unconfirmed group reported higher levels of breathing issues, chest pain/tightness, sore throat/hoarseness, and blurred vision than the Confirmed group (*p*s = 0.004–0.015).

Of these participants, 177 (Unknown group: n = 31; Unconfirmed group: n = 88; Confirmed group: n = 58) reported experiencing ongoing symptoms after the 3 weeks of illness. Significant group differences were found in 11/47 ongoing symptoms (Sidak α = 001; see **Figure 5** and **Supplementary Table 9**). *Post hoc* tests (Sidak α = 0.017) showed that, compared with the Unknown group, both the Confirmed and Unconfirmed groups reported higher levels of fatigue, difficulty concentrating, brain fog, tip-of-the-tongue (ToT) problems, muscle/body pains, fast/irregular pulse, semantic disfluency, chest pain/tightness, limb weakness, and loss of smell/taste (*p*s < / = 0.001). The Unconfirmed group also experienced higher level of night waking ($p = 0.001$) than the Unknown group. There were no significant differences in ongoing symptoms between the Confirmed and the Unconfirmed groups.

Characterizing Symptom Profiles

While data on individual symptoms are useful in identifying highly specific predictors, these are too numerous for more systematic analysis, which require data-reduction. A stated aim of this study was to identify symptom profiles that may be informative as to underlying pathology.

Initial Symptom Factors

To group the initial symptoms, we included 34 symptoms in the PCA after excluding paralysis and seizures (experienced by less than 10% of the participants). A total of 164 participants reported on their symptoms during the first 3 weeks of illness (the factor analysis coded here as 1 = *Very severe*, 3 = *Not at all*). The Kaiser-Meyer-Olkin (KMO) test (value 0.861) and Bartlett's test of sphericity [$\chi^2(528) = 2{,}250$, $p < 0.001$] showed the data were suitable for factor analysis. We employed the varimax rotation. Initially, nine factors were obtained with eigenvalue > 1.0, which was reduced to five via Cattell's Scree test (Kline, 2013). Assessments were conducted of 4, 5, and 6 factor solutions for interpretability and robustness. The ratio of rotated eigenvalue to unrotated eigenvalue was higher for the 5-factor solution than for the 4- or 6-factor solutions, and this structure was also the most interpretable. We thus proceeded with a 5-factor solution, which explained 50.59% of item variance with last rotated eigenvalue of 1.998.

We labeled the new components as "F1: Neurological/Psychiatric," "F2: Fatigue/Mixed," "F3: Gastrointestinal," "F4: Respiratory/Infectious," and "F5: Dermatological" (see **Table 3** for factor loadings). We computed the factor scores using the regression method (see **Supplementary Table 10** for factor scores).

People who went on to experience ongoing symptoms showed higher factor scores in the Fatigue/Mixed symptom factor during the initial illness [$F_{(2,\ 158)} = 23.577$, $p < 0.001$], but did not differ in any other initial symptom factor. Pairwise analysis revealed that those who recovered were significantly less likely to experience Fatigue/Mixed symptoms than those with mild/moderate ($p < 0.001$) or severe ($p < 0.001$) ongoing symptoms (**Figure 6**).

Ongoing Symptom Factors

We performed a second PCA using the symptoms experienced since the initial phase (after the first 3 weeks), including 45 symptoms. Paralysis and seizures were excluded (experienced by less than 10% of the participants). A total of 149 participants reported on their symptoms over the time since the first 3 weeks of illness (the factor analysis coded here as 1 = *Very severe and often*, 5 = *Not at all*). The KMO test (value 0.871) and Bartlett's test of sphericity [$\chi^2(861) = 3{,}302$, $p < 0.001$] showed suitability for factor analysis. We employed the varimax rotation. PCA showed 11 components with eigenvalues > 1.0, and this was reduced to 6 via inspection of the eigenvalue gradient (scree plot). The ratio of rotated eigenvalue to unrotated eigenvalue was higher for the 7-factor solution, followed by the 6-factor. The 6- and 7-factor solutions were differentiated by subdivision of the second factor, reducing the degree of cross-loading. However, the 7-factor solution was less interpretable and less robust to

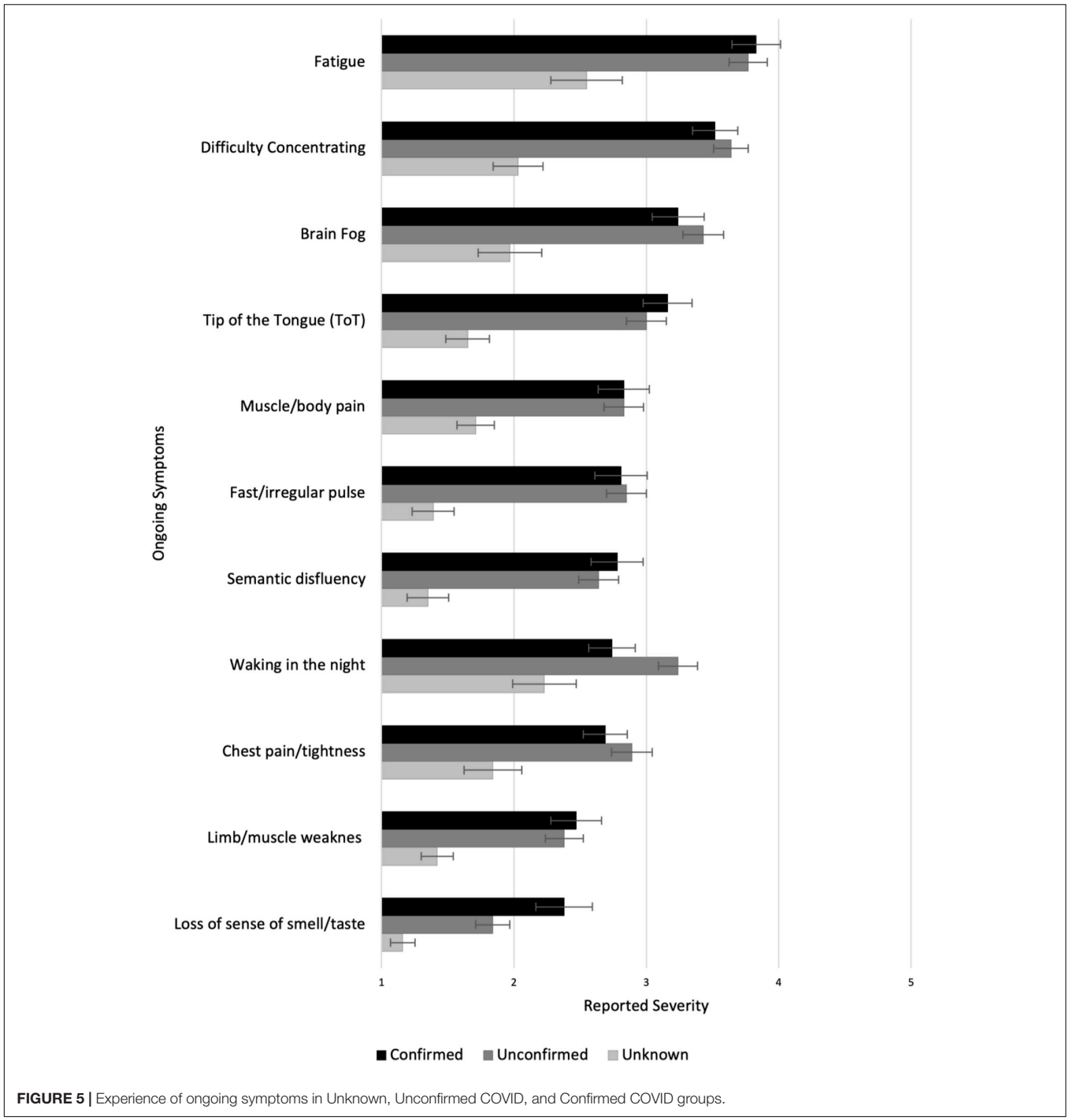

FIGURE 5 | Experience of ongoing symptoms in Unknown, Unconfirmed COVID, and Confirmed COVID groups.

removal to cross-loaders (the presence of which can be accepted from a pathology perspective, given that multiple mechanisms can produce the same symptom). As such, we proceeded with the 6-factor solution, which explained 54.17% of item variance and had a last rotated eigenvalue of 2.227.

We labeled the new components as "F1: Neurological," "F2: Gastrointestinal/Autoimmune," "F3: Cardiopulmonary/Fatigue," "F4: Dermatological/Fever," "F5: Appetite Loss," and "F6: Mood" (see **Table 4** for factor loadings). We computed the factor scores using the regression method (see **Supplementary Table 11** for factor scores).

In order for cognitive symptoms [brain fog, forgetfulness, tip-of-the-tongue (ToT) problems, semantic disfluency and difficulty concentrating] to be used as a dependent variable, these were isolated and a PCA run separately. A single component emerged, with all the cognitive symptoms loading homogeneously highly (see **Supplementary Table 12**). The KMO test (value 0.886) and Bartlett's test of sphericity [$\chi^2(10) = 564$, $p < 0.001$]

TABLE 3 | Factors and loadings from the "Initial Symptoms" PCA.

	Component				
Symptom	**F1 Neurological/Psychiatric**	**F2 Fatigue/Mixed**	**F3 Gastrointestinal**	**F4 Respiratory/Infectious**	**F5 Dermatological**
Disorientation	**0.763**				
Delirium	**0.688**				
Visual disturbances	**0.639**				
Confusion	**0.630**	0.431			
Altered consciousness	**0.617**	0.364			
Speech difficulty	**0.583**				
Blurred vision	**0.518**	0.374			
Hallucinations	**0.502**				
Drowsiness	**0.453**	0.362			
Anxiety	**0.416**				
Numbness	**0.367**	0.346			
Fatigue		**0.753**			
Chest pain/tightness		**0.631**		0.313	
Muscle/body pains		**0.585**			
Headache		**0.543**	0.368		
Limb weakness		**0.541**			0.301
Dizziness	0.395	**0.530**			
Brain fog	0.466	**0.523**			
Eye-soreness	0.325	**0.511**			
Diarrhea			**0.738**		
Nausea		0.307	**0.707**		
Vomiting			**0.696**		
Abdominal pain		0.315	**0.649**		
Acid reflux		0.323	**0.403**		
Sore throat			**0.338**		
Fever				**0.717**	
Cough				**0.609**	
Breathing issues		0.479		**0.592**	
Loss of appetite				**0.526**	
Loss of smell/taste				**0.361**	
Rash					**0.785**
Itchy welts					**0.782**
Foot sores			0.426		**0.586**
Face/lips swelling				0.367	**0.490**

The bold indicates items loading above 0.5; non bold numbers are those loading above 0.3.

indicated suitability for factor analysis, and the single 5-item factor explained 76.86% of variance.

Current Symptoms

The current symptoms assessed were the same as the ongoing symptoms, but rated dichotomously as either currently present or absent. To estimate the degree to which current symptoms aligned with the factors established for the ongoing period, we generated a quasi-continuously distributed variable according to how many of the high loading (> / = 0.5) items from the ongoing factors were recorded as present currently. Using this *sum scores by factor* method (Tabachnick et al., 2007; Hair, 2009), each score was subsequently divided by the number of items in that factor producing quasi "factor scores" that were comparable and indicative of "degree of alignment" of current symptoms to established factors.

To assess the stability and specificity of symptom profiles between these periods, serial correlations were conducted for corresponding and non-corresponding factors. Correlations of the same factor across time points were materially higher (> 0.2) from the next highest correlation among the 5 non-corresponding factors, with Williams tests (Steiger, 1980) giving the narrowest gap at $p = 0.003$ (Neurological: $r = 0.676$, $t = 5.712$; Gastrointestinal/Autoimmune: $r = 0.531$, $t = 3.778$; Cardiopulmonary/Fatigue: $r = 0.678$, $t = 7.272$; Dermatological/Fever: $r = 0.523$, $t = 3.364$; Appetite Loss: $r = 0.591$, $t = 5.017$; Mood: $r = 0.490$, $t = 4.803$). This consistency suggests that while particular symptoms may fluctuate, the profile of symptoms—once grouped into an adequately supported factor—is moderately stable for individuals, and can be relatively well represented by a "snapshot" of current symptoms. For completeness, an additional factor analysis was

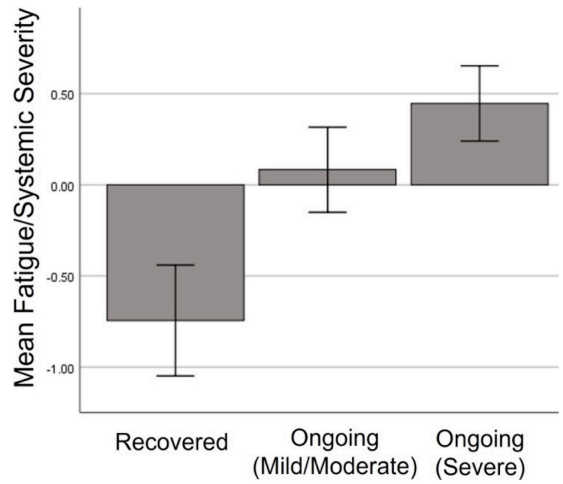

FIGURE 6 | Severity of Fatigue/Mixed symptom factor during initial illness among those who went on to full recover, or have ongoing mild or severe symptoms.

conducted on the current symptoms, which are reported in **Supplementary Table 13**.

One symptom factor showed change over time since infection, suggesting higher severity in those who had been ill for longer: Number of weeks since infection (positive test/first symptoms) was positive correlated with severity of ongoing severity of Cardiopulmonary/Fatigue symptoms [$r(147) = 0.271$, $p < 0.001$; **Figure 7**] and, to a weaker extent, current alignment with the same factor [$r(147) = 0.206$, $p = 0.012$], however, only the former association survived correction for multiple comparisons (Sidak $\alpha = 0.0085$).

Cognitive Symptoms

Within those currently experiencing symptoms ($n = 126$), 77.8% reported difficulty concentrating, 69% reported brain fog, 67.5% reported forgetfulness, 59.5% reported tip-of-the-tongue (ToT) word finding problems and 43.7% reported semantic disfluency (saying or typing the wrong word).

Symptoms experienced during the initial illness significantly predicted both ongoing and current cognitive symptoms (**Figure 8**). A linear regression with backward elimination found that the best model contained the Neurological/Psychiatric, Fatigue/Mixed, Gastrointestinal, and Respiratory/Infectious symptom factors and explained 20% of variance ($R_{adj}^2 = 0.2$, $p < 0.001$). **Table 5** shows that the Fatigue/Mixed symptoms factor ($\eta'_p{}^2 = 0.129$) was the better predictor followed by the Neurological/Psychiatric symptom factor ($\eta'_p{}^2 = 0.092$). For current cognitive symptoms, the best model contained both the Neurological/Psychiatric and Fatigue/Mixed symptom factors, together explaining 13.9% of variance ($p < 0.001$). Of the two, the Fatigue/Mixed factor was the better predictor ($\eta'_p{}^2 = 0.110$). No interactions between factors contributed significantly and were thus not included in the final models.

A similar, but much stronger, pattern emerged when considering the predictive value of ongoing (non-cognitive) symptoms (**Figure 8**). Using backward elimination to factors with significance ($p < 0.05$), all factors except Dermatological/Fever remained in the model, which explained over 55% of variance ($R_{adj}^2 = 0.558$, $p < 0.001$). The effect size ($\eta'_p{}^2$) for each factor is given in **Table 5**. The Gastrointestinal/Autoimmune and Cardiopulmonary/Fatigue factors were the biggest contributors to the model. Indeed, in an extreme elimination model in which contributing factors were limited to two or fewer, these two factors alone explained 38% of variance retaining strong significance ($p < 0.001$). No interactions between factors contributed significantly and were thus not included in the final models. Ongoing symptoms also predicted current cognitive symptoms. The best model explained 36% of the variance ($p < 0.001$) and included the Neurological, Gastrointestinal/Autoimmune and Cardiopulmonary/Fatigue factors and an interaction between the Gastrointestinal/Autoimmune and Cardiopulmonary/Fatigue factors. Of these, Cardiopulmonary/Fatigue symptoms were the strongest predictor ($\eta'_p{}^2 = 0.208$), with Neurological ($\eta'_p{}^2 = 0.118$) and Gastrointestinal/Autoimmune ($\eta'_p{}^2 = 0.115$) being relatively equal.

Current symptom factors also strongly predicted current cognitive symptoms (**Figure 8**). The backward elimination model left three contributing factors: Neurological, Cardiopulmonary/Fatigue and Appetite Loss. Together these explained around 50% of variance ($R_{adj}^2 = 0.494$). Of these, Cardiopulmonary/Fatigue was the stronger predictor ($\eta'_p{}^2 = 0.306$). Indeed, when the model was limited to just this factor, this model still explained 43% of the variance.

There was a significant association between degree of cognitive symptoms and duration of illness. Those who had been ill for longer were more likely to report having had cognitive symptoms throughout the ongoing illness [$r(147) = 0.262$, $p = 0.001$] and to be experiencing them at the time of test [$r(147) = 0.179$, $p = 0.03$] (**Figure 7**).

Experiences and Impact of Long COVID

Here we limited analysis to all those who reported some degree or period of ongoing symptoms following COVID-19 [i.e., excluding those who reported being totally asymptomatic throughout or feeling completely better very quickly after initial illness ($n = 15$)]. Of the remaining 146 participants, 108 (74%) self-identified as experiencing or having experienced "Long COVID."

We examined the impact and experiences of ongoing illness (**Table 6**). In most cases, the nature and degree of negative experience of ongoing symptoms scaled with perceived severity. The change in symptoms over time differed between severity subgroups [$\chi^2(6) = 37.52$, $p < 0.001$, $V = 0.367$]. The $C++$ (Severe) subgroup were more likely to report that symptoms were consistent over time, while those with mild/moderate ongoing symptoms were more likely to report improvement in symptoms. As might be expected, the R subgroup were alone in reporting complete resolution of symptoms after recovery from the initial illness (**Supplementary Table 14**).

TABLE 4 | Factors and loadings from the exploratory factor analysis of ongoing "since then" symptoms PCA.

	Component					
Symptom	**F1 Neurological**	**F2 Gastrointestinal/ Autoimmune**	**F3 Cardiopulmonary/ Fatigue**	**F4 Dermatological/ Fever**	**F5 Appetite Loss**	**F6 Mood**
Disorientation	**0.695**					0.323
Confusion	**0.651**					
Delirium	**0.639**					
Speech difficulty	**0.619**					
Altered consciousness	**0.607**					0.316
Visual disturbances	**0.604**			0.386		
Hallucinations	**0.576**			0.386		0.301
Pins & needles	**0.561**	0.399				
Numbness	**0.559**					
Blurred vision	**0.531**	0.369		0.348		
Head pressure	**0.501**	0.428				
Drowsiness	**0.490**					
Hot flushes		**0.624**		0.306		
Nausea		**0.608**				
Diarrhea		**0.591**				
Abdominal pain		**0.576**		0.309		
Headache		**0.565**	0.301			
Muscle/body pains		**0.563**	0.524			
Eye-soreness	0.305	**0.488**			0.342	
Dizziness	0.435	**0.477**	0.373			
Weight gain		**0.471**			−0.396	
Acid reflux		**0.456**				
Incontinence		**0.393**				
Breathing issues			**0.793**			
Chest pain/tightness			**0.727**			
Fatigue		0.391	**0.619**			
Cough			**0.580**	0.330		
Fast/irregular pulse		0.430	**0.553**			
Night waking			**0.536**			
Limb weakness	0.428	0.457	**0.466**			
Difficulty sleeping			**0.457**		0.356	0.345
Sore throat	0.308	0.324	**0.388**			
Face/lips swelling				**0.678**		
Foot sores				**0.646**		
Itchy welts				**0.562**		
Rash		0.303		**0.549**		
Fever				**0.461**		
Loss of smell/taste				**0.421**		
Excess thirst		0.305	0.316	**0.390**		
Vomiting		0.321		**0.385**		
Weight loss					**0.752**	
Loss of appetite					**0.637**	
Depression						**0.715**
Anxiety	0.316					**0.683**
Vivid dreams		0.337				**0.428**

The bold indicates items loading above 0.5; non bold numbers are those loading above 0.3.

Long COVID has significant impact on individuals' lives. Over 54.6% of those with ongoing symptoms had experienced long periods unable to work and 34.5% had lost their job due to illness, 63.9% reported difficulty coping with day-to-day activities, 49.6% had had difficulty getting medical professionals to take their symptoms seriously, and 43.7% felt that they had experienced a trauma, while 17.6% had experienced financial difficulty as a result of illness. These impacts scaled with symptom

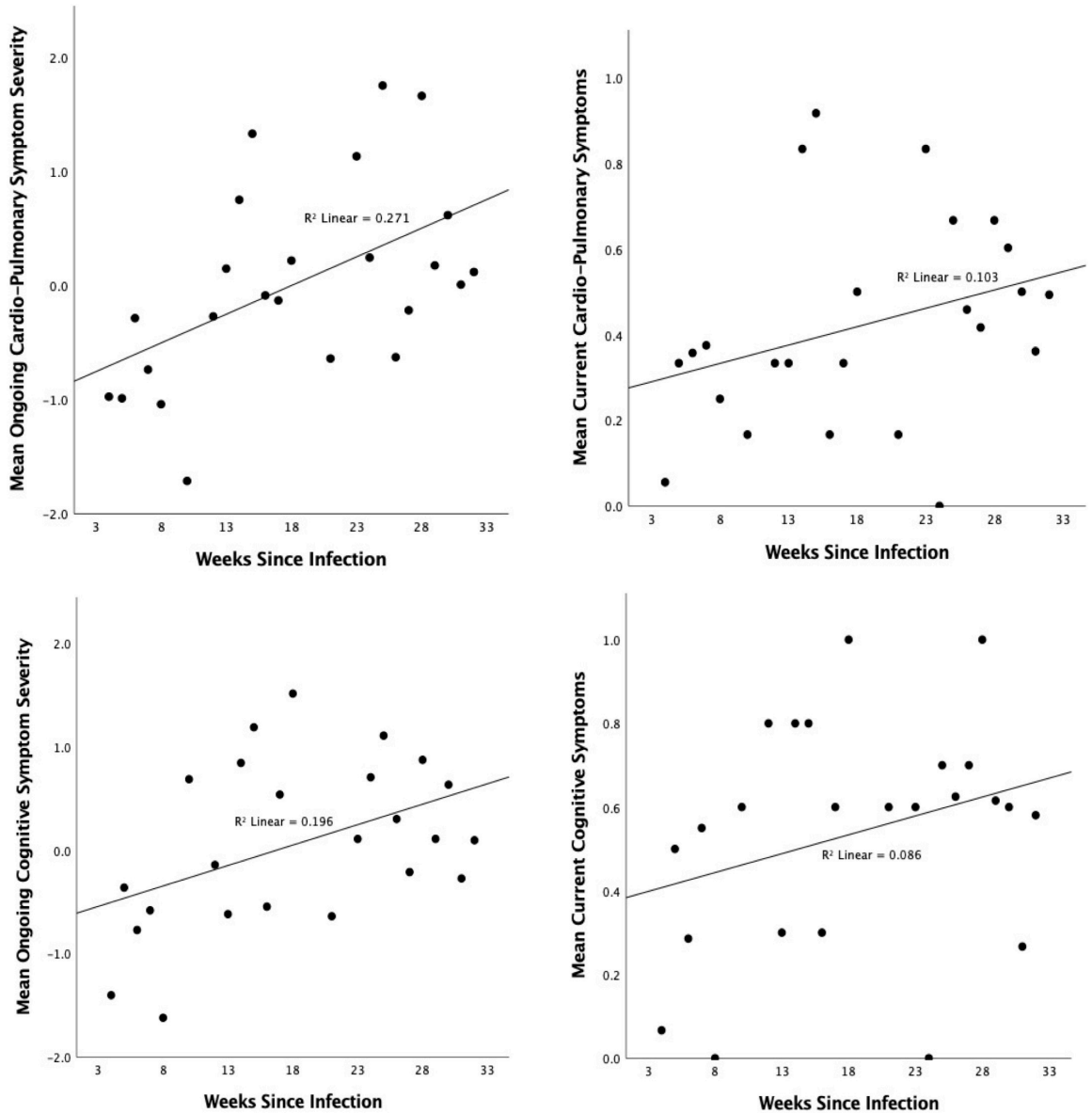

FIGURE 7 | Association between number of weeks since infection and severity of **(top)** Cardiopulmonary/Fatigue Symptoms and **(bottom)** cognitive symptoms in the entire period since the initial infection **(left)** and the past 1–2 days **(right)**. Higher scores indicate higher symptom severity.

severity. Those with severe ongoing symptoms were more likely to report being unable to work for a long period due to illness [$\chi^2(2) = 46.42$, $p < 0.001$, $V = 0.564$], having difficulty coping with day-to-day requirements [$\chi^2(2) = 20.23$, $p < 0.001$, $V = 0.372$], having difficulty getting medical professionals to take their symptoms seriously [$\chi^2(2) = 23.05$, $p < 0.001$, $V = 0.397$], and losing their job due to illness [$\chi^2(2) = 24.39$, $p < 0.001$, $V = 0.409$]. In contrast, the *R* subgroup tended to report experiencing none of the above [$\chi^2(2) = 52.73$, $p < 0.001$, $V = 0.601$].

We further compared job-loss with the No COVID group ($n = 185$). Those with ongoing symptoms were more likely to have lost their job than those who had not experienced COVID-19 [$\chi^2(1) = 26.74$, $p < 0.001$, $V = 0.297$]. The most common reason for job-loss among those with ongoing symptoms was illness [$\chi^2(1) = 56.85$, $p < 0.001$, $V = 0.432$], while the most common reason in the No COVID group was economy [$\chi^2(1) = 7.67$, $p = 0.006$, $V = 0.159$].

DISCUSSION

Nature of Illness and Symptom Profiles

Here we report the initial findings from a cross-sectional/longitudinal study investigating cognition post-COVID-19. One aim of this first publication was to

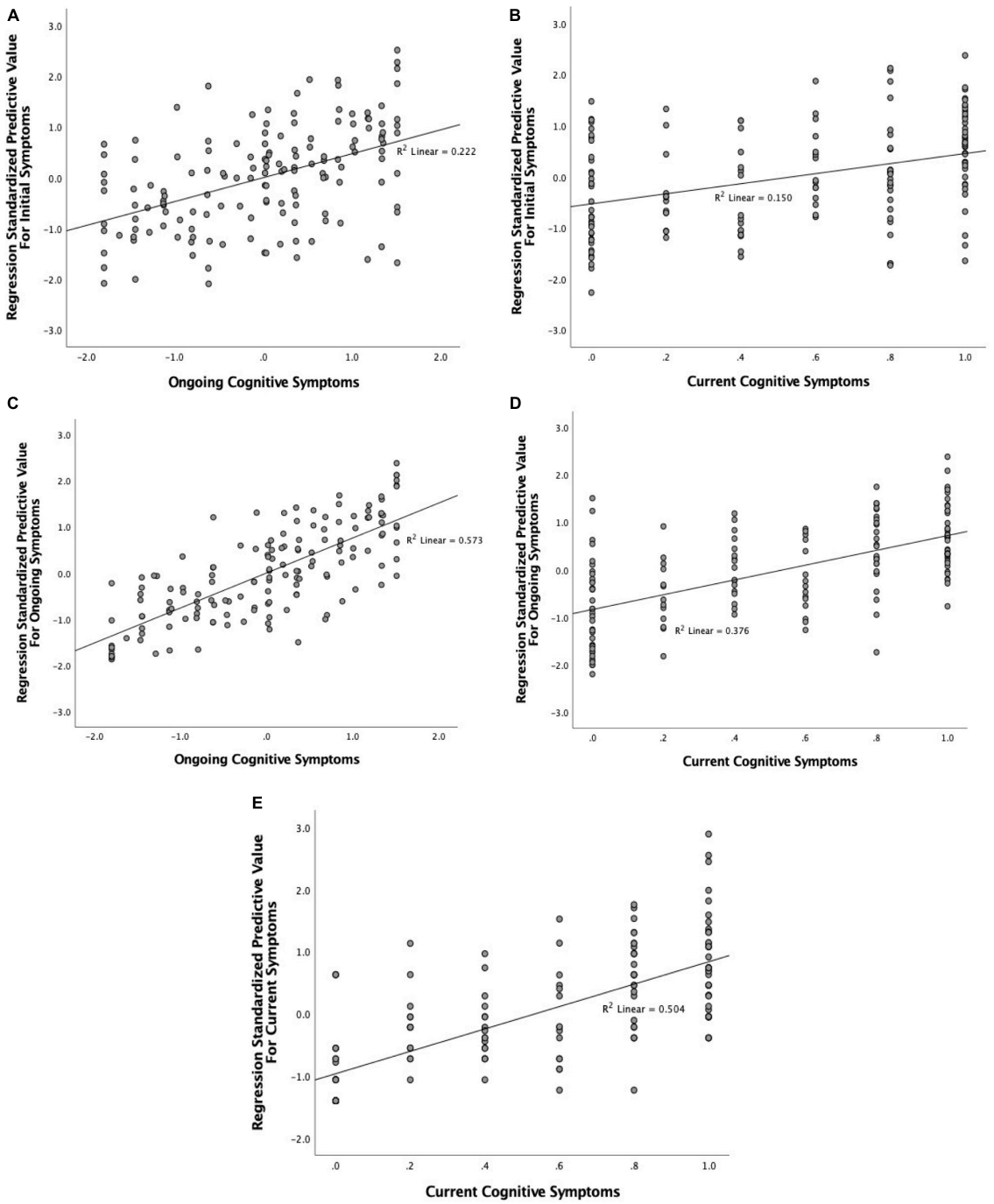

FIGURE 8 | Association between combined regression model predicted value for **(A)** initial symptom factors and ongoing cognitive symptoms; **(B)** initial symptom factors and current cognitive symptoms; **(C)** ongoing symptom factors and ongoing cognitive symptoms; **(D)** ongoing symptom factors and current cognitive symptoms; and **(E)** current symptom factors and current cognitive symptoms.

characterize the "COVID and Cognition Study" (COVCOG) sample. Within the COVID group, we recruited specifically to get good representation of those who were experiencing or had experienced ongoing symptoms. Indeed, 74% identified with the term "Long COVID." Our final sample had a relatively even spread of those that had fully recovered at the time of test (42), or had mild/moderate (53) or severe (66) ongoing symptoms. Medical history did not differ between those experiencing ongoing symptoms and those who recovered. However, in terms of health behaviors, those with ongoing symptoms were in general "healthier," being more likely to have previously been consuming less fatty food and more fruits

TABLE 5 | Regression models predicting variation in the cognitive symptom factor (ongoing and current) from non-cognitive symptom factors (initial, ongoing, and current).

	R_{adj}^2	Effect size ($\eta'_p{}^2$) of Independent Variable					Interactions
IV: Initial symptoms							
		Neurological/ Psychiatric	**Fatigue/Mixed**	**Gastrointestinal**	**Respiratory/ Infectious**	**Dermatological**	
Ongoing Cognitive Symptoms	0.2 $p < 0.001$	0.092	0.129	0.029	0.029	n.s.	
Current Cognitive Symptoms	0.139 $p < 0.001$	0.057	0.110	n.s.	n.s.	n.s.	
IV: Ongoing symptoms							
		Neurological	**Gastrointestinal/ Autoimmune**	**Cardiopulmonary/ Fatigue**	**Dematological/ Fever**	**Appetite loss**	**Mood**	**GI/AI × Card-Pul**
Ongoing Cognitive Symptoms	0.558 $p < 0.001$	0.236	0.309	0.325	n.s.	0.056	0.043	
Current Cognitive Symptoms	0.36 $p < 0.001$	0.118	0.115	0.208	n.s.	n.s.	n.s.	0.038
IV: Current symptoms								
Current Cognitive Symptoms	0.494 $p < 0.001$	0.074	n.s.	0.306	n.s.	0.021	n.s.	

Only partial eta squared ($\eta'_p{}^2$) effect size is given here, as beta coefficients are not meaningful for already standardized variables.

and vegetables. This result is counterintuitive and may reflect insufficient controls for confounding demographic variables relating to socio-economic status. Nonetheless potential links between lifestyle and nutrition and COVID-19 recovery warrant further investigation.

The nature of the initial illness was found to have a significant impact on the likelihood and severity of ongoing symptoms. Despite this sample almost entirely comprised of non-hospitalized patients, those with more severe initial illness were more likely to have ongoing symptoms, and for those symptoms to be more severe. This suggests even in "community" cases, initial infection severity is a predictor of vulnerability to Long COVID. In an analysis of all symptoms experienced during the initial illness, there were several that were predictive of presence or severity of ongoing symptoms. In particular, individuals with severe ongoing symptoms were significantly more likely to have experienced limb weakness during the initial illness than those that recovered. However, some differences in severity ratings between ongoing subgroups were small despite being statistically significant, which warrant caution in interpreting the results.

We asked participants to retrospectively report on symptoms over three time periods: initial illness, ongoing illness, and currently experienced. Given the highly heterogenous nature of Long COVID, we used principal component analysis (PCA) with the aim to ascertain whether there may be different phenotypes of the condition within our sample—that is to say, that there may be certain types of symptoms that tend to (or not to) co-occur. For both the initial and ongoing illness, the symptom factors resemble those found in previous studies (e.g., Davis et al., 2021; Whitaker et al., 2021; Ziauddeen et al., 2021), with some quite coherent cardiopulmonary clusters, and other less specific "multisystem" profiles which may reflect more systemic issues such as inflammation, circulation, or endocrine function.

Predictors of Cognitive Difficulties

A large proportion of our sample reported cognitive difficulties. We isolated the cognitive symptoms for the ongoing and current illness and computed a single factor including only these. Using this, we investigated which (non-cognitive) symptom factors during both the initial and ongoing illness explained significant variance in severity of cognitive symptoms.

Together, the Fatigue/Mixed, Neurological/Psychiatric, Gastrointestinal and Respiratory/Infectious symptom factors during the initial illness explained around 20% of variance in ongoing ("since then") cognitive symptoms, and a similar model (containing only Neurological/Psychiatric and Fatigue/Mixed symptom factors) explained nearly 14% of variance in current cognitive symptoms. These findings strongly suggest that experience of neurological symptoms during the initial illness are significant predictors of self-reported cognitive impairment. While only one factor is named "Neurological" both this and the Fatigue/Mixed factor contain clear elements of neurological involvement. Indeed, headache, dizziness, and brain fog all loaded more highly on the Fatigue/Mixed factor than on the Neurological/Psychiatric factor (which was more characterized by disorientation, visual disturbances, delirium, and altered consciousness). This suggests different types of neurological involvement, potentially reflecting neuroinflammation (the Fatigue/Mixed factor) and encephalitis (the Neurological/Psychiatric factor), respectively. It is of note then that both these factors independently predicted subjective cognitive problems. Both inflammation and encephalitis have been proposed as mechanisms through which COVID-19 may

TABLE 6 | Experiences and impact of Long COVID in different ongoing symptom severity groups.

	Now Recovered (*R*) (*n* = 27**)	Ongoing (Mild/Moderate) (*C* +) (*n* = 53)	Ongoing (Severe) (*C* + +) (*n* = 66)	Chi-square tests
Identify as experiencing "Long COVID"				$\chi^2(4) = 85.75$, $p < 0.001$, $V = 0.542$
Yes	3 (11.1%)	43 (81.1%)	62 (93.9%)	
No	16 (59.3%)	2 (3.8%)	–	
Other	8 (29.6%)	8 (15.1%)	4 (6.1%)	
Change of symptoms after initial illness				$\chi^2(6) = 37.52$, $p < 0.001$, $V = 0.367$
No ongoing symptoms after initial recovery	5 (18.5%)	–	–	
Different symptoms at different times	8 (29.6%)	28 (52.8%)	39 (59.1%)	
Improvement in symptoms over time	5 (18.5%)	18 (34%)	9 (13.6%)	
Symptoms have been very consistent	3 (11.1%)	7 (13.2%)	17 (25.8%)	
I don't know/N/A	6 (22.2%)	–	1 (1.5%)	
Cycle of symptoms after initial illness				n.s.
Cycle every few days	3 (11.1%)	11 (20.8%)	14 (21.2%)	
Cycle every few weeks	3 (11.1%)	13 (24.5%)	19 (28.8%)	
Cycle monthly	2 (7.4%)	7 (13.2%)	9 (13.6%)	
No cycling	12 (44.4%)	19 (35.8%)	23 (34.8%)	
N/A	7 (25.9%)	3 (5.7%)	1 (1.5%)	
Impact of Long COVID				
Long period unable to work (due to illness)	2 (7.4%)	15 (28.3%)	50 (75.8%)	$\chi^2(2) = 46.42$, $p < 0.001$, $V = 0.564$*
Difficulty coping day-to-day activities	6 (22.2%)	28 (52.8%)	48 (72.7%)	$\chi^2(2) = 20.23$, $p < 0.001$, $V = 0.372$*
Difficulty getting medical professionals to take symptoms seriously	1 (3.7%)	21 (39.6%)	38 (57.6%)	$\chi^2(2) = 23.05$, $p < 0.001$, $V = 0.397$*
Lost job due to illness	1 (3.7%)	9 (17%)	32 (48.5%)	$\chi^2(2) = 24.39$, $p < 0.001$, $V = 0.409$*
Feeling that you have experienced a trauma	4 (14.8%)	21 (39.6%)	31 (47%)	$\chi^2(2) = 8.44$, $p = 0.015$, $V = 0.240$
Financial difficulty (as a result of illness)	1 (3.7%)	7 (13.2%)	14 (21.2%)	n.s.
None of the above	18 (66.7%)	9 (17%)	1 (1.5%)	$\chi^2(2) = 52.73$, $p < 0.001$, $V = 0.601$*

**Denotes p-values below Sidak-correct alpha at 0.007 for the impact of Long COVID.*

***Excluding a small portion of participants who reported asymptomatic or feeling completely better very quickly from the Recovered subgroup (n = 15).*

impact the brain (Bougakov et al., 2021) and the presence of indications of neuro-inflammation have been found in post-mortem studies (Matschke et al., 2020). It will be an important next step in the investigation to explore whether the neurological and (possible) inflammatory symptom factors explain variance in performance in cognitive tests.

Participants' experience of ongoing Neurological, Cardiopulmonary/Fatigue, Gastrointestinal/Autoimmune, Mood and Appetite Loss symptom factors all predicted current cognitive symptoms, together explaining around over 55% of variance. Unlike the initial symptom factors, the vast majority of neurological symptoms were contained within the Neurological factor for ongoing symptoms, with only headache and dizziness loading more strongly into the Gastrointestinal/Autoimmune factor. This latter factor was instead more characterized by symptoms associated with systemic illness—potentially endocrine, or reflecting thyroid disruption—including diarrhea, hot flushes and body pains. An additional predictor here was Cardiopulmonary/Fatigue symptoms, a factor which was quite narrowly characterized by symptoms associated with breathing difficulties. Alone, the Gastrointestinal/Autoimmune and Cardiopulmonary/Fatigue factors explained a large proportion of the variance (36%), suggesting these were the biggest contributor to individual differences in cognitive symptoms. These findings suggest that the symptoms linked with cognitive issues are not so specifically neurological as during the initial illness, but may also incorporate problems with heart and lung function (potentially implying hypoxia, which can induce hypoxic/anoxic-related encephalopathy; Guo et al., 2020) and with other ongoing ill health that is harder to label (resembling symptoms of the menopause, Crohn's disease, hypothyroidism, and a number of other conditions), but may imply systemic inflammation. Again, these associations align with previous findings, in which cardiopulmonary and cognitive systems clustered in the same factor (Ziauddeen et al., 2021).

In terms of current symptoms, the Cardiopulmonary/Fatigue factor again emerged as a significant predictor, this time paired with Neurological and Appetite Loss symptom factors and explaining nearly 50% of variance. It is potentially notable that both the cognitive and Cardiopulmonary/Fatigue factors showed positive correlation with length of illness, suggesting either that the same disease process underpinning both increases in severity over time, or that the relationship between the two may be the result of both being symptoms more commonly still experienced in those with longer-lasting illness. Longitudinal investigation within individuals would be necessary to disambiguate this.

Impact of Long COVID

Of those experiencing Long COVID, more than half (and 75% of those with severe symptoms) reported long periods unable to work due to illness. These findings chime with evidence from other studies on Long COVID (e.g., Davis et al., 2021; Ziauddeen et al., 2021). Notably, Davis et al. (2021) found that in their sample 86% of participants reported that it was the cognitive dysfunction *in particular* that was impacting their work (30% severely so). The reported experiences of those with Long COVID—many of whom were at least 6 months into their illness at the time of completing the study—suggest that in addition to broader economic challenges associated with the pandemic, society will face a long "tail" of workforce morbidity. It is thus of great importance—not just for individuals but for society—to be able to prevent, predict, identify and treat issues associated with Long COVID, and including treatment for cognitive symptoms as part of this policy.

A major roadblock to progress in management and treatment of Long COVID is that clinicians do not have the appropriate information or experience. A significant number (over 50% of those with severe symptoms) of our sample reported struggling to get medical professionals to take their symptoms seriously. Part of this issue will be the nature of the symptoms experienced. Patients whose symptoms cannot be, or are not routinely, clinically measured (such as cognitive symptoms; Kaduszkiewicz et al., 2010) are at greater risk of "testimonial injustice"—that is, having their illness dismissed by medical professionals (De Jesus et al., 2021). The novel and heterogenous nature of Long COVID also provides a particular challenge for clinicians dealing with complex and undifferentiated presentations and "medically unexplained symptoms" (Davidson and Menkes, 2021). The data presented here demonstrate that cognitive difficulties reported by patients can be predicted by severity and pattern of symptoms during the initial stages of infection, and during the ongoing illness. These findings should provide the foundation for clinicians to assess the risk of long-term (6 months +) cognitive difficulties, as well as for researchers to investigate the underlying mechanism driving these deficits. In our next paper, we will explore the association between general and cognitive symptoms and performance on cognitive tasks, with the aim of establishing whether self-reported cognitive issues translate into "objective" deficits on cognitive evaluations.

Some have argued that cognitive changes following COVID-19 infection may reflect changes related to experience of lockdown or social isolation (perhaps via development of depression or anxiety). There is indeed some evidence that pandemic-related changes in lifestyle impact cognition (e.g., Fiorenzato et al., 2021; Okely et al., 2021). However, many of these studies did not record COVID-19 infection history (Okely et al., 2021; Smirni et al., 2021) so it is difficult to ascertain to what degree these findings may have been related to COVID-19 infection. One study that did control for this (Fiorenzato et al., 2021) identified significant declines in self-reported attention and executive function, however, showed reduced reports of forgetfulness compared with pre-lockdown. Our results show that, compared to individuals who experienced a (probable) non-COVID-19 illness during the pandemic, those with suspected or confirmed COVID-19 infection experienced greater levels of fatigue, difficulty concentrating, brain fog, tip-of-the-tongue (ToT) word finding problems and semantic disfluency, but did not differ in levels of anxiety and depression. Meanwhile there was little difference between those that did and did not have biological confirmation of their COVID-19 infection. This strongly suggests that self-reported cognitive deficits reported in our sample are associated with COVID-19 infection, rather than the experience of illness, or pandemic more generally.

Limitations and Future Research

While the findings of this study are notable, there are a number of limitations in design and execution which warrant caution in interpreting the results.

Being unable to bring participants into the lab for clinical assessment, this study relied on online retrospective self-report of symptoms sometimes experienced some months previously. We thus must be cognizant of potential issues of misremembering and that questionnaires may not have been completed in an environment conducive to concentration and reflection. The manner of reporting symptoms differed between different reporting times, with a longer list and more reporting options (reflecting both severity and regularity) for the "ongoing" period. In particular, our binary present/absent reporting approach for currently experienced symptoms was not able to reflect current severity and did not lend itself to factor analysis. Using the *sum scores by factor* method (Tabachnick et al., 2007; Hair, 2009) to calculate alignment of currently experienced symptoms with the symptom factors got around some of these issues, future studies should keep lists consistent to allow for direct comparison of symptom profiles at the different time points. A similar issue is that symptoms information was not collected for the "No COVID" group, or (in terms of current symptoms) for those that reported having recovered. This would have been highly useful in order to establish the degree to which symptoms (particularly those which might be expected to be exacerbated by lockdowns, such as depression, anxiety, fatigue) were more common in those that had previously experienced COVID-19 than those that had not. It would also be useful to ask both the COVID and No COVID groups about their living situation at the time of completing the study, such as whether lockdown or any social restrictions were taking place and how much these measures were affecting their physical and psychological health. It would also have been useful to assess whether people who reported having "recovered"

showed symptomatology similar to the "No COVID" group, or remained distinct.

Due to the intensive performance focus of the current investigation, our study had a relatively smaller sample size than is feasible in an epidemiological cohort. Characterizing the sample, we found that those who had experienced COVID-19 infection—and within these, those with more severe ongoing symptoms—tended to be older and more educated. We do not believe that these features reflect vulnerabilities toward COVID-19 or Long COVID, but rather the biases in our recruitment and target populations. Our sample was recruited from English speaking countries (the United Kingdom, Ireland, United States, Canada, Australia, New Zealand, or South Africa) and the majority were from the United Kingdom, which may not be representative of people from other parts of the world. Where possible, we controlled for age, sex, education, and country of residence, which should mitigate some of these biases, however, these sampling discrepancies should be kept in mind. We furthermore specifically targeted our recruitment to those self-identifying as experiencing Long COVID, and we advertised the study as investigating memory and cognition in this group. Our sample may thus have been biased toward those individuals with more severe symptoms and cognitive symptoms in particular (as these individuals may be more motivated to take part). Overrepresentation of Long COVID sufferers is not a serious issue outside of prevalence studies, however, our reported rates of cognitive symptoms within the Long COVID cohort should be treated with caution. It is reassuring, however, that the figures for these symptoms within our cohort are comparable to those seen in much larger studies not explicitly investigating cognition (e.g., Davis et al., 2021; Ziauddeen et al., 2021).

Finally, much of the analysis in this study was necessarily exploratory, as too little was known at the time of study design to form many clear hypotheses. To handle this, multiple comparisons were conducted, for which the alpha adjustments entailed that only the very strongest effects survived at conventional statistical thresholds. This high type 2 error rate means that it is likely that more than just these findings would be confirmed on replication, and because a stated aim of this study was to generate hypotheses that could be tested in later, more targeted research, we have additionally reported the uncorrected results. Similarly, in terms of investigating symptom profiles, we did not aim to present a "definitive" set of factors, but to provide stratifiers and covariates for future analysis, particularly of cognitive test performance, and changes over time. While this study is not able to identify a specific mechanism, it may be able to lay the groundwork with sufficient breadth and detail to inform future mechanistic investigation.

CONCLUSION

The COVID and Cognition study is a cross-sectional/longitudinal study assessing symptoms, experiences and cognition in those that have experience COVID-19 infection. Here we present the first analysis in this cohort, characterizing the sample and investigating symptom profiles and cognitive symptoms in particular. We find that particular symptom-profiles—particularly neurological symptoms—during both the initial infection and ongoing illness were predictive of experience of cognitive dysfunction. The symptoms and experiences reported by our sample appear to closely resemble those reported in previous work on Long COVID (e.g., Davis et al., 2021; Ziauddeen et al., 2021) which suggests that our, smaller, sample might be generally representative of the larger Long COVID patient community. The participants in this study are being followed up over the course of the next 1–2 years, and it is hoped that future publications with this sample will provide valuable information as to the time-course of this illness.

The severity of the impact of "Long COVID" on everyday function and employment reported in our sample appear to reflect previous studies (e.g., Davis et al., 2021) and is notable, particularly given the large proportion of healthcare and education staff in our sample. All of these issues should be of interest to policy makers, particularly when considering the extent to which large case numbers should be a concern in the context of reduced hospitalizations and deaths due to vaccination. While we do not yet know the impact of vaccination on Long COVID numbers, there are reasons to believe that high levels of infection among relatively young, otherwise healthy individuals may translate into considerable long-term workforce morbidity.

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 Psychology Research Ethics Committee, University of Cambridge. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LCh and PG designed the study. PG, SY, RL, AS, AB, LCu, and LCh recruited and collected data. PG, AB, SY, MH, and LCh analyzed the data. LCh, PG, SY, and AB wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.804922/full#supplementary-material

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Rehabilitation at the Time of Pandemic: Patient Journey Recommendations

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Purpose: The World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) a pandemic in March 2020, causing almost 3.5 million coronavirus disease (COVID-19) related deaths worldwide. The COVID-19 pandemic has imposed a significant burden on healthcare systems, economies, and social systems in many countries around the world. The access and delivery of rehabilitation care were severely disrupted, and patients have faced several challenges during the COVID-19 outbreak. These challenges include addressing new functional impairments faced by survivors of COVID-19 and infection prevention to avoid the virus spread to healthcare workers and other patients not infected with COVID-19. In this scoping review, we aim to develop rehabilitation recommendations during the COVID-19 pandemic across the continuum of rehabilitation care.

Materials and Methods: Established frameworks were used to guide the scoping review methodology. Medline, Embase, Pubmed, CINAHL databases from inception to August 1, 2020, and prominent rehabilitation organizations' websites were searched.

Study Selection: We included articles and reports if they were focused on rehabilitation recommendations for COVID-19 survivors or the general population at the time of the COVID-19 pandemic.

Data Extraction: Two of our team members used the pre-tested data extraction form to extract data from included full-text articles. The strength and the quality of the extracted recommendations were evaluated by two reviewers using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.

Results: We retrieved 6,468 citations, of which 2,086 were eligible after removing duplicates. We excluded 1,980 citations based on the title and the abstract. Of the screened full-text articles, we included 106 studies. We present recommendations based on the patient journey at the time of the pandemic. We assessed the evidence to be of overall fair quality and strong for the recommendations.

Conclusion: We have combined the latest research results and accumulated expert opinions on rehabilitation to develop acute and post-acute rehabilitation recommendations in response to the global COVID-19 pandemic. Further updates are warranted in order to incorporate the emerging evidence into rehabilitation guidelines.

Keywords: COVID-19, pandemic, rehabilitation, scoping review, GRADE, physiotherapy, occupational therapy, ICU rehabilitation

INTRODUCTION

SARS-n-CoV-2 (a novel coronavirus), causing severe respiratory disease, was first formally identified in Wuhan City, China, on December 31, 2019, and within a few months spread globally World Health Organization [WHO] (2020). The World Health Organization (WHO) declared the disease caused by the novel coronavirus COVID-19, a pandemic on March 11, 2020. COVID-19 has impacted nations worldwide, regardless of climate, population, and location World Health Organization [WHO] (2020). The impact of the pandemic has been devastating and long-lasting, not only to health and healthcare systems but to social systems and economies as well, with subsequent burdens at the community level.

In order to prevent the spread of the disease, the general population has been impacted through restrictions that have limited access to primary care, elective and non-elective surgeries, urgent care, outpatient rehabilitation, and post-acute rehabilitation, both in patients with COVID-19 and without COVID-19 infection. Frail older adults are at the greatest risk for severe complications and mortality after COVID-19 infection due to age-related comorbidities (such as diabetes, hypertension, and frailty), which impair their ability to fight severe COVID-19 related pneumonia (Meftahi et al., 2020; Perrotta et al., 2020; Stawicki et al., 2020; United Nations, 2020). Data collected in South Korea, Italy, France, Germany, England, and Spain indicate that the mortality rate from COVID-19 infection increased by 12% per year after the age of 70-years (Goldstein and Lee, 2020).

Rehabilitation is essential after recovery from numerous health conditions such as acute stroke (Smith et al., 2020), cardiac events, and infectious diseases (Besnier et al., 2020; Scherrenberg et al., 2020). The pandemic has led to frequent cancelation of elective surgeries, a step taken with the aim of decreasing hospital utilization, preserving Intensive Care Unit (I.C.U.) capacity, conserving Personal Protective Equipment (P.P.E.) and allowing for redeployment of healthcare workers to care for those with COVID-19 infection. As a result, rehabilitation services are in higher demand since the beginning of the global pandemic. However, the rehabilitation community has faced a number of challenges in the context of COVID-19. These challenges include: (1) Addressing multifactorial functional impairments seen among COVID-19 survivors because of lung, heart, kidney, vascular endothelium, muscular and central nervous system effects of the disease (Centre for Disease Control Prevention, 2021); (2) Infection prevention to avoid virus spread to healthcare workers and other patients not infected with COVID-19; (3) Provision of acute rehabilitation; (4) Provision of post-acute rehabilitation after discharge from acute hospital, and (5) Transitioning to a telehealth care-delivery model. Adaptations were necessary to: facilitate care for a population with complex medical and functional impairments (COVID-survivors); prevent infection; preserve P.P.E., and accommodate facility and/or local policies to mitigate the spread of COVID-19 (Levi et al., 2020; Miles et al., 2020; Salawu et al., 2020).

A large number of COVID-19 patients ended up hospitalized and admitted to the intensive care unit. Many of these patients ended up on ventilator machines and intubated, ultimately impacting speech and swallowing function, respiratory function, and overall physical function, and these patients will be benefited from timely and comprehensive rehabilitation care. But, there is a paucity of evidence on rehabilitation recommendations during COVID-19 (Simpson and Robinson, 2020) which may contribute to high rates of unmitigated disability following coronavirus infections. Rooney et al. (2020) Clinic closures and restrictions placed on rehabilitation personnel entering certain high-risk facilities have contributed to a substantial reduction in rehabilitation volume delivered to frail older adults (Falvey et al., 2020). There is clear evidence that rehabilitation services are associated with improvements in physical and cognitive function (Zhang et al., 2019). Therefore,

failure to provide rehabilitation services may leave patients vulnerable to avoidable hospitalizations (such as those from fall-related trauma), worsening disability, higher caregiver burden, and lower quality of life. For individuals with frailty, the negative impacts of reduced rehabilitation service may be magnified given their higher vulnerability to functional decline (Ferrante et al., 2018), leading to further declines in functional reserve and increased vulnerability to adverse events (Hosey and Needham, 2020).

Thus, there is an urgent need to develop rehabilitation recommendations that aim to provide guidance to rehabilitation institutions and professionals on safe and effective practices across the continuum of rehabilitation care during the COVID-19 pandemic (Thornton, 2020). These recommendations can be used to help inform the public that rehabilitation is an essential medical intervention that has been poorly prioritized during the pandemic, leading to unnecessary suffering and added disability burden for those infected with COVID-19, as well as those who have been unable to receive needed care because of COVID-19 related restrictions. In response to the global pandemic, we launched a COVID task force in the American Congress of Rehabilitation Medicine (ACRM) to help address the lack of contemporary research assessing the impact of COVID-19 on rehabilitation. The task force comprises a multidisciplinary team of clinicians and researchers with a diversity of rehabilitation and health services expertise across the continuum of rehabilitation settings. The purpose of this paper is to develop rehabilitation recommendations during the COVID-19 pandemic across the continuum of rehabilitation care.

MATERIALS AND METHODS

We used the framework proposed by Arksey and O'Malley (2005) and Levac et al. (2010) to guide the scoping review methodology. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) guidelines to warrant a high quality of research reporting (Tricco et al., 2018).

Development of Research Questions

The main concepts of interest are the COVID-19 pandemic and rehabilitation (including physiotherapy, physical therapy, occupational therapy, speech-language pathology, physiatry, and other rehabilitation services). The outcomes of interest were rehabilitation recommendations based on research data, consensus, or expert opinions.

Identifying Relevant Studies

A health sciences librarian developed and implemented literature searches in Medline, Embase, Pubmed, CINAHL, and gray literature including major rehabilitation websites/organizations from inception to August 1, 2020. Our multidisciplinary study members helped conceptualize the search strategy (which was based on the concepts of the COVID-19 pandemic and rehabilitation) with multiple text words and subject headings (e.g., MeSH) describing each concept. This search strategy was limited to English. The search strategies are detailed in the **Supplementary Materials**.

Selection Criteria

Studies were included if they discussed rehabilitation recommendations for COVID-19 patients, survivors, or the general population at the time of the COVID-19 pandemic.

Screening and Study Selection

Search results were uploaded to the Covidence platform (Covidence Systematic Review Software, 2021). After removing duplicates, two of four team members (MZ, AS, VM, AN) independently reviewed the titles and abstracts following the inclusion/exclusion criteria. If there were insufficient details to make an informed decision, the article was retrieved for review. To confirm eligibility, two of four team members (MZ, AS, VM, AN) independently assessed the full-text articles using the same inclusion criteria. Any disagreement was resolved through consensus or third-party adjudication by a senior reviewer (AN).

Data Extraction

A standardized data extraction form was created by the research team. Two of four team members (MZ, AS, VM, AN) then used the pre-tested data extraction form to extract data from included full-text articles.

Quality Assessment

Two reviewers (MZ, VM) evaluated the strength and the quality of the extracted recommendations using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach of selected full-text articles using the Oxford Level of Evidence (Guyatt et al., 2008). There are four possible categories for strength of recommendation evidence: (1) strong recommendation for; (2) weak recommendation for; (3) weak recommendation against, and (4) strong recommendation against. **Figure 1** shows the GRADE strength categories and outlines the clinical application of recommendations based on level of strength. There are three categories for quality of recommendation: (1) Good, (2) Fair, and (3) Poor. We present the quality and strength of key recommendations throughout the results of the review.

Summarizing and Reporting the Findings

The extracted recommendations were organized into several sections. These sections were decided with input from coauthors (group of experts in rehabilitation sciences). We reported a brief summary of the studies along with the strength and the quality of recommendations.

RESULTS

Of the 6,468 citations retrieved, 2,086 were eligible for screening after removing duplicates. We excluded 1,980 after the title and abstract screening. Of the screened full-text articles, 106

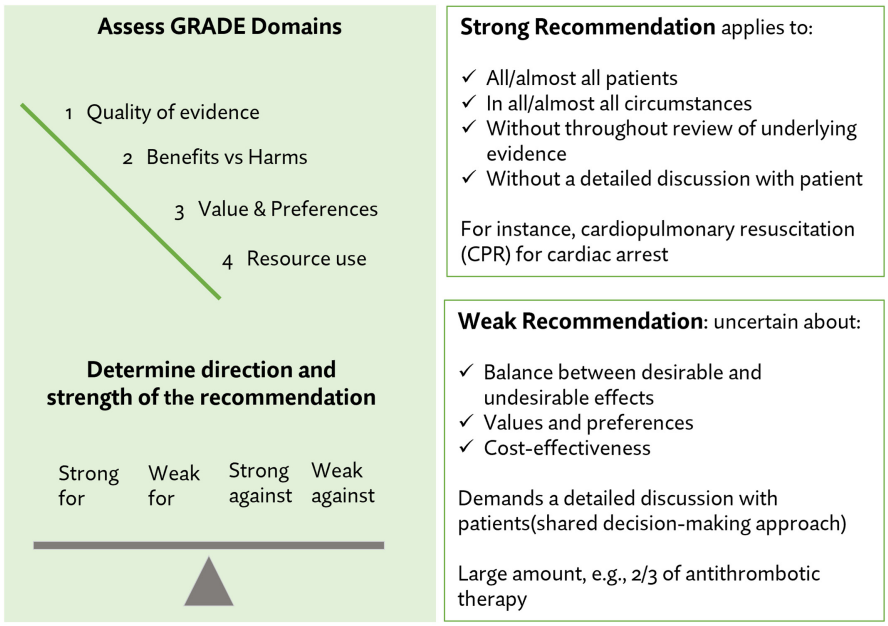

FIGURE 1 | Strength and quality assessments for individual recommendations (Guyatt et al., 2008).

studies from 22 countries (including low-income, middle-income and high-income) reported COVID-19 related recommendations (**Figure 2**). Of these articles, 46 articles reported rehabilitation recommendations across patients' journeys. A reference list of the 46 articles is provided in the **Supplementary Materials**.

The Extracted Recommendations

In this guideline, we present recommendations focused on the patient journey at the time of the pandemic. Another manuscript presented the health system-related recommendations (Negm et al., 2022). **Figure 3** summarizes the structure of the recommendation.

Quality and Strength of the Recommendations

Using the GRADE approach to evidence quality assessment, we assessed the evidence to be overall of fair quality and strong for the recommendations made (**Table 1**). The strength of each individual recommendation is reported in the **Supplementary Table**.

Acute Care/I.C.U. Rehabilitation

We identified 17 publications that addressed the acute or I.C.U. rehabilitation domain. Publication dates ranged from March 30, 2020, to August 1, 2020 (Amatya and Khan, 2020; Arenivas et al., 2020; Chinese Association of Rehabilitation Medicine et al., 2020; Hosey and Needham, 2020; Kalirathinam et al., 2020; Masiero et al., 2020; Nakamura et al., 2020; Pinto and Carvalho, 2020; Qu et al., 2020; Recommendations AHSSAGC, 2020; Sañudo et al., 2020; Sheehy, 2020; Thomas et al., 2020; Vitacca et al., 2020; Yu P. et al., 2020; Handu et al., 2021; Kurtais Aytür et al., 2021). Recommendations were from 11 countries [Canada ($n = 3$), Australia ($n = 2$), Brazil ($n = 1$), China ($n = 3$), Italy ($n = 2$), Japan ($n = 1$), Belgium ($n = 1$), Spain ($n = 1$), Turkey ($n = 1$), United Kingdom ($n = 1$), United States ($n = 3$), one study included data from multiple countries (Australia, Belgium, Canada)]. Seventeen institutions participated in developing these guidelines, including hospitals, scientific societies, and universities (**Supplementary Table**). Of the 17 publications, eight were developed by rehabilitation or medical professions, and five were developed by researchers. The other four publications did not report the group involved in developing the recommendations. Of the 17 publications, 16 were developed based on expert opinion and/or clinical experience, and a single study was developed based on a combination of both evidence-based methods and expert opinion.

Summary of Key Recommendations

- In patients with COVID-19 pneumonia or acute respiratory distress syndrome (ARDS), include a multidisciplinary/holistic care program for pulmonary rehabilitation tailored to the unique needs of each patient, giving meticulous attention to the delivery of evidence-based critical care interventions, to early comprehensive rehabilitation that targets physical and neuropsychological recovery, and for the evaluation of adequate social support.
- If indicated, use airway clearance techniques including positioning, active breathing cycle, manual and ventilator hyperinflation, percussion and vibrations, positive expiratory pressure therapy (P.E.P.), assisted or stimulated cough maneuvers, airway suctioning, and mechanical insufflation-exsufflation.

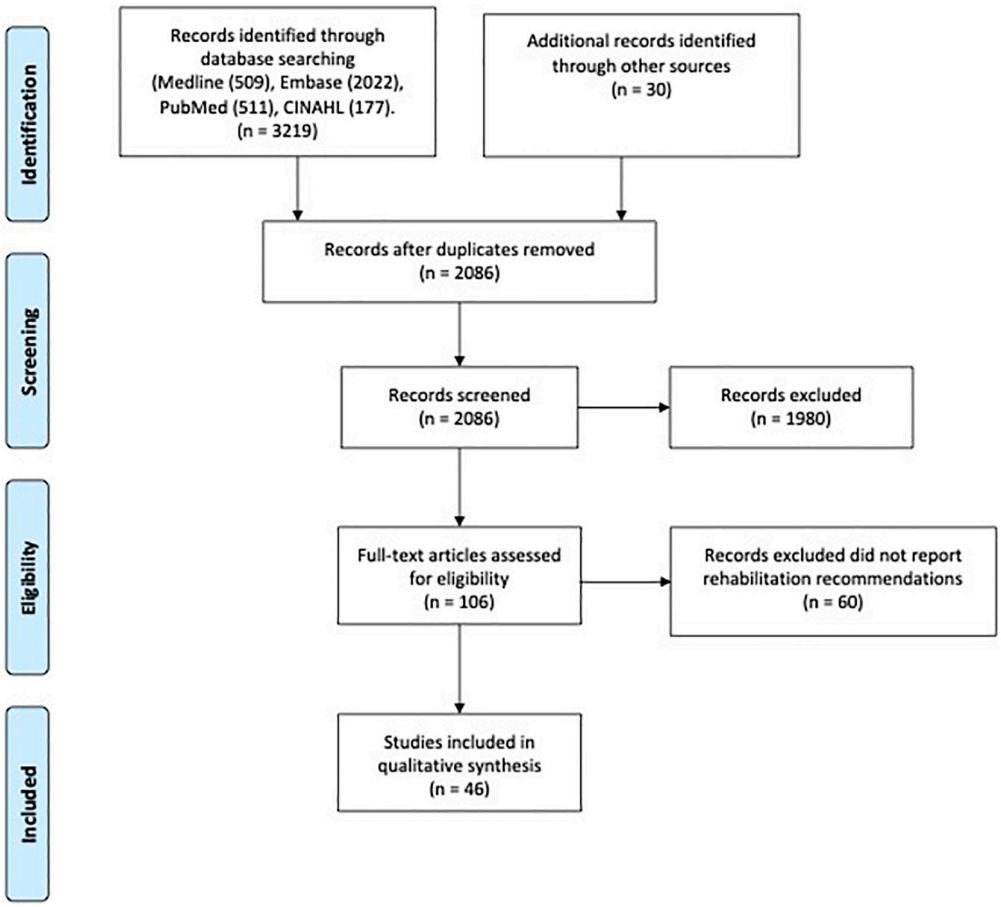

FIGURE 2 | PRISMA flow diagram.

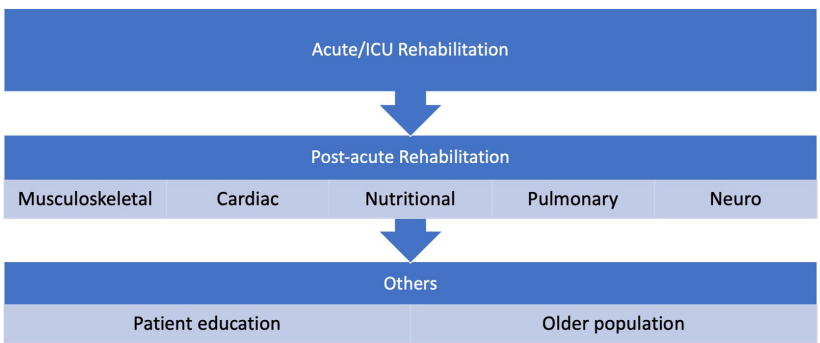

FIGURE 3 | Structure of patient journey recommendations.

- Positioning management: When physiological status permits, gradually change positioning in more vertical anti-gravity postures, such as raising the bed head.
- Carry out positioning management in 30-min sessions, three sessions per day. Prone position ventilation is implemented in patients with ARDS for 12 h and above.
- In the supine position, place the lower edge of the pillow on one-third of the scapula to prevent head hyperextension and place a pillow below the popliteal fossa to relax the lower limbs and abdomen.
- Ensure safety and integrity of tubing and lines to prevent inadvertent disconnection or detachment during mobilization and rehabilitation interventions.

- Monitor vital signs during rehabilitation sessions and vital sign responses to rehabilitation interventions.
- Consider intensity and duration of rehabilitation activities and sessions and adjust accordingly for patients with poor physical status.
    - Lower intensity and shorter duration of activities, exercises, with sessions only for patients with poor physical status.
    - Keep single rehabilitation sessions to less than 30 min to reduce fatigue.
    - Passive, active-assisted, active range of motion or resistance exercises may be performed to maintain or improve joint integrity, range of motion, and muscle strength.
- Mobility/mobilization/exercises may include side-to-side position changes, bed mobility, sitting at the bed edge, moving from the bed to chair, sitting in a chair, standing, stepping in place, walking, tilt table, standing hoists, upper/lower cycle ergometry, and exercise programs; and active range of motion (R.O.M.) exercises through the full available range.
- The treatment plan for patients receiving sedatives or unconscious includes in-bed cycling, passive R.O.M. exercises, stretching exercises, and neuromuscular electrical stimulation.
- Indicate reconditioning interventions in weaned patients and those with prolonged weaning from mechanical ventilation and oxygen use to improve physical function and capacity and address motor and cognitive effects of prolonged immobilization in I.C.U.
- Neuropsychologists assess and treat varied cognitive presentations in acute rehabilitation settings. Build cognitive flexible evaluation methods that can be adapted to the patient's functional level.
- Utilize neuropsychologists to provide emotional support and use evidence-based interventions to promote mental health and coping skills.
- In individuals with suspected or confirmed COVID-19 infection in the I.C.U. who are not mechanically ventilated, registered dietitians (RD) should work with the multidisciplinary team to ensure adequate energy and protein intake.
- When needs cannot be met orally, enteral nutrition (EN) is the preferred feeding route. If EN is not suitable or accepted/ has to be initiated in a timely manner to treat and prevent any further malnutrition.

Post-acute Rehabilitation

We identified 25 publications that addressed post-acute rehabilitation. Publication dates ranged from February 4 to July 5, 2020 (Barker-Davies et al., 2020; Bartolo et al., 2020; Bij de Vaate et al., 2020; Boldrini et al., 2020; Brugliera et al., 2020; Chen et al., 2020; Chinese Association of Rehabilitation Medicine et al., 2020; Galiuto and Crea, 2020; Gómez-Moreno et al., 2020; Jangra and Saxena, 2020; Kho et al., 2020; Mammi et al., 2020; Pandian and Sebastian, 2020; Piepoli, 2020; Polastri et al., 2020; Qu et al., 2020; Sañudo et al., 2020; Schmidt et al., 2020; Sheehy, 2020; Vitacca et al., 2020; Wade, 2020; Yang and Yang, 2020; Yu H.P. et al., 2020; Zhao et al., 2020; Handu et al., 2021; Kurtais Aytür et al., 2021). Recommendations were from 12 countries [Canada ($n = 2$), China ($n = 5$), India ($n = 2$), Italy ($n = 8$), Mexico ($n = 1$), Denmark ($n = 1$), United States ($n = 2$), Netherlands ($n = 1$), Portugal ($n = 1$), Spain ($n = 1$), Turkey ($n = 1$), United Kingdom ($n = 2$), one study included data from multiple countries (China, Denmark, United States)]. Twenty-five institutions participated in developing these guidelines including hospitals, scientific societies, and universities (**Supplementary Table**).

Of the 25 publications, nine were developed by rehabilitation or medical professions, and eight were developed by researchers. Other (Besnier et al., 2020) publications did not report the group involved in developing the recommendations. Of the 25 publications, 22 were developed based on expert opinion and/or clinical experience, two were developed using evidence-based methods including systematic review, survey, and observational studies, and one study was developed based on a combination of both evidence-based methods and expert opinion.

TABLE 1 | Recommendations quality.

Standard	Rating
Establishing transparency	Fair
Management of C.O.I.* in the guideline development group	Fair
Recommendation development group composition	Good
Recommendation development (evidence-based)	Fair
Establishing evidence foundations and rating strength for each of the recommendations	Fair
Articulation of recommendations	Fair
External review	Not Reported
Updating	Fair
Implementation issues	Not Reported

** C.O.I., Conflict of interest.*

Summary of Key Recommendations

A) Neurorehabilitation

- The role of occupational therapists or healthcare professionals with similar training should include:
    - Prevention, detection, and monitoring of delirium.
    - Assessment and management of impairments in physical and cognitive functioning.
    - Evaluation of emotional coping strategies for patients.
    - Addressing mental health and psychosocial needs of patients and/or caregivers.
- Inpatient rehabilitation settings: Ensure the adequate delivery of interventions and development of individual rehabilitation plans for patients directly admitted from the acute care wards, including patients recovering from COVID-19 with disabling sequelae.
- Patients with neurological conditions requiring rehabilitation coming from acute units outside hospitals should be admitted

if tested as COVID-19 negative using throat and nasal swabs and after confirming absence of fever and cough (or other symptoms suggestive of COVID-19 infection).

Use psychosocial support to manage emotional disturbance, changes in self-esteem and self-confidence, and similar constructs with techniques such as cognitive-behavioral therapy and motivational interviewing (Bartolo et al., 2020; Chinese Association of Rehabilitation Medicine et al., 2020; Kho et al., 2020; Pandian and Sebastian, 2020; Qu et al., 2020; Sheehy, 2020; Wade, 2020).

B) Nutritional Rehabilitation and Speech Therapy

- Early assessment of nutritional status with consequent addition of energy and protein through oral food supplements, or if not tolerated, transition to artificial nutrition.
- Speech-Language Pathology role should include:
    - Assessment and management post-extubation dysphagia upon decompensation and respiratory compromise.
    - Assessment of basic cognitive and communication functions.
    - Assessment and treatment of voice impairments caused by prolonged intubation.
- Implement early nutritional supplement protocol for non-critical COVID-19 patients with severe inflammatory status and anorexia, which can lead to a significant reduction in food intake.
- When counseling patients with suspected or confirmed COVID-19 infections who are in their homes or the outpatient setting, R.D.s' advice to patients and their families should include the following:
    - Adequate energy and protein intake by meeting at least the recommended dietary allowance for energy and protein-based on age and sex.
    - If the oral dietary intake is inadequate, nutrient-dense foods and beverages, including oral nutritional supplements, should be recommended to increase energy and protein intake.
    - Beverages should be recommended to increase energy intake; if an individual is unable to eat solid foods due to difficulty coordinating chewing and breathing.
    - Micronutrient supplements help counteract for inadequate oral intake to address deficiencies.
    - Small frequent meals and snacks should be recommended to avoid nausea, vomiting, and shortness of breath.
    - Provide foods that require little handling, preparation, or effort to eat.

Adequate intake of fluids to stay hydrated throughout the day and evening. Use rehydration drinks if the patient is experiencing vomiting and diarrhea (Brugliera et al., 2020; Chinese Association of Rehabilitation Medicine et al., 2020; Kho et al., 2020; Sheehy, 2020; Handu et al., 2021).

C) Musculoskeletal and Cardiorespiratory Rehabilitation

- Standardized rehabilitation evaluation including:
    - Clinical evaluation: physical examination, imaging tests, laboratory tests, lung function tests, nutrition screening, and ultrasonography.
    - Exercise and respiratory function assessment: (i) respiratory muscle strength: maximum inspiratory pressure/maximum expiratory pressure; (ii) muscle strength: manual muscle testing using the Medical Research Council scale; or isokinetic muscle testing; (iii) joint R.O.M. test; (iv) balance function evaluation: Berg Balance Scale; (v) aerobic exercise capacity: 6-min walk test and cardiopulmonary exercise testing; and (vi) physical activity evaluation: International Physical Activity Questionnaire and Physical Activity Scale for the Elderly.
    - Evaluation of activities of daily living (A.D.L.): The Barthel index or equivalent instruments.
- The role of occupational therapists or healthcare professionals with similar training should include:
    - Optimizing bed and seating positioning using pressure relief principles (e.g., mattress).
    - Assessment and management of A.D.L.s and instrumental activities of daily living (IADLs) to encourage early mobilization.
    - Provision of assistive devices for A.D.L.s, communication, seating, and mobility.
    - Facilitate functional independence/autonomy and preparing patients for discharge.
- The role of physical therapy or healthcare professionals with similar training includes:
    - Assessment of exercise and functional capacity.
    - Monitoring of pre-existing comorbid conditions.
    - Exercise training and/or physical activity coaching.
    - Enhance mobility, A.D.L., and IADL.
- According to the cognitive and emotional dysfunction level, an individual can choose a first-line physical therapy under general practitioner supervision or an integrated treatment program in a COVID-19 rehabilitation clinic (if available).
- Aerobic exercises are tailored based on the patient's underlying COVID-19 disease and remaining dysfunction. Aerobic exercises, such as walking, slow jogging, and swimming, should begin at a low intensity then gradually increase. A total of 3 to 5 sessions should be carried out every week, each session lasting 20–30 min. Patients should use intermittent exercises if they are prone to fatigue.
- Progressive resistance training is recommended for strength training: 8 to 12 repetitions per set, 1 to 3 sets for each target muscle group, with 2-min rest intervals between sets, at a frequency of 2 to 3 sessions/week for six weeks.
- Patients with comorbid balance disorders should perform balance training.

- Adjust the exercise program plan to accommodate the patients' home environment. Help patients identify safe, alternative spaces for aerobic training according to current government/jurisdictional COVID-19 guidelines.
- Use COVID-19 illness severity to determine the exercise intensity:
    - For mild COVID-19 illness, (i) Exercise intensity measured by Modified BORG Dyspnea Scale $\leq$ 3 points; (ii) Exercise frequency should be twice a day, duration 15–45 min each session, 1 h after meals; and (iii) examples of types of exercise include Tai chi, breathing exercise, or square dancing.

For moderate COVID-19 illness, (i) Exercise intensity should be between rest [1.0 metabolic equivalents (M.E.T.s)] and light exercise (< 3.0 M.E.T.s); (ii) Exercise frequency should be twice a day, 1 h after a meal, duration should be based on the individual's physical status, and each session lasts 15–45 min. Individuals should perform intermittent exercise if they are prone to fatigue; (iii) examples of types of exercise include stepping, Tai chi, breathing exercises (Barker-Davies et al., 2020; Bij de Vaate et al., 2020; Chen et al., 2020; Chinese Association of Rehabilitation Medicine et al., 2020; Gómez-Moreno et al., 2020; Kho et al., 2020; Mammi et al., 2020; Piepoli, 2020; Qu et al., 2020; Schmidt et al., 2020; Sheehy, 2020; Vitacca et al., 2020; Wade, 2020; Yu H.P. et al., 2020).

D) Pulmonary/Cardiorespiratory Rehabilitation

- Respiratory assessment should include evaluation of dyspnea, thoracic activity, diaphragmatic activity and amplitude, respiratory muscle strength (maximal inspiratory and expiratory pressures), respiratory pattern, and frequency. Cardiac status should also be assessed.
- Determine respiratory rehabilitation goals
    - The short-term goal of pulmonary rehabilitation should be to lessen dyspnea and reduce anxiety and depression.
    - The long-term goal of pulmonary rehabilitation should be to reserve the patient's function, improve quality of life, and accelerate return to the community.
- Primary intervention measures for pulmonary rehabilitation include airway clearance, reduction of dyspnea, breathing control, physical activity, and exercise.
- Airway clearance techniques: in patients with chronic airway disease, forced expiratory techniques should be used in the early stages of airway clearance after discharge to expel sputum and reduce coughing and energy consumption; positive expiratory pressure/OPEP can be used as aids.
- Breathing control: (i) positioning: An upright sitting position. If a patient has shortness of breath, a semi-sitting position should be used; (ii) maneuvers: the patient slowly inhales through the nose and slowly exhales through the mouth while the shoulders and neck accessory muscles are relaxed.
- In the post-acute phase, inspiratory muscle training should be included if inspiratory muscles are weak.
- Two sessions of 10 min of pulmonary rehabilitation every week for six weeks following discharge from acute care showed a significant improvement in pulmonary function, endurance, quality of life, and depression.

Breathing exercise: if shortness of breath, wheezing, and difficulty in expelling sputum occur in patients after discharge, breathing exercise (such as posture management, adjustment of breathing rhythm, thoracic expansion training and mobilization of respiratory muscle groups) should be used (Chinese Association of Rehabilitation Medicine et al., 2020; Jangra and Saxena, 2020; Polastri et al., 2020; Qu et al., 2020; Sañudo et al., 2020; Sheehy, 2020; Vitacca et al., 2020; Yang and Yang, 2020; Zhao et al., 2020; Kurtais Aytür et al., 2021).

E) Cardiac Rehabilitation

- Give cardiovascular protection during COVID-19 infection and prescribe adequate cardiac rehabilitation programs to survivors of the disease.
- Home-based cardiac rehabilitation (C.R.) programs should comprise the same main components as center-based programs.
- Telemonitoring should include technology-assisted assessments, which range from using a logbook and structured telephone calls to the use of wearable sensors, such as heart rate monitors, accelerometers, or remote E.C.G. telemetry monitoring.
- Patient-related factors (cardiovascular risk, digital skills and personal preferences) and provider-related factors (such as logistical conditions, including staff training and availability of technological equipment) determine the approach and the degree of technological sophistication to use for telemonitoring.
- The video conferencing technologies is used to allow patients to meet with the cardiac rehabilitation team. Video conferencing is a useful tool to decrease the mental and physical consequences of social isolation caused by the COVID-19 pandemic.

A hybrid approach is recommended if patients' safety is a concern. The hybrid approach begins with supervised sessions in a cardiac rehabilitation unit; the sessions start with a low-intensity exercise prescription to promote patients' confidence and adherence, followed by weekly telephone calls to discuss exercise progression and any concerns (Galiuto and Crea, 2020; Schmidt et al., 2020).

Education/Social Interventions

We identified eight publications that addressed education and social interventions (Barker-Davies et al., 2020; Chinese Association of Rehabilitation Medicine et al., 2020; Griffin, 2020; Jalali et al., 2020; Qu et al., 2020; Sheehy, 2020; Wade, 2020; Kurtais Aytür et al., 2021). Publication dates ranged from April 19 to July 5, 2020. Recommendations were from 5 countries [Canada (n = 1), China (n = 2), Iran (n = 1), Turkey (n = 1), United Kingdom (n = 3)]. Eight

institutions participated in developing these guidelines, including hospitals, scientific societies and universities (**Supplementary Table**).

Of the eight publications, one was developed by physicians, and two were developed by researchers. Other (United Nations, 2020) publications did not report the group involved in developing the recommendations. Of the eight publications, seven were developed based on expert opinion and/or clinical experience, and a single study was developed based on a combination of both evidence-based methods and expert opinion.

Summary of Key Recommendations

- Education includes many specific areas: patient self-management; caregivers (family and professional) being taught how to support self-management; caregivers being taught to accelerate practice and/or to provide care safely; caregivers being encouraged to facilitate social integration; teaching patients and others as appropriate, about the disease and its management; and setting expectations for all parties.
- Patient education: (1) Advocacy, videos, and booklets are used to help patients understand the disease and treatment process; (2) patients are encouraged to take regular rest and have sufficient sleep; (3) patients are encouraged to eat a balanced diet; (4) patients are advised to stop smoking.

Timing of Rehabilitation Services in Persons With COVID-19 Infection

We identified nine publications that addressed the start and stop rehabilitation criteria (Aytür et al., 2020; Chinese Association of Rehabilitation Medicine et al., 2020; Kalirathinam et al., 2020; Kemps et al., 2020; Qu et al., 2020; Sheehy, 2020; Thomas et al., 2020; Vitacca et al., 2020; Yang and Yang, 2020). Publication dates ranged from March 30 to July 16, 2020. Recommendations were from 8 countries [Turkey ($n = 1$), China ($n = 3$), United Kingdom ($n = 1$), Netherlands ($n = 1$), Australia ($n = 1$), Belgium ($n = 1$), Canada ($n = 2$), Italy ($n = 1$), one study included data from multiple countries (Australia, Belgium, Canada)]. Nine institutions participated in developing these guidelines, including hospitals, scientific societies and universities (**Supplementary Table**).

Of the nine publications, two were developed by researchers and four were developed by rehabilitation and medical professionals. Other (Perrotta et al., 2020) publications did not report the group involved in developing the recommendations. Of the nine publications, eight were developed based on expert opinion and/or clinical experience, and one study was developed based on a combination of both evidence-based methods and expert opinion.

Summary of Key Recommendations

- **Start Criteria:** Zhao et al. recommended that "In the critically ill COVID-19 patient, respiratory rehabilitation can be initiated once all of the following criteria are met: (1) respiratory system: (i) fraction of inspired oxygen ≤ 0.6, (ii) SpO2 $\geq$ 90%, (iii) respiratory rate $\leq$ 40 breaths/min (bpm), (iv) positive end expiratory pressure $\leq$ 10 cmH2O (1 cmH2O = 0.098 kPa), (v) absence of ventilator resistance, and (vi) absence of unsafe hidden airway problems; (2) cardiovascular system: (i) systolic blood pressure $\geq$ 90 and $\leq$ 180 mmHg, (ii) mean arterial pressure (M.A.P.) $\geq$ 65 and $\leq$ 110 mmHg, (iii) heart rate $\geq$ 40 and $\leq$ 120 beats/min, (iv) absence of new arrhythmia or myocardial ischemia, (v) absence of shock with lactic acid level $\geq$ 4 mmol/L, (vi) absence of new unstable deep vein thrombosis and pulmonary embolism, and (vii) absence of suspected aortic stenosis; (3) nervous system: (i) Richmond Agitation-Sedation Scale score: -2 to $+2$ and (ii) intracranial pressure $<$ 20 cmH2O; and (4) other: (i) absence of unstable limb and spinal fractures, (ii) absence of severe underlying hepatic/renal disease or new progressively worsening hepatic/renal impairment, (iii) absence of active hemorrhage, and (iv) temperature $\leq$ 38.5 C" (Zhao et al., 2020).
- **Exercise Stop Criteria:** For patients with COVID-19, delay the exercise program if fever or other signs and/or symptoms of COVID-19 infection exist. Assess exercise continuation individually. In general, patients with mild to moderate symptoms can gradually resume the exercise program after one week with no fever and 48 h with no symptoms. If possible, do not suspend cardiac rehabilitation components but provide them using telerehabilitation tools.
- For critically ill patients, it is recommended by Zhao et al. (2020) that "early rehabilitation to be discontinued immediately if the following conditions occur: (1) Respiratory system: (i) SpO2 $<$ 90% or decrease by $>$ 4% from baseline, (ii) respiratory rate $>$ 40 bpm, (iii) ventilator resistance, and (iv) artificial airway dislodgement or migration; (2) cardiovascular system: (i) systolic blood pressure $<$ 90 or $>$ 180 mmHg, (ii) M.A.P. $<$ 65 or $>$ 110 mmHg, or $>$ 20% change compared with baseline, (iii) heart rate $<$ 40 or $>$ 120 beats/min, and (iv) new arrhythmia and myocardial ischemia; (3) nervous system: (i) loss of consciousness and (ii) irritability; and (4) other: (i) discontinuation of any treatment or removal of monitoring tube connected to the patient; (ii) patient-perceived heart palpitations, exacerbation of dyspnea or shortness of breath, and intolerable fatigue; and (iii) falls inpatient" (Zhao et al., 2020).

Special Consideration for Geriatric Rehabilitation

We identified eight publications that addressed rehabilitation of older adults (Alliance, 2020; Chen et al., 2020; Etard et al., 2020; Gómez-Moreno et al., 2020; Ismail, 2020; Jiménez-Pavón et al., 2020; Verduzco-Gutierrez et al., 2020; Zeng et al., 2020). Publication dates ranged from February 4 to July 6, 2020. Recommendations were from 8 countries [France ($n = 1$), Mexico ($n = 1$), Egypt ($n = 1$), United States

($n = 3$), China ($n = 2$), Spain ($n = 1$), Denmark ($n = 1$), and Canada ($n = 1$), two studies included data from multiple countries (China, Denmark, United States; Spain, United States)]. Eight institutions participated in developing these guidelines, including hospitals, scientific societies, and universities (**Supplementary Table**).

Of the eight publications, four were developed by researchers and three were developed by rehabilitation and medical professionals. The last publication did not report the group involved in developing the recommendations. Of the eight publications, six were developed based on expert opinion and/or clinical experience, and two were developed using evidence-based methods including systematic review, survey and observational studies.

Summary of Key Recommendations

- Comprehensive Geriatric Assessment (C.G.A.) for frail seniors with rehabilitative needs should remain a priority. C.G.A. includes interprofessional geriatric assessment, physical assessment findings, analysis and synthesis of the clinical profile, and development of a collaborative plan and follow-up plan of care.
- Consider prehabilitation with the frail or at-risk patient. Prehabilitation includes interventions that aim to preventing or reducing physical impairments caused by physical stressors. Examples include cancer or surgical prehabilitation to improve treatment-related morbidity and mortality, and psychological health outcomes.
- Recognize that caregivers are essential to the care of frail seniors and are key in many settings to the provision of care. Caregivers often serve as a liaison between patients and clinicians and are involved in day-to-day decision-making and care delivery. They should therefore be included in the healthcare teams' communication and care planning. Caregivers should be given access to necessary resources. In the context of the current pandemic, caregivers will require personal protective equipment (P.P.E.) with instruction in proper donning and doffing techniques.
- Exercise frequency: The international guidelines of physical activity for older people recommend five days per week. At the time of the pandemic, which is associated with quarantine or lockdown, the exercise frequency should increase to 5–7 days per week with adaptation in volume and intensity (Jiménez-Pavón et al., 2020).
- Exercise volume: The guidelines recommend at least 150–300 min per week of aerobic exercise and two resistance training sessions per week. Under restriction of movement due to the COVID-19 pandemic, it should increase to 200–400 min per week across 5–7 days to offset the lower levels of daily physical activity. A minimum of 2–3 days per week of resistance exercise should be recommended. Mobility training, balance and coordination exercises should be performed on all the training days (Jiménez-Pavón et al., 2020).
- Exercise intensity: The guidelines suggest moderate intensity for most of the sessions and some amount of vigorous exercise weekly. Because vigorous-intensity exercise may inhibit the immune system, especially in sedentary people, moderate-intensity (40–60% heart rate reserve or 65–75% of maximal heart rate) should be recommended for older people during restriction of movement due to COVID-19 pandemic (Jiménez-Pavón et al., 2020).
- A number of measures have been recommended to reduce the risk of COVID-19 outbreak in institutions caring for older adults:
    - Lockdowns, suspension of visits and personal aids, secured supply chains, isolation of cases, extended barrier measures, sanitation, limitation of internal activities, etc.
    - Public information and communication campaigns should be directed to protect older adults, make them noticeable, and offer strong psychological support to the nursing staff.
    - Reinforce the communication between nursing staff and families at the end of a resident's life and after death.
    - A palliative approach of care should be proposed within the impacted institutions after accounting for ethical considerations to decrease the burden on general hospitals.
- Physiatrist outpatient in-person visits can be transitioned to virtual physical exams (telemedicine), which can be delivered using virtual workflow (before, during, and after the visit) during natural disasters such as the current pandemic due to COVID-19.

DISCUSSION

In this review, we pooled rehabilitation recommendations for various settings, including acute care, critical care, and different post-acute settings. Recommendations for education interventions and special consideration for older adult rehabilitation were also presented. Most of the recommendations were based on expert opinions and/or consensus. Based on the GRADE approach, the overall quality of the recommendations was deemed fair, and most of the individual recommendations were graded as strong.

Overall, the evidence suggests that continuity of rehabilitation services is critically important to maintain function and participation among patients during the COVID-19 pandemic. Yet, many barriers exist across healthcare settings. Globally, healthcare systems have needed to rapidly adapt to the different waves of the current pandemic. Telehealth has been one of the areas with higher development, emerging as a good approach to keep many aspects of healthcare, including rehabilitation, running during this time. Technology has been a key tool to help provide this continuity of healthcare attention to our patients and will likely continue having a significant role in the

future. Even though the role of telerehabilitation is not yet fully understood, it is definitely "here to stay" as part of our future healthcare practice. Our guidelines acknowledge this change and include telerehabilitation recommendations and strategies to help rehabilitation professionals deliver care.

The recommendations for critical care/I.C.U. and acute settings address the need for a multidisciplinary care program in patients with COVID-19 pneumonia or acute respiratory distress syndrome (ARDS), including pulmonary rehabilitation, physical and neuropsychological recovery, and nutritional support provided early on and tailored to the unique needs of each patient. The recommendations for post-acute rehabilitation address the importance of individual assessment of neurorehabilitation, speech, musculoskeletal, respiratory, and cardiac rehabilitation following the specific protocols provided. Education of patients, caregivers and families is at the center of disease management. Specific criteria to start or stop a rehabilitation services are also provided, as are recommendations for frail seniors. The recommendations can be used to guide rehabilitation professionals in their decision-making and patient management.

We acknowledge the limitations of this review which include lack of higher levels of evidence among primary studies [e.g., randomized controlled trials (R.C.T.s)]. Although systematic reviews and meta-analyses of R.C.T.s and/or observational studies provide a more measured approach for efficacy of a treatment, we did not include them in our review as we did not find enough primary studies to conduct a systematic review on COVID-19 rehabilitation recommendations. Most publications in our review were expert opinion and clinical recommendations without systematic reviews. We synthesized and summarized the eligible publications with the best available recommendations.

The COVID-19 pandemic and the evidence addressing it are rapidly evolving. The recommendations included in this article will be updated in the near future to incorporate the most recent evidence. The COVID-19 vaccine may decrease the impact of COVID-19 and might modify some of the approaches proposed in this document, as they reflect evidence published before vaccine introduction.

In conclusion, we have combined the latest research findings and expert opinions to develop acute and post-acute rehabilitation recommendations. Further ongoing updates are warranted in order to incorporate the emerging evidence into rehabilitation guidelines.

AUTHOR CONTRIBUTIONS

All authors were involved in critical revision and approval of the manuscript's design, conception, and analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.781226/full#supplementary-material

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REVIEW
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Cognitive Assessment in SARS-CoV-2 Patients: A Systematic Review

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Background: Patients with post-infective severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) often show both short- and long-term cognitive deficits within the dysexecutive/inattentive spectrum. However, little is known about which cognitive alterations are commonly found in patients recovered from SARS-CoV-2, and which psychometric tools clinicians should consider when assessing cognition in this population. The present work reviewed published studies to provide a critical narrative of neuropsychological (NPs) deficits commonly observed after SARS-CoV-2 infection and the tests most suited for detecting such cognitive sequelae depending on illness severity.

Methods: This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and was pre-registered on Prospective Register of Systematic Reviews (PROSPERO) (CRD42021253079). Observational studies quantitatively assessing cognition in patients with post-infective SARS-CoV-2 were considered. From 711 retrieved articles, 19 studies conducted on patients with SARS-CoV-2 without medical comorbidities were included and stratified by disease severity.

Results: The majority of studies (N = 13) adopted first-level tests. The most frequently administered screeners were the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE)—with the former more likely to detect mild, and the latter moderate/severe deficits. Among second-level tests, those assessing attention and executive functions (EFs) were highly represented. Remotely-delivered tests yielded lower percentages of cognitive impairment. Overall, cognitive domains often found to be impaired were EFs, attention, and memory.

Conclusion: Cognitive sequelae in patients with post-infective SARS-CoV-2 can be detected with NPs testing. Depending on the psychometric test features, the likelihood

of observing cognitive deficits can vary. Further studies on larger sample sizes are needed to investigate the clinical usefulness of second-level tools. The primary goal of preventative health services should be the early detection and intervention of emerging cognitive deficits.

Keywords: SARS-CoV-2, COVID-19, neuropsychology, psychometrics, cognitive impairment

KEY POINTS

- Cognitive sequelae are prevalent in patients with SARS-CoV-2, while the likelihood of observing such sequelae varies depending on the test used.
- Among patients with SARS-CoV-2, MoCA is more likely to detect mild cognitive deficits, whereas MMSE moderate/severe deficits.
- Studies using domain-specific tests are needed, to investigate whether some specific cognitive functions are more impaired than others.
- A standardized protocol for cognitive assessment in patients with SARS-CoV-2 should be made available to clinicians.

INTRODUCTION

The novel human-infecting coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) causes a multi-organ disease (COVID-19) that can impact the central nervous system (CNS; Coolen et al., 2020; Boscutti et al., 2021). Coronaviruses are known to elude the immune response and spread to cells other than those of the respiratory tract and have shown the ability to be neuro-invasive (Xu et al., 2005; Arabi et al., 2015). Several mechanisms by which SARS-CoV-2 can damage the CNS have been hypothesized. These include direct infection, viruses entering through blood circulation and neuronal pathways, hypoxic and immune injury, as well as binding to the angiotensin-converting enzyme 2 (ACE2) receptor (Baig et al., 2020). The neurotropism of SARS-CoV-2 allows it to escape the host immune response and achieve latency, which possibly causes both acute and long-term neurological effects, such as cognitive dysfunction (Blomberg et al., 2021). Indeed, post-mortem studies have found brain alterations among patients deceased because of COVID-19. Specifically, subcortical microbleeds and macrobleeds, asymmetric olfactory bulbs, and ischemic lesions have been observed through structural brain magnetic resonance imaging (Coolen et al., 2020). Furthermore, post-mortem histological/immunohistochemical analyses revealed the presence of astrogliosis in several regions (e.g., olfactory bulb, basal ganglia, and cerebellum), activation of microglia, and infiltration of cytotoxic T lymphocytes primarily in the cerebellum and brainstem (Matschke et al., 2020). Nonetheless, our understanding of such mechanisms remains limited, and most of the available evidence comes from previous SARS-CoV infections, post-mortem studies, and mouse transgenic models (Bao et al., 2020).

Health clinics are seeing an influx of patients with cognitive problems who were otherwise healthy prior to COVID-19 infection (Esposito et al., 2021; Nersesjan et al., 2022). From the emerging evidence and current understanding of the mechanism of SARS-CoV-2 action in the CNS, one can expect to a range of cognitive impairments that can either occur during the acute phase or manifest as long-term sequelae. Regarding short-term complications, deficits in working memory (WM), set-shifting, divided attention, and processing speed have been reported, with most patients showing mild-to-moderate symptoms (Varatharaj et al., 2020). Presently, we have limited ability to discuss the long-term cognitive consequences of COVID-19. However, in line with structural brain alterations found post-mortem across deceased patients, along with neuroimaging alterations found in COVID-19 patients with cognitive deficits (Douaud et al., 2022), we can expect that COVID-19 survivors would show long-term cognitive difficulties. Therefore, the cognitive evaluation of patients with COVID-19 should include first-level tests—i.e., screeners that usually provide a global index of general cognitive functioning—as well as second-level tests—i.e., tests that are able to provide an accurate evaluation of domain-specific cognitive functions, such as attention, speed of processing, executive functions (EFs), learning, and memory.

Given the past outbreaks of coronaviruses as well as current reports of COVID-19-related neurological complications, a large number of patients with COVID-19 will likely experience cognitive symptoms during or after the active phase, which will in turn negatively affect their psycho-social and functional outcomes (Jacobs et al., 2020). For these reasons, several studies have attempted to identify and characterize early cognitive sequelae associated with COVID-19 (Douaud et al., 2022). A detailed and longitudinal evaluation should be always considered in COVID-19 patients with cognitive complaints to monitor the emergency, the frequency, the severity, and subject-specific profile of cognitive dysfunction, given the high rate of inter-individual variability. This heterogeneity is primarily due to contextual factors that are known to impact cognition. First, the severity of SARS-CoV-2 infection, along with its medical management, seems to affect cognitive outcomes. As a matter of fact, a higher rate of cognitive impairment was found among patients with COVID-19 who experienced delirium relative to those without delirium (Mcloughlin et al., 2020). Second, hypoxemic respiratory failure, duration of intubation, or time elapsed from extubation to assessment are all known to impact cognitive performance (Turon et al., 2018; Sasannejad et al., 2019)—although a recent study did not find significant associations between the type of ventilation and cognitive impairment (Jaywant et al., 2021). Additionally, while the

premorbid cognitive status of individuals who recovered from COVID-19 is often unknown, possible pre-existing cognitive dysfunction, age, and general medical comorbidities impairing cognition may all play a pivotal role (Gunstad et al., 2010; Wu et al., 2011; Seliger et al., 2015; Kim et al., 2016). As a matter of fact, lower cognitive ability was found to be a key risk factor associated with the likelihood of SARS-CoV-2 infection/hospitalization (Batty et al., 2020).

Other aspects that are likely responsible for the high degree of heterogeneity in cognitive dysfunction include elements associated with cognitive evaluation: first-level and second-level tests may have different psychometric and diagnostic properties toward COVID-19-related cognitive impairment (Block et al., 2017), similar to how remote and in-person administration might not always elicit comparable results (Bilder et al., 2020).

The purpose of this systematic review is to identify which NPs (NPs) tests are best able to capture the cognitive complications following COVID-19. First, we review all published articles that included all first- and second-level NPs testing. Second, we classify these findings based on disease severity, so that it becomes possible to determine which test is most useful to characterize a specific cognitive domain at a given level of illness severity. Third, for each test, we report the percentage of patients with deficits. Finally, we note differences between in-person *vs.* remote administration, when available.

METHODS

The present systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA, Page et al., 2021); PRISMA checklist is provided in **Supplementary Table 1**.

This systematic review was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO)—identification number: CRD42021253079 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=253079).

Search Strategy

The online search strategy was conducted on 30 October 2021 through two of the major public scientific databases, PubMed and Scopus. The following search terms were entered: ("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND ("cognitive impairment" OR "cognitive deficit" OR "neuropsychology"). For Scopus, the fields of search were title, abstract, and keywords; for PubMed, the fields of search were title and abstract only. Additional studies that were manually retrieved have been included. No date limit was set and only contributions written in English were included. Gray literature was not searched for.

Inclusion and Exclusion Criteria

Observational studies (cross-sectional and longitudinal) quantitatively assessing patients with COVID-19 for different modalities, components, and functions of cognition by means of standardized tests were considered for eligibility. Abstracts, reviews, meta-analyses, opinion papers, research protocols, qualitative studies, case series studies, articles with no standardized tests administered to patients with COVID-19, and articles that present samples with severe comorbidities known to impact cognitive functioning were excluded.

Bias Assessment

Formal quality assessment was performed by four independent raters (AD, IL, LN, and GF) by means of the Standard Quality Assessment Criteria (SQAC, Kmet et al., 2004). Disagreements were solved *via* discussion with a fifth independent rater (BB). Non-applicable items were removed from the SQAC (range = 0–20).

Study Selection Process and Data Collection

The study selection process is shown in **Figure 1**.

The search, conducted from May 2021 to October 2021, provided 711 potentially relevant articles. After the removal of duplicates, 346 articles were available for screening—along with nine articles identified through manual search. The screening was performed independently by three of the authors (AD, IL, and LN) who were blinded to each other's decisions *via* Rayyan[1]. Disagreements were resolved by reaching a consensus. From the initial pool, 65 articles were then assessed for eligibility, of which 46 were excluded based on exclusion criteria. A total of 19 studies were included in this review. Taken together, the studies included in this review assessed 1.197 patients infected by SARS-CoV-2.

Data extraction was performed by four independent Authors (AD, IL, LN, and GF), whereas a fifth independent rated (BB) checked the extracted data and resolved disagreements. The following variables were extracted from included studies: authors and year; study design (cross-sectional *vs.* longitudinal); number of patients; age; education; sex; disease severity and duration; time between infection and assessment; modality of assessment (in person *vs.* remote); tests that were administered; first- *vs.* second-level assessment; cognitive domains or behavioral aspects that were assessed; and scores on NPs tests.

RESULTS

Study Categorization

In light of the high heterogeneity in COVID-19 severity, included articles were stratified according to disease severity to better understand the prevalence and nature of cognitive deficits. Studies were stratified as follows: severe, if patients required intensive care unit (ICU) admission and/or invasive ventilation (N = 5); moderate, if patients required hospitalization (N = 3); and mild, if no hospitalization was needed (N = 1). Whenever a study included patients with different degrees of severity, or severity was not specified, the study was categorized as having a mixed population (N = 10).

Outcome Overview

A summary of the included articles and their data are provided in **Table 1**. Five studies investigated severe patients, three moderate

[1]https://rayyan.qcri.org/welcome

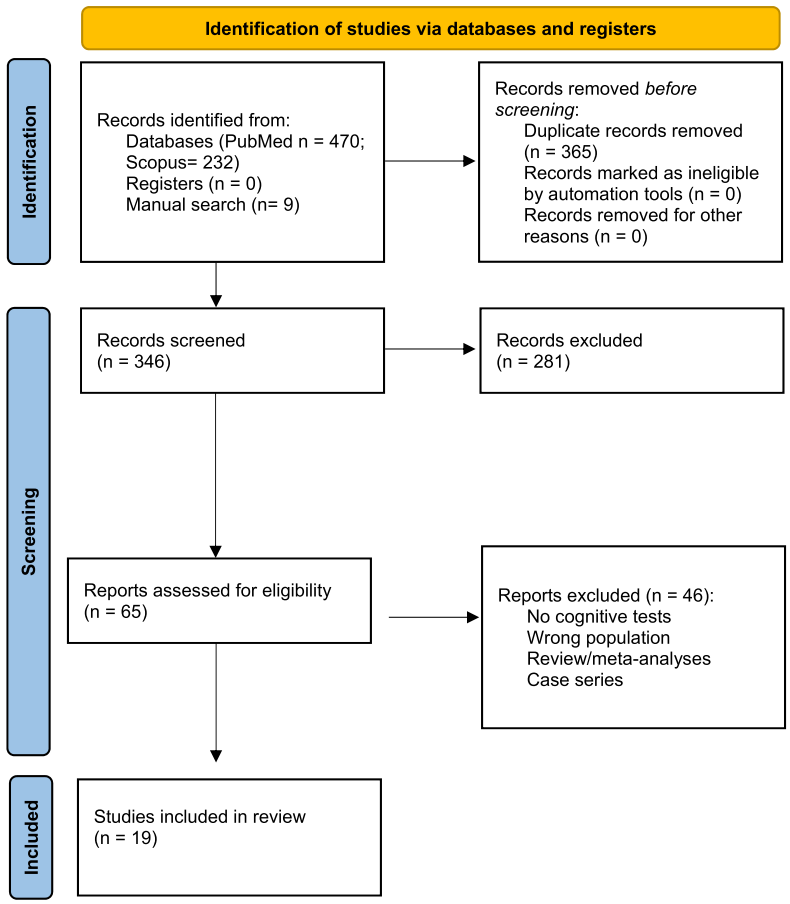

FIGURE 1 | PRISMA 2020 flow diagram for the systematic review, which included searches of Pubmed and Scopus databases.

patients, and one mild patients, whereas 10 featured patients with mixed or unspecified severity.

The mean SQAC scores was 17.8/20 ± 1.8/20 (17/18 for articles with non-applicable items). In 14 studies, NPs' assessment took place in person, while five studies tested patients remotely. In one study the assessment took place both in-person and remotely.

In total, 13 studies used a first-level assessment tool, with the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) being the most frequently administered test, followed by the Mini Mental State Examination (MMSE; Folstein et al., 1975), and the Telephone Interview for Cognitive Status (TICS; Brandt et al., 1988). Additionally, six studies investigated specific NPs domains with second-level assessments.

Overview of Neuropsychological Assessment in Patients With COVID-19

Neuropsychological Assessment in Severe Patients

Within articles including *severe* patients (N = 5), two administered the NPs evaluation in person while three did it remotely.

Furthermore, four out of five studies used a first-level assessment, with MoCA and MMSE being the most commonly used, followed by TICS. One study (Zhou et al., 2020) used the following second-level tests: Trail Making Test (TMT), Sign Coding Test (SCT), Continuous Performance Test (CPT), and Digit Span Test.

In addition, two studies from mixed categories reported NPs scores separately for severe patients (Alemanno et al., 2021; Heyns et al., 2021): their findings are therefore reported in this section. Both studies assessed cognition through in-person evaluation, administering MoCA (Alemanno et al., 2021; Heyns et al., 2021), and MMSE (Alemanno et al., 2021), respectively.

All studies investigating global cognition in severe patients with the MoCA encompassed in-person assessments and identified pathological scores in 46% (7 out of 15 patients, Heyns et al., 2021) and 70% (22 out of 31 patients, Alemanno et al., 2021) of patients, respectively. Latronico et al. (2022) assessed patients longitudinally after hospital discharge and found that 25% (25/98) of patients were pathological on MoCA at 3 months after discharge, 22% (17/77) pathological after 6 months, and 13% (7/51) pathological after 12 months.

The MMSE was administered both in-person (Alemanno et al., 2021; Pistarini et al., 2021) and remotely

TABLE 1 | List of included studies.

References	Study type	*N* (diagnosis modality)	Age (year)	Sex% males	Education (years)	Disease severity	Disease duration	Time of assessment from onset	Assessment modality	Assessment level	Cognitive test: % of patients with deficit (n of patients with deficit/N)
Aiello et al., 2022	Cross sectional	100 of which 55 RCD + and 45 RCD- (not reported)	*RCD+:* 66.13 ± 13.84 *RCD–:* 63.33 ± 11.4	*RCD+:* 61% M *RCD–:* 86% M	*RCD+:* 11.2 ± 3.63 *RCD–:* 11.02 ± 3.89	Mixed	40.6 ± 26.72 (2–113) [days] 42.31 ± 26.26 (5–129) [days]	74.13 ± 41.02 (7–241) [days] 76.43 ± 35.33 (26–186) [days]	In person	I level	*RCD+:* MMSE: 20% (11/55) MOCA: 23.6% (13/55) *RCD–:* MMSE: 2.2% (1/45) MOCA: 4.4% (2/45)
Alemanno et al., 2021	Longitudinal	87 (PCR)	67.23 ± 12.89	71% M	N/A	*N* = 31 severe *N* = 47 moderate (18 BPAP, 29 Venturi Mask) *N* = 9 mild	12.39 ± 6.51 [intubation; days] N/A N/A N/A	5–20 days	In person	I level	*Severe:* MMSE: 12.9% (4/31) MoCA: 72% (22/31) *Moderate (BPAP):* MMSE: 55.6% (10/18) MoCA: 94.4% (17/18) *Moderate (Venturi Mask):* MMSE: 48.3% (14/29) MoCA: 89.6% (26/29) *Mild*: MMSE: 44.4% (4/9) MoCA: 77.8% (7/9)
Almeria et al., 2020	Cross-sectional	35 (PCR)	47.6 ± 8.9	45.7% M	12.6 ± 4.6	Mixed	10.8 ± 9.2 [days]	10–35 days after hospital discharge	In person	II level	TAVEC: 2.9% (1/35) WMS-IV: no deficit Digit Forward: no deficit Digit Backwards: 8.6% (3/35) letter and numbers: no deficit TMT A: 2.9% (1/35) TMT B: 8.6% (3/35) SDMT: 5.7% (2/35) Stroop: 2.9% (1/35) Phonemic Fluency: 11.4% (14/35) Semantic Fluency: 5.7% (2/35) BNT: 2.9% (1/35)
Boesl et al., 2021	Cohort	100 (PCR or antibodies)	45 [20–79]	33% M	N/A	Mixed	N/A	184.5 [days]	In person	I level	MoCA: 30% (30/100)
Del Brutto et al., 2021	Longitudinal	52 (serology)	59.4 ± 10.6	38% M	N/A	Mild	N/A	N/A	In person	I level	MoCA: 21% (11/52)

(Continued)

TABLE 1 | (Continued)

References	Study type	*N* (diagnosis modality)	Age (year)	Sex% males	Education (years)	Disease severity	Disease duration	Time of assessment from onset	Assess-ment modality	Assess-ment level	Cognitive test: % of patients with deficit (n of patients with deficit/N)
Ferrucci et al., 2021	Cross-sectional	38 (not reported)	53.45 ± 12.64	71% M	12.39 ± 3.24	Moderate	9.84 ± 3.95 [days of hospitalization]	132.86 ± *36.62*	In person	II level	BRB-NT: 60.5% (23/38) SRT: 26.3% (10/38) SPART: 15.8% (6/38) SDMT: 42.1% (16/38) PASAT: 10.5% (4/38) WLG: 7.9% (3/38)
Heyns et al., 2021	Cross-sectional	135 of which 38 assessed cognitively (PCR)	72.0 [58.0–86.0]	49.6% M	N/A	*N* = 15 severe *N* = 23 moderate	>7 days of hospitalization	N/A	In person	I level	*Severe:* MoCA: 46.7% (7/15) *Moderate:* MoCA: 60.9% (14/23)
Lamontagne et al., 2021	cohort	100 of which 50 COVID-19 patients (PCR) and 50 HCs	*COVID*: 30.8 ± 7.79 *HC:* 29.14 ± 9.87	*COVID*: 42% M *HC:* 28% M	*COVID*: N/A *HC:* N/A	mixed	N/A	123.63 ± 94.71 [days post diagnosis]	Remote	II level	ANT:% N/A
Latronico et al., 2022	Longitudinal	114 (admission to ICU)	60 [52-66]	77% M	N/A	Severe	N/A	3, 6, and 12 months post discharge	In person	I level	*3 months post discharge* MoCA: 25% (25/98) *6 months post discharge* MoCA: 22% (17/77) *12 months post-discharge* MoCA: 13% (7/51)
Mazza et al., 2021	Longitudinal	130 cognitively assessed (PCR)	58.85 ± 12.8	66% M	12.58 ± 3.68	Mixed	N/A	90.1 ± 13.4 [days] after hospital discharge	In person	II level	BACS: 16% (21/130) deficit in at least one function 17% (22/130) deficit in at least 2 functions 14% (18/130) deficit in at least 3 functions 10% (14/130) deficit in at least 4 functions 5% (7/130) deficit in at least 5 functions Executive functions: 50% of impaired patients Psychomotor coordination: 57% of impaired patients
Mcloughlin et al., 2020	Longitudinal	71 (PCR)	61 [24–91]	72% M	N/A	Mixed	N/A	N/A	Remote	I level	TICS-m:% N/A

(Continued)

TABLE 1 | (Continued)

References	Study type	*N* (diagnosis modality)	Age (year)	Sex% males	Education (years)	Disease severity	Disease duration	Time of assessment from onset	Assess-ment modality	Assess-ment level	Cognitive test: % of patients with deficit (n of patients with deficit/N)
Miskowiak et al., 2021	Longitudinal	29 (PCR)	56.2 ± 10.6	59% M	14.3 ± 3.9	Moderate	N/A	3 months post hospital discharge	In person	II level	SCIP-D: 59–65% VLT-L:% N/A WMT:% N/A VFT:% N/A VLT-D:% N/A PMT:% N/A TMT-B:% N/A
Monti et al., 2021	Longitudinal	39 (PCR)	56 ± 10.5	89% M	N/A	Severe	23–44 days in hospital 7–16 days in ICU	51–71 days after ICU discharge	Remote	I level	Itel-MMSE: 2.6% (1/39)
Patel et al., 2021	Cohort	77 (not reported)	61.3 ± 15.67	36.4% M	N/A	Mixed	37.03 ± 31.8 [days]	N/A	In person	I level	MoCA: 80.5% (62/77)
Pilotto et al., 2021	longitudinal	126 (hospitalization)	64.8 ± 12.6	50% M	N/A	Mixed	11.6 ± 8.8	6 months after hospital discharge	In person	I level	MoCA: 17.5% (22/126)
Pistarini et al., 2021	Cross sectional	27 of which 20 COVID-19 positive and 7 post-COVID patients (nasal swab)	64.13 ± 15.85	37.5% M	11.15 ± 4.88	Severe	N/A	10 days after symptom onset N/A	In person	I level	*COVID-19 positive:* MMSE: 35% (7/20) *Post-COVID:* MMSE: 5% (1/7)
Solaro et al., 2021	Cohort	32 (nasal swab)	53.77 ± 4.81	59% M	N/A	moderate	16.54 ± 9.08 [days]	N/A	In person	I level	MoCA: 36.7% (13/32) Mean MoCA score: 20(8)
Soldati et al., 2021	Cross-sectional	23 (not reported)	53.6 ± 11.7	78% M	12.7 ± 3.5	Severe	12.3 ± 7 [days; ICU stay]	37–115 [days]	Remote	I level	TICS: 13% (3/23)
Zhou et al., 2020	Cross-sectional	29 (recovered from COVID-19)	47 ± 10.54	62% M	12.59 ± 2.78	Severe	N/A	N/A	Remote	II level	TMT: no deficit SCT: no deficit CPT:% N/A DST: no deficit

M, male; PCR, Polymerase Chain Reaction; RCD+, at risk for cognitive deficits; RCD–, not at risk for cognitive deficits; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; FAB, Frontal Assessment Battery; N/A, not available; itel-MMSE, Italian telephone version of MMSE; TICS, telephone interview for cognitive status; BPAP, Biphasic Positive Airway Pressure; SCIP-D, Screen for Cognitive Impairment in Psychiatry Danish Version; VTL-L: VLT-L, verbal learning test-learning; WMT, working memory test; VFT, verbal fluency test; VLT-D, verbal learning test-delayed recall; PMT, psychomotor speed test; TMT-B, Trail Making Test B; BRB-NT, Brief Repeatable Battery of Neuropsychological Tests; SRT, Selective Reminding Test; SPART, Spatial Recall Test; SDMT, Symbol Digit Modalities Test; PASAT, Paced Auditory Serial Addition Test; WLG, Word List Generation Test (WLG); TAVEC, Test de Aprendizaje Verbal Espa na-Complutense; WMS-IV, Wechsler Memory Scale –IV; BNT, Boston Naming Test; BACS, Brief Assessment of Cognition in Schizophrenia; SCT, Sign Coding Test; CPT, Continuous Performance Test; DST, Digital Span Test; TICS-m, Modified Telephone Interview for Cognitive Status.

(Monti et al., 2021). Scores on MMSE highlighted relatively low yet the variable prevalence of pathological scores—specifically 13% (4 out of 31, Alemanno et al., 2021) and 2.5% (1 out of 39, Monti et al., 2021). Pistarini et al. (2021) divided their sample into patients with acute COVID-19 and post-COVID, and found cognitive deficits in 35% (7 out of 20) and 5% (1 out of 7), respectively. It is worth noting that Alemanno et al. (2021) administered both MoCA and MMSE to the same patients, revealing different proportions of impairment when using the two tests.

The study, such as the TICS reported that only 3 out of 23 patients (13%) had pathological scores (Soldati et al., 2021).

Finally, in Zhou et al. (2020), patients with COVID-19 showed cognitive deficits in sustained attention, assessed with the CPT. When compared with healthy controls, patients with COVID-19 showed lower correct number and higher missing numbers on CPT 2 and CPT 3, error detection rate, and missed detection rate.

Neuropsychological Assessment in Moderate Patients

Studies with samples of *moderate* severity (N = 3) all performed in-person NPs assessments; one study used the first-level (MoCA, Solaro et al., 2021) and two studies used the second-level (Ferrucci et al., 2021; Miskowiak et al., 2021) tests. The two studies from mixed categories reported NPs outcomes separately for moderate samples (Alemanno et al., 2021; Heyns et al., 2021): their findings are therefore reported in this section. Both studies assessed cognition through in-person evaluation administering MoCA (Alemanno et al., 2021; Heyns et al., 2021) and MMSE (Alemanno et al., 2021).

Studies administering the MoCA test found pathological scores in 60% (14 out of 23, Heyns et al., 2021) and 36% (13 out of 32; Solaro et al., 2021) of patients. Alemanno et al. (2021) further subdivided moderate patients into those requiring Bilevel Positive Airways Pressure (BPAP) ventilation or Venturi mask; they found MoCA deficits in 94% of those with BPAP (17 out of 18), and in 89% of those requiring Venturi mask (26 out of 29). Using the MMSE in the same subpopulations, Alemanno et al. (2021) found deficits in 55% of those requiring BPAP and in 49% of patients requiring Venturi mask (10 out of 18 and 14 out of 29, respectively). Among studies using multi-domain screenings, one study (Ferrucci et al., 2021) administered in-person the Brief Repeatable Battery of Neuropsychological Test (BRB-NT; Amato et al., 2006); 60% of the sample (N = 38) was impaired in at least one subtest. The most frequently impaired cognitive domains were processing speed, visual/verbal short-term memory, long-term memory, and language (especially semantic verbal fluency). Finally, Miskowiak et al. (2021) administered the Screen for Cognitive Impairment in Psychiatry Danish Version (SCIP-D) (Purdon, 2005; Jensen et al., 2015) in the presence of a heterogeneous proportion of patients with deficits, depending on the cut-off considered (62% were globally impaired when considering a less conservative criterion, while 37% when considering a stricter cut-off). The most frequent impairments were in the domains of WM, verbal fluency, and psychomotor speed.

Neuropsychological Assessment in Mild Patients

The study investigating *mild* patients assessed cognition through in-person administration of MoCA (Del Brutto et al., 2021). Another study from mixed category assessed mild patients (in-person MoCA and MMSE) reporting NPs outcomes for each disease severity group separately (Alemanno et al., 2021); its findings are therefore reported in this section. MoCA pathological scores were found in 21% (11 out of 52, Del Brutto et al., 2021) and 77% (7 out of 9, Alemanno et al., 2021) of patients. The MMSE scores were pathological in 4 out of 9 patients (44%, Alemanno et al., 2021).

Neuropsychological Assessment in Mixed Patients

Finally, studies with *mixed* or unspecified severity samples (N = 10) assessed cognition both in-person (N = 8) and remotely (N = 2). The first-level assessment was performed in 7 out of 10 studies, with MoCA being the most commonly administered test, followed by MMSE and TICS.

The results of two of the studies categorized as mixed (Alemanno et al., 2021; Heyns et al., 2021) are reported here as they reported results separately for disease severity that have been included in the previous sections of this manuscript.

Aiello et al. (2022) administered both MoCA test and the MMSE in-person, dividing patients with COVID-19 in two groups: being those at risk of developing cognitive deficit or not at risk of developing cognitive deficit (RCD + and RCD–). The authors found pathological scores on MoCA in 23% (RCD+, 13 out of 55) and 4% (RCD–, 2 out of 45) of patients. Whereas, MMSE scores were found to be pathological in 20% (RCD+, 11 out of 55) and 2% (RCD–, 1 out of 45) of the sample. Studies administering MoCA test in-person on mixed populations found pathological scores in 80% (62 out of 77, Patel et al., 2021), 30% (30 out of 100, Boesl et al., 2021), and, finally, 17% (22 out of 126, Pilotto et al., 2021) of patients. One study (Mcloughlin et al., 2020) investigated cognition through a modified-version of TICS administered from remote; here, the authors compared the cognitive profiles of COVID-19 patients with and without delirium: mean cognitive scores were similar among the two groups, but exact percentages were not reported by the authors.

Regarding studies with second-level assessment in mixed samples, Almeria et al. (2020) conducted a thorough in-person NPs evaluation. The authors found 12 out of 35 (34%) patients showing cognitive impairments. Specifically, those with mild neurological symptoms (e.g., anosmia or headache) had lower scores on WM tests; patients that needed oxygen therapy had lower scores on verbal and visual memory, attention, WM, processing speed, and EFs. Finally, patients that stayed in the ICU showed lower scores only on EFs. Mazza et al. (2021) administered the Brief Assessment Cognition Schizophrenia (BACS; Keefe et al., 2004) to 130 patients, showing that 16% had pathological scores on at least one function, 17% in two, 14% in three, 11% in four, 5% in five, and 1.5% showing pathological scores in each domain. Finally, Lamontagne et al. (2021) evaluated 50 healthy controls and 50 patients with COVID-19, who were classified into patients with acute COVID-19, Post-Acute Sequelae of COVID-19 (PASC), and post-PASC. After remotely administering the Attention Network Test (ANT;

Fan et al., 2002), which evaluates the attentional networks of alerting, orienting, and executive control by means of reaction times, researchers reported a selective impairment only on executive functioning in the PASC phase.

DISCUSSION

The goal of this review is to provide clinicians with an overview of first- and second-level NPs tests that have been used *de visu* and remotely to assess cognition among patients with COVID-19.

Results from included studies corroborate that cognitive dysfunction is a common feature among patients with SARS-CoV-2. Although the cognitive sequelae of SARS-CoV-2 infection seem consistently captured by both global examinations and domain-specific assessments, vastly different degrees of impairment were found, depending on first- *vs.* second-level tests, modality of administration (i.e., in person *vs.* remote), and disease severity.

The cognitive domains found to be most frequently impaired were EFs, attention, and memory, as assessed both by first- (e.g., Alemanno et al., 2021) and second-level (Ferrucci et al., 2021; Miskowiak et al., 2021) tests.

Regarding first-level tests, studies administering the MoCA found a remarkably higher proportion of pathological scores among moderate patients (Alemanno et al., 2021; Heyns et al., 2021) when compared with severe patients (Alemanno et al., 2021; Heyns et al., 2021). Similarly, studies using the MMSE in severe patients found a relatively low prevalence of pathological scores (Alemanno et al., 2021; Monti et al., 2021), whereas these were much higher in moderate and mild patients (Alemanno et al., 2021). In particular, the prevalence of impairment was consistently lower when assessed through MMSE as compared with MoCA (mild: 4 patients/9 MMSE vs. 7/9 MoCA; moderate: 14/29 MMSE vs. 26/29 MoCA; and severe: 4/31 MMSE vs. 22/31 MoCA; Alemanno et al., 2021). With regards to the lower proportion of cognitive deficits in severe *vs.* moderate patients, it is possible that patients presenting with severe symptomatology (e.g., requiring invasive ventilation), or more aggressive treatments (e.g., intubation) experienced less extensive hypoxic damage to the brain, which is instead typically associated with moderate-to-severe COVID-19 presentations (Alemanno et al., 2021). By contrast, moderate patients might have suffered from hypoxic states for prolonged time, thus showing more severe neurocognitive sequelae (Sasannejad et al., 2019). Furthermore, studies assessing severe patients with COVID-19 may have suffered from a selection bias in that patients with more critical health conditions may have been excluded from the data collection process because the NPs evaluation was not feasible. This may also explain why a lower proportion of cognitive deficits was found among severe patients with COVID-19. Taken together, albeit very preliminary in nature, these findings are in line with previous literature, suggesting that, across patients with COVID-19, MoCA may have higher sensitivity in detecting mild cognitive deficits (Pinto et al., 2019), whereas the MMSE could be more useful for patients who present with severe impairments (Tsoi et al., 2015). With respect to the TICS—administered remotely to either severe (Soldati et al., 2021) or mixed (Mcloughlin et al., 2020) patients, a relatively low prevalence of impaired performance was found, preliminarily suggesting that this test has limited usefulness in this population.

It is worth noting that the proportion of pathological scores within the *mild* category is highly variable among the two studies here included (Alemanno et al., 2021; Del Brutto et al., 2021). The one that reported remarkably high proportions of deficits (Alemanno et al., 2021) has two issues that limit the generalizability of findings: first, the sample size was small ($N = 9$); second, the majority of patients included and assessed were older adults aged 75 years and above (62.56 ± 20.06; mean age and standard deviation [SD]). Therefore, the higher rate of cognitive impairment could be linked to age-related risk factors rather than to the disease itself. This hypothesis seems corroborated by the fact that Del Brutto et al. (2021), who assessed 52 participants aged 59.4 ± 10.6 years, only found 21% of the sample being impaired on MoCA. Taken together, these findings suggest that more sensitive and reliable tests are likely needed to assess cognitive impairments in mild patients.

With regards to the second-level assessment, three studies focus on clinical populations examined with mixed illness severity (Almeria et al., 2020; Lamontagne et al., 2021; Mazza et al., 2021), two studies focused on patients with moderate illness severity (Ferrucci et al., 2021; Miskowiak et al., 2021), and only one was conducted on severely ill patients (Zhou et al., 2020). The included studies mostly evaluated attention and/or EFs using different tests, thus not allowing for direct comparisons. Nonetheless, the following tests were frequently used: Trail Making Test A and B (TMT-A/B; Zhou et al., 2020; Almeria et al., 2020; Miskowiak et al., 2021), Symbol Digit Modality Test (SDMT; Almeria et al., 2020; Ferrucci et al., 2021), Continuous Performance Test (CPT; Zhou et al., 2020), Paced Auditory Serial Addition Task (PASAT; Ferrucci et al., 2021); Digit Forward and Backward, Fluency tests, and Stroop test (Almeria et al., 2020). However, once again, patients with moderate illness severity showed a higher prevalence of cognitive impairment (Ferrucci et al., 2021; Miskowiak et al., 2021) when compared to those with mixed-severity (Almeria et al., 2020; Zhou et al., 2020). Accordingly, Almeria et al. (2020) found that patients requiring O_2 therapy, but not ICU admission, showed impairment in several cognitive domains (e.g., memory, attention, and EFs) whereas patients who needed to be intubated only showed deficits on EFs.

Drawing definitive conclusions about *mixed* samples is complicated by the fact that patients showed symptoms ranging from mild to severe. Since different illness severities are associated with different cognitive profiles, it remains challenging to disentangle the effect of illness severity on the overall proportion of pathological scores.

Similarly, the lack of studies investigating II-level cognitive deficits in mild populations does not allow us to infer which type of test is more appropriate to characterize the cognitive profile of patients with mild COVID-19 symptoms. Arguably, if such patients present with subtle alterations, domain-specific tests, rather than global screeners, may be more useful in this context.

Some considerations are necessary when discussing the modality of assessment (in-person *vs.* remote). First, studies assessing patients with COVID-19 remotely either used telephone-based tools (Monti et al., 2021; Soldati et al., 2021) or an iPad-based assessment (Zhou et al., 2020). In one of these studies where MMSE was administered remotely to patients with severe COVID-19 (Monti et al., 2021), the proportion of patients found to be impaired was lower when compared with a study where the same test was administered in-person to patients with severe COVID-19 (Alemanno et al., 2021). This raises the possibility that remote NPs assessment may underestimate the actual prevalence of cognitive deficits among patients with COVID-19, especially when a global screener is used.

The studies hereby reviewed present several methodological limitations, the main one being the inconsistency of disease severity classifications across studies. A clearer consensus categorization is needed to be able to compare results across studies. Additionally, several studies did not include relevant demographic characteristics of patients enrolled (e.g., years of education, medical comorbidities, or disease duration). This hampers a proper interpretation of results and makes comparison between study populations fraught with problems. Finally, most studies were significantly underpowered, including less than 30 participants ($N = 4$).

CONCLUSION

Our review of the literature highlights the following points: (i) The MoCA may be able to catch subtle cognitive alterations, at least on patients with moderate COVID-19, whereas the MMSE is more indicated for severe cognitive deficits; (ii) although several second-level NPs assessments have consistently indicated the presence of attentive and executive deficits, the limited amount of available evidence does not allow to draw specific conclusions, and research is needed to deeply characterize cognitive deficits following COVID-19 infection; and (iii) in-person NPs evaluation seems to be the best choice to investigate cognitive deficits in this population.

Despite the low methodological rigor of this nascent field of research, the early identification and characterization of cognitive consequences following COVID-19, across all degrees of disease severity, remains of paramount importance. While the older population is certainly that with the greatest vulnerability to cognitive decline, the possible downstream cognitive consequences of COVID-19 infection in younger, mild, or asymptomatic cases are emerging (Ortelli et al., 2022). Based on our review, we recommend the implementation of both baseline and follow-up NPs screenings that are consistent with disease severity classification.

Finally, because cognition actively impacts an individual's capacity to work effectively, drive, manage finances, participate in daily family activities or make informed decisions, specific prevention and intervention programs that remediate cognitive deficits will be an important next step to achieve independent functioning and improved quality of life among many patients who endured COVID-19.

AUTHOR CONTRIBUTIONS

AD, BB, AN, IL, and PB: conceptualization. AD, BB, AN, IL, LN, and GF: investigation. BB, AN, IL, and LN: methodology. AD, BB, AN, and IL: writing – original draft. AD, AN, IL, LN, and GF: formal analysis. AD, BB, AN, IL, EZ, NS, and PB: writing – review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.909661/full#supplementary-material

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Natural, longitudinal recovery of adults with COVID-19 using standardized rehabilitation measures

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Background: While studies recommend rehabilitation following post-hospitalization recovery from COVID-19, few implement standardized tools to assess continued needs. The aim of this study was to identify post-hospitalization recommendations using an interdisciplinary needs assessment with standardized rehabilitation measures. A secondary aim was to use these tools to measure recovery over a 30-day period.

Materials and methods: Using a 30-day longitudinal design, we completed weekly rapid needs assessments in this convenience sample of 20 people diagnosed with COVID-19 discharged from the hospital to home. We computed summary statistics and used the Wilcoxon Signed Rank Test to assess change over the 4-week course of the study with alpha level = 0.05.

Results: Our sample (65% male, 47% over 50 years of age, 35% White, 37% with a confirmed diagnosis of diabetes, and 47% obese) included no patients who had required mechanical ventilation. Initial assessments demonstrated the majority of our participants were at an increased risk of falls, had disability in activities of daily living (ADL) and instrumental activities of daily living (IADL), mild cognitive impairment, and dyspnea. At the 30-day follow-up, most were independent in mobility and basic ADLs, with continued disability in IADLs and cognitive function.

Discussion: In this sample of patients who were not mechanically-ventilated, early and individualized rehabilitation was necessary. The results of this study suggest patients would benefit from a multi-disciplinary team needs assessment after medical stabilization to minimize fall risk and disability, and to prevent secondary complications resulting from post-hospital deconditioning due to COVID-19.

KEYWORDS

COVID-19, rehabilitation, multi-disciplinary, function, cognition, mobility

Introduction

As more people contract and recover from the Corona virus, knowledge of acute, post-acute and long-term physiological, physical, cognitive, and psychological sequelae evolve (Huang et al., 2021). Studies have reported people with COVID-19 who require hospitalization demonstrate long-term fatigue, cognitive difficulty, dyspnea, taste and smell impairments, muscle weakness, and poor cardiovascular endurance (Huang et al., 2021; Lopez-Leon et al., 2021; Wu et al., 2021; Zhang et al., 2021). Post-hospitalization, patients also commonly report anxiety, depression, post-traumatic stress disorder, and ICU-related neuropathy (Carenzo et al., 2021; Heesakkers et al., 2022). The majority of patients recovering from COVID-19 demonstrate impairments that hinder or restrict participation in activities of daily living (ADL), instrumental activities of daily living (IADL), the ability to live independently, return to work, and resume previous levels of social activity. Studies suggest early rehabilitation is associated with shorter recovery times and faster return to everyday activities (Choi et al., 2008; Coleman et al., 2017).

While studies recommend rehabilitation during the acute and post-acute phases of recovery (Demeco et al., 2020; Gutenbrunner et al., 2020; Sivan et al., 2020), little is known about the *depth* of rehabilitation needs because researchers have not utilized standardized assessment tools. Current studies examine patients 6–12 months post COVID-19 using screening tools too broad to provide detailed information about patients living in their home environment (Huang et al., 2021; Wu et al., 2021; Xiong et al., 2021; Zhang et al., 2021; Heesakkers et al., 2022). While longitudinal studies of sequelae offer critical information, a profile of the natural recovery during the early period after hospitalization is critical to improve recommendations for rehabilitation. The primary aim of this study was to identify post-hospitalization needs and services required for those diagnosed with COVID-19 using an interdisciplinary needs assessment with standardized rehabilitation tools. The secondary aim of this study was to report the natural course of recovery for people hospitalized with COVID-19 over a 30-day period using these standardized rehabilitation assessments.

Materials and methods

We employed a modified, rehabilitation-oriented, rapid needs assessment using a longitudinal design to assess people who were discharged from hospital to home with a diagnosis of COVID-19 between April and December 2020. While a traditional needs assessment involves a reiterative process in which participants communicate needs to the researcher, in a *rapid needs assessment*, the timing for understanding health care needs is critical, thus the team begins with hypothetical, but informed areas of evaluation (Lee, 2019).

The team completed baseline measurements within 5°days of hospital discharge. We then assessed patients weekly over a 30-day period post-hospitalization using a battery of standardized tools utilizing nursing, occupational therapy, physical therapy, and social work utilizing cellular telephones, FaceTime, or Zoom platforms. Inclusion criteria included people at least 18 years of age, English speaking, diagnosed with COVID-19, hospitalized and subsequently discharged home, able to consent with or without caregiver assistance, and with internet access. Exclusion criteria included individuals who were discharged or met the criteria for hospice, demonstrated current drug or alcohol dependency, or who were pregnant. This study was approved by the Institutional Review Board of The University of Oklahoma Health Sciences Center (IRB#11988).

Patient recruitment

During the course of this study, the IRB required research to be conducted virtually due to COVID-19 restrictions. We recruited participants from a convenience sample of patients admitted to a Level I Trauma Hospital on an academic health sciences center campus. We consented and provided participants a COVID Assessment Kit either personally prior to hospital discharge, or a combination phone call and front door drop-off. We utilized the "Evaluation for Consent" tool because people with COVID-19 are more likely to demonstrate cognitive impairment (Resnick et al., 2019; Sasannejad et al., 2019).

Data collection

Advanced practice registered nursing staff (APRN), occupational therapists (OT)s, physical therapists (PT)s, and social work staff (SW) completed virtual interviews and physiological, physical, functional, cognitive, and mental health assessments. All study personnel utilized the secure Research Electronic Data Capture (REDCap) system to enter data.

Baseline assessments utilized:

Evaluation to sign consent

Either APRN or SW staff determined each participant's cognitive eligibility to consent using procedures described by Resnick et al. (2019).

Sociodemographic information/medical history

Advanced practice registered nursing staff staff obtained sociodemographic, medical, and mental health history using the hospital chart and interview.

Charlson co-morbidity index

This assessment characterizes patient comorbidities based on the International Classification of Function. Each co-morbidity has an associated weight from 1 to 6 based on the adjusted risk of mortality or resource use. The sum of all weights results in a single comorbidity score where "0" indicates no comorbidities. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use (Charlson et al., 1987).

Weekly standardized outcome tools

Physiological measures

Multi-dimensional dyspnea profile

The MDP assesses dyspnea intensity, sensory quality, unpleasantness, and affective distress using 12 items rated on a 0–10 numerical scale. The reliability, validity, and responsiveness to clinical change of the MDP in use for both acute and follow-up care is well-established (Meek et al., 2012; Banzett et al., 2015).

Physical performance measures

SQUEGG hand strength test

The SQUEGG hand grip dynamometer measures grip strength up to 220°pounds using a smartphone application usable in the home environment. Traditional hand grip dynamometers have excellent reliability and validity (Mathiowetz, 2002).

Five times sit to stand test

The 5xSTS assesses strength, transitional movements, balance, and fall risk by documenting time required for a person to come to a complete stand from a sitting position five times. The 5xSTS has good reliability and validity (Schaubert and Bohannon, 2005; Bohannon, 2006; Tiedemann et al., 2008).

Timed up and go with manual and cognitive versions

The TUG comprises three separate tests to assess fall risk; under normal situations, with added physical stress (manual) and with divided attention (cognitive). Examiners assess the time it takes for a person to rise from a seated position, walk three meters, turn around, and return to sitting (normal), while carrying a glass 3/4 full of water (manual), and while counting backward by 3 or 4 from 100 (cognitive). TUG scores are predictive of fall risk with an 87% success rate, and have excellent reliability (Shumway-Cook et al., 2000; Hofheinz and Schusterschitz, 2010).

Borg rating of perceived exertion

The Borg RPE provides an estimate of heart rate during physical activity based on a rating scale ranging from 6 to 20 (Borg, 1982). Researchers have reported a high correlation between perceived exertion rating multiplied by 10, and the actual heart rate during physical activity (Borg, 1982; Marissa et al., 2008; Tabacof et al., 2022).

Functional performance measures

Barthel index

The Barthel index uses an ordinal scale to measure and monitor change in activities of daily living (**Table 3**), with scores based on current ability (de Morton et al., 2008; Della Pietra et al., 2011). The Barthel index delivered by phone has excellent inter-relater reliability (Kappa = 0.90 with 985% CI, 0.85–0.94).

Lawton instrumental activities of daily living scale

The Lawton IADL Scale uses an interview format to assess independent living skills like phone use, shopping, food preparation, medications, finance, housekeeping, and laundry (Lawton and Brody, 1969). We modified scoring for more differentiation between participants using scores of 0 (dependent), 1 (partial assistance), and 2 (independent). The maximum score of 16 indicates self-reported independence. The tool demonstrates very high internal consistency and inter-rater reliability (Siriwardhana et al., 2018).

Cognitive and psychological screening measures

Montreal cognitive assessment-5 minute protocol

The MoCA is a short cognitive screen predictive of mild cognitive impairment by assessing language, orientation, and memory using three items totaling a possible 15 points. The MoCA has good reliability and validity in differentiating cognitively impaired patients with executive domain impairment from those without and has excellent 30-day test-retest reliability (Pendlebury et al., 2013).

Patient health questionnaire-9

The PHQ-9 is a measure of depression using scores on nine items ranging from 0 (not occurring at all) to 3 (occurring nearly every day) for the "last 2°weeks" (Maurer, 2012). The PHQ-9 can be used to make a tentative diagnosis of depression in at-risk populations. When used as a screen for depression, the PHQ-9 has fair sensitivity and very good specificity (Maurer, 2012).

Generalized anxiety disorder-7

The GAD-7 is a measure of generalized anxiety with its potential causes using a seven-item scale with scores ranging from 0 (not occurring at all) to 3 (occurring nearly every day). Modeled after the PHQ9, it is quick (2–5 min) and effective when used within a primary health care setting, and can be self-administered or completed by interview, either electronically or in person (Roy-Byrne et al., 2009).

Procedures

The research team attended 8°h of study protocol training and received online written protocols for future reference. Training included strict study protocol adherence, standardizing assessments, assessing, and referral for patients experiencing medical deterioration, and documentation using the secure REDCap data collection system.

The COVID Home Care Kit contained an electronic scale, blood pressure cuff, mobile oxygen saturation monitor, SQUEEG hand strength dynamometer, and a 3-meter measuring tape. After receiving the kit, research personnel contacted participants to set up FaceTime, Zoom, and biomedical assessment tool technology. Personnel delivered the baseline assessments within 5°days of hospital discharge, and spread baseline assessments over 72 h to relieve patient and caregiver burden. Because anxiety is associated with COVID-19 (Heesakkers et al., 2022), our protocol included additional 5-min phone check-ins by nursing to assess physiological measures and recommend primary care physician follow-up if needed. Nursing staff tapered the frequency of these phone calls over 4°weeks calling 7°days during Week 1, 3°days during Week 2, 2°days during Week 3, and 1°day during Week 4. Disciplines communicated regularly about the time of scheduled visits to minimize risk of fatigue caused by multiple calls and assessments during the 30-day period. We asked participants at risk for falls, with significant ADL/IADL dependence, or with immediate health concerns to call his or her primary care physician for an appointment or referral for home health services.

Data analysis

Upon completion of the study, one researcher downloaded and analyzed all data using a combination of Microsoft Excel and SAS 9.4 (Carey, NJ, United States). Personnel computed summary statistics including means and 95% CI for all continuous variables, along with percentages for each categorical variable. To analyze change over the 4-week course of the study in each continuous variable, we utilized the Wilcoxon Signed Rank test with an alpha level equal to 0.05.

Results

Sample description

We enrolled the first 20 patients diagnosed with COVID-19 who consented upon discharge from a Level 1 Trauma Hospital on our academic campus. One patient dropped out immediately after enrolling, making our resulting sample size 19. Several patients failed to complete portions of the assessments, or did not participate after 1 or 2°weeks. Two thirds of participants self-identified as male and almost half were over 50 years of age. One third (35%) self-identified as Caucasian, with an additional 10% White-Hispanic. Although 85% had a BMI classification of overweight or obese (overweight = 16%, obesity type I = 32%, obesity type II = 26%, and obesity type III = 11%), two thirds responded their general health prior to COVID-19 was good, very good, or excellent (64%). Education ranged from high school or GED level through college graduate level. More than half of respondents reported living alone (**Table 1**).

Only 16% of our participants reported being every day or someday smokers and none used vaping devices. While 7% reported previous diagnoses of anxiety or depression, none reported thoughts of suicide, either currently, or in the past. The mean Charlson Comorbidity Index score was 3 out of a maximum score of 37, representing a low risk of either mortality or high levels of resource use. While nearly three quarters (74%) revealed their chief complaint requiring hospitalization was shortness of breath, no one in this cohort required full ventilation and only 16% required bi-level positive airway pressure (Bi-PAP) assistance with breathing. Almost half (47%) of the participants in this study were hospitalized 6–10 days. Only 16% of participants in the study received inpatient physical or occupational therapy, and none had a referral for outpatient or home health therapy services (**Table 1**).

Physiological measures

The mean Week 1 Multidimensional Dyspnea Profile score was 64 (M = 64.3, 95% CI: 44.3–84.3), which dropped significantly to 13 (M = 13.2, 95% CI: −7.2 to −33.6) by week 4 (p = 0.0059). Heart rate also decreased significantly from 94.9 at Week 1 to 91.0 at Week 4 (p = 0.01). Other vital signs, including blood pressure, oxygen saturation levels, and weight remained stable over the 4°weeks following discharge (**Table 1**). Percentage of participants reporting fatigue dropped from 75% at Week 1, to 31% at Week 4 (p = 0.0031).

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TABLE 1 Socio-demographic, patient chart data (n = 20), and data gathered by nursing staff over time reported at weeks 1 and 4 (mean values with 95% CI) (n = 15).

Gender (n = 17, two missing–preferred not to answer)	
Female	35.3%
Male	64.7%
Age (n = 19)	
0–39	31.6%
40–49	21.1%
50–59	26.3%
60–69	15.8%
80+	5.3%
Race/ethnicity (n = 18, one missing, preferred not to answer)	
Caucasian	50.0%
Hispanic (white)	2%
Asian	11.1%
Mixed	11.1%
BMI classification (n = 19)	
Underweight	10.5%
Normal weight	5.3%
Overweight	15.8%
Obese (I)	26.3%
Obese (II)	10.5%
Obese (III)	10.5%
Education (n = 19)	
HS degree or GED	26.3%%
Some college	21.1%
College degree	21.1%
Preferred not to answer	31.6%
Self-reported health status prior to COVID-19 (n = 15, four preferred not to answer)	
Excellent	7.1%
Very good	35.7%
Good	21.4%
Fair	35.7%
Chief complaint requiring hospitalization: (n = 19)	
Fatigue	5.26%
Fever	10.5%
Shortness of breath	73.7%
Other	10.5%
Number of days hospitalized (n = 19)	
0–5 days	21.1%
6–10 days	47.4%
11–15 days	15.8%
16–20 days	5.3%
Number of days requiring full ventilation (n = 19)	
None	100%
Number of days requiring bi-level positive airway pressure (BiPAP) assistance with breathing (n = 19)	
None	84.2%
Eight days	5.3%
Nine days	10.5%

(Continued)

TABLE 1 (Continued)

Percentage of patients requiring supplemental oxygen at discharge (*n* = 16, missing three)	
No	62.5%
Yes	37.5%
Smoking status (*n* = 19)	
Every day smoker	5.3%
Some day smoker	10.5%
Never smoked	47.4%
Prefers not to answer	31.6%
Vaping status (*n* = 19)	
Not currently using	100%
Self-reported previous diagnosis of anxiety or depression (*n* = 19)	
Yes	7.1%
No	21.4%
Unsure	71.4%
Self-reported previous thoughts of suicide (*n* = 19)	
No	100%
Self-reported current thoughts of suicide (*n* = 19)	
No	100%
Referral to physical or occupational services during hospitalization (*n* = 19)	
Yes	15.8%
No	84.2%

Nursing assessments	Week one	Week four	*P-value**
Multidimensional dyspnea profile MDP)	64.3 (44.3, 84.3)	13.2 (−7.2, 33.6)	**0.0059**
Weight	211.0 (177.7, 244.2)	205.0 (159.0, 250.9)	0.3750
Heart rate	94.9 (84.7, 105.0)	91.0 (79.9, 102.1)	0.01221
Systolic blood pressure (BP)	124.7 (114.4, 135.0)	127.6 (115.5, 139.6)	0.02563
Diastolic blood pressure (BP)	78.3 (72.3, 84.4)	79.8 (72.0, 87.5)	0.9302
Oxygen saturation levels	93.7 (92.4, 95.1)	94.2 (92.9, 95.4)	0.2773

*Wilcoxon signed rank test.

Physical performance measures

The five times sit to stand test improved during the 4-week study from a mean 17.5 s to a mean 12.6 s (p = 0.0009). Participants did not fall below the cut-off time suggestive of further assessment for fall risk (12 s), during the course of the study. Timed Up and Go (TUG) scores improved during the 4-week study from a mean 15.1 s during Week 1, to a mean 12.1 s during Week 4 (p = 0.0419). Participants fell below the cut-off value suggestive of fall risk (13.5 s) after week two, meaning their fall risk was within an acceptable range. Both the Dual Task TUG (TUG-DT) and the Cognitive TUG (TUG-COG) also improved with mean values of 14.3 s and 20.5°s respectively during Week 1, to 12.1 s and 13.7 s during Week 4. These versions of the TUG represent a participant's ability to engage cognitively or physically while executing complex motor tasks and acceptable fall risk levels are 14.5 and 15 s, respectively (Table 2).

BORG Perceived Rate of Exertion scores dropped dramatically during each of these physical exertion tests with highs of 10.7/20 during the 5xSTS test during Week 1 to 8.4/20 during the TUG-COG during Week 4. Final RPE scores for all these tasks fall within either the fairly light or very light ranges and are acceptable for physical tasks like those represented by the 5xSTS and the TUG (Table 2). Hand grip during the study changed from a mean 65 pounds in the dominant hand during week one, to a mean 78.2 pounds with the dominant hand during week four (p = 0.0020) (Table 2).

Functional performance measures

Barthel ADL Index scores indicated all participants were independent in bowel continence, bladder continence, and toilet use upon discharge from the hospital. Barthel scores for bathing, dressing, hygiene (grooming), and transfers all approached or scored independence by the end of 4°weeks. Participants significantly improved in ambulation independence, beginning with a mean score of 9.0 points and ending with a mean score of 13.0 points (p = 0.0156). The ability to climb stairs was low at Week 1 with a mean of score of 5.4, and remained low at Week

TABLE 2 Physical therapy data.

	Week one	Week two	Week three	Week four	*P-value**
Five times sit to stand (STS)					
Five times sit to stand (sec)	17.5 (15.1, 19.9)	8.3 (6.6, 9.9)	13.1 (11.2, 14.9)	12.6 (10.9, 14.3)	**0.0009**
Borg for 5xSTS	10.7 (8.5, 12.8)	9.2 (7.2, 11.2)	7.8 (6.5, 9.2)	8.3 (6.0, 10.5)	**0.0146**
Timed up and go (TUG)					
TUG (sec)	15.1 (11.5, 18.6)	13.5 (9.9, 17.1)	11.6 (8.6, 14.7)	12.1 (8.9, 15.3)	**0.0419**
Borg for TUG	9.2 (8.0, 11.8	8.5 (6.7, 10.3)	7.5 (6.5, 8.4)	8.0 (5.9, 10.1)	0.1289
Manual TUG	14.3 (11.7, 16.9)	13.6 (10.5, 16.7)	12.3 (9.7, 15.0)	12.1 (9.4, 14.7)	0.0563
Borg for manual TUG	9.9 (8.0, 11.8)	8.6 (6.8, 10.5)	7.5 (6.6, 8.4)	8.3 (6.1, 10.6)	0.0508
Cognitive TUG	20.5 (13.8, 27.3)	17.1 (12.2, 22.1)	14.8 (10.8, 18.8)	13.7 (10.9, 16.6)	**0.0369**
Borg for cognitive TUG	9.4 (7.5, 11.4)	8.9 (6.8, 10.9)	7.8 (6.7, 9.0)	8.4 (6.2, 10.6)	0.0581
Squegg (hand grip strength)	65.0 (41.0, 88.9)	74.3 (50.5, 98.2)	77.3 (48.6, 106.0)	78.2 (56.5, 100.0)	**0.0020**

Mean values (with 95% CI) for the Five Times Sit to Stand test (5xSTS) in seconds, the Timed up and Go test (TUG) in seconds, and the Squegg hand grip strength test in pounds, and associated Borg rating of perceived exertion (RPE) using the 6–20 range scale during 4°weekly time points (n = 14). **P-value* represents the difference in test values between week 1 and week 4, calculated by the Wilcoxon signed rank test. Bold values represent significance at the alpha = 0.05 level.

4 with a mean score of 6.1 points. BORG Rating of Perceived Exertion scores demonstrated significant decreases in bathing, with a mean change from 10.3 to 7.8 points (p = 0.0156), in dressing with a mean change from 8.9 to 7.8 points (p = 0.0313), in bed and chair transfers with a mean change from 8.5 to 6.3 points (p = 0.0313), and in ambulation with a mean change from 12.5 to 9.2 points (p = 0.0195) Perceived exertion remained high for climbing stairs (Table 3).

Lawton IADL scores revealed participants were independent in their ability to use the phone at Week 1. In more physically and mentally complex tasks, while participants improved significantly in their ability to shop (mean change from 0.9 to 1.4, p = 0.0125), prepare food (mean change from 1.4 to 1.8, p = 0.0125), and do housekeeping (mean change from 1.0 to 1.6, p = 0.0313), scores did not indicate independence. While many Borg RPE scores for IADLs changed during the 4°weeks after discharge from the hospital, the changes were not significant (Table 3).

Cognitive and psychological screening measures

The mean 5-min Montreal Cognitive Assessment test score in Week 1 was 11.7 points, indicating mild cognitive impairment. While this score improved to 13.3 points at Week 4, the difference was not significant (p = 0.10). Several participants demonstrated significant cognitive impairment that did not change or even declined during the course of the study (Table 3).

The mean GAD-7 total score during Week 1 was 5.9 points, which remained relatively consistent over the 4°weeks of the study ending with a mean during Week 4 of 4.5 points (p = 0.34). No individual variables of the GAD-7 changed significantly over time. The mean PHQ-9 score in Week 1 was 8.9 points, which reduced to a mean of 5.5 points in Week 4 (p = 0.10). No individual portions of the PHQ-9 changed significantly over time (Table 4).

Discussion

The primary aim of this study was to identify post-hospitalization needs and services that would allow patients diagnosed with COVID-19 to be as safe and independent as possible in their home settings using an interdisciplinary rapid needs assessment. In our sample of patients, discharge planning did not appear to include functional level or prognosis. Chart reviews revealed that 80% of our participants had not received any type of rehabilitation therapy and, when asked, were uncertain about how to progress their activity levels, or how to balance movement with rest. One partial explanation may be that training by professionals might have been poorly retained due to cognitive deficits, which were prevalent in week one. Further, we found significant impairments in physiologic, physical, functional, and cognitive performance which indicated the need for referral for a multi-disciplinary assessment and rehabilitation. These findings suggest a thorough assessment by nursing, occupational therapy, physical therapy, and social work staff could assist in clarifying post-discharge needs for patients transitioning to home after hospitalization for COVID-19.

The secondary aim of this study was to report the natural course of COVID-19 recovery over a 30-day period using standardized assessment tools. We found that while many measurements returned to normal or near normal over time, patients demonstrated increases in fall risk and loss of independence during their first few weeks at home, and required assistance with basic self-care. Caregivers were also impacted as they were unable to work unless they left impaired patients at home alone during initial recovery. Participants in our study

TABLE 3 Occupational therapy data.

	Week one	Week two	Week three	Week four	*P-value**
Barthel scale [maximum possible points for each category is in ()]For all Borg scale scores, 6 = minimal exertion					
Feeding (10)	10.0**	10.0**	10.0**	10.0**	***
Borg for feeding	7.1 (5.7, 8.4)	6.5 (5.8, 7.2)	6.2 (5.9, 6.4)	6.3 (5.8, 6.8)	0.1250
Bathing (5)	4.0 (2.9, 5.1)	4.2 (2.9, 5.4)	4.6 (3.7, 5.5)	4.5 (3.4, 5.6)	0.5000
Borg for bathing	10.3 (7.9, 12.7)	8.8 (6.0, 11.5)	7.6 (5.6, 9.5)	7.8 (5.3, 10.3)	**0.0156**
Personal hygiene (grooming) (5)	4.7 (4.0, 5.4)	5.0**	4.6 (3.7, 5.5)	5.0**	1.0000
Borg for hygiene (grooming)	8.9 (7.0, 10.9)	7.5 (5.7, 9.3)	7.3 (5.2, 9.3)	7.2 (4.7, 9.7)	0.0625
Dressing (10)	9.0 (7.9, 10.1)	9.6 (8.7, 10.5)	9.6 (8.7, 10.5)	10.0**	0.25
Borg for dressing	8.9 (6.8, 10.9)	8.4 (6.5, 10.4)	8.2 (6.4, 10.0)	7.8 (5.8, 9.8)	**0.0313**
Bowel control (10)	10.0**	10.0**	10.0**	10.0**	***
Borg for bowel control	7.1 (5.6, 8.5)	6.3 (5.6, 7.1)	6.3 (5.6, 7.1)	6.7 (5.6, 7.8)	0.7500
Bladder control (10)	10.0**	10.0**	10.0**	10.0**	***
Borg for bladder control	6.5 (5.7, 7.2)	6.0**	6.0**	6.3 (5.6, 7.0)	1.0000
Toilet transfers (10)	10.0**	9.6 (8.7, 10.5)	9.6 (8.7, 10.5)	10.0**	***
Borg for toilet transfers	8.0 (6.4, 9.6)	7.3 (5.7, 8.8)	6.1 (5.9, 6.3)	6.1 (5.9, 6.3)	0.0625
Chair/bed transfers (20)	14.3 (13.4, 15.3)	15.0**	14.6 (13.7, 15.5)	15.0**	0.5000
Borg for chair/bed transfers	8.5 (6.8, 10.2)	7.8 (6.3, 9.2)	7.1 (6.1, 8.1)	6.3 (5.8, 6.8)	**0.0313**
Ambulation (15)	9.0 (5.7, 12.3)	9.6 (5.0, 14.2)	11.7 (8.0, 15.3)	13.0 (9.5, 16.5)	**0.0156**
Borg for ambulation	12.5 (9.7, 15.3)	10.4 (6.2, 14.7)	9.0 (5.7, 12.3)	9.2 (6.0, 12.5)	**0.0195**
Stair climbing (20)	5.4 (2.5, 8.2)	5.6 (2.0, 9.1)	5.6 (2.0, 9.1)	6.1 (2.4, 9.8)	0.2500
Borg for stair climbing	12 (8.4, 15.6)	10.7 (5.1, 16.4)	9.3 (3.7, 15.0)	10.0 (4.4, 15.6)	0.1563
Lawton Instrumental Activities of Daily Living (IADL) scale (ranges from 0 = dependent through 2 = independent)					
Ability to use the phone	2.0**	2.0**	2.0**	2.0**	***
Borg for using phone	7.1 (5.5, 8.8)	6.9 (4.9, 8.9)	7.3 (6.8, 5.1)	7.5 (4.9, 10.1)	***
Shopping	0.9 (0.4, 1.4)	1.3 (0.6, 1.9)	1.5 (1.0, 2.0)	1.4 (0.7, 2.1)	**0.0125**
Borg for shopping	11.0 (7.2, 14.8)	9.9 (6.5, 13.3)	8.3 (5.6, 11.0)	6.9 (5.7, 8.0)	0.0625
Food preparation	1.4 (0.9, 1.9)	1.4 (0.8, 1.9)	1.5 (1.1, 1.9)	1.8 (1.5, 2.1)	**0.0125**
Borg for food prep	7.6 (6.1, 9.2)	6.9 (5.4, 8.4)	7.5 (5.2, 9.7)	7.0 (5.0, 9.0)	0.3125
Housekeeping	1.0 (0.5, 1.5)	0.8 (0.2, 1.4)	1.5 (0.9, 2.0)	1.6 (1.0, 2.1)	**0.0313**
Borg for housekeeping	10.3 (7.6, 13.0)	6.8 (5.6, 8.1)	6.9 (5.8, 8.0)	6.8 (5.3, 8.2)	0.0625
Laundry	0.9 (0.4, 1.5)	1.1 (0.5, 1.7)	1.4 (0.8, 2.0)	1.8 (1.4, 2.1)	0.0625
Borg for laundry	9.6 (6.3, 12.9)	7.4 (6.0, 8.8)	7.9 (4.7, 11.1)	7.3 (4.6, 9.9)	0.0625
Mode of transportation	1.3 (0.8, 1.9)	1.3 (0.7, 2.0)	1.5 (0.9, 2.1)	1.8 (1.3, 2.3)	0.5000
Borg for transportation	8.1 (5.8, 10.4)	6.6 (5.1, 8.1)	6.7 (5.6, 7.7)	5.8 (5.8, 7.0)	0.0625
Responsibility for own medications	1.7 (1.4, 2.1)	1.8 (1.4, 2.1)	1.8 (1.4, 2.1)	1.9 (1.6, 2.1)	**
Borg for medications	6.4 (5.9, 6.8)	6.2 (5.9, 6.5)	6.2 (5.8, 6.6)	6.0 **	0.5000
Ability to handle finances	1.5 (1.1, 1.9)	1.7 (1.3, 2.1)	1.8 (1.6, 2.1)	2.0**	0.1250
Borg for finances	6.7 (6.0, 7.4)	6.1 (5.9, 6.3)	6.0**	6.0**	0.2500

Five minute montreal cognitive assessment	**Week One**	**Week Four**	***P-value***
Language (4)	2.7 (2.0, 3.4)	3.1 (2.5, 3.7)	0.5313
Orientation (6)	5.8 (5.5, 6.1)	6.0 **	1.0000
Memory (5)	3.4 (2.5, 4.3)	4.2 (3.3, 5.1)	0.4375
Total–5-Min MoCA (15)	11.7 (10.3, 13.1)	13.3 (12.1, 14.5)	0.1016

Mean values (with 95% CI) for the Barthel index for activities of daily living and the Lawton instrumental activities of daily living (IADL) scale in points [maximal points in ()], as well as the Borg RPE (rating of perceived exertion) using the 6 (minimal exertion)–20 (maximal exertion) range during these activities. **P-value* represents the difference in test values between week 1 and week 4, calculated by the Wilcoxon signed rank test. **Scores across individuals are equal so no CI is available. ***Unable to compute because the mean difference between week 1 and week 4 ≈ 0. Bold values represent significance at the alpha = 0.05 level.

TABLE 4 Social work data.

	Week one	Week four	*P-value**
Generalized Anxiety Disorder-7 (GAD-7), with scores ranging from 0 (not at all) to 3 (nearly every day) over the last 2°weeks			
Feelings of nervousness	0.9 (0.3, 1.6)	0.9 (0.4, 1.5)	0.8125
Inability to stop worrying	0.9 (0.3, 1.5)	0.4 (0, 0.7)	0.3750
Excessive worry	0.7 (0.1, 1.3)	0.7 (0, 1.4)	1.0000
Restlessness	0.8 (0.2, 1.3)	0.5 (0.1, 1.0)	0.7500
Difficulty in relaxing	0.5 (0, 1.0)	0.2 (−0.1, 1.0)	0.3750
Easy irritation	1.2 (0.6, 1.8)	1.2 (0.5, 1.8)	1.0000
Fear something awful will happen	0.9 (0.3, 1.5)	0.5 (−0.2, 1.2)	0.1250
Total GAD-7 score	5.9 (2.4, 9.3)	4.5 (1.6, 7.4)	0.3438
Patient Health Questionnaire–9 (PHQ-9) with values ranging from 0 (not at all) to 3 (nearly every day) over the last 2°weeks			
Little interest or pleasure in doing things.	1.1 (0.5, 1.8)	0.6 (0.2, 1.1)	0.1250
Feeling down, depressed, or hopeless.	0.9 (0.2, 1.1)	0.4 (0.0, 0.7)	0.1563
Trouble falling or staying asleep, or sleeping too much.	1.4 (0.6, 2.1)	1.2 (0.2, 2.1)	0.5313
Feeling tired or having little energy.	1.9 (1.2, 2.7)	1.5 (0.6, 2.3)	0.4063
Poor appetite or overeating.	1.4 (0.7, 2.0)	0.6 (−0.1, 1.4)	0.3438
Feeling bad about yourself or that you are a failure or have let yourself or your family down.	0.4 (−0.1, 1.0)	0.2 (−0.1, 0.5)	0.5000
Trouble concentrating on things, such as reading the newspaper or watching television.	0.7 (0.2, 1.2)	0.6 (−0.1, 1.3)	0.4844
Moving or speaking so slowly that other people could have noticed. Or the opposite being so fidgety or restless that you have been moving around a lot more than usual.	1.1 (0.3, 1.8)	0.5 (0.1, 0.8)	0.2500
Thoughts that you would be better off dead, or of hurting yourself.	0.0**	0.0**	***
Total PHQ-9 score	8.9 (5.4, 12.3)	5.5 (2.3, 8.8)	0.0986

Mean values (with 95% CI) for the Generalized Anxiety Disorder-7 (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9). **P-value* represents the difference in test values between week 1 and week 4, calculated by the Wilcoxon signed rank test. **Scores across individuals are equal so no CI is available. ***Unable to compute because the mean difference between week 1 and week 4 = 0.

did not demonstrate significant improvement in cognition over the 4-week period.

Physiological measures

In this study, researchers monitored physiological measures of dyspnea, blood pressure, heart rate, and weight over 4°weeks. During week one, 75% of participants experienced dyspnea, compared to week four levels of 31%. This compares to a meta-analysis by Fernández-de-Las-Peñas et al. (2021), in which dyspnea decreased from a baseline level of 13.2%, to 27.2% at 60 days, and 26.3% at 90 days. Within our study, we found a significant decrease in heart rate, an insignificant decrease in weight and an insignificant increase in oxygen saturation levels. Patients with persistent dyspnea may benefit from referrals to professionals versed in respiratory and cardiac rehabilitation to improve their breath support and reduce their energy expenditure during functional activities.

Participants in this study were not highly impacted by comorbid conditions as evidenced by their mean Charlson Co-Morbidity Index score of three. Patients with comorbidities did experience poorer outcomes. Early identification of potential comorbidities during initial assessment, as well as enhanced attention to those potential complications during acute care, and discharge planning could assist in preventing secondary complications. Patients with comorbid conditions may also require enhanced time and rehabilitation hours compared to their counterparts without these conditions (Charlson et al., 1987; Choi et al., 2008).

Physical performance measures

The participants in this study demonstrated significant levels of debilitation during their first week post hospitalization as evidenced by poor scores on the TUG, the 5x sit to stand, and the SQUEGG hand grip dynamometer. In previous studies, researchers have provided results on a 6-min Walk test. While none of our participants had the physical capacity to complete this test at hospital discharge, the 6-min walk test would have added a component of cardiovascular endurance to our measures, a factor we failed to adequately capture. By the end of week two, participants transitioned quickly to a safe level of walking and transfers and were no longer considered at fall risk. Although no participants reported falls in the 4°weeks after hospitalization, fall risk was high given their mobility status at discharge. While the physical performance assessments we utilized demonstrated improvement over the 30-day acute outpatient term, all three

versions of the TUG along with the 5xSTS were probably unnecessary. Grip strength also increased significantly over 4°weeks, an important finding, as higher hand strength is associated with less mortality (Sayer and Kirkwood, 2015; De Biase et al., 2020).

Functional performance

Participants in this study were independent in bowel and bladder control upon hospital discharge, however required assistance with all ADLs and basic mobility tasks until week four. Assessment scores suggested that patients continued to require assistance with bathing, ambulation, and stair climbing, even at week four. Participants with stalled performance scores also continued to have higher rates of perceived exertion.

Considering IADLs, our participants were independent with telephone use upon discharge although one reported shortness of breath while talking on the phone. While scores for financial and medication management quickly improved to normal, the OT assessment team reported these scores may have reflected ability versus observed performance, given the participant's cognitive scores. Participants continued to be partially dependent in the IADL skills of shopping, food preparation, housekeeping, laundry, and transportation at week four. Most participants continued to need assistance due to mild shortness of breath and had Borg scores greater than seven. In support of our findings, Carenzo et al. (2021) reported 87% of the participants in their study were independent in self-care by 8°weeks post-hospitalization. Our findings suggest OT and PT referrals for patients with even mild ADL and IADL disability could minimize risk of secondary complications resulting from COVID-19 (He et al., 2015).

Cognitive and psychological performance

Similar to other studies (Hampshire et al., 2021; Jaywant et al., 2021), our participant's demonstrated mild cognitive impairment, particularly in the areas of language and memory. While these scores did not improve significantly over the 4-week trial they did trend upwardly. Participants continued to report problems with word-finding and short-term memory at week four and many requested information about how to enhance recovery. Hampshire et al. (2021) reported cognitive impairment and word-finding difficulty in their participants, and Jaywant et al. (2021) found impaired working memory in 55% of participants, impaired speed of processing in 40% of participants, and divided attention in 46% of participants recovering from COVID-19. Referrals to speech-language pathology and/or occupational therapy might enhance cognitive and communication ability (McGuire et al., 2006).

Unlike other studies (Xiong et al., 2021; Zhang et al., 2021), our participants did not experience significant or persistent self-reported anxiety and depression. Patients did report fears of re-infection, anxiety about financial concerns, and anxiety about not returning to baseline functional levels. The majorities of participants in our sample were married or had a caregiver staying with them. It is possible that social support moderated the level of anxiety noted in other studies (Viseu et al., 2018; Zhao et al., 2018). Clearly, mood should be monitored following COVID-19 as symptoms of depression and anxiety affect cognitive performance in older adults (Baune et al., 2006).

Limitations

Because our samples of patients were never ventilator dependent, they most likely did not exhibit the most severe symptoms, therefore generalization to that population may be limited. Our sample size was relatively small, with some loss to follow-up. Our participants tired from meeting the demands of multiple phone calls on different days from multiple disciplines, suggesting a more streamlined approach may be beneficial. We were dependent on patient interpretation of test results as we did not conduct face-to-face assessments. We did ask caregivers to provide input when cognition may have impacted participant response reliability.

Conclusion

We examined the post-discharge needs of patients hospitalized with COVID-19 and followed their natural recovery over 30 days without intervention. Our physiological, physical, cognitive, and functional findings suggest patients would benefit from assessment and intervention from a multi-disciplinary to address the range of deficits patients may experience as they recover from COVID-19. Early rehabilitation may shorten recovery time and allow patients to return to normal activities; foundational for an optimal quality of life.

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 University of Oklahoma Health Sciences

Center IRB. 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

CC contributed to the study conceptualization and design, developed the study manual and training, collected data and contributed significantly to the development of this manuscript. SJ contributed to the study design, led all team members in RED Cap training, collected and analyzed data, developed tables, and authored significant sections of the manuscript. HM and VL participated in data collection and manuscript development. AC-L, SD, WR, and TF participated in study conceptualization and design, trained team members, collected data, and edited all portions of the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Neuropsychological impairment in post-COVID condition individuals with and without cognitive complaints

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One of the most prevalent symptoms of post-COVID condition is cognitive impairment, which results in a significant degree of disability and low quality of life. In studies with large sample sizes, attention, memory, and executive function were reported as long-term cognitive symptoms. This study aims to describe cognitive dysfunction in large post-COVID condition individuals, compare objective neuropsychological performance in those post-COVID condition individuals with and without cognitive complaints, and identify short cognitive exams that can differentiate individuals with post-COVID symptoms from controls. To address these aims, the Nautilus project was started in June 2021. During the first year, we collected 428 participants' data, including 319 post-COVID and 109 healthy controls (18–65 years old) from those who underwent a comprehensive neuropsychological battery for cognitive assessment. Scores on tests assessing global cognition, learning and long-term memory, processing speed, language and executive functions were significantly worse in the post-COVID condition group than in healthy controls. Montreal Cognitive Assessment, digit symbol test, and phonetic verbal fluency were significant in the binomial logistic regression model and could effectively distinguish patients from controls with good overall sensitivity and accuracy. Neuropsychological test results did not differ

between those with and without cognitive complaints. Our research suggests that patients with post-COVID conditions experience significant cognitive impairment and that routine tests like the Montreal Cognitive Assessment, digit symbol, and phonetic verbal fluency test might identify cognitive impairment. Thus, the administration of these tests would be helpful for all patients with post-COVID-19 symptoms, regardless of whether cognitive complaints are present or absent.

Study registration: www.ClinicalTrials.gov, identifiers NCT05307549 and NCT05307575.

KEYWORDS

COVID-19, post-COVID-19 condition, NeuroCOVID, neuropsychological test, cognitive function

Introduction

Since the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020, it has been an ongoing challenge for healthcare systems worldwide. Until the development and implementation of vaccines, most efforts focused on the disease's acute phase. With a large part of the population now vaccinated and more defined treatment strategies being made available, concerns about mortality have somewhat decreased. However, a significant number of people who have been infected have persistent symptoms, causing disability or decreased quality of life. The post-COVID-19 condition (PCC) occurs approximately 3 months from the onset, with symptoms lasting for at least 2 months, cannot be attributed to alternative diagnoses, and impact everyday functioning (Soriano et al., 2022). PCC is more common in the more severe COVID-19 forms, but it still affects patients who are not hospitalized (Chen et al., 2022). Regarding age, PCC affects both young and old persons, even though it occurs more frequently in the elderly (Daugherty et al., 2021; Cohen et al., 2022). Moreover, women are more likely than men to have PCC (Davis et al., 2021).

PCC is characterized by a wide variety of symptoms, either fixed or fluctuating. They may arise for the first time or continue from the acute phase in a milder or more severe form (Soriano et al., 2022). The most prevalent symptoms include fatigue, pain, headaches, dyspnea, changed smell and taste, cognitive impairment, and mental health issues. These symptoms most likely belong to numerous syndromes, resulting from various pathophysiological processes across the disease spectrum. Proposed mechanisms to explain the pathogenesis of PCC include organ damage in the acute infection phase, a persistent hyperinflammatory state, viral activity associated with a host viral reservoir, or an incompetent antibody response (Proal and VanElzakker, 2021). In addition to acute disease, other factors such as previous comorbidities (Cellai and O'Keefe, 2020), psychological disorders (Mazza et al., 2020), or lifestyle changes due to the pandemic (Galea et al., 2020) may explain this chronicity.

Cognitive dysfunction is one of the most reported symptoms of PCC and generates more significant disability or a decrease in quality of life. In long-COVID studies, brain fog and cognitive dysfunction are self-reported in around 70–80% of patients (Davis et al., 2021; Guo et al., 2022; Ziauddeen et al., 2022). Patients with critical forms of the disease, severe neurological manifestations, or older individuals are more likely to have long-term cognitive dysfunction, according to previous investigations involving patients who experienced acute respiratory distress syndrome from causes other than the SARS-CoV-2 virus (Hopkins et al., 2005; Denke et al., 2018). However, for unknown reasons, cognitive dysfunction also occur frequently in young people with non-severe forms of COVID-19 (Davis et al., 2021).

Initial neuropsychological evaluations supported people's self-reported data. Attention, memory, and executive function were impaired in participants discharged from the hospital or who recently recovered from a moderate or mild case of COVID-19 (Almeria et al., 2020; Woo et al., 2020; Zhou et al., 2020; Silva et al., 2021). From an online assessment platform, nine computerized cognitive tests were employed in a prospective evaluation with a sample size of more than 84,000 participants. In tests of reasoning, problem-solving, spatial planning, and target detection, 12,689 people who suspected they had COVID-19 performed worse than those who did not report the disease. Depending on the severity of COVID-19, these cognitive deficiencies had varying degrees of impact on several tests (Hampshire et al., 2021).

Studies that focused on long-term cognitive symptoms have confirmed the initial findings with case studies or small samples. A study on 740 people conducted 7 months after the COVID-19 diagnosis using cut-off scores [defined as a

Z-score $\leq$ 1.5 standard deviation (SD) below measure-specific age-, educational level-, and sex-adjusted norm of classical standardized tests] found impairments in all domains assessed, ranging from 10% in attention and working memory to 24% in verbal encoding (Becker et al., 2021). Another study on 66 PCC subjects selected according to cognitive complaints also found low scores across domains ranging from 15 to 52% in attention and 12 to 32% in executive functions (García-Sánchez et al., 2022). However, both these studies lacked a control group. Delgado-Alonso et al. (2022) compared the results of a paper and pencil and computerized testing of a sample of 50 people with post-COVID cognitive complaints with 50 healthy controls (HCs). They found impaired attention-concentration, episodic memory, visuospatial processing, and executive functions (Delgado-Alonso et al., 2022). Guo et al. (2022) compared 181 people with PCC and 185 HCs by using several online experimental tasks, and only found impairments in memory but not executive functions or language.

Despite existing research, more data is needed to comprehend COVID-19's impacts on cognition. This study aims first to describe the cognitive dysfunctions in a large PCC and compare them with a HC group. Our second aim is comparing the objective performance in individuals with and without subjective cognitive complaints. We expect to find more affectation in PCC individual with cognitive complaints. Finally, we aim to detect the neuropsychological tests that better discriminate patients from controls, to be proposed as short cognitive screenings. We selected a neuropsychological battery using instruments typically utilized in clinical settings, but we also included the recognition of emotions because of its sensitivity to the orbital cortex (Adolphs, 2002). To date, no study has been published that evaluates social cognition in PCC individuals. We expect to find more affectations in emotion recognition in PCC group.

Materials and methods

Participants

The sample comprised 428 participants from the Nautilus Project (ClinicalTrials.gov IDs: NCT05307549 and NCT05307575). Three hundred and nineteen participants with PCC and 109 HCs were evaluated at the Neuropsychology and COVID-19 Units across 16 hospitals in Catalonia, Madrid, and Andorra, coordinated by the Consorci Sanitari de Terrassa (Terrassa, Barcelona, Spain). The inclusion criteria for the PCC group were as follows: (a) confirmed diagnosis of COVID-19 according to WHO criteria with signs and symptoms of the disease during the acute phase; (b) at least 12 weeks after infection; and (c) age between 18 and 65 years. The exclusion criteria were: (a) established diagnosis before COVID-19 disease of psychiatric, neurological, neurodevelopmental disorder, or systemic pathologies known to cause cognitive deficits, and (b) motor or sensory alterations that impede the neuropsychological examination. The HCs did not have COVID-19 (no positive test or compatible symptoms), and the same exclusion criteria were applicable to the PCC group. All participants were native Spanish speakers.

Procedure

The overall procedure consisted of two sessions. In the first session, various questionnaires were administered to collect information about demographic factors, previous comorbidities, and data on COVID-19. Participants provided information on their age, sex, formal education, citizenship, ethnicity, profession, and income. They were questioned about their medical history and behavior related to their health. Moreover, they were also asked about their COVID-19 experience, including their symptoms, treatment, hospitalization, and time since diagnosis. We also collected information on their post-COVID symptoms, including cognitive ones.

Each participant underwent a cognitive assessment with a comprehensive neuropsychological battery in the second session. We used the Montreal Cognitive Assessment (MoCA) as a general cognitive screening tool (Nasreddine et al., 2005; Ojeda et al., 2016). The Matrix subtest from the Wechsler Adult Intelligent Scale (WAIS) III was used to assess abstract reasoning (Wechsler, 1999). To assess verbal memory, we used the Spanish version of Rey's Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996; Alviarez-Schulze et al., 2022). Visual memory was evaluated with the 30-min delayed recall test from the Rey–Osterrieth Complex Figure Test (ROCF) (Meyers and Meyers, 1996). The copy trial of the ROCF evaluated the visuo-constructive abilities. The WAIS-III Digit Span subtest was used to measure verbal attention (digit span forward) and working memory (digit span backward) (Wechsler, 1999). Visual scanning, tracking, and motor speed were assessed by the digit symbol test from the WAIS-III (Wechsler, 1999). Parts A and B of the Trail Making Test (TMT) were administered to measure visual scanning, motor speed and attention, and mental flexibility (Reitan, 1958). The Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1989; Peña-Casanova et al., 2009) was used to evaluate verbal fluency and language. The number of words beginning with the letters P, M, and R recalled in 1 min was recorded. Semantic fluency was evaluated using the category "animals" (Ardila et al., 2006). The number of correct animals recalled in 1 min was considered. The Stroop test consists of three subtests: words, colors, and color words that conflict with the color in which they are presented. Here, the interference score was calculated as a measure of cognitive inhibitory control (Golden, 2005). The Boston Naming Test (BNT) was used to evaluate language

(Allegri et al., 1997). Emotion recognition was assessed with the Reading the Mind in the Eye Test (Fernández-Abascal et al., 2013). The Word Accentuation Test (TAP) was included as an estimate of premorbid IQ (Gomar et al., 2011). In addition to cognitive measures, we used the Chalder Fatigue Scale (CFQ) (Jackson, 2014) to assess fatigue, the Generalized Anxiety Disorder 7-item scale (GAD-7) (Spitzer et al., 2006; García-Campayo et al., 2010) to assess anxiety, and the Patient Health Questionnaire-9 (PHQ-9) (Diez-Quevedo et al., 2001; Kroenke et al., 2001) to assess depression. All evaluations were performed by trained neuropsychologists.

The recruitment was carried out between June 2021 and June 2022. The study was conducted with the approval of the Drug Research Ethics Committee (CEIm) of Consorci Sanitari de Terrassa (CEIm code: 02-20-107-070) and the Ethics Committee of the University of Barcelona (IRB00003099). All participants provided written informed consent.

Statistical analyses

Descriptive statistics were conducted for all the variables of the study. Group differences in demographics were examined by conducting two-tailed Student's *t*-tests. The Fisher's exact test assessed a comparison of binarized measures between the two groups. One-way analysis of covariance (ANCOVA) was performed to determine differences in cognitive functioning among groups, including age, sex, education, and estimated IQ as nuisance variables. Graphical representations and descriptive statistics were used to study the assumptions. The effect size was calculated using the value partial eta squared (η_p^2). We used logistic regression to assess the additive contribution of neuropsychological variables in classifying the PCC and HC. We used age, years of education, and sex as covariables. Results were presented as odds ratios with 95% confidence intervals (CIs). We reported the accuracy, sensitivity, and specificity, and positive and negative predictive values. The area under the ROC curve (AUROC) was also calculated. Analyses were performed using IBM SPSS Statistics 27.0 (IBM Corporation, Armonk, NY, USA) and R Statistical Software (version 4.2.0; The R Foundation for Statistical Computing Platform). The critical level for statistical significance was set at $\alpha = 0.05$. A Bonferroni adjustment was made for ANCOVA analyses such that statistical significance was accepted when $p < 0.0025$.

Results

Table 1 shows the socio-demographic characteristics and comorbidities of the PCC and HC groups. The PCC group had a higher proportion of women (77 vs. 62%), were older, had less formal education, and had a lower estimated IQ than the control group. Therefore, age, sex, educational level, and estimated IQ were covariates in comparing cognitive results between the two groups. Compared to the HC group, respiratory disease, high blood pressure, and obesity were more prevalent among PCC participants. On average, patients had a positive test 320 days before their neuropsychological evaluation (SD = 156.66 days, range: 84–795 days).

Regarding the severity of the disease, 150 (47%) PCC patients were hospitalized, of which 77 (51.3%) were admitted to the intensive care unit (ICU). The remaining 169 (53%) individuals with PCC were outpatients and had a mild illness at home. Of those, 139 (82.2%) had disturbance of activities of daily living, and 30 (17.8%) continued to carry out their activities as usual. Table 2 shows symptoms reported by participants with PCC at the time of assessment. Fatigue, pain, and headache were the most reported post-COVID general symptoms, whereas cognitive complaints, depressive, and anxiety manifestations were the most frequently reported among the neuropsychiatric symptoms.

After adjusting for covariates and considering the Bonferroni correction for the number of comparisons (which leaves us with a significance level of $p = 0.0025$), there was a statistically significant poor performance of PPC group in MoCA, matrix reasoning, RAVLT sum, RAVLT delayed recall, digit symbol, Stroop words, Stroop colors, Stroop interference, phonetic fluency, and semantic fluency than in HC group (Table 3 and Figures 1, 2).

The PCC group showed statistically significant higher scores of CFQ (PCC: mean = 6.21, SD = 4.33 vs. HC: mean = 1.73, SD = 3.07; $t = -9.730$, $p < 0.001$, $d = 1.104$), GAD-7 (PCC: mean = 6.73, SD = 5.55 vs. HC: mean = 3.18, SD = 3.12; $t = -6.178$, $p < 0.001$, $d = 0.702$), and PHQ-9 (PCC: mean = 9.13, SD = 6.64 vs. HC: mean = 3.08, SD = 2.79; $t = 9.004$, $p < 0.001$, $d = 1.023$) than those of the HC group. We reanalyzed the data by taking fatigue, anxiety, and depression scale scores as covariates. After adjusting for these variables, there was a statistically significant poor performance of the PPC group in MoCA ($F = 10.120$; $p = 0.002$; partial $\eta^2 = 0.025$), RAVLT sum ($F = 4.843$; $p = 0.028$; partial $\eta^2 = 0.012$), digit symbol ($F = 7.448$; $p = 0.007$; partial $\eta^2 = 0.019$), Stroop word-colors ($F = 5.757$; $p = 0.017$; partial $\eta^2 = 0.015$), phonetic fluency ($F = 5.802$; $p = 0.016$; partial $\eta^2 = 0.015$), semantic fluency ($F = 6.055$; $p = 0.014$; partial $\eta^2 = 0.015$), and Reading the Mind in the Eyes test ($F = 7.576$; $p = 0.006$; partial $\eta^2 = 0.019$). However, no result remained statistically significant after Bonferroni correction (see Supplementary Table).

We focused on the neuropsychological variables that better distinguished patients and controls. We performed binomial logistic regression using the group as the outcome and the significant variables after the Bonferroni correction in the comparison between the two groups as predictors. We added demographic variables (age, years of formal education, and sex) as covariables. Linearity of the continuous variables for the logit of the dependent variable was assessed using the Box–Tidwell

TABLE 1 Socio-demographic characteristics and comorbidities for the PCC and HC groups.

	PCC	HC		
	***n* = 319*M* (SD)Range**	***n* = 109*M* (SD)Range**	***t***	***p***
Age (years)	49.06 (9.13)24–65	46.10 (9.31)23–62	2.901	0.004
Education (years)	13.78 (3.34)8–20	15.57 (2.93)8–20	5.300	<0.001
IQ estimation*	101.51 (7.87)85–116	104.79 (6.58)85–116	4.235	<0.001
	***n* (%)**	***n* (%)**	**χ^2**	***P***
Sex (% female)	84 (77.7%)	68 (62.4%)	7.817	0.005
Change of employment status (post-COVID)	126 (39.5%)	9 (8.3%)	36.722	<0.001
Previous comorbidities				
Heart disease	11 (3.5%)	3 (2.8%)		
Respiratory disease	40 (12.5%)	5 (4.6%)	6.635	0.036
Chronic kidney disease	3 (0.9%)	0		
High blood pressure	47 (14.7%)	5 (4.6%)	9.055	0.011
Dyslipidemia	46 (14.4%)	11 (10.1 %)	2.430	0.297
Diabetes mellitus	13 (4.1%)	3 (2.8%)		
Obesity	99 (31.3%)	16 (14.7%)	12.469	0.002
Chronic liver disease	10 (3.2%)	0		
Tobacco smoking	22 (7.0%)	27 (24.8%)	26.348	<0.001

PCC, post-COVID condition; HC, healthy control; M, mean; SD, standard deviation.
*By means of Word Accentuation Test.

procedure (Box and Tidwell, 1962). A Bonferroni correction was applied using all 19 terms in the model, resulting in statistical significance being accepted when $p < 0.00263$ (Tabachnick and Fidell, 2014). Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable. The logistic regression model was statistically significant ($\chi^2_{(3)} = 87.862$, $p < 0.001$). The link test was nonsignificant, indicating good model specification. The Hosmer–Lemeshow goodness-of-fit test was non-significant, indicating good model fit ($\chi^2_{(8)} = 12.639$, $p = 0.125$). The model explained 28.0% (Nagelkerke R^2) of the variance. Of the nine predictor variables, three made significant contributions to the model: total MoCA [odds ratio (OR) = 0.731], digit symbol test (OR = 0.973), and phonetic fluency (OR = 0.977) (**Table 4**). The model demonstrated overall classification accuracy of 74.5%, with a sensitivity of 89.9% and a specificity of 30.6%. The positive predictive value was 78.63%, and the negative predictive value was 51.56%. The AUROC 0.788 (95% CI: 0.744–0.832), which is an acceptable level of discrimination (Hosmer et al., 2013; **Figure 3**).

To evaluate whether the cognitive complaint is a determining factor in worse neuropsychological performance, we formed two groups: subjects who reported cognitive complaints (CC) ($n = 123$, 38.6%) and those who did not notice cognitive changes (NCC) ($n = 196$). The groups were similar in age (NCC: mean = 49.11, SD = 9.829 vs. CC: mean = 48.97, SD = 7.941); education (NCC: mean = 13.68, SD = 3.266 vs. CC: mean = 13.93, SD = 3.461), and estimated IQ (NCC: mean = 101.86, SD = 8.162 vs. CC: mean = 100.95, SD = 7.382), but the CC group had significantly more days since the positive test than the NCC group (CC: mean = 370, SD = 199.329, NCC: mean = 288, SD = 111.748; $t = -4.193$, $p < 0.001$, $d = 0.546$). Additionally, the CC group had 87 (70.7%) women compared to the 112 (57%) in the NCC group ($\chi^2_{(1)} = 5.947$, $p = 0.015$). There were no differences in GAD-7 scores (NCC: mean = 6.44, SD = 5.67 vs. CC: mean = 7.20, SD = 5.35) between groups. However, the scores of the CFQ (NCC: mean = 7.94, SD = 6.39 vs. CC: mean = 11.06, SD = 6.62) and the PHQ-9 (NCC: mean = 5.37, SD = 4.37 vs. CC: mean = 7.60, SD = 9.91) were significantly higher in the CC group than in the NCC group (CFQ: $t = -4.488$, $p < 0.001$, $d = 0.530$; PHQ-9: $t = -4.065$, $p < 0.001$, $d = 0.481$). Thus, we compared the neuropsychological performance of both groups controlling for sex, days of evolution, fatigue, and depression. We did not find significant differences at the Bonferroni level in the neuropsychological variables between participants with cognitive complaints and those without.

Discussion

The present study aimed to characterize the cognitive impairment of a large sample of participants with PCC.

TABLE 2 Post-COVID-19 condition reported symptoms at the time for neuropsychological assessment (N = 319).

Symptom	Cases (%)
Fatigue	209 (65.5)
Joint pain/body aches	140 (43.9)
Headaches	136 (43.3)
Dyspnea on exertion	122 (38.2)
Limb weakness	98 (30.7)
Paresthesia	87 (27.3)
Altered smell	98 (30.7.1)
Chest pain	70 (21.9)
Altered taste	64 (20.1)
Dizziness	68 (21.3)
Cough	53 (6.6)
Menstrual cycle alteration	8 (10.3)*
Sore throat	37 (11.6)
Nasal congestion	36 (11.3)
Loss of appetite	33 (10.3)
Dermatologic issues	27 (8.5)
Conjunctival congestion	24 (7.5)
Diarrhea	23 (7.2)
Loss of hair	22 (6.9)
Nausea	18 (5.6)
Neuropsychiatric symptoms	
Overall cognitive complains (subjective)	123 (38.6)
Memory deficits	110 (34.5)
Lack of concentration	106 (33.2)
Brain fog	97 (30.4)
Problems with language	79 (24.7)
Problems with executive functioning	73 (22.9)
Depressive symptoms	101 (31.7)
Anxiety	98 (30.7)
Post-traumatic stress	43 (13.5)
Difficulty sleeping	40 (12.5)
Obsessive-compulsive symptoms	16 (5)
Psychotic symptoms	3 (0.94)

PCC, post-COVID condition.
*% women < 45 years (n = 78).

Previous studies have shown that people who had COVID-19 performed worse than comparable healthy subjects in all cognitive domains, namely attention, executive functions, memory, and language (Becker et al., 2021; Delgado-Alonso et al., 2022; García-Sánchez et al., 2022; Guo et al., 2022; Zhao et al., 2022). Compared to the HCs, we found lower functioning of the PCC sample in tests of all domains other than attention and visuoconstructive functions.

Contrary to other authors (Becker et al., 2021; Delgado-Alonso et al., 2022; García-Sánchez et al., 2022), we did not find differences in attention between groups. Performance in TMT-A, a test in the attention domain, was not significant, although it was before the Bonferroni correction. García-Sánchez et al. (2022) highlighted the attentional deficits linked to COVID-19, but they used the CPT, a specific attention test that allow to separate between attentional accuracy and responsiveness speed, to detect a slight decrease in attentional abilities. Processing speed is a key component of attention as most attention tests are speed sensitive. Delgado-Alonso et al. (2022) found impaired attention. However, they collapsed several tests, such as Stroop, Symbol Digits Modalities Test, and reaction time tests, in addition to TMT-A and digit span forward, in the domain named attention and processing speed (Delgado-Alonso et al., 2022). Processing speed was affected also in our PCC group. Similar to us, Becker et al. (2021) measured attention with routine tests in clinical settings. They reported a 10% affectation when taking one standard deviation of the Z-score in reference to the HCs. However, this impairment was more prevalent in hospitalized patients, and therefore probably in more severe cases. A total of 24% of our PCC participants underwent critical care, which is risk factor for impairment in attention and processing speed (Hopkins et al., 1999). Neuroinflammatory reactions occur with severe systemic infection, as well as mild COVID-19 infections. A pattern of activated white matter microglia similar to that associated with the chemo-brain has been identified in individuals with SARS-CoV-2 infection (Fernández-Castañeda et al., 2022). PPC patients' mental processing speed likely stems from impairments in complex brain networks rather than specific dysfunctions. The evidence points to an attentional deficit in PCC patients, but the poor results in several tests potentially reflect processing speed issues.

Regarding the memory domain, we found an obvious impairment of verbal learning similar to other authors (Becker et al., 2021; Delgado-Alonso et al., 2022), but we did not find impaired visuoconstructive functions and visual memory. Chronic inflammation has been linked to neuronal impairment, especially in the hippocampus (Belarbi and Rosi, 2013). It has been suggested that patients with PCC could suffer from a chronic inflammatory condition (Maamar et al., 2022). This could explain these memory problems, especially in those who have had milder forms of COVID-19. In addition, affectations in the hippocampus have been related to memory loss at 3 months post-COVID (Lu et al., 2020).

We found that the performance of the Reading the Mind in the Eyes test also differed between PCCs and controls. However, Bonferroni's corrections were applied, and the differences did not reach the criteria for significance. To date, no studies have been published that evaluate social cognition in PCC individuals even though impaired social cognition can result in difficulties with social communication (Henry et al., 2006). Surprisingly, the Eye test did not correlate with depression and anxiety scores in our PCC participants. Social cognition is affected in depressed individuals (Nejati et al., 2012; Weightman et al., 2014). It has been proposed that the association between decreased social

TABLE 3 Adjusted* means for the neuropsychological variables for PCC and HC groups.

	PCC		HC				
	N	M_{adj} (SE)	*N*	M_{adj} (SE)	*F*	*p*	η_p^2
MoCA	**310**	**26.02 (0.14)**	**106**	**27.54 (0.24)**	**28.196**	**<0.001**	**0.064**
Matrix reasoning	**308**	**16.09 (0.25)**	**107**	**17.97 (0.43)**	**13.715**	**<0.001**	**0.032**
RAVLT sum	**311**	**44.24 (0.47)**	**107**	**48.09 (0.81)**	**16.703**	**<0.001**	**0.039**
RAVLT immediate recall	311	8.88 (0.15)	107	9.58 (0.26)	5.436	0.020	0.013
RAVLT delayed recall	**310**	**8.77 (0.17)**	**107**	**9.83 (0.29)**	**9.982**	**0.002**	**0.023**
RAVLT recognition	308	12.16 (0.13)	107	12.91 (0.23)	7.696	0.006	0.018
ROCFT copy	311	32.91 (0.21)	107	32.83 (0.35)	0.050	0.815	0.000
ROCFT delayed recall	311	18.93 (0.32)	107	19.43 (0.56)	0.532	0.466	0.001
Digit span forward	311	5.58 (0.06)	106	5.94 (0.11)	7.424	0.007	0.018
Digit span backward	313	4.42 (0.06)	106	4.66 (0.11)	3.346	0.068	0.008
Digit symbol	**310**	**64.39 (0.93)**	**107**	**73.82 (1.62)**	**24.743**	**<0.001**	**0.058**
TMT-A	310	38.053 (1.1)	107	32.92 (2.02)	5.032	0.025	0.012
TMT-B	306	88.39 (3.13)	107	71.64 (5.40)	7.180	0.008	0.017
Stroop words	**309**	**93.16 (1.18)**	**106**	**100.72 (2.06)**	**10.166**	**0.002**	**0.024**
Stroop colors	**309**	**64.08 (0.75)**	**106**	**70.42 (1.32)**	**17.293**	**<0.001**	**0.040**
Stroop word-colors	**309**	**38.38 (0.57)**	**106**	**48.85 (0.99)**	**23.065**	**<0.001**	**0.053**
Phonetic fluency (PMR)	**312**	**41.66 (0.65)**	**107**	**47.08 (1.13)**	**17.122**	**<0.001**	**0.039**
Semantic fluency (animals)	**311**	**20.94 (0.29)**	**107**	**23.28 (0.50)**	**15.818**	**<0.001**	**0.037**
BNT	311	52.09 (0.26)	107	52.89 (0.46)	2.055	0.152	0.005
Eye test	310	22.26 (0.20)	107	23.47 (0.35)	8.509	0.004	0.020

PCC, post-COVID condition; HC, healthy control; MoCA, Montreal Cognitive Assessment; RAVLT, Rey's Auditory Verbal Learning Test; ROCFT, Rey–Osterrieth Complex Figure Test; TMT, Trail Making Test; BNT, Boston Naming Test.

*Adjusted by years of education, estimated IQ, age, and sex.

η_p^2 effect size is as follows: $\eta_p^2 = 0.009$, small; $\eta_p^2 = 0.059$, medium; $\eta_p^2 = 0.139$, large.

The results after Bonferroni correction are indicated in bold font ($p < 0.0025$).

cognition and psychosocial issues in depressed individuals may be mediated by executive functions (Knight and Baune, 2019). The affectation of emotion recognition found in our sample could be explained by the reduction in gray matter in the orbito-frontal cortex seen in a large-sample of the COVID-19 re-imaging study (Douaud et al., 2022).

The neuropsychological profile observed in our data, which is consistent with the mild executive dysfunction syndrome reported by Bertuccelli et al. (2022) in a recent meta-analysis, indicates that individuals infected with COVID-19 are likely to develop neurodegeneration and dementia in the future. Periodical neuropsychological follow-up of PCC individuals is recommended to control the progression of cognitive deficits. We are unsure whether they will continue, resolve, or worsen. This monitoring will also enable us to ensure that the tests used to identify these deficiencies are the best ones available. In any case, the focus of clinical and research professionals should always be on creating interventions for cognitive stimulation.

Interestingly, our results are significant after removing the effect of many variables and performing the Bonferroni correction for multiple comparisons. Group differences were small-to-medium, as indicated by effect size calculations. Low effect size has also been reported by other authors (Delgado-Alonso et al., 2022; García-Sánchez et al., 2022). However, our results might have clinical relevance despite the small or medium effect size. It is a relatively young sample (<65 years of age) with cognitive impairments, which may affect the functionality. In our sample, we do not use objective measures to evaluate the functionality. However, 39.5% of PCC subjects had employment status changes, compared to 8.3% of HCs. Further investigation that additionally examines the mental health, quality of life, and functionality of PCC patients is needed.

Several studies have revealed that subjects with PCC present high levels of fatigue, depression, and anxiety (Fernández-de-Las-Peñas et al., 2021; Mattioli et al., 2021), which are correlated with cognitive deficits (Mattioli et al., 2021; Delgado-Alonso et al., 2022; García-Sánchez et al., 2022; Whiteside et al., 2022). Our results are consistent with those of previous reports. Fatigue, depression, and anxiety explain part of our sample's variance in cognitive performance, as evidenced by the reduction of cognitive differences between the PCC and HC groups after controlling for these factors. In PCC patients, depression, anxiety, and executive dysfunction have been found to predict fatigue (Calabria et al., 2022). However, it is unknown how depression and cognitive impairment are related causally. Depression plays a role in poor cognitive function. However, it cannot be ruled out that post-COVID symptoms such as cognitive deficits may cause depression. It is also possible that the same illness process causes cognitive impairment and depression, but more research is required to draw exact conclusions about the connection between depression and cognitive deficits.

We found that the neuropsychological tests that best discriminate between PCC and HCs are the MoCA, digit symbol test, and phonetic fluency. The model obtained

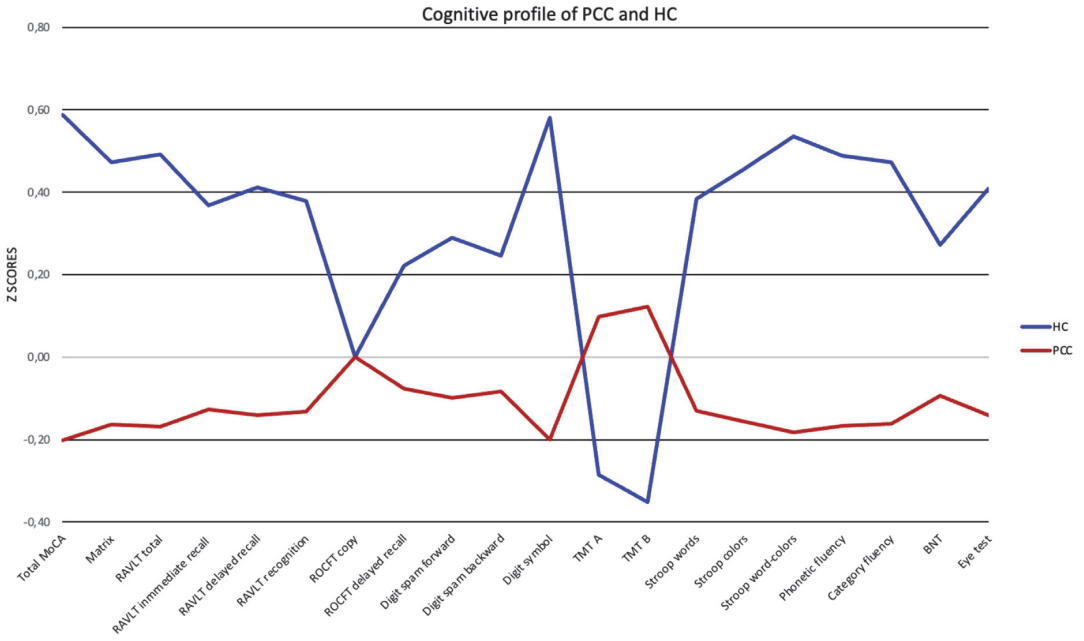

FIGURE 1
Cognitive profile for PCC and HC. Healthy controls (HC) in blue, PCC in red. Data are presented as *Z*-scores. Lower *Z*-scores indicate poorer performance, except for TMT (time), where lower *Z*-scores mean better performance.

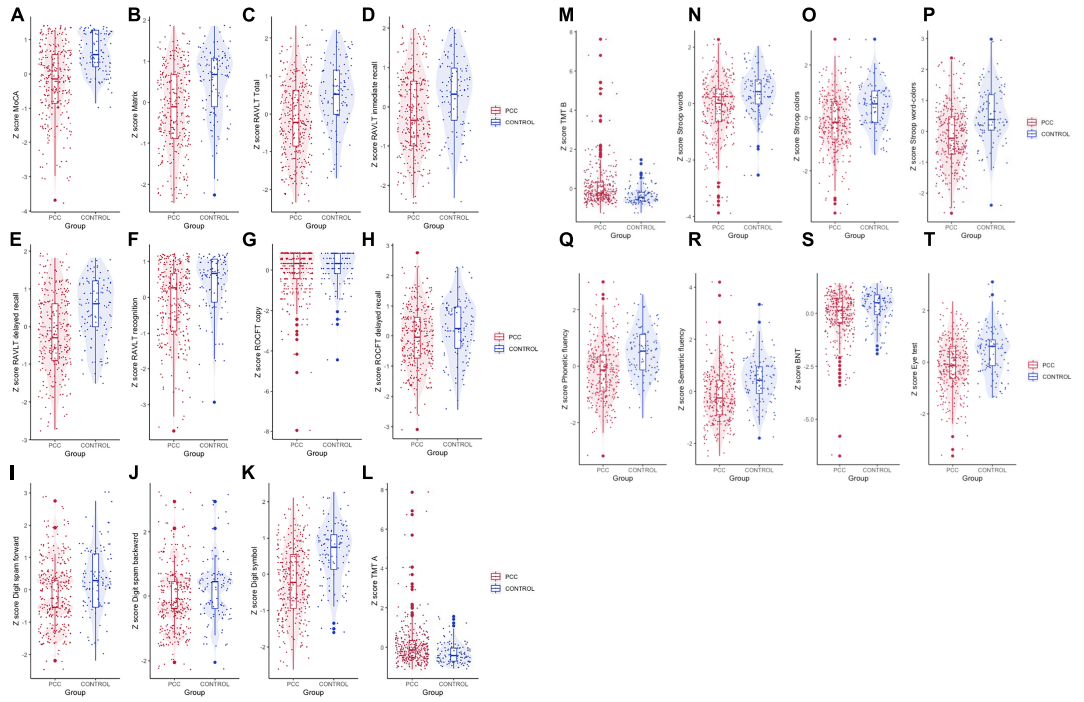

FIGURE 2
Violin plot for cognitive variables of PCC and HC groups. Data are presented as *Z*-scores. **(A)** MoCA, **(B)** matrix reasoning, **(C)** Rey's Auditory Verbal Learning test (RAVLT) total (sum of 5 trials), **(D)** RAVLT immediate recall, **(E)** RAVLT delayed recall, **(F)** RAVLT recognition, **(G)** Rey–Osterrieth Complex Figure Test (ROCFT) copy, **(H)** ROCFT delayed recall, **(I)** digit spam forward, **(J)** digit spam backward, **(K)** digit symbol test (coding), **(L)** Trail Making Test (TMT) A, **(M)** TMT B; **(N)** Stroop test words, **(O)** Stroop test colors, **(P)** Stroop test word-colors (interference), **(Q)** phonetic fluency (PMR), **(R)** semantic fluency (animals), **(S)** Boston Naming Test (BNT), and **(T)** Reading the Mind in the Eyes test (Eye test).

TABLE 4 Logistic regression classifying participants in PCC and HC groups based on significant neuropsychological results.

	B	SE	Wald	df	*p*	Odds ratio	95% CI for odds ratio	
							Lower	Upper
Total MoCA	−0.313	0.065	22.927	1	<0.001	0.731	0.643	0.831
Digit symbol	−0.027	0.008	11.382	1	<0.001	0.973	0.958	0.989
Phonetic fluency	−0.023	0.011	4.782	1	0.029	0.977	0.956	0.998
Constant	12.529	1.792	48.904	1	<0.001	276,250.358		

MoCA, Montreal Cognitive Assessment.

differentiates acceptably well, has good sensitivity, and correctly identifies PCCs. Two of the tests showing discrimination power are usual screening tools for mild cognitive impairment (MCI) (Nasreddine et al., 2005; González-Blanch et al., 2011). According to a recent meta-analysis, MoCA has already demonstrated its efficacy in detecting cognitive impairments associated with COVID-19 in the first 6 months (Crivelli et al., 2022). Our results reveal that the sensitivity of MoCA to detect cognitive impairment extends well beyond the first 6 months. Digit symbols are a susceptible test for brain damage. This task has not been related to brain structure or function, rather its deficient performance has been linked to various biological or functional pathologies (Lezak et al., 2012). On the other hand, verbal fluency, both phonetic and semantic, has also been shown to discriminate between people with MCI and healthy people, particularly semantic fluency (McDonnell et al., 2020). Semantic fluency does not appear in our model, but phonetic fluency does. It seems that performance in phonetic fluency tests is more sensitive in discriminating between people with PCC and healthy people. Distinct brain structures are involved in these language processing components: word retrieval in semantic fluency depends on semantic associations and each association's meaning, whereas phonetic fluency involves uncommonly used procedures requiring more effort (Bayles et al., 1989).

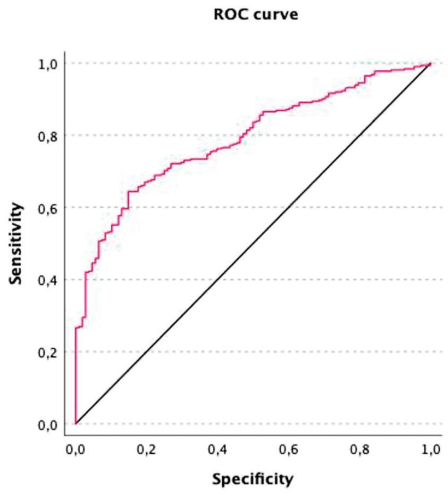

FIGURE 3
Receiver operating characteristic (ROC) curve for discrimination between PCC and controls based on MoCA, digit symbol, and phonetic fluency. The model's total diagnostic accuracy is summarized by the AUROC. A value of 0 represents a completely inaccurate test, and a value of 1 represents a completely accurate test. AUC = 0.788 (95% CI: 0.744–0.832).

Contrary to what we expected, we found no differences in the neuropsychological performance between participants who presented a cognitive complaint and those who did not. According to Calabria et al. (2022), our scores on depression and fatigue were higher in the cognitive-complaint subjects than in those without it. However, patients with cognitive complaints were not cognitively poorer than patients without them, and their increased complaining may have been due to their high levels of depression and fatigue. Our data suggest that anyone with PCC may have cognitive impairment influencing their functionality and quality of life, even if they do not complain. In fact, Zhao et al. (2022) found poor performance on sustained attention tasks up to 9 months after infection in a sample of people who did not seek post-COVID care. Cognitive function screening should be protocolized in the evaluation of people with PPC, even without cognitive complaints.

When interpreting the results, it is essential to consider the limitations and strengths of the current study. Our control group is not optimal, because we had to control some variables statistically. We aimed to match the PCC sample by age, sex, and education. Enrolling people who have not had the disease proved increasingly difficult. Although we could have used old samples from other studies, we wanted to control for the "pandemic" effect (i.e., lockdowns and stress) so that the control group experienced the same environmental circumstances, with the only difference being that they did not experience the infection. Another limitation refers to the choice of instrument to assess visuoconstructive skills and verbal memory. We used the ROCF test, which was normal for both the copying and memory parts. However, tests used by other authors are better suited to measure visual memory and it is possible that our test has not been adequate enough to assess visual memory impairment in COVID-19 patients. We did not investigate associations between cognitive status and biomarkers of clinical severity (i.e., ferritin or CRP). To understand the pathogenesis of cognitive dysfunction in COVID-19 patients, future studies with bigger samples are required to assess these characteristics.

However, our sample size is reasonably large, representing the full spectrum of severity of COVID-19. Moreover, the sample includes both individuals with and without cognitive complaints. This allows the results to be extrapolated to the entire PCC population. In addition, the selection of the sample has been made by ruling out comorbidities that could cause cognitive impairment, which means that we have a clean sample.

Conclusion

To conclude, despite the methodological limitations, the results of our study, with a large, representative sample of individuals with PCC and a large HC group, show that people with PCC present significant impairments in global cognition, learning and long-term memory, processing speed, language, and executive functions. Even though it has been almost a year since the COVID positive test, these impairments are still observed. We also provide evidence that cognitive deficits can affect anyone with PCC, regardless of whether they experience cognitive complaints. Further, we believe that all patients with post-COVID-19 symptoms would benefit from the routine use of three assessing tools such as MoCA, digit symbol, and verbal fluency test to rule out cognitive impairment. These tests are currently utilized in research and clinical settings. They are simple to conduct and accurate, making them popular among healthcare professionals and patients alike. Healthcare professionals will find our results to be clinically helpful when evaluating cognition in PCC.

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 Drug Research Ethics Committee (CEIm) of Consorci Sanitari de Terrassa, Terrassa, Barcelona, Spain (CEIm code: 02-20-107-070) Ethics Committee of the University of Barcelona (IRB00003099). The patients/participants provided their written informed consent to participate in this study.

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MA, MG, CJ, and BS designed the study. NC and NAUTILUS-Project Collaborative Group collected the data. MA performed the statistical analyses and wrote the first version of the manuscript. CJ revised the manuscript critically for important intellectual content. All authors revised the manuscript drafts and approved the final manuscript.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.1029842/full#supplementary-material

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Cognitive impairments in patients with subacute coronavirus disease: Initial experiences in a post-coronavirus disease clinic

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Background: A significant number of patients experience persistent cognitive impairment after coronavirus disease (COVID-19). This study aimed to investigate the cognitive function of patients in the subacute phase of COVID-19 and to identify the clinical factors associated with cognitive sequelae.

Materials and methods: Data from patients who visited the psychiatric department of our post-COVID clinic between March and May 2022 were analyzed. The results of neuropsychiatric function tests, including the digit span forward (attention/processing speed) and backward (working memory) tests, the trail making test part A (attention/processing speed) and part B (executive functioning), and the Stroop word color interference test (executive functioning), as well as clinical data from 40 patients in the subacute phase of COVID-19 were analyzed. We calculated the frequency of impairments in each cognitive measure, defined as a z-score of ≤ -1.5 standard deviations below measure-specific age- and sex-adjusted norms.

Results: Of the participants, 72.5% (n = 29) had impairments in at least one cognitive domain. Impairment in executive function was the most frequent (64.9%), followed by impairments in processing speed/attention (52.5%) and working memory (42.5%). Age was inversely correlated with T scores in all cognitive function tests.

Conclusion: Regular examination of cognitive function is needed, especially in elderly individuals, regardless of the subjective symptom manifestations.

KEYWORDS

long COVID, cognitive function, subacute phase, cognitive sequelae, neurocognitive function test

Introduction

Coronavirus disease (COVID-19) has caused more than 550 million confirmed cases of infection and over 6.3 million deaths worldwide by the end of June 2022 (WHO, 2022). A substantial proportion of individuals with COVID-19 have reported persistent symptoms beyond the acute illness, and these cases are referred to as "long COVID" (Taquet et al., 2021; O'Laughlin et al., 2022). According to recent literature, long COVID can be divided into two categories: (1) subacute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities present from 4 to 12 weeks beyond acute COVID-19, and (2) chronic or post-COVID-19 syndrome, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 which are not attributable to alternative diagnoses (Nalbandian et al., 2021). After the acute phase of infection, fatigue and neurological and psychiatric symptoms are the most frequent symptoms during the chronic COVID-19 phase aside from respiratory, gastrointestinal, and cardiologic problems (Nasserie et al., 2021; Badenoch et al., 2022). Thus, the impact of COVID-19 varies among individuals, and long-term symptoms can have devastating effects (Praschan et al., 2021).

Brain fog, a term used to describe slow or sluggish thinking, is one of the most common symptoms reported by individuals who have survived COVID-19 (Heneka et al., 2020). Up to 80% of COVID-19 survivors have reported subjective cognitive decline from the acute to the chronic phase (Cirulli et al., 2020; Davis et al., 2021; Graham et al., 2021; Mazza et al., 2021; Guo et al., 2022a). Cognitive decline is often reported in the chronic phase and lasts for a long time (Ermis et al., 2021). In a cohort study including 273,000 COVID-19 survivors, neuropsychiatric symptoms were first reported after 90 days in a third of survivors, and many survivors who developed symptoms at an early stage also had symptoms that lasted up to 180 days (Taquet et al., 2021). In a systematic review that included studies reporting the results of objective neurocognitive tests, the onset of cognitive symptoms varied from the acute to the chronic phase of COVID-19 and persisted even 7 months after discharge (Crivelli et al., 2022). Therefore, when cognitive decline begins and how long it lasts are important concerns to be investigated.

In terms of cognitive domains, declines in attention, executive function, fluency, and memory have been commonly reported. Studies with patients in the acute phase of COVID-19 have reported declines in executive function, attention, memory, and verbal fluency (Groiss et al., 2020; Beaud et al., 2021; Hellmuth et al., 2021; Tolentino et al., 2021). Studies on post-COVID-19 patients also found cognitive deficits in verbal fluency, attention, executive function, and delayed memory (Davis et al., 2021; Ermis et al., 2021; Hosp et al., 2021; Miskowiak et al., 2021; Méndez et al., 2021). In a cohort study with 81,000 subjects including 12,000 confirmed COVID-19 cases, cognitive deficits were more evident in complex tasks requiring reasoning, planning, and problem solving as opposed to more basic working memory functions such as completing the digit span test (Hampshire et al., 2020). In a study focusing on long COVID, memory and executive function showed declines, but of the two domains, only the decline in memory remained significant after controlling for demographic variables (Guo et al., 2022b).

Several mechanisms underlying the neural damage caused by COVID-19 have been suggested, including direct invasion of SARS-CoV-2 into the brain or degenerative spread of the disease through olfactory pathways, abnormal ischemic or hemorrhagic events in the brain, neuroinflammation, and excessive immune responses (Douaud et al., 2022; Guo et al., 2022b). Importantly, this evidence was particularly strong in the presence of neurological symptoms (Helms et al., 2020; Kandemirli et al., 2020). Therefore, investigations of the neurocognitive decline associating with each phase of COVID-19, as well as demographic and clinical characteristics would be a cornerstone in revealing the pathophysiology of neurocognitive dysfunction caused by COVID-19.

An increasing number of studies have investigated the clinical correlates of COVID-19 infection (Davis et al., 2021; Douaud et al., 2022; Hampshire et al., 2022). Severe respiratory symptoms during the acute phase, older age, and hyposmia are associated with cognitive deficits. A recent long-COVID study with a community-based sample reported that fatigue/mixed symptoms during the initial illness predicted post-COVID cognitive symptoms, and different ongoing symptoms explained variance in individual cognitive tasks (Guo et al., 2022a,b).

In Korea, the peak of the COVID-19 pandemic occurred in March 2022 (WHO, 2022). Although an increasing number of patients complain of neurocognitive sequelae after the acute phase, reports of their incidence are insufficient. Myongji

Hospital, which received the first Korean patient with COVID-19, is one of the representative hospitals specializing in infectious diseases and launched the "Purple Clinic," the first for managing long-COVID in South Korea in March 2022. During the first 3 months of the Purple Clinic, 3,058 patients presented, and most patients were in the subacute phase of COVID-19. Therefore, we focused on identifying the characteristics and clinical correlates of cognitive impairment during the subacute phase of COVID-19. Many prior studies have reported cognitive impairments during the chronic/post-COVID phase. The subacute phase has been included in some studies but not in others as the phase classification for COVID-19 was still under discussion. We believe that investigation of the discrete subacute phase, or at least the early phase of chronic COVID-19, could demonstrate the transition of neurocognitive sequelae throughout long COVID.

Materials and methods

Participants

This study was approved by the Institutional Review Board of Myongji Hospital and was performed in accordance with the approved protocols and guidelines (MJH-2022-06-027). Data were collected from the Purple Clinic in Myongji Hospital, the first specialized clinic to care for patients with long COVID in Korea, from March to May 2022. During the first 3 months of the Purple Clinic, 3,058 patients presented, 59 of whom were referred for psychiatric consultation owing to their depressed mood, anxiety, or brain fog symptoms. Among the 59 patients, 40 patients in the subacute phase [between 28 and 90 days after the confirmation of COVID-19 using reverse transcription polymerase chain reaction (RT-PCR)] were finally included in the study.

Subjective symptoms

In the Purple Clinic, all patients completed a subjective symptom checklist, which included 31 symptoms in eight categories: cardiopulmonary (coughing, productive sputum, shortness of breath, palpitations, chest pain, and edema), neurological (headache, dizziness, sleep disturbance, memory impairment, and tingling), gastrointestinal (abdominal discomfort, heartburn, abdominal pain, diarrhea, and nausea or vomiting), psychiatric (decreased attention, depression, and anxiety), general (fatigue, generalized weakness, and weight loss), ear-nose-throat (hyposmia and hypogeusia), eye (blurred vision and eye irritation), and others (hair loss and skin rash, dysmenorrhea, vaginal bleeding, bladder-related symptoms, foamy urine, and sexual dysfunction).

Neuropsychological and cognitive function tests

Selected cognitive function tests [the digit span test, the trail making test (TMT), and the Stroop word color interference test], considering previous studies, were performed before visiting the psychiatric clinic (Biagianti et al., 2022). The tests provided data on three cognitive domains (attention/processing speed, working memory, and executive function) (**Table 1**). The time required to complete each test was recorded. We defined impairment in each measure as a z-score of ≤ -1.5 standard deviations (SD) below the measure-specific age- and sex-adjusted norms. To reduce the use of the computationally cumbersome z-score, which can be positive or negative, we adopted the T-score system in the final analysis. The T-score is composed of a scale that ranges from 5 SD below the mean to 5 SD above the mean. Thus, for example, a raw score that fell exactly five SD below the mean would be equal to a T score of 0, a raw score that fell at the mean would be equal to a T of 50, and a raw score of five SD above the mean would be equal to a T of 100.

Validated neuropsychological scales that measure mood [the Hospital Anxiety and Depression Scale, HADS (Snaith, 2003)], sleep quality [the Pittsburgh Sleep Quality Index, PSQI (Buysse et al., 1989)], distress after trauma [the Impact of Event Scale, IES (Weiss, 2007)] and fatigue severity [the Fatigue Severity Scale, FSS (Lee et al., 2013)] were also routinely used before visiting the psychiatric clinic to assess the referred patients' symptoms on the day of presentation to the clinic. The HADS is a self-rating measure comprising seven items each for anxiety and depression. Each item is rated on a 4-point Likert scale ranging from 0 to 3, and the total score for depressive and anxiety symptoms ranges from 0 to 21 points each. The PSQI measures seven subdomains: subjective sleep quality, sleep latency, sleep time, usual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction. Each domain, rated on a 0–3-point scale, yields a total score ranging from 0 to 21, with higher scores indicating lower sleep quality. The FSS is a 9-item self-rating measure of the degree of fatigue experienced over the preceding week. Each item is rated from 1 to 7. The final FSS score is given by the average value divided by nine after adding the scores of each item. A higher score indicates higher

TABLE 1 Observed cognitive domains and respective neuropsychological tests.

Cognitive domain	Neuropsychological test
Attention/processing speed	Digit span forward
	Trail making test part A
Working memory	Digit span backward
Executive function	Trail making test part B
	Stroop word color interference test

fatigue. The IES is a 22-item self-report measure that assesses the subjective distress caused by traumatic events. Items are rated on a 5-point scale ranging from 0 to 4. The IES yields a total score ranging from 0 to 88, with higher scores indicating higher stress levels.

Statistical analysis

We performed a descriptive analysis of the clinical variables. Spearman's rho coefficient was calculated to determine the correlation between cognitive function and clinical characteristics. An additional multivariate regression analysis was performed, including age, HADS, PSQI, IES, and FSS results as independent variables. The Mann–Whitney test was used to assess the difference between the presence of subjective symptoms and cognitive function (T score). The threshold for statistical significance was $\alpha = 0.05$, and all tests were two-tailed. Statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

Results

Sample characteristics

The demographic and clinical profiles of the participants are presented in Table 2. Forty patients in the subacute phase of COVID-19 were included in the study. The average age of the patients was 53.74 ± 16.46 years, and 51.95 ± 19.17 days had passed from SARS-CoV-2 infection confirmation using RT-PCR. The neuropsychiatric scales showed that the participants experienced significant levels of depression, anxiety, and sleep disturbances.

TABLE 2 Demographic and clinical characteristics of the participants ($n = 40$).

Characteristics	$n = 40$, Mean ± SD
Sex	
Female,% (n)	82.9% (33)
Age	53.74 ± 16.46
>60 years,% (n)	48.0% (19)
Days from the SARS-CoV-2 confirmation using RT-PCR	51.95 ± 19.17
Number of subjective symptoms	14.21 ± 5.87
HADS: Anxiety score	13.58 ± 4.92
HADS: Depression score	13.18 ± 3.90
FSS score	5.41 ± 0.23
IES score	41.08 ± 26.09
PSQI	12.47 ± 4.28

HADS, Hospital Anxiety and Depression Scale; FSS, Fatigue Severity Scale; IES, Impact of Event Scale; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; RT-PCR, reverse transcription polymerase chain reaction.

Frequency of subjective symptoms during the subacute phase of coronavirus disease

The average number of complained symptom was 14. Psychiatric, neurological, and general symptoms were also common (Table 2). The frequency of subjective symptoms among the participants is shown in Figure 1. In our previous report (Jung et al., 2022), the symptoms with higher prevalence in the post-acute (more than 4 weeks since the diagnosis of COVID-19) group were fatigue, decreased attention, depression, cognitive decline, blurred vision, hair loss, bladder symptoms, sexual dysfunction, and dysmenorrhea. Fatigue was the most common symptom among the patients.

Cognitive function during the subacute phase of coronavirus disease

Neuropsychological test scores are presented in Table 3. The analysis indicated that 72.5% ($n = 29$) of the participants demonstrated scores of ≤−1.5 SD, compared with the adjusted norm, in at least one cognitive function test. Regarding each cognitive domain, impairments in executive function were the most frequent (64.9%, ≤−1.5 SD of the TMT-B or Stroop word color interference test results), followed by those in attention/processing speed (52.5%, ≤−1.5 SD of the digit span forward or TMT-A results) and working memory (42.5%, ≤−1.5 SD of the digit span backward results).

Correlates of cognitive function

Age was inversely correlated with T scores in all cognitive function tests (Table 4). According to multivariate regression analyses, age predicted lower cognitive function after adjustment for other clinical characteristics, including HADS, FSS, PSQI, and IES scores (Table 5).

Regarding each subjective symptom (Table 6), patients with headaches had lower digit span backward scores than those without headaches (average ranking: 23.32 vs. 15.71, $p = 0.039$). Patients with subjective memory impairment and weight loss had lower TMT-A scores than those without subjective memory impairment (average ranking: 23.03 vs. 15.58, $p = 0.036$) and weight loss (average ranking: 22.20 vs. 14.30, $p = 0.028$). Furthermore, there was a trend level of difference in the TMT-A results between patients with and without hyposmia (21.27 vs. 13.64%, $p = 0.051$). When multiple linear regression was performed, including all 17 symptoms, no symptoms significantly predicted the results of the cognitive tasks. Note that there were 31 symptoms on the checklist, and 17 symptoms with at least 10 cases in each group (with or without symptoms) were included in the comparisons. Nausea/vomiting, diarrhea,

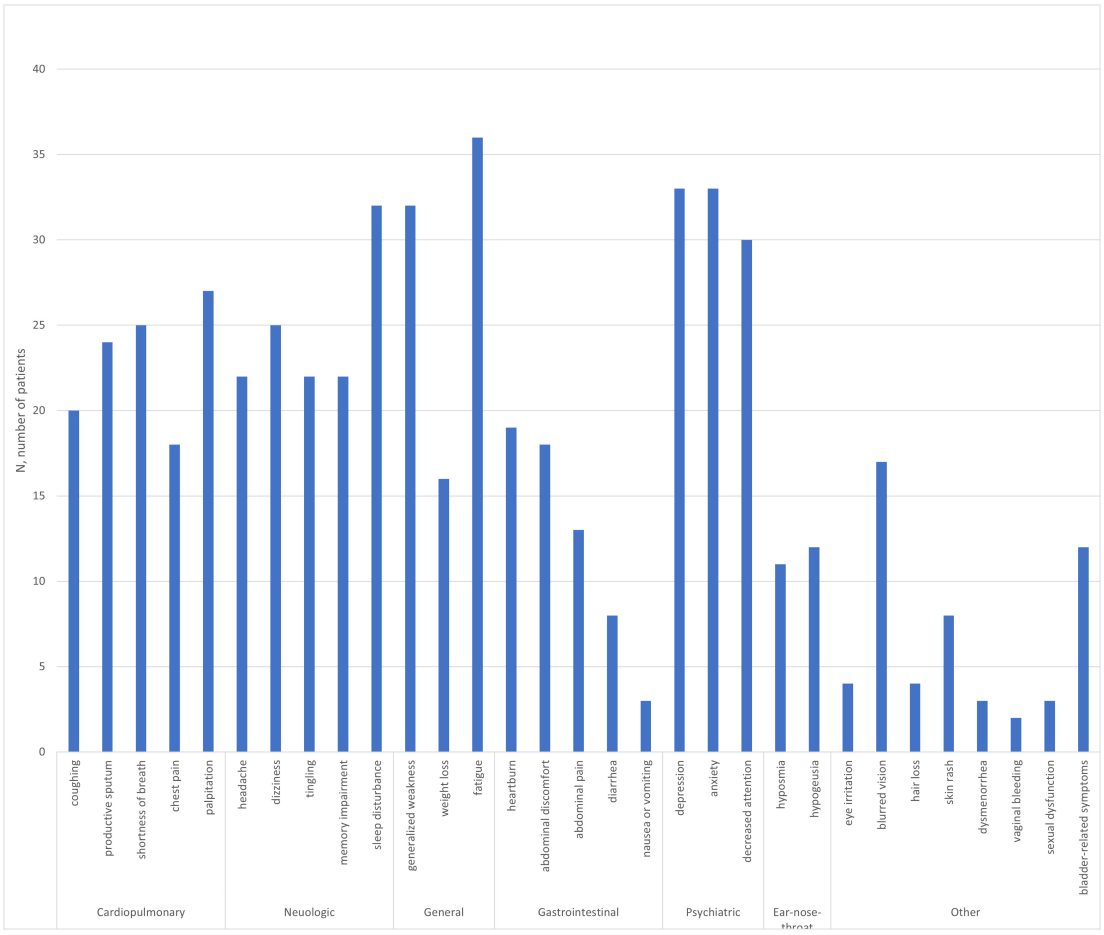

FIGURE 1
Subjective symptoms of the patients with subacute coronavirus disease referred to the psychiatric clinic (n = 40).

TABLE 3 Computerized neurocognitive test scores in the patients with subacute COVID-19.

Characteristics	Average direct score ± SD	T-score ± SD	Participants with ≤1.5 SD,% (n)
Digit span forward, n = 40	6.28 ± 1.38	45.18 ± 15.85	35.0 (14)
Digit span backward, n = 40	4.88 ± 1.33	45.65 ± 9.96	22.5 (9)
Trail making test part A (s), n = 38	38.97 ± 27.08	45.82 ± 16.13	34.2 (13)
Trail making test part B (s), n = 36	62.28 ± 35.82	48.89 ± 16.48	36.1 (13)
Stroop word color interference test (s), n = 38	41.58 ± 29.35	36.50 ± 12.18	63.2 (24)

s, second; SD, standard deviation; COVID-19, coronavirus disease.

eye symptoms, hair loss, dysmenorrhea, abnormal vaginal bleeding, and sexual dysfunction were excluded due to the small number of cases. On the other hand, depression, anxiety, insomnia, decreased attention, fatigue, and loss of energy were excluded because of the small number of cases without such symptoms (non-cases). This was an inevitable result because the study population was referred to a psychiatric clinic due to these symptoms. The effects of the psychiatric symptoms and fatigue on cognitive function were investigated by comparisons (Tables 4, 5).

Discussion

This study is the first in Korea to examine cognitive sequelae in patients in the subacute phase of COVID-19. The strength of this study is that cognitive functions were examined within a specific period, between 28 and 90 days after the confirmation of COVID-19, using objective cognitive tests. The examinations using objective cognitive tests showed that a significant number of patients had impairments in executive

TABLE 4 Correlation between the T scores in the cognitive tests and clinical characteristics.

	Attention/processing speed		Working memory	Executive function	
	Digit span forward	Trail making test part A	Digit span backward	Trail making test part B	Stroop word color interference test
Age	−0.638**	−0.750**	−0.639**	−0.745**	−0.852**
Days from the SARS-CoV-2 confirmation using RT-PCR	0.289	0.208	0.128	0.308	0.154
HADS: Anxiety score	−0.128	−0.226	−0.173	−0.230	−0.101
HADS: Depression score	−0.259	−0.211	−0.119	−0.123	−0.191
FSS score	0.020	0.085	0.177	0.142	0.024
IES score	0.164	0.086	−0.007	0.045	0.087
PSQI	−0.045	0.159	0.248	0.274	0.164
Number of subjective symptoms	0.077	0.076	−0.064	0.027	0.019

HADS, Hospital Anxiety and Depression Scale; FSS, Fatigue Severity Scale; IES, Impact of Event Scale; PSQI, Pittsburg Sleep Quality Index; RT-PCR, reverse transcription polymerase chain reaction. **$p < 0.001$.

TABLE 5 Linear regression results for cognitive function by age and other clinical characteristics.

Predictor	Cognitive task	*F*	*P*	*B*	*t*	Adjusted R^2
Age	Digit span forward	4.830	<0.001	−0.598	−4.342	0.383
	Trail making test part A	4.683	0.003	−0.417	−3.267	0.387
	Digit span backward	6.932	<0.001	−0.374	−4.478	0.490
	Trail making test part B	8.485	<0.001	−0.670	−5.364	0.576
	Stroop word color interference	8.456	<0.001	−0.546	−5.853	0.561

Age, Hospital Anxiety and Depression Scale; Impact of Event Scale; Pittsburg Sleep Quality Index, and Fatigue Severity Scale results were entered as independent variables. Variables that showed significant results ($p < 0.05$) are presented in the table as predictors.

function and attention/processing speed. In particular, the older the patient, the more severe the cognitive impairment compared to age-adjusted norms. Routine inspection using objective neurocognitive tools is required for early detection, especially in elderly patients.

The results of our study are consistent with those of previous studies that investigated the prevalence of cognitive deficits in patients in the subacute phase. In particular, one study investigated cognitive function using the Montreal Cognitive Assessment in 53 hospitalized patients and 61.5% of patients had deficits in cognitive function, primarily in executive function, attention, language, and delayed recall (Ermis et al., 2021). Another study that conducted cognitive function tests at the 12th week of diagnosis with 130 patients discharged after treatment for COVID-19 reported that executive function and psychomotor coordination were impaired in 50–75% of patients (Mazza et al., 2021). All participants in our study had confirmed SARS-CoV-2 infection during the Omicron-variant era, and the severity of acute symptoms was relatively low. Our results suggest that observation of cognitive sequelae is needed even in patients who suffered from mild symptoms in the Omicron era and did not require hospitalization in the acute phase. Further, this argument is strengthened by a recent case-control study that reported significant cognitive decline and brain structural changes after SARS-CoV-2 infection regardless of hospitalization (Douaud et al., 2022).

There is now a large body of literature on neurocognitive sequelae associating with cognitive domains and clinical characteristics. With respect to cognitive domains, more evident impairments in higher cognitive functions were reported in a large cohort study of 12,689 individuals who were suspected to have COVID-19 (Groiss et al., 2020). This study did not specify the time since COVID-19 was confirmed, and the degree of severity of respiratory symptoms in the subjects varied. In a study focusing on 181 cases of long COVID, memory exhibited the only significant decline among the cognitive domains after controlling for age, sex, country, and education level (Guo et al., 2022b). In that study, there was a significant group difference in reaction time on the executive function test, but this dropped below significance after adjustment. In another study with 100 subjects visiting a Neuro-COVID-19 clinic, short-term memory and attention were the most commonly impaired domains (Davis et al., 2021). This study included 50 non-hospitalized SARS-CoV-2 laboratory-positive individuals and 50 laboratory-negative individuals. In our study, the most commonly impaired domain was executive function (Stroop word color interference and TMT-B), followed by attention/processing speed (digit span forward and TMT-A). We defined impairments in each measure as a z-score of ≤−1.5 SD below the measure-specific age- and sex-adjusted norms. However, education level was not controlled for, and there was no control group in our study. It is also necessary to consider that the tasks representing each cognitive domain differed by study. Otherwise, cognitive

TABLE 6 Comparisons of the cognitive test results across the subjective symptoms.

		Attention/processing speed		Working memory	Executive function	
		Digit span forward	Trail making test part A	Digit span backward	Trail making test part B	Stroop word color interference test
Palpitation	*Z*	−1.196	−0.783	−0.276	0.000	−0.424
	p	0.245	0.441	0.799	1.000	0.707
Shortness of breath	*Z*	−0.531	−0.559	−0.471	−0.436	−1.049
	p	0.613	0.582	0.654	0.668	0.337
Dizziness	*Z*	−0.546	−0.144	−0.766	−0.570	−0.086
	p	0.592	0.888	0.460	0.587	0.936
Sputum	*Z*	−0.305	−1.040	−0.320	−0.869	−0.247
	p	0.765	0.304	0.765	0.400	0.819
Headache	*Z*	−1.927	−0.723	−2.081*	−1.187	−1.402
	p	0.055	0.476	**0.039**	0.240	0.195
Tingling	*Z*	−1.827	−0.477	−1.838	−0.591	−0.592
	p	0.072	0.639	0.067	0.561	0.593
Memory impairment	*Z*	−0.314	**−2.094***	−0.670	−1.076	−1.232
	p	0.769	**0.036**	0.510	0.287	0.257
Coughing	*Z*	−0.305	−1.040	−0.320	−0.869	−0.247
	p	0.765	0.304	0.765	0.400	0.819
Heartburn	*Z*	−0.156	−0.963	−0.156	−1.179	−0.307
	p	0.879	0.341	0.879	0.243	0.775
Abdominal discomfort	*Z*	−0.453	−0.244	−0.099	−0.480	−0.146
	p	0.667	0.822	0.923	0.636	0.892
Chest pain	*Z*	−0.795	−0.061	−0.524	−0.745	−1.005
	p	0.443	0.964	0.606	0.463	0.357
Weight loss	*Z*	−0.791	**−2.188***	−0.819	−1.537	−0.983
	p	0.437	0.028	0.420	0.127	0.360
Abdominal pain	*Z*	−1.062	−0.534	−1.326	−0.702	−0.795
	p	0.303	0.610	0.195	0.489	0.460
Hypogeusia	*Z*	−0.782	−0.633	−0.061	−0.147	−0.309
	p	0.443	0.544	0.964	0.900	0.775
Hyposmia	*Z*	−1.368	**−1.967**	−1.272	−1.155	−0.873
	p	0.177	**0.051**	0.210	0.255	0.428
Blurred vision	*Z*	−1.395	−0.842	−0.863	−0.998	−1.290
	p	0.163	0.400	0.388	0.318	0.197
Bladder-related symptoms	*Z*	−1.499	−0.641	−0.199	−0.316	−1.19
	p	0.134	0.521	0.842	0.752	0.234

Bold values represent the $p \leq 0.051$. *$p < 0.05$.

impairment in this study may be characteristic of subacute patients who experienced relatively milder symptoms during the Omicron era. The absence of a memory test in the battery of day-of-visit cognitive tests is a limitation of our study. Taken together, memory, executive function, and attention domains need to be investigated according to the phases and characteristics of subjects with COVID-19.

In terms of clinical characteristics, as patients aged, cognitive function declined more than the age-and sex-adjusted norms in all cognitive domains. Previous studies have also shown that cognitive decline in patients with post-COVID syndrome is more prominent in older patients (Kouzuki et al., 2021; Badenoch et al., 2022; Douaud et al., 2022). Interestingly, in our study, significance was maintained after adjusting for the severity of psychiatric symptoms and fatigue. Furthermore, severity of psychiatric symptoms was not related to age (**Supplementary Table 1**). This suggests that cognitive decline could be a sequela of the viral disease, not merely a symptom related to fatigue, mood, or anxiety.

Several mechanisms of cognitive decline after COVID-19 have been suggested, and structural and functional imaging studies are accumulating (Hosp et al., 2021; Aoun Sebaiti et al., 2022); however, many aspects remain unknown. Although the purpose of our study was not to elucidate the underlying mechanisms, our results provide some clues. Our study found that the frequency of executive function decline was common in the subacute phase and was not associated with other subjective ongoing symptoms. In contrast, attention, processing speed, and working memory deteriorated more in participants who reported subjective memory loss (TMT-A), weight loss (TMT-A), and headache (digit span backward) than in participants who did not. The gray matter thickness and tissue contrast

in the orbitofrontal cortex, which is associated with executive function, were significantly reduced in COVID-19 survivors compared to controls, and this significance was maintained after excluding patients hospitalized for severe symptoms (Douaud et al., 2022). In a previous study with immune markers, an increased systemic inflammation index in the acute phase predicted further cognitive decline in processing speed and coordination but did not predict declines in executive function (Mazza et al., 2021). These results suggest that deterioration of executive function might be a symptom independent of the severity of systemic inflammation. Further studies with the same group after the systemic symptoms disappeared are needed to clarify this.

Headache is one of the most common neurological symptoms among the general population. Headache was correlated with the results of the digit span backward test, which showed the smallest percentage of decline in our study, as well as in a prior large cohort study (Groiss et al., 2020). In another study, headache severity was associated with performance on the word recognition test, category fluency, and pictorial associative memory (Guo et al., 2022b). Therefore, whether this correlation is disease specific or a more general manifestation needs to be investigated in studies with control groups. In addition, factor analysis studies to identify the features of long COVID are important.

Interestingly, participants with hyposmia tended to show decreased performance on the TMT-A at the trend level (p = 0.051). In addition, there were no differences in age or other psychiatric symptom scale results between the hyposmia and non-hyposmia groups (**Supplementary Table 2**). Decreased performance on the TMT-A, which reflects a concentration problem, has been frequently found in neuroinflammatory conditions, such as chronic fatigue and chemobrain syndrome (Aoun Sebaiti et al., 2022). Consistent with this result, COVID-19-related hyposmia has recently been shown to be associated with viral persistence and neuroinflammation (de Melo et al., 2021). The presence of hyposmia in the subacute phase may be attributed to ongoing neuroinflammation, which further affects cognitive function.

This study has several limitations. First, our results cannot be generalized to all patients with subacute COVID-19 because the data were obtained from patients who had been referred to a psychiatric clinic. However, depression, anxiety, and other psychiatric symptom severities were not associated with cognitive functional outcomes (**Tables 4**, **5**). Second, we could not check all cognitive domains, including memory function, because the tests were conducted on the day of presentation for patients who visited from afar owing to their long-COVID. Third, although the checklist contained a total of 31 symptoms covering all systems, we could not compare cognitive function based on all subjective symptoms owing to the small number of cases or non-cases in some symptoms. In addition, the difference in cognitive function by clinical symptoms was not significant in multiple linear regression; therefore, these results need to be taken as exploratory demonstrations for future research. A large-scale longitudinal study is required to determine the cognitive trajectory of COVID-19 patients. Fourth, it is difficult to establish the extent to which cognitive change is due to COVID-19 infection specifically, or other factors related to the pandemic period, which has been one of the most stressful conditions for many people, regardless of infection status. We showed that cognitive decline was not correlated with current psychiatric symptoms, but a comparison with a non-infected control group would be preferable.

Nevertheless, this study has several strengths. First, this is the first study to report the objective cognitive sequelae of patients with COVID-19 in South Korea and showed that the characteristics were consistent with results from other countries. Second, this study demonstrated cognitive function in patients in the subacute phase of COVID-19 and suggested that the cognitive sequelae of COVID-19 could start before the chronic phase, especially among older patients. Third, this study showed a separate cognitive decline that was not fully explained by psychiatric symptoms and explored the relationship between cognitive sequelae and the systemic symptoms of COVID-19.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) of Myongji Hospital. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

SL and WL: conceptualization. JC: data curation, validation, visualization, and writing—original draft. SL: formal analysis and supervision. All authors contributed to writing—review and editing, investigation, and methodology.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.994331/full#supplementary-material

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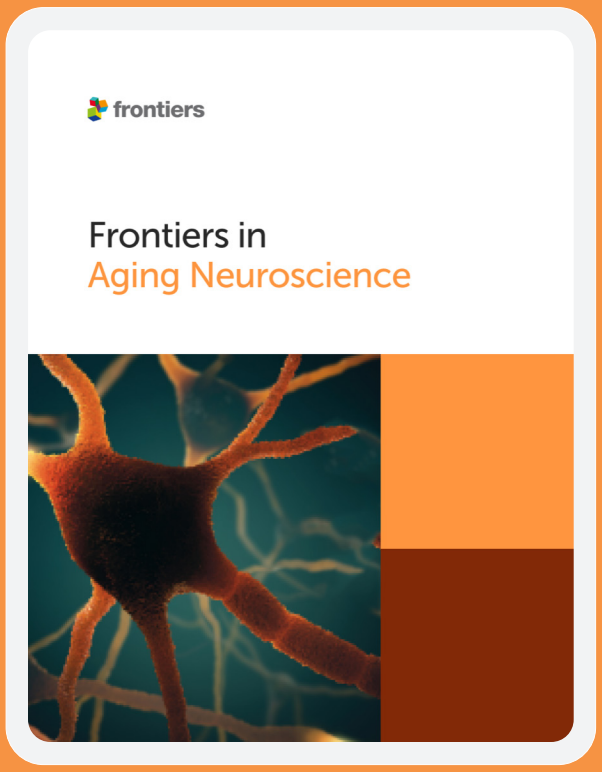

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