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Post COVID-19: Analysing and addressing the challenges faced by patients following intensive care treatment for COVID-19

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Published in
Frontiers in Medicine
Frontiers in Sociology
Frontiers in Psychology

ISSN 1664-8714
ISBN 978-2-8325-4102-9
DOI 10.3389/978-2-8325-4102-9

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Citation

Auriemma, V., Piazza, O., Scarpati, G., Iorio, G., eds. (2023). *Post COVID-19: Analysing and addressing the challenges faced by patients following intensive care treatment for COVID-19*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-4102-9

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frontiers | Frontiers in Sociology

TYPE Editorial
PUBLISHED 28 November 2023
DOI 10.3389/fsoc.2023.1332156

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 02 November 2023
ACCEPTED 17 November 2023
PUBLISHED 28 November 2023

CITATION
Auriemma V, Iorio G, Scarpati G and Piazza O (2023) Editorial: Post COVID-19: analysing and addressing the challenges faced by patients following intensive care treatment for COVID-19. *Front. Sociol.* 8:1332156. doi: 10.3389/fsoc.2023.1332156

Editorial: Post COVID-19: analysing and addressing the challenges faced by patients following intensive care treatment for COVID-19

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KEYWORDS

doctor–patient, intensive care, post COVID-19, social wellbeing, psychic wellbeing

Editorial on the Research Topic
Post COVID-19: analysing and addressing the challenges faced by patients following intensive care treatment for COVID-19

Introduction

This Research Topic has aimed to reflect the significant consequences of the pandemic for COVID-19 survivors; therefore, it offers readers the opportunity to understand all those factors that have influenced and continue to influence patients' distress and opportunities for recovery, with the aim of best ensuring that the consequences of the pandemic do not develop into chronic injuries.

The key concept throughout the Research Topic was transdisciplinarity, as reflected both in the scientific differentiation of the papers received and in the very organization of the various authors within each paper. So, given the nature of the topic, which falls between medicine, sociology, social work and psychology, it was possible to obtain a more comprehensive assessment of the complexity of the current situation (Auriemma et al., 2023).

Although the health perspective focuses primarily on understanding the physiological aspects of COVID-19, it was possible to capture, through the papers presented, the different ways in which patients were able to restore their wellbeing not only physiologically, but also socially, especially through the support they received from medical professionals as many papers describe and from local health services after discharge from intensive care units (ICUs).

Review and opinion contributions

Among the various works that confirmed and lent luster to our main objective, we certainly find Di Rosa's review, whose aim was to reflect on the specific area of the interaction between health care and social care (and vice versa). This field, as obvious as it is, does not

always receive the right attention, whose roles increasingly go by the wayside despite the enormous amount of work being done. Therefore, the author showed how medicalization in emergency management has undermined or, at least, weakened the comprehensive approach to the person and vulnerability profiles that should inspire social and health integration (Di Rosa). The author, also described the relationship that exists between health systems and social systems and the effects of the COVID-19 pandemic on it, pointing out and specifying how much that weak link that, especially in certain parts of the world, was present has been undermined.

By reading Deng's text, however, it is possible to delve, in small steps, into the other focus of our call, that of physiological care processes. Indeed, it is possible to understand how the early application of prone ventilation, for COVID-19 patients, offered a survival advantage, all of which generated, as consecon a lower expected mortality in patients with severe ARDS (Deng and Zou).

Empirical results: quantitative data and original research

The empirical work section opens with a very interesting paper by Agnoletti et al. who present readers with an innovative and functional method for coping with the increase in intensive care unit beds related to pandemic COVID-19, demonstrating the feasibility and efficiency of a dynamic model of hospital reorganization.

The aim of the study by Wang et al. was to explore the application and effect of the "WeChat cloud service" in the emergency intensive care unit. A kind of tele-medicine, or, at least, tele-support. The research was conducted on 774 patients admitted within the intensive care unit between February 2020 and June 2021. The authors pointed out that, there was a significantly better situation due to lower costs and lower delirium situations. Claiming that the "WeChat cloud service" was helpful in preventing and controlling coronavirus disease 2019 during the outbreak and improving patient experience (Wang et al.).

Instead, authors Snoubar et al., proposed an article starting with a description of the qualitative-quantitative research conducted on the effect of COVID-19 fear toward the future. They analyzed 204 Turkish social workers who were engaged in the front lines against the pandemic. In general, social workers were found to be extremely concerned about contracting COVID-19. However, the authors also pointed out that female social workers had a greater fear of contracting the infection than males. Social workers and frontline committed health workers can use these findings to develop effective intervention programs reduce fears related to COVID-19 (Snoubar et al.).

To enrich our review, it is also possible to read the work of Zulbaran-Rojas et al. The authors present work that investigates the consequences of being in the intensive care unit for long periods of time. Dwelling on one risk in particular, namely the deconditioning of lower extremity muscles, especially in critically ill patients. The study is described as a double-blind, randomized controlled trial through which the safety and efficacy of electrical stimulation in the lower limbs was examined. Therefore, the researchers' goal was to have empirical evidence in the use of electrostimulation to prevent muscle decay (Zulbaran-Rojas et al.).

Another very interesting study for our call is the work of Naorungroj et al. The authors described the characteristics and outcomes of intrahospital mortality of patients hospitalized for COVID-19. This paper is presented as a retrospective review on the medical records of patients with COVID-19 infection admitted to the intensive care unit of Siriraj Hospital between January 2020 and December 2021. The authors hypothesized a strategy based on appropriate selection of patients to be admitted to the ICU and to implement solutions to limit disease progression to prevent intubation (Naorungroj et al.).

One of the most outstanding studies in this call is the descriptive study by Yoo et al. The authors conducted interviews with caregivers of patients admitted to intensive care units during the COVID-19 pandemic. Their goal was to analyze the impact of listening to music on their psychological wellbeing. To collect this information, three questionnaires were administered, the first being the Korean version of the Center for Epidemiologic Studies Depression Scale, and the second being the World Health Organization Quality of Life Scale. Finally, a third, *ad-hoc* constructed questionnaire was used with the aim of collecting information on participants' engagement in musical activities, thus generating a data set that led to interesting results (Yoo et al.).

Regarding the cross-sectional study by Habibi Asgarabad et al. we note how the aim was to assess the validity and reliability of the General Health Questionnaire, characterized by 12 items and administered to patients hospitalized with COVID-19 in 2020. The authors pointed out that among the factorial models, using the three-factor model (successful coping, self-esteem and stress) proved to be the most suitable. So, overall, the results revealed some very interesting data, which had only been hypothesized before. That is, mental distress in patients with COVID-19 is related to high perceived stress and, more importantly, low sleep quality, which is easy to hypothesize because of the noise and intensive care units, but interesting to highlight with empirical data (Habibi Asgarabad et al.).

Within our call we find, also, an experimental study by Maslova et al., which was conducted in the post-COVID-19 paradigm to assess the quality of life after 9 months after leaving the ICU of critically ill patients. Two hospitalization conditions were analyzed, the first involving the use of medical oxygen for therapy and the second involving the non-use of medical oxygen for therapy in addition to outpatient treatment. This represents one of the first studies in the current literature to report the quality of life of patients who responded to treatment 9 months after COVID-19 (Maslova et al.).

Another very interesting study is represented within the work of Kuryllo et al. The authors' goal was to observe how patients admitted to the intensive care unit may exhibit muscle weakness up to a year or more after discharge. Within this study was analyzing neuromuscular progression by distinguishing the results between women and men, however, the study found no sex differences in the parameters assessed in the 3- to 6-month follow-up; the significant difference, however, was found in the 6- to 12-month follow-up (Kuryllo et al.).

The study by Hajkova et al. examined the impact of anxiety and depression symptoms during the first phase of pandemic

COVID-19. Therefore, the authors highlighted behavioral, cognitive and emotional changes in the Czech population. The authors' goal was, therefore, to show what has been widely hypothesized, namely, that increased anxiety and depression are symptoms that have characterized the experience of many due to loneliness and reduced close relationships (Hajkova et al.).

The study protocol by Sum et al. observes the residual symptoms manifested by patients in the post-acute and rehabilitation stages include fatigue, dyspnea and insomnia. The double-blind, randomized, placebo-controlled study aimed to evaluate the efficacy and safety of the combination of the two formulas [named "COVID-19 Rehab Formula (CRF)"] in treating the residual symptoms of COVID-19 (long COVID). In addition, evaluating the efficacy and safety of CRF in treating residual symptoms of COVID-19 with a scientifically rigorous design (Sum et al.).

The clinical study by Chi et al. explored the risk factors associated with postoperative hypoxemia in elderly patients recovered from COVID-19 disease and undergoing surgery for hip fracture in the short term. The authors conducted the study within three hospitals in China and found statistically significant differences among patients, and also followed the classification of the American Society of Anesthesiologists by comparing it with the presence of sputum symptoms, preoperative hypoxemia, and pulmonary inflammation from chronic obstructive pulmonary disease. So, it is interesting to note empirically how secondary risks can seriously affect respiratory disease (Chi et al.).

Conclusion

The main objective of this call, which we felt was fully achieved, was to highlight some of the insights that can be gained from a transdisciplinary exploration in the analysis of patients and health care and non-health care personnel during COVID-19. This allowed, in this way, to generate a pool of research from around the world, highlighting the different ways of operating, assessing and operationalizing the same disease. Consequently, it is important to analyze and delve into any type of theory while avoiding dwelling only on those theories that reflect on understanding others as only a matter of biological input, as the aspect of cultural interaction remains at the core of any discourse. We live in a historical period where isolated sectorization does not lead to any interesting discoveries, so the sciences need transdisciplinarity as m, as seen in this Research Topic, contributing to a common knowledge that can place the person at the center of all scientific discourse, avoiding scientistic reductionism and allowing researchers and scholars to draw on the broadest possible sources. In conclusion, the wonderful and ambitious goal that we editors from distant disciplines had set for ourselves and which the authors of each paper masterfully fulfilled, we must emphasize that today, despite the post-pandemic, it is possible to reflect from this to face the new challenges that the future holds. Mixing the techniques used in these papers, rather than emphasizing a different one than has always been used, to compare the results. So, transdisciplinarity as a deeper way of approaching science and future research.

Author contributions

VA: Writing—original draft, Writing—review & editing. GI: Writing—original draft, Writing—review & editing. GS: Writing—original draft, Writing—review & editing. OP: Writing—original draft, Writing—review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers in Medicine

ORIGINAL RESEARCH
published: 03 February 2022
doi: 10.3389/fmed.2021.833942

Impact of the "WeChat Cloud Service" Option for Patients in an Emergent Intensive Care Unit During an Epidemic in Tai Zhou China

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OPEN ACCESS

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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *12 December 2021*
Accepted: *28 December 2021*
Published: *03 February 2022*

Citation:
Wang J, Qin J, Tung T-H, Chen J, Zheng N, Lu L, Jin Y and Lin N (2022) Impact of the "WeChat Cloud Service" Option for Patients in an Emergent Intensive Care Unit During an Epidemic in Tai Zhou China. Front. Med. 8:833942. doi: 10.3389/fmed.2021.833942

To explore the application and effect of "WeChat cloud service" in the emergency intensive care unit (EICU) in the context of an epidemic, we examined 774 patients admitted to an EICU between February 2020 and June 2021. Patients admitted from February 2020 to December 2020 were selected as the control group ($n = 503$) and those from January 2021 to June 2021 comprised the observation group ($n = 271$). There were no statistically significant differences in gender, age, disease, and length of stay in the EICU between the groups. The control group received the general (routine) daily service, such as communicating with families through in-person information transmission, and receiving self-provided drugs and daily supplies during the specified visiting time; the observation group received the "WeChat cloud service" providing the chance of communication, supplies, and payment through the platform at any time. We used a T-test and $\chi 2$-test to analyse the incidence of delirium, labour costs, and patient and family satisfaction throughout ICU treatment for comparison. Results indicated that the observation group had lower labour costs, less incidence of delirium, and greater patient and family satisfaction than the control group. The "WeChat cloud service" was beneficial for preventing and controlling coronavirus disease 2019 during the epidemic and providing an improved patient experience.

Keywords: pandemic, COVID-19, WeChat, EICU, delirium

INTRODUCTION

The severe acute respiratory syndrome coronavirus causes an infectious disease known as coronavirus disease 2019 (COVID-19) that mainly involves pulmonary lesions. It is characterised by rapid onset, strong infection, and rapid changes in the physical condition of infected persons (1, 2). As of the time of the writing of this paper, the National Health Committee has incorporated pneumonia caused by COVID-19 as a Class B infectious disease as stipulated in the "Law of the People's Republic of China on Prevention and Control of Infectious Diseases," and adopted prevention and control measures for Class A infectious diseases. In the period during the COVID-19 pandemic, medical institutions have implemented prevention and control regulations and suggestions

by stopping or strictly restricting visits by hospitalised patients' families (Office of the National Health Commission, Office of the State Administration of Traditional Chinese Medicine. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia [trial version 6] at http://www.kankyokansen.org/uploads/uploads/files/jsipc/protocol_V6.pdf). Intensive care unit (ICU) patients have reduced immunity and a heightened risk of nosocomial infection, which are the key points of epidemic prevention and control (3). Thus, some nursing modes, such as traditional visits, are no longer suitable for providing nursing care to severe patients, and it is necessary to explore new nursing modes that actively create a good treatment environment for patients and meet the various needs of patients and their families (4, 5). "WeChat cloud service" is the integration of a "cloud visit" wherein the online delivery of hospitalisation expenses, online purchases of daily supplies for patients, and free delivery to the hospital are all managed over the WeChat platform. Therefore, we assessed the use of the WeChat cloud service with patients in an emergency ICU (EICU) to determine if it can offer superior comfort and humanistic care for patients and their families by reducing the incidence of delirium and improving the satisfaction of patients and their families.

TABLE 1 | Patient demographics and their conditions requiring treatment in the EICU ($n = 774$).

Characteristics/conditions		Control group	Observational group	x^2/t	*P*
Gender	Male	340	190	0.517	0.472
	Female	163	81		
Age (years)		62.71 ± 17.08	63.36 ± 18.94	−0.482	0.63
Disease or condition	Trauma—non-surgical	142	68	7.637	0.266
	Trauma—surgical	56	23		
	Sepsis	84	47		
	Cardiovascular disease	63	52		
	Cerebrovascular diseases	55	27		
	Poisoning	33	15		
	Other	70	39		
Average length of stay in EICU (days)		7.36 ± 8.10	6.48 ± 5.98	1.703	0.089

MATERIALS AND METHODS

Participants

A total of 774 patients admitted to the EICU of Taizhou Hospital of Enze Medical Centre in Zhejiang province, China, from February 2020 to June 2021 were selected for participation in this study. Inclusion criteria were patients (1) who were hospitalised in the EICU for more than 24 h; (2) who provided informed consent for themselves and their families to participate; (3) who had consciousness or Richmond Agitation Sedation Scale (RASS) > -3; (4) who could read and fill in the questionnaire by themselves; and (5) whose families had smartphones and could skilfully use WeChat functions. Exclusion criteria were patients who (1) had disputes with the EICU or died while in the EICU; (2) did not agree, or whose families did not agree, to participate or cooperate; and (3) dropped out during their time in the EICU. A total of 503 patients admitted from February 2020 to December 2020 were selected as the control group, and 271 patients admitted between January 2021 and June 2021 were selected as the observation group. There were no statistically significant differences in gender, age, disease, and length of stay in the EICU between the two groups (see **Table 1**). This study was reviewed and approved by the hospital ethics committee.

Study Design

In this study, the method of before and after comparison was adopted. The time period was taken as the cut-off point, and the study samples were selected. The conventional nursing mode (control group) and wechat cloud service nursing mode (observational group) were, respectively, adopted. **Table 1** showed that there was no statistical difference between observational and control groups.

Sample Size Determination

The study design were based on the literature reviews and integrated the resources of the hospital. The wechat cloud service system with service items was established. All courses were applied in keeping with the principles of our institutional ethics committee and in accordance with the Declaration of Helsinki. All of the participants' data were kept anonymous. This study was approved by the Institution Review Board of Taizhou Hospital of Zhejiang Province in China.

For the determination of study sample, we exported the data from the EICU electronic nursing shift system. Patients with conscious and RASS score >-3 were screened out by Excel ($n = 774$). According to the patient information, ICDSC delirium score of the patient during EICU hospitalisation was derived from the electronic nursing shift system for statistical analysis of the data. The satisfaction questionnaire is a self-designed questionnaire with a total of 10 mandatory items, and each item is divided into very satisfied, relatively satisfied, satisfied and dissatisfied. The paper and wechat qr code scanning methods are used to investigate, and the final results are statistically analysed with each result accounting for more than 30%, as shown in the figure. Labour cost data: Before and after wechat cloud service, according to doctor-patient communication and business needs during EICU treatment, the average number of patients' family members returning to and from the hospital was counted for statistical analysis.

Procedure

The control group was offered the general daily service. Under this service, the EICU arranges visits from 15:00 to 15:30 every Monday, Wednesday, Friday, and Sunday when patients' families can visit outside the EICU window if they have

TABLE 2 | The incidence of delirium between the control group and "WeChat" group ($n = 774$).

Item	*n*	Cases with delirium *n*	Incidence of delirium %	x^2/T	*P*
Control group	503	89	17.60%	6.665	0.010
Observation group	271	29	10.70%		

negative nucleic acid test results. Before the visit, the nurses made various preparations for each patient, including adjusting their posture; providing basic nursing monitoring, treatment, and support services; checking inpatient account arrears; and managing the quantity of self-provided drugs. Meanwhile, the attendants checked the patient's daily supplies, including nursing pads and disposable gloves. During the WeChat visit, the patient communicates with his or her family through in-person information transmission. Meanwhile, the nurses and attendants communicate with a family member one-on-one according to the situation regarding any inpatient account arrears, the patients' self-provided drugs as verified by doctors, and an account of the daily supplies.

The observation group was offered the "WeChat cloud service" through which patients in the EICU could communicate with their families online during the visiting time specified every day or whenever needed. The procedure was as follows: (1) Preliminary preparation: Applying for the department's mobile phone and WeChat account used for special communication and ensuring that the WeChat accounts of directors, head nurses, responsible nurses, and tube bed doctors, including first-line and second-line doctors of EICU, are added to the department's WeChat account. The head nurse was responsible for establishing a total of 13 WeChat communication groups according to the number of beds using the department's mobile phone and WeChat account. Next, the director, head nurse, responsible nurse, and tube bed doctors joined the WeChat communication groups. The patients' families could join the corresponding communication groups by scanning a QR code. (2) Implementation: (i) After each communication group was established, a group announcement was issued to inform the patients' families about related matters such as not initiating video chatting by themselves. (ii) From 14:00 to 15:00 every day, the designated nurse responsible recorded a video of 2 min or less describing the patient's current condition for each severely ill patient in their charge. Meanwhile, for conscious patients, the designated responsible nurse scheduled video calls according to the needs of each patient. (iii) The EICU arranged visits from 15:00 to 15:30 every Monday, Wednesday, Friday, and Sunday, when the patient's families could visit outside the EICU window upon providing a negative nucleic acid test result. During the visit, video calls were arranged according to the needs of the patient and their families. (iv) In the communication group, the patient's families could ask via text or voice about any concerns they had regarding the patient's treatment and condition outside of the specified times (15:30 to 16:00 on Monday, Wednesday, Friday, and Sunday), and the doctors or nurses could reply later (whenever they were able to). (v) The purchase list of disposable living supplies and payment QR codes was provided according to the needs of patients. Their families could scan the payment QR code directly and pay for disposable living supplies, which were delivered at no cost. (vi) When an inpatient account balance was insufficient, the primary nurse communicated with the family through the communication group to confirm the payment amount and provide the payment QR code to charge. The communication platform also provided online purchases and in-hospital distribution of self-provided drugs. (vii) After the patient was transferred out of the EICU, the responsible nurse sent the patient and their family a QR code to access the satisfaction questionnaire, informed them about how to leave the group, and provided timely updates of the names of active members. (viii) It was uniformly stipulated that the communication group of the patient in the EICU will be called the "communication group of xx in Bed x" and the idle group will be called the "communication group in Bed x."

Observation Index

The Intensive Care Delirium Screening Checklist (ICDSC) for patients in the EICU with consciousness or RASS ≥ -3 was used to evaluate their delirium symptoms; a score of ICDSC > 3 indicated the occurrence of delirium. The incidence of delirium was calculated as the number of patients with delirium/the total number of patients included in the evaluation. The incidence of delirium was statistically compared between the two groups.

The satisfaction of patients and their families was measured using a patients' satisfaction questionnaire created by the EICU and included patient's feedback on, nursing quality, medical service attitude, and medical quality. The satisfaction evaluation was completed by the patients and their families using a QR code or fill in the paper questionnaire described in the questionnaire. Next, we exported the evaluation data and tabulated recovery rates and scores: the recovery rate of the satisfaction questionnaire = the number of satisfaction questionnaires collected per month/the total number of satisfaction questionnaires given out (which is equal to the number of transferred patients from the EICU per month).

The number of visits to the hospital patients' families needed was determined according to the condition of the patients, patient needs, and the needs of medical staff. We counted the number of visits family members made to the hospital and calculated the difference between the visits (the control group visits—the observation group visits).

Statistical Analysis

In this study, all data were analysed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA). The descriptions of all of the measurement data (patients' age, length of stay in the EICU) and counting data (patients' gender, disease, incidence of delirium, recovery rate of the satisfaction questionnaire) were expressed as mean ± SD and number (%), respectively. For univariate analysis, the two-sample independent *t*-test method and χ^2-test were adopted to assess differences in the mean value of continuous variables and percentage of categorical variables between observational and control groups. A $p < 0.05$

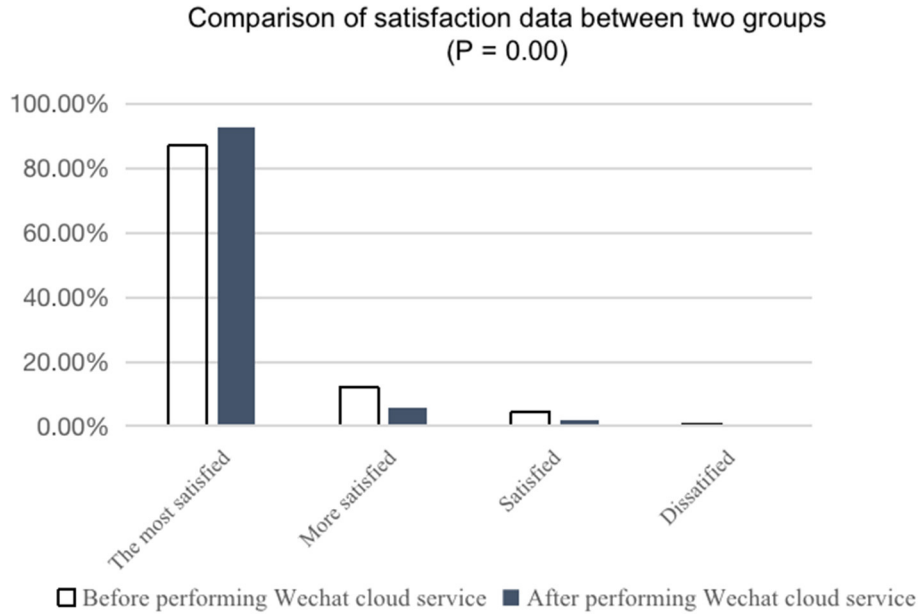

FIGURE 1 | Comparison of "satisfaction" data between the two groups.

was considered to represent a statistically significant difference between two test populations.

RESULTS

Incidence of Delirium

According to the ICDSC delirium score system, patients with consciousness or RASS ≥ -3 were assessed promptly if the patients experienced consciousness changes. A score of ICDSC > 3 indicated the occurrence of delirium. The statistical results between the two groups are shown in **Table 2**.

Patient and Family Satisfaction

The satisfaction evaluation was completed by scanning the QR code or Fill in the paper questionnaire for the self-report satisfaction questionnaire in the WeChat cloud service communication group. Next, the satisfaction data were exported for analysis. The results are as shown in **Figure 1**.

Hospital Travel Labour Costs for Patients' Families

After the implementation of the WeChat cloud service, the average number of patients' families needed at the hospital was reduced by 4 ± 2.18 compared with the control group. Thus, the labour cost of hospital travel for families of patients using the WeChat option was extremely low.

DISCUSSION

Patients in the EICU have critical conditions and high mortality rates (3). To ensure that the patients have adequate rest time and prevent cross-infection, the management mode of "no company, no visitors" is often adopted in these units. However, the establishment of the biological-psychological-social medical mode has highlighted the importance of the social and psychological needs of patients and their families and their impact on biological health (6–8). Hence, visitation is recognised as important for emotional communication between patients and their families in addition to the need for communication between medical staff and patients' families (9). The new epidemic era inevitably brought about the exploration of new visiting modes (10). With the development of communication technology and the popularity of smartphones and the WeChat application, video visitation, including WeChat video visitation, has been explored for use in intensive care units (ICUs) in recent years (11–17). On the basis of various studies on "cloud visits," we examined a WeChat cloud service platform that encompasses chat and payment functions for patients and their families. The platform was constructed to integrate group-building, video chatting, and payment processing.

Patients in the EICU are also often prone to delirium due to disease and predisposing factors. Delirium aggravates the condition of illness, is not conducive to treatment, and can delay a patient's recovery (18). The prevention and treatment of delirium require a systematic diagnosis and treatment programme composed of multiple projects, objectives, and methods. Currently, ABCDEF and eCASH strategies with delirium emphasise that family care and maximising humanistic care are important (19–21). Some studies (22–25) have found that it can significantly promote the management of delirium by prolonging ICU visiting time and increasing communication opportunities with patients and families. Meanwhile, the consensus among delirium experts is that paying attention to communication with patients and their families reduces the

occurrence of delirium and promotes the recovery of delirium (18). Using the cloud visiting function of the WeChat cloud service makes communication with patients and families more flexible and convenient as it is not limited by time and region. In addition, our results indicate it is effective for the prevention and treatment of delirium in EICU patients.

Using the payment function of the WeChat cloud service makes it possible to purchase patients' living supplies and self-provided drugs, and make hospitalisation payments online. Meanwhile, it can reduce the number of visits of patients' families; such a reduction is needed to save labour costs and meet the requirements of epidemic control by reducing gathering among hospital personnel and among members of the general public within the hospital when a family member is admitted. In addition, the recovery rate of the satisfaction questionnaire increased from 41.5 to 81.5% by scanning the QR code instead of the paper questionnaire, and the satisfaction scores of patients and families improved.

Limitations

There were several limitations should be discussed in this study. Firstly, despite the benefits of the WeChat service reported in this study, only one hospital was included, and it is located in a county-level area where the technological and cultural sophistication of patients and their families is relatively low. Thus, there were certain limitations in the use of WeChat cloud services for some patients, especially older adult patients who are less likely to use smartphones and may need a younger person to assist, thereby creating an indirect means of communication between the older person, the hospital, and the patient or other family members. Secondly, additional instruction or practise may be needed for people with different cultural levels to successfully adopt the technology for use for patients in EICUs. Meanwhile, the "WeChat cloud service" is used to establish communication groups according to the number of beds. The information of patients being admitted into and moving out of the hospital, and the participation and withdrawal of families should be updated timely by a special person to ensure ordering. Thirdly, it is difficult to investigate whether between the experimental group and the control group there were differences in all medical-physiological variables related to the health status of the patient during the period of hospitalisation in the ICU (therefore on the progression of the disease and on healing), that is, to assess whether, between the two groups, there were significant variations in some parameters, detectable with the common equipment present in the ICU, which could have a relationship with the implementation of the "weChat" system namely with this direct and continuous communication with family members. Fourthly, although the satisfaction questionnaire is a self-designed questionnaire, it can be used after reliability and validity test, it was difficult to exclude the error caused by the satisfaction measurement results. At the same time, the questionnaire design does not distinguish between family members and patients themselves, which may also produce certain bias to the results of the survey. Finally, this study only focused on the overall satisfaction of the questionnaire, and there is no sub-dimensions results. Future studies with further verify the effectiveness of wechat cloud service in patients' satisfaction would make these results more convincing.

CONCLUSION

The application of the "WeChat cloud service" in EICU can help hospitals meet the psychological needs of patients and their families, reduce the incidence of delirium in patients in EICU, improve the satisfaction among patients and their families, and reduce the cost of labour. Additionally, the WeChat cloud service can effectively reduce gatherings, which is especially critical during an epidemic era. Thus, the service is recommended as worthy for application in clinics.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was exempted from informed consent and approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province (Approval number: K20211219) in China.

AUTHOR CONTRIBUTIONS

JW conducted the literature search, designed the study, and collected the data and interpreted it. JQ administrated the project. T-HT revised the manuscript. JC, NZ, LL, and YJ interpreted the data and edited critically revised the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We thank the emergency intensive care unit for their contributions to this study. We thank Editage for their editing services. We thank Nongmu Lin for helping to communicating.

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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.

frontiers in Medicine

METHODS
published: 18 March 2022
doi: 10.3389/fmed.2022.819134

Description of an Integrated and Dynamic System to Efficiently Deal With a Raging COVID-19 Pandemic Peak

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OPEN ACCESS

Edited by:
Ornella Piazza,
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Reviewed by:
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Geremia Zito Marinosci,
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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *20 November 2021*
Accepted: *14 February 2022*
Published: *18 March 2022*

Citation:
Agnoletti V, Gamberini E, Circelli A, Martino C, Santonastaso DP, Bolondi G, Bastoni G, Spiga M, Ceccarelli P, Montaguti L, Catena F, Poletti V, Lusenti C, Lazzari C, Altini M and Russo E (2022) Description of an Integrated and Dynamic System to Efficiently Deal With a Raging COVID-19 Pandemic Peak. Front. Med. 9:819134. doi: 10.3389/fmed.2022.819134

Background: This study aimed to describe an innovative and functional method to deal with the increased COVID-19 pandemic-related intensive care unit bed requirements.

Methods: We described the emergency creation of an integrated system of internistic ward, step-down unit, and intensive care unit, physically located in reciprocal vicinity on the same floor. The run was carried out under the control of single intensive care staff, through sharing clinical protocols and informatics systems, and following single director supervision. The intention was to create a dynamic and flexible system, allowing for rapid and fluid patient admission/discharge, depending on the requirements due to the third Italian peak of the COVID-19 pandemic in March 2021.

Results: This study involved 142 COVID-19 patients and 66 non-COVID-19 patients who were admitted; no critical patient was left unadmitted and no COVID-19 severe patients referring to our center had to be redirected to other hospitals due to bed saturation. This system allowed shorter hospital length-of-stay in general wards (5.9 ± 4 days) than in other internistic COVID-19 wards and overall mortality in line with those reported in literature despite the peak raging.

Conclusion: This case report showed the feasibility and the efficiency of this dynamic model of hospital rearrangement to deal with COVID-19 pandemic peaks.

Keywords: COVID-19, intensive care unit, high dependency unit, step-down unit, hospital admission criteria, bed management, bed occupancy rate, patients throughput

INTRODUCTION

Since its onset, the COVID-19 pandemic has pressured healthcare systems worldwide. We previously described a functional and dynamic strategy that allowed our intensive care unit (ICU) to deal with the first two peaks of the pandemic, in March and October 2020, that in our community reached 8.2 cases per 1,000 inhabitants (1).

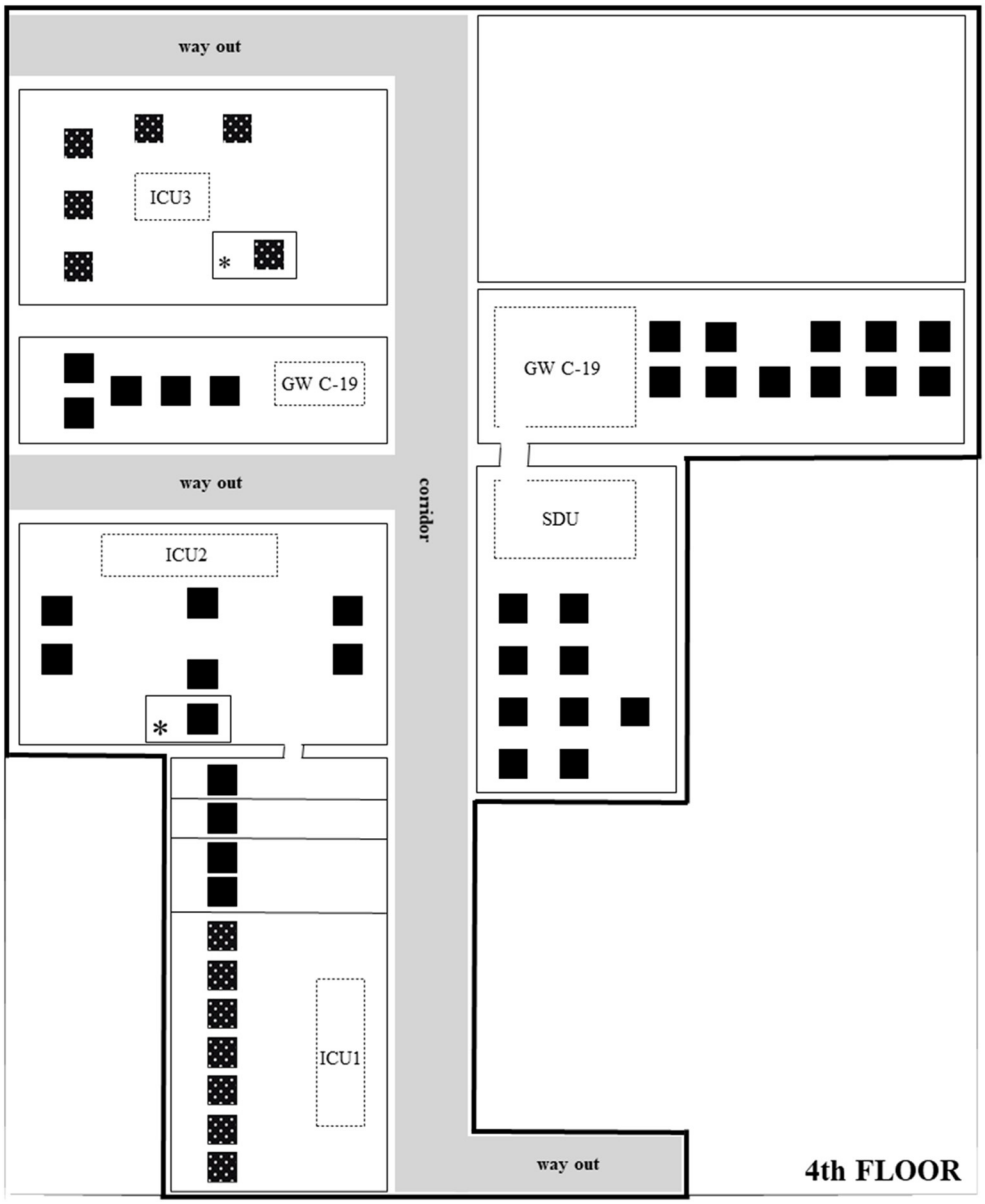

FIGURE 1 | Critical area on the 4th floor. Planimetry and bed location of the 4th floor, under the direct control of the intensive care department. Full-black beds,COVID-19 patients; Spotted-black beds, non-COVID-19 patients; Asterick, supra-numerary beds, usually not in use, open only for emergency; Dotted rectangles with unit name, medical positions and monitor areas physically separated from patient's open-space.

The setting is a public hospital of 450 beds, which is a reference point for a population of about 210,000 people. Before COVID-19, the ICU consisted of 18 beds, whereas during the pandemic, 6 non-COVID ICU beds and 9 step-down unit (SDU) beds were opened.

This case study aimed to show how this dynamic system has been furtherly implemented to deal with the third and strongest pandemic peak, in March 2021, reaching a local incidence of 13.3 positive cases per 1,000 inhabitants (62% increase).

Abbreviations: ICU, Intensive Care Unit; SDU, Step-Down Unit; PPNR, Patient-Per-Nurse Ratio; HFNC, High Flow Nasal Cannulae; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO_2, Oxygen Saturation; GW_{C19}, General Ward Covid-19; LOS, Length-Of-Stay; SD, Standard Deviation; ICU_{C19}, Intensive Care Unit Covid-19; ICU_{no-C19}, Intensive Care Unit No Covid-19; HDU, High Dependency Unit; ED, Emergency Department.

METHODS

As the third peak was arising, all the hospital non-COVID wards were promptly resized and relocated. Strategically, the first units

TABLE 1 | Clinical description of the patients admitted in the different units during the pandemic peak.

	GW_{C19}	SDU	ICU_{C19}	ICU_{no-C19}
Number of patients admitted	76	41	25	66
Men/women	46/30	28/13	19/6	36/30
Mean (SD) age, in years	63.7 (9.2)	61.4 (12.5)	58.3 (12.4)	61.8 (13.4)
Mean (SD) length-of-stay (LOS), in days	5.9 (4.0)	7.0 (4.6)	8.6 (6.7)	4.0 (5.3)

GW_{C19}, General (Internal Medicine) Ward COVID-19; SDU, Step Down Unit; ICU_{C19}, Intensive Care Unit COVID-19; ICU_{no-C19}, Intensive Care Unit Non-COVID-19.

left empty were those close to the ICU-SDU (4th floor) and to the COVID-internal medicine (6th floor).

With respect to the previous strategy, a further internistic COVID unit, General Internal Medicine Ward COVID-19 (GW_{C19}), of 16 beds was carved out on the 4th floor, next to the SDU (**Figure 1**). It was staffed by an intensivist physician, with an 8:1 patient-per-nurse ratio (PPNR), wherein nurses were not ICU-trained. Two monitored beds (oxygen saturation, non-invasive or invasive blood pressure, and ECG) for patients needing high flow nasal cannulae (HFNC) were available. Admission criteria to this general ward were the following: patients positive to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with radiologic evidence of pulmonary interstitiopathy, dyspnea, oxygen saturation (SpO_2) $\geq$ 92% on room air, and low oxygen supplementation (less 10 L/min). Clinical factors, such as fever, hypertension, and diabetes mellitus, were considered risk factors for possibly severe evolution (2).

The 4th floor, under the control of the intensive care department, thus counted on the following: 16 GW_{C19} beds, 1 intensivist, 8:1 PPNR; 9 beds SDU, 1 intensivist, and 3:1 PPNR (at least 1 ICU-trained nurse); 11 ICU1 beds, 2 intensivists (1 during the night shift), and 2:1 PPNR; 7 ICU2 beds, 2 intensivists (1 during the night shift), and 2:1 PPNR; 6 ICU3 beds, 1 intensivist, and 2:1 PPNR (**Figure 1**). Admission criteria to SDU were previously described (1).

This was made possible by a drastic 50% reduction of the planned operating room activity, actuated for safety reasons, that allowed to recover a sufficient number of anesthetists to be employed at the 4th floor. In Italy, anesthesia and intensive care still constitute a single residency program, thus specialists are certified and trained to manage complex patients with one or more ongoing organ failure.

In March 2021, the Italian Ministry of Health published new guidelines on the management of isolation of severe COVID-19 patients: (3) 21 days after the first SARS-CoV-2 positivity, if asymptomatic or with a negative molecular test, they were considerable non-infective and transferable to non-COVID units. This increased the fluidity in the management of bed occupancy.

TABLE 2 | Summary of the provenience and the discharge destination of all the patients treated at the 4th floor integrated system led by the intensive care department.

4th floor unit	$GW_{C19,\ n\ (\%)}$	SDU, n (%)	$ICU_{C19,\ n\ (\%)}$	$ICU_{no-C19,\ n\ (\%)}$
Patients coming from (admission):				
COVID-19 wards				
ED	41 (53.9)	8 (19.5)	1 (4)	19 (28.8)
GW_{C19}	-	26 (63.4)	8 (32)	-
GeW_{C19}	24 (31.5)	-	-	-
SDU	11 (14.4)	3 (7.3)	11 (44)	1 (1.5)
ICU_{C19}	-	4 (9.7)	-	-
$oICU_{C19}$	-	-	5 (20)	-
Non-COVID-19 wards				
GW_{no-C19}	-	-	-	40 (60.6)
ICU_{no-C19}	-	-	-	6 (9.1)
Total number (%)	76 (100)	41 (100)	25 (100)	66 (100)
Patients going to (discharge):				
COVID-19 wards				
GW_{C19}	-	20 (42.5)	-	-
oGW_{C19}	9 (14.2)	6 (12.7)	1 (7.4)	-
SDU	10(15.9)	-	7 (50)	-
ICU_{C19}	-	11 (23.4)	-	-
$oICU_{C19}$	-	10 (21.2)	5(35.7)	-
RW_{C19}	-	-	1 (7)	-
Non-COVID-19 wards				
GW_{no-C19}	-	-	-	44 (63.8)
ICU_{no-C19}	-	-	-	9 (13)
RW_{no-C19}	-	-	-	16 (23.2)
Home	44 (69.8)	-	-	-
Total number (%)	63 (100)	47 (100)	14 (100)	69 (100)

The upper part of the table shows from where the patients were admitted to the different units. The lower part of the table shows to which units the patients were discharged. $oICU_{C19}$ refer to nearby hospital ICUs collapsed during the pandemic peak, which referred 5 of their supernumerary patients to our ICU_{C19}. Other patients were carried from the ambulances directly from nearby provinces to our emergency department. As soon as they were stabilized and a bed was available in their local ICU or hospital, they were discharged outside our hospital. A geriatric ward (GeW_{C19}) was also available for elderly patients in our hospital, although not described in the paper. When a patient fulfilled the admission criteria, he was admitted to the GW_{C19} despite the advanced age, upon bed availability. ED, Emergency Department; GW_{C19}, General (Internal Medicine) Ward Covid-19; oGW_{C19}, Other General (Internal Medicine) Ward Covid-19 not led by intensivists; GeW_{C19}, Geriatric Ward Covid-19, GW_{no-C19}; SDU, Step Down Unit; ICU_{C19}, Intensive Care Unit Covid-19; $oICU_{C19}$, Other Intensive Care Unit Covid-19 in a different hospital; RW_{C19}, Rehabilitation Ward Covid-19; GW_{no-C19}, General Ward No Covid-19; ICU_{no-C19}, Intensive Care Unit No Covid-19; RW_{no-C19}, Rehabilitation Ward No Covid-19.

RESULTS

In March 2021 (31 days), a total of 142 COVID-19 patients and 66 non-COVID-19 patients were admitted to the 4th floor. **Table 1** describes the characteristics of these patients. The 4th-floor setting allowed to admit every patient to a level of intensiveness appropriate for their clinical status.

Mean length-of-stay (LOS) (*SD*) in days was 5.9 (4) for GW_{C19}, 7 (4.6) for SDU, 8.6 (6.7) for ICU COVID-19 (ICU_{C19}), and 4 (5.3) for ICU non-COVID-19 (ICU_{no-C19}). The mortality rate was 2.6% for GW_{C19}, 20% for SDU, 36% for ICU_{C19}, and 9.2% for ICU_{no-C19}, in line with available literature (4, 5).

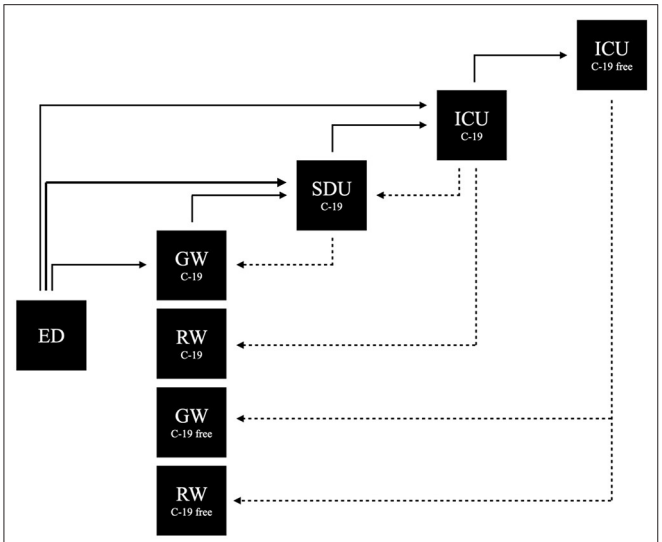

FIGURE 2 | Patient COVID-19 flow. Patients flow between the different units during the pandemic peak. For the number of patients refere to **Table 2**. ED, Emergency department; GW C-19, General ward COVID-19; RW C-19, Rehabilitation ward COVID-19; SDU C-19, Step down unit COVID-19; ICU C-19, Intensive care unit COVID-19; ICU C-19 free, Intensive care unit no-COVID-19; GW C-19 free, General ward no-COVID-19; RW C-19 free, Rehabilitation ward no-COVID-19.

Table 2, **Figure 2** summarize the overall flow of patients between different units.

Mean ($\pm$ *SD*) LOS in GW_{C19} was shorter than in other internistic COVID-19 wards: 5.9 (4) days vs. 11.8 (5) days ($p < 0.0001$; unpaired *t*-test). This is probably due to the higher rapidity by which patients were transferred to a higher level of care through early detection of clinical deterioration and simple transfer systems or to the mindset of intensivists used to working with short timescales. All patients with severe COVID-19 who were referred to our hospital have been hospitalized, none needed to be referred to other hospitals, thanks to a system that avoided hospital bed saturation.

DISCUSSION

The decision to staff the GW_{C19} with anesthesiologists/intensivists was proposed by the hospital direction due to staff contingency. The director of anesthesia and ICU and the collaborators agreed with this setting, to ease and improve the management of patient discharge from ICU and SDU, trying to avoid bed saturation. Being part of the same team, sharing the same protocols, informatics system (Margherita 3), and coordinators allowed considerable time-saving. This was an efficient solution to maintain a safe and balanced hospital environment.

Differently from the previous report from March and April 2020, SDU worked more as a high dependency unit (HDU), at a semi-intensive care level, more complex than a common step-down unit (6). Furthermore, 8 patients were transferred from ICU_{C19} to SDU without requiring invasive ventilation; of the 41 patients admitted in SDU, only 11 needed escalation to ICU_{C19} for higher monitoring or orotracheal intubation; 34 patients were admitted directly from the emergency department (ED) to SDU. These data seem to testify to the high intensity of care reached in SDU at this third wave.

A limitation of this report is that, by its nature of case study, it is not matched with a comparative system. Moreover, at first superficial sight, the employment of intensivists in GW_{C19} and SDU might seem a waste of resources. In our experience, this has allowed many physicians to cyclically work at a lower intensity, periodically decompressing from the stress and pressure of a year in an ICU_{C19}, interacting with conscious patients experiencing better outcomes, thus reducing burnout problems (7).

A further limitation of this system is that it worked in our specific context, whereas, it might not be applicable for hospitals acting as referral centers for a much wider general population and it might also not be applicable to regions where the incidence rate is much higher, determining a dramatic pandemic wave.

The model of differential intensity for hospital care management (high-intensity for ICU, medium-intensity for SDU, and low-intensity for GW), handled by a single intensive care unit, determined a sort of independence of the 4th floor from the hospital. The 4th floor was able to admit COVID-19 patients from other units/floors as needed from their clinical status evaluated by a consultant, but internally there was no need for hospital bed-manager coordination, counseling requests, bureaucracy, and time-wasting procedures.

CONCLUSION

The use of a COVID-19 "critical floor" from the general ward to ICU is an example of system adaptability. The effort made by intensivists was useful for patients in terms of quality of care and doctors in terms of occupational stress and mental health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

VA conceived the study and wrote the article. EG, AC, CM, DS, and GBo worked in COVID-19 ICU and wards and helped to write the article. GBa, MS, and PC coordinated the nursing staff in the management of the ward. LM, FC, CLu, MA, CLa, and VP collaborated to review the manuscript. ER helped to write the manuscript and provided supervision. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors thank all the colleagues (physicians, nurses, and healthcare operators) who cannot be mentioned in this article, who bravely and restlessly collaborated to face this year of COVID-19 pandemic.

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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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GENERAL COMMENTARY
published: 24 May 2022
doi: 10.3389/fmed.2022.884942

Commentary: Lung Recruitment, Individualized PEEP, and Prone Position Ventilation for COVID-19-Associated Severe ARDS: A Single Center Observational Study

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Keywords: COVID-19, prone position, endotracheal tube (ETT), ventilation, prone position tube (PPT)

A Commentary on

Lung Recruitment, Individualized PEEP, and Prone Position Ventilation for COVID-19-Associated Severe ARDS: A Single Center Observational Study
by Sang, L., Zheng, X., Zhao, Z., Zhong, M., Jiang, L., Huang, Y., Liu, X., Li, Y., and Zhang, D. (2021). Front. Med. 7:603943. doi: 10.3389/fmed.2020.603943

OPEN ACCESS

Edited by:
Giuliana Scarpati, University of Salerno, Italy

Reviewed by:
Sachit Anand, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, India

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Specialty section:
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

Received: *27 February 2022*
Accepted: *15 April 2022*
Published: *24 May 2022*

Citation:
Deng M and Zou W (2022) Commentary: Lung Recruitment, Individualized PEEP, and Prone Position Ventilation for COVID-19-Associated Severe ARDS: A Single Center Observational Study. Front. Med. 9:884942. doi: 10.3389/fmed.2022.884942

The worldwide outbreak of "coronavirus disease 2019" (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has topped 5,916,373 deaths with more than 420 million diagnosed cases as of 24 February 2022 (1). Patients with acute hypoxemic respiratory failure or acute respiratory distress syndrome (ARDS) used to be treated with oxygen and ventilation (2). Approximately 3.2% of patients with COVID-19 required intubation and invasive ventilation in mainland China (2).

Early application of prolonged prone position ventilation provides a survival advantage with expected lower mortality in patients with severe ARDS (3) and has been widely used in Wuhan for critically ill patients with COVID-19 by improving mechanics and gas exchange (2). However, prone position ventilation was associated with an increased safety risk of displacement or dislocation of the endotracheal tube due to the gravity and the tape getting damp from oral secretion (4), especially in prolonged prone ventilation and patients with severe COVID-19 infection. In view of this, it is prudent to avoid unnecessary displacement or dislocation of the endotracheal tube in prone-position-ventilated patients with COVID-19 in order to avoid adverse events and unnecessary exposure of the virus to the environment.

In our previous study, we applied a custom-designed prone position tube (PPT) (**Figure 1A**) for patients undergoing prone position surgery (**Figure 1B**) (4, 5). Unlike those traditional tubes and tube-securing devices, the PPT tube and the fixation device are integrated with the following advantages: (1) it is designed with a fixture that attaches to the tube to keep the sides of the cord firm; (2) the fixation method is more effective and easier to manage, and the fixing effect is more reliable; (3) once fixed, the binding cord will not be affected by the sterilizing fluid, blood, or fluids leaking from the mouth; (4) the tube is reinforced with a steel wire to prevent patients from biting the tube; (5) the displacement rate of the tube in our previous research was lower compared with that of the Haider Tube-Guard reported by Buckley et al. (4, 6). We found that the application of PPT could significantly reduce the incidence of tube displacement compared to the conventional endotracheal tube.

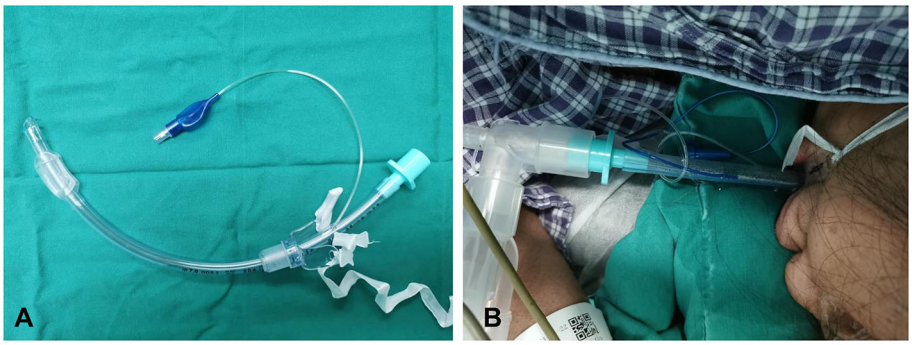

FIGURE 1 | The prone position tube. **(A)** The prone position tube is designed as a whole unit with a fixture that is affixed to the tube to increase the stabilization. **(B)** The prone position tube was applied for a patient undergoing prone position surgery.

The tube and fixation ensure safe ventilation and simultaneously do not interfere with the procedure in the mouth or the airway, and this tube will be particularly beneficial for patients with COVID-19 who require prolonged ventilation in the prone position.

It is essential to guarantee a perfect hold of the prolonged prone position ventilation for the patients with COVID-19 to avoid possible displacement or dislocation of the endotracheal tube. According to our experience, the PPT can provide effective airway protection. Under the present emergency condition of COVID-19, we recommend that this PPT be used in prone position ventilation of patients with COVID-19.

AUTHOR CONTRIBUTIONS

MD and WZ wrote the paper. WZ revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from the National Natural Science Foundation of China (81974172 ad 82171236 to WZ) and the Key Research and Development Program of Hunan Province (2021SK2018 to WZ).

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frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 06 September 2022
DOI 10.3389/fpsyg.2022.985202

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

RECEIVED 03 July 2022
ACCEPTED 15 August 2022
PUBLISHED 06 September 2022

CITATION
Snoubar Y and Zengin O (2022) Fear of being infected with COVID-19 virus among the medical social workers and its relationship to their future orientation.
Front. Psychol. 13:985202.
doi: 10.3389/fpsyg.2022.985202

Fear of being infected with COVID-19 virus among the medical social workers and its relationship to their future orientation

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COVID-19 has been studied extensively for its direct effects on healthcare workers. Despite this, very little is known about the effect of COVID-19 fear on future orientation. Studying medical social workers' fear of being infected with COVID-19 and their future orientation was the primary method used to examine this relationship. 204 Turkish medical social workers on the pandemic's front lines were included in the total sample. Social workers were found to be extremely concerned about contracting COVID-19. Although only gender is a significant predictor of the fear of contracting COVID-19 infection, the study also found that female social workers have a higher fear of infection than males. Also, no correlation exists between social workers' vaccination status and their fear of contracting COVID-19. There was a weak negative correlation between social workers' fear of contracting COVID-19 and their future orientation, but in general, social workers had a positive future orientation. Medical social workers and front-line health care providers can use these findings to develop effective and culturally appropriate intervention programs to reduce COVID-19 concerns and foster a forward-looking outlook.

KEYWORDS

COVID-19, medical team, fear, future orientation, medical social worker

Background

In health care settings, social work has a critical role to play. During the COVID-19 pandemic, social and psychological needs of patients and their families were of the utmost importance. Yet the pandemic and the virus's spread have created numerous barriers to social justice, health care system incompetence, social exclusion, and racism for hospital social workers, despite their methods for providing support to patients. As a result of these challenges, social workers face a variety of situations in which they work with the health care team, including in the home (Ross H. et al., 2021). As a result, the COVID-19 pandemic had a significant impact on

the clinical role of the social worker in supporting family members who had lost loved ones in the pandemic. In spite of this influence, social workers in the medical field were inspired to look for creative solutions through technology and innovation in clinical work (Fox et al., 2021; Snoubar, 2021). Since oncology patients are more susceptible to infection with COVID-19 due to their weakened immune systems, the use of a video phone to communicate with these patients has raised questions about whether or not direct patient contact is the best method for delivering the best care. The social worker had difficulty assessing body language and the inadequacy of feedback in this type of communication. Dissatisfaction with the job and negative thoughts about a future social work practice may result from this challenge. However, some useful alternatives have been developed that help patients communicate with their families (Di Ciero, 2021; Snoubar, 2021). In cases where these alternatives helped patients improve their emotional and social wellbeing by giving them access to safe technological means of communicating with their loved ones (Walter-McCabe, 2020), it was still difficult to help patients with cancer who were being diagnosed over the phone by an interpreter who had limited ability to read body language, recognize anxiety, communicate empathically, and correct misunderstandings as they occurred (Boparai et al., 2021). Many families, especially those disadvantaged or marginalized, lack access to technology and thus cannot benefit from these services as the rest of the population does. This may hinder the attainment of social justice in the health care field, despite the positive outlook on these innovations in the use of technology in social work practice remotely. This may put the social worker concerned about the future of social justice (Liburd et al., 2020). This crisis has led to new roles and mechanisms for medical social workers to create a supportive work environment and enhance cooperation among the various team members (Chen and Zhuang, 2020). As this disease has affected their and their clients' wellbeing, the COVID-19 pandemic has caused anxiety in social workers in various fields, particularly health care. As a result of the stress and sadness brought on by the pandemic, many social workers found it difficult to practice and adhere to normal standards, and they also suffered from a lack of motivation (Aaslund, 2021). The National Association of Social Workers (NASW) has provided numerous resources to assist social workers in addressing the fears and anxieties of the pandemic. Other resources available on the homepage include advocacy for COVID-19, legal resources for people in special populations and those with special health needs, social work safety, and the use of technology to support clients. Self-care during the Coronavirus Pandemic and ethics resources are also available (NASW, 2020). Additionally, the medical field's response to the COVID-19 pandemic has been characterized by innovation and renewal by devising the most effective ways to mitigate the pandemic's severity and enabling them to obtain informal support from family and friends.

In spite of the fact that medical social work is one of the oldest areas of social work science and practice, it did not show the desired progress in Turkey due to a lack of academic studies and professional personnel (Zengin, 2011). Therefore, conducting a wide range of studies on medical social workers in Turkey is critical to gathering data that can help improve their performance and increase their sense of wellbeing in the field (Ceylan et al., 2016; Gokler, 2021). However, this crisis has left social workers with many negative effects that require dealing with them for social workers to maintain their wellbeing and avoid diseases related to stress and mental health. It's important to look at social workers' negative feelings and fears about COVID-19 to determine what level of compatibility and stability is necessary for social workers to face the future positively. Medical social workers' perspectives on the future, shaped by their experiences working on the front lines during the pandemic, are the focus of this study's future orientation.

The impact of COVID-19 on the medical social workers

Preliminary research shows that the pandemic has psychological and social effects that accelerate the spread of the epidemic and lead to high levels of depression and anxiety in the general population. Affected by COVID-19, health care workers are among the most vulnerable to mental health issues and require early psychosocial intervention (Ornell et al., 2020). Social workers, as well as other members of the health care team, have been negatively impacted by the pandemic. In addition to emotional exhaustion and depersonalization, which is considered a risk factor for mental health and their impact on the quality of their professional life, occupational burnout, and post-traumatic stress syndrome are among the most important of these negative effects that appear on the health care team during direct work on the front lines (Buselli et al., 2020; Carmassi et al., 2020; Johnson et al., 2020; Luceño-Moreno et al., 2020; Salehi et al., 2021). Social workers who work in emergency rooms may be more vulnerable to these effects, as they may experience anxiety and fear of contracting the disease (Shaukat et al., 2020). Medical social workers are an essential part of the health care delivery team because of the nature of their services and the roles they play (Herod and Lymbery, 2008). They aid those who are afflicted by long-term, life-threatening illnesses in obtaining the treatment they require and coping with the emotional and physical consequences of their condition for themselves and their loved ones (Alagaban, 2018). Working in a multidisciplinary team has led to the development of these roles, which have the primary responsibility of providing information about

mental illnesses. It was the social workers' job to connect patients and their families with medical professionals. The responsibilities of this role varied depending on the context in which they performed it as part of the multidisciplinary team (Gehlert, 2011). In times of epidemics and pandemics, social work can have a significant impact on the mental health of the public. The social worker helps to alleviate feelings of fear and anxiety that are linked to a person's overall sense of wellbeing. There is a pressing need for social workers in this time of crisis to do things that will help people build or rebuild their capacities by creating the right social conditions (Barker, 1999). However, in the crisis of the COVID-19 pandemic, social workers faced the most difficult times in the history of social work by working in the front lines with the multidisciplinary health care team face to face with cases infected with the virus and in a stressful atmosphere (Redondo-Sama et al., 2020). Family support strategies, proactive meetings and contact between dying people and their loved ones are some of the psychosocial support interventions that can be used before and after death (Selman et al., 2020). In the course of treating those infected with the virus, social workers played a particularly delicate and crucial role. They bolstered the medical team's support for patients and their families by implementing these interventions (Johns et al., 2020). Social workers are one of the most vulnerable to burnout and personal safety risks because of their position and the roles they play in the health care team (Queen and Harding, 2020). It's difficult and stressful to deal with the effects of this pandemic on patients and coworkers, and doing so necessitates support and wellbeing maintenance through good self-care (Vo, 2021). Mental health needs to be prioritized and fatigue from working with patients must be eliminated if social workers are to continue fulfilling the responsibilities they have as members of the specialized team in their full potential (Hansel, 2020). During the COVID-19 pandemic, self-care by social workers is an essential tool for coping with stress and anxiety about the disease itself. It is critical that social workers learn and practice self-care practices in these trying times. People who work in healthcare will be under increasing pressure to manage their own wellbeing while also trying to help others, so it is essential that social workers develop strategies for managing their own wellbeing as the pandemic continues (Miller and Reddin Cassar, 2021). For social workers, this could have a significant impact on their mental health and future direction. Vaccination and the development of many vaccines may decrease fear of disease and increase a positive outlook toward the future.

The study

This study aims to examine the relationship between fear of being infected with COVID-19 and the level of future orientation for the medical social workers and their relationship to some demographic and social variables. Following are the sub-goals of this research:

1. Recognize the degree of fear of being infected with COVID-19 in the social workers.
2. Recognize the degree of future orientation of the social workers.
3. Identify the relationship between the degree of fear of being infected with COVID-19 and the level of future orientation of the social workers.

In light of these objectives, this study seeks to answer the following questions:

1. What is the degree of fear of being infected with the COVID-19 among the social workers?
2. What is the degree of future orientation for the social workers?
3. Is there a statistically significant relationship between the degree of fear of being infected with COVID-19 among the social workers and each variable (age-gender—number of years of experience—vaccination status)?
4. Is there a statistically significant relationship between the level of future orientation of the social workers and each of the variables (age—gender—number of years of experience—vaccination status)?
5. Is there a statistically significant relationship between the degree of fear of being infected with COVID-19 and the level of future orientation of the social workers?

Methodology

Sample

This quantitative, cross-sectional, and descriptive study was designed to examine the fear of being infected with COVID-19 and their future orientation levels of medical social workers. For this purpose, the data of social workers in Turkey were collected using an electronic questionnaire due to the COVID-19 pandemic conditions. As of 2012, 600 social workers are working under the Ministry of Health in Turkey (Topuz and Öz, 2014). There is no data on the current number. Since the Ministry of Health employs an average of 100 new social workers every year, it is thought that approximately 1,600 social workers work in the Ministry of Health today. By accessing the online platforms used by social workers working in the state hospitals affiliated to the Ministry of Health, 204 social workers were reached with the improbable, purposive sampling method.

Study materials

After reviewing studies that are relatively close to the subject of the study, the researchers found that because the subject of the current study was relatively recently studied, the previously developed measures or tests were incompatible with the subject. Additionally, the pre-made measure or test represents the task to be measured and other tasks, so it might not be relevant for the current study task. Also, we found that some pre-made tests whose standards are derived from a sample differ in nature from the sample being studied. Therefore, this study is based on using a scale designed by researchers after reviewing the research and studies conducted in the past 2 years on the negative effects of COVID-19 infection on the social workers. The research team also reviewed the scale to ensure its relevance to the cultural and social context of the sample under study. The scale consists of 17 phrases that are divided into two parts:

The first section, which consists of 8 statements, is concerned with measuring the degree of fear of being infected with COVID-19.

The second section, which consists of 9 phrases, is concerned with measuring the degree of future orientation.

In addition to the primary data (gender, age, marital status, number of years of experience, vaccination status).

Procedure

Quantitative research methods were used to collect data from social workers working in the medical field in Turkey. Questions were developed to collect demographic data, and a 17-statement scale was used to collect data on fear of infected with COVID-19 and future orientation. In preparing the scale, many scales (Alipour et al., 2020; Chandu et al., 2020; Kumar et al., 2020; Nikčević and Spada, 2020; Silva et al., 2020) were viewed that we benefited from in designing the scale statements. The scale was written in Turkish; we sent the scale to two academics whose academic interests are social work practices in the field of health and then pre-test. The questionnaire was distributed to all social workers working in the medical field electronically through several channels and access their communication groups, emails, and phone calls. Informed consent is also placed at the beginning of the questionnaire, which indicates the confidentiality of information, how it is stored and used, and the social worker's right to withdraw at will. The data collection process lasted from September 15, 2021, to October 15, 2021, and during this process, 204 social workers were reached.

Statistical analysis

In the analysis phase of the data, firstly, missing data analysis was performed, and it was seen that there was no missing data. Descriptive statistics and histogram graphs were used to examine the fear of being infected with COVID-19 and the level of future orientation of healthcare workers. Multiple regression analysis was used to determine whether age, gender, and vaccination status significantly predicted fear of being infected with COVID-19 and future orientation. In the regression analysis, the predictors were included in the analysis simultaneously. Gender and vaccination status were included in the analysis as dummy variables. For the gender variable, the male category was determined as the reference category (female = 1, male = 0), while the non-vaccinated category (vaccinated = 1, unvaccinated = 0) was determined as the reference category for the vaccination status variable.

The assumptions of the multiple regression analysis were checked. As a result of the analysis, it was seen that there was no extreme value. Durbin-Watson values showed that the errors were independent in both regression models. When the standardized residuals histogram and normal P-P graph diagrams are examined, it is seen that the errors show a distribution similar to the normal distribution. Standardized predicted values and scatter plots of standardized residuals showed that the data provided homoscedasticity and linearity assumptions of variances. When the VIF (variance inflation factor) and tolerance values are examined, it is seen that there is no multi-collinearity problem between the variables.

Research ethics

Ethical approval and written consent were obtained from the Research Ethics Committee of... University (2021/15.09). Informed consent was obtained from all participants in the study. Confidentiality was maintained by not requesting names or any other information identifying the social workers involved. The subjected were informed of their right to withdraw from the investigation at any time.

Findings

Descriptive statistics were determined in order to examine the fear of being infected with COVID-19 and the level of future orientation of social workers working in the field of health. In addition, histogram charts showing the score distributions of social workers were used. The results of descriptive statistics are given in **Table 1**, and histogram graphics are given in **Figures 1**, **2**.

TABLE 1 Descriptive statistics of fear of being infected with COVID-19 and future orientation variables.

	Fear of being infected with COVID-19	Future orientation
N	204	204
Average	22.593	30.152
Standard deviation	6.468	6.654
Median	22.00	30.00
Skewness	0.022	−0.434
Kurtosis	−0.627	−0.130
Min	8.00	10.00
Max	37.00	42.00
Range	29	32

As seen in Table 1, the skewness value of the distribution (0.022) for fear of being infected with COVID-19 is close to zero. The fact that the skewness value is close to zero indicates that the fear of being infected with COVID19 scores generally gather around the average. When the histogram graph in Figure 1 is examined, it is seen that the majority of the scores are around the mean. Accordingly, it can be inferred that social workers' fear of being infected with COVID-19 is generally at a moderate level. The skewness value of the distribution of forward orientation scores (−0.434) and the histogram in Figure 2 shows that the distribution is slightly skewed to the left. The skewed distribution to the left indicates that the scores are relatively high. Accordingly, it can be deduced that the expectations of social workers for the future are generally positive.

Table 2 shows that the social workers who took part in the study had an average age of 30.82 years, but they had been in the field for an average of 6.92 years. A bachelor's degree is held by nearly three-quarters of the participants, despite the fact that women make up slightly more than half (54.9 percent). Of the participants, only 28.9 percent had the COVID-19 virus, while 89.2 percent had the vaccine. Almost a quarter of the social workers (25.5%) said they didn't want to work in health facilities because of the pandemic and instead wanted to work in another field.

Multiple regression analysis was performed to identify the variables that predicted social workers' fear of contracting COVID-19. The standard (β) and non-standard (B) regression coefficients obtained as a result of the analysis are given in Table 3.

As seen in Table 3, the created multiple regression model predicts the dependent variable significantly [$F(3, 200) = 3.010$, $p = 0.031$]. Variables in the model explain 4.3% of the variance in fear of being infected with COVID-19 (R^2 = .043). Of the variables in the model, only gender significantly predicts fear of being infected with COVID-19. Female social workers have a higher fear of being infected with COVID-19 than males (β = 0.213, $p = 0.003$). Age (β = 0.031, $p = 0.664$) and vaccination status (β = 0.001, $p = 0.991$) do not significantly predict fear of being infected with COVID-19. According to this finding, there is no relationship between age and vaccination status and fear of being infected with COVID-19.

Multiple regression analysis was performed to determine the variables that predicted the future orientation of social workers. The standard (β) and non-standard (B) regression coefficients obtained as a result of the analysis are given in Table 4.

As seen in Table 4; multiple regression model, in which age, gender and vaccination status variables were predictors, did not significantly predict the dependent variable [$F(3, 200) = 0.422$, $p = 0.737$]. Age (β = 0.035, $p = 0.634$), gender (β = There was no significant relationship between −0.049, $p = 0.503$) and vaccination status (β = −0.051, $p = 0.473$) with future orientation.

Pearson product-moment correlation coefficient was calculated to determine the relationship between fear of contracting COVID-19 and future orientation. As a result of the analysis, it was found that there was a weakly significant negative relationship between these two variables ($r = -0.29$, $p < 0.001$).

Discussion

The COVID-19 pandemic has caused many burdens on people. Among these people, health personnel are at the forefront. Social workers working in the field of health are also included in this group. Increasing responsibilities and risks in both work and home life negatively affected social workers (Dubey et al., 2020; Pedrosa et al., 2020; Urooj et al., 2020). In a qualitative study conducted by Ross A. M. et al. (2021) with social workers working in hospitals, social workers had to cope with feelings of overwhelm and powerlessness due to the conditions and uncertainty they were in during the pandemic process. At the same time, safety concerns regarding the risk of exposure to COVID-19 were evident during this period. In our study, it can be said that social workers' fear of being infected with COVID-19 is at a significant level. In the model established for the relationship of sociodemographic variables with the fear of being infected with COVID-19 in our study, only gender among the sociodemographic variables significantly predicts the fear of being infected with COVID-19. In this direction, the fear of being infected with COVID-19 among female social workers was found to be higher than that of males. This situation may be related to the excess of responsibilities related to home life from the perspective of women's gender. This result agrees with Aughterson et al.'s (2021) study indicated the continuous and exacerbated anxiety of female health workers due to the fear of transmitting the virus to them and thus transmitting it to their families and loved ones. Also, it agrees with Abdelghani et al.'s (2020) study results, which indicates a higher level of fears of infection of COVID-19 among the health care team

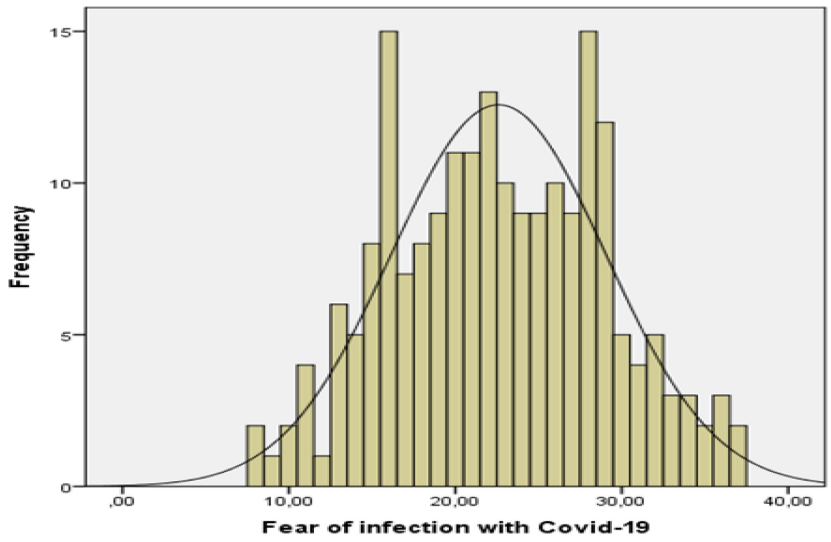

FIGURE 1
Histogram of fear of being infected with COVID-19 scores.

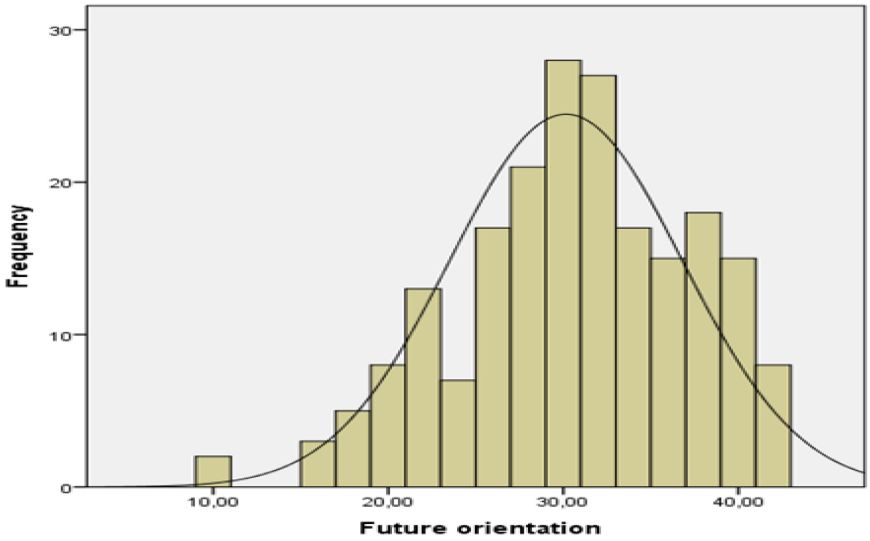

FIGURE 2
Histogram of future orientation scores.

in general and an increase in these fears among females in particular. In addition, one study indicated that social workers fear that their older relatives and other family members may infect COVID-19 because of their direct work in the medical field (Senreich et al., 2021). This finding can also be linked to female fear of the stigma associated with COVID-19 in Eastern societies compared to Western societies (Wahed et al., 2020). According to our findings, there is no significant relationship between the vaccination status of social workers and the fear of being infected with COVID-19. This situation can be explained by the existence of social workers who do not believe in vaccines and diseases and therefore have less fear of being infected with COVID-19.

As stated in the study of Ross A. M. et al. (2021), social workers believe that there is a better future for the post-pandemic period. In our study, the expectations of social workers for the future are generally positive. However, no significant relationship was found between sociodemographic and vaccination status variables and future orientation. In addition to all these, as a result of the analysis carried out to determine the relationship between the fear of being infected with COVID-19 and the future orientation, it was found that

TABLE 2 The social demographics of the sample.

	N	%
Age		
22–25	42	20,6
26–28	66	32,4
29–34	52	25,5
35 and above	44	21,5
Gender		
Female	114	55,9
Male	90	44,1
Marital status		
Single	106	52
Married	98	48
Educational level		
Bachelor's degree	157	77
Postgraduate	47	23
Being infected with COVID-19		
Yes	59	28,9
No	145	71,1
Getting a COVID-19 vaccine		
Yes	182	89,2
No	7	3,4
Indecisive	15	7,4
Field change request due to pandemic		
Yes	52	25,5
No	152	74,5

there was a weakly significant negative relationship between these two variables. The study was conducted during the period when the effectiveness of vaccination against COVID-19 was proven, and cases of infection decreased globally, which may have impacted the future orientation.

Strengths and limitations

To the authors' knowledge, the current study is the first to investigate the relationship between fear of being infected with COVID-19 and future orientation in medical social workers. Besides, many limitations must be identified. This study was based on the quantitative approach, the mixed method may be more suitable for this type of study, but the conditions resulting from COVID-19, the precautionary measures, and the pressures faced by social workers working in the medical field due to the pandemic were taken into account when designing the methodology. However, we recommend that studies be conducted in a mixed manner to determine the concerns and concerns of social workers and their attitudes toward the future. Furthermore, the sample was identified with social workers working in the medical field, and this may not be generalized to mean social workers working in various fields during the pandemic.

Conclusion and implications for social work and health

Since this study is one of the first studies examining the relationship between social workers' fear of being infected with COVID-19 and the trend toward the future, it contributes to the social work literature in the medical field. The findings of this study provide indicators that alert social workers to the potential association between fear of contracting COVID-19 and future orientation to help develop psycho-spiritual assessments that are in line with the cultural context with a supportive focus for females based on their health, family, and community status. These results draw attention to the necessity of conducting research and developing policies focusing on the role of working with serious medical conditions in the results of the future orientation of female social workers.

Evidence indicates the spread of fear and mental health-related diseases among the medical team during the COVID-19 pandemic. Therefore, the medical care team must be aware of the relationship between fear of being infected with COVID-19 and future orientation. This may be beneficial for social work practice as social workers are in the process of preparing to deal with the mental health implications associated with the COVID-19 pandemic. For example, a recent study found that social workers could work with client emergencies despite a lack of resources and remain committed to providing services to their clients despite their concerns and situations related to their personal and family life (Senreich et al., 2021). However, the severe stresses associated with the pandemic and brought about by the nature of work in the medical field underscores the need for social workers for an integrated tool to alleviate the stresses associated with COVID-19 and anxiety about the disease itself. Self-care is one of the most important pillars that empower social workers and prepare them to support clients and the health care team (Miller and Reddin Cassar, 2021). All healthcare workers need psychological counseling and comprehensive mental health services because of their risk of developing PTSD and developing a range of negative consequences of COVID-19 (McFadden et al., 2021). Where social workers can contribute to providing support to the health care team by developing the policies of the institution, it is also assumed that social workers develop knowledge and practice skills related to the mental health needs of the health care team, such as trauma-informed care practices for group and individual trauma (Bender et al., 2021). Social worker intervention may be beneficial in supporting the wellbeing of health care workers, helping them manage emotional stress, and relieving fears (Aughterson et al., 2021). This is important because our current study found that social workers' fear of being infected with COVID-19 has reached a

TABLE 3 Results of multiple regression model predicting fear of being infected with COVID-19.

The dependent variable	Predictor	B	SE	β	*t*	*P*
Fear of being infected with COVID-19	Constant	20.166**	2.465		8.183	<0.001
	Age	0.028	0.065	0.031	0.435	0.664
	Sex (Female = 1)	2.767*	0.925	0.213	2.992	0.003
	Vaccination status (Vaccinated = 1)	0.016	1.449	0.001	0.011	0.991

$R = 0.208$, $R^2 = 0.043$.
$F(3, 200) = 3.010$, $p = 0.031$.
*$p < 0.01$, **$p < 0.001$.

TABLE 4 Results of multiple regression model predicting future orientation.

The dependent variable	Predictor	B	SE	β	*t*	*P*
Future orientation	Constant	30.496*	2.584		11.803	<0.001
	Age	0.032	0.068	0.035	0.476	0.634
	Sex (Female = 1)	−0.650	0.970	−0.049	−0.671	0.503
	Vaccination status (Vaccinated = 1)	−1.093	1.519	−0.051	−0.719	0.473

$F(3, 200) = 0.422$, $p = 0.737$.
$R = 0.079$, $R^2 = 0.006$.
*$p < 0.001$.

significant level. Therefore, the social worker needs strategies to deal with these expected feelings when working on the front lines to fight against the disease. Also, female social workers may be more at risk of developing a mental disorder associated with working in the front lines in the medical field than males. Thus, social workers need to provide support to each other.

Data availability statement

The original contributions presented in this 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 the ethical approval and written consent were obtained from the Research Ethics Committee of Karabük University (2021/15.09). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YS and OZ contributed to the conception and design of the study and wrote sections of the manuscript. YS organized the database and wrote the first draft of the manuscript. OZ performed the statistical analysis. Both authors contributed to manuscript revision, read, and approved the submitted version.

Funding

Open Access funding provided by the Qatar National Library.

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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frontiers | Frontiers in Sociology

TYPE Brief Research Report
PUBLISHED 09 November 2022
DOI 10.3389/fsoc.2022.1039003

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Sociological Theory, a section of the journal Frontiers in Sociology

RECEIVED 07 September 2022
ACCEPTED 20 October 2022
PUBLISHED 09 November 2022

CITATION
Sena B and De Luca E (2022) Managing the end of life in COVID patients. The role of palliative care in emergency departments during the pandemic. *Front. Sociol.* 7:1039003. doi: 10.3389/fsoc.2022.1039003

Managing the end of life in COVID patients. The role of palliative care in emergency departments during the pandemic

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Managing COVID-19 patients has been an extremely difficult and dramatic task, especially for emergency departments during the strongest waves of the pandemic in Italy. Medical staff and health professionals were redeployed from their work setting to COVID units; many were overwhelmed by the deaths of so many patients in a very short time. This work aimed to explore palliative care health professionals' and physicians' perceptions of end-of-life care management in COVID units during the first two waves of the pandemic in Italy. Qualitative data was collected through 24 semi-structured in-depth interviews. The participants were palliative care medical and health professionals redeployed, or in a supporting role, COVID units from the most affected areas of northern and central Italy. The interview questions were focused on four thematic areas concerning different aspects of the role and responsibilities of the palliative care specialist (physician and healthcare professional). A brief presentation of the main sociological literature on end-of-life management in hospital contexts will be firstly presented and discussed to offer a theoretical frame. Subsequently, some of the most significant results that emerged from our research will be illustrated concerning the role played by palliative care professionals during the pandemic and the relevance of the palliative care approach in emergency contexts.

KEYWORDS

COVID-19, end-of-life care, palliative care, emergency departments, interprofessional care

Introduction

In the most critical phases of the COVID-19 pandemic, the management of the end of life has been an extreme difficult task, especially in the emergency and intensive care departments. The high number of patients affected by COVID-19 (from now on only COVID) quickly saturated these wards, which had very few resources available to cope with this new emergency. Many doctors and health professionals were suddenly forced to come out of their daily routine and they have been overwhelmed by the deaths of so many patients, and it has been reported, in some cases, severe psychological, occupational and physical consequences (Leo et al., 2021; Silverman et al., 2021; Søvold et al., 2021).

In Italy, especially during the first wave of pandemic, with its rapid increase in COVID cases and deaths, mostly in the north of the country, healthcare personnel often found themselves managing the end of life of COVID patients alone. Relatives and caregivers were not allowed to stay, assist, and often, even to see their beloved once admitted in the hospital. In the most critical period of the pandemic, the increasing difficult situation of many COVID wards, and their limited resources and capacity, has even led the Italian Society of Anaesthesia (SIAARTI, 2020) to issue emergency guidelines for doctors. These guidelines recommended doctors to reserve intensive care or eventual escalation of treatments (such as endo tracheal intubation, invasive ventilation, etc.) only for patients who could have a higher probability of "therapeutic success". The decision was solely based on doctors' clinical judgement without any involvement from other professionals and the family members, therefore without the wider consensus generally expected in any end of life decision.

However, the second wave of infections also saw strong pressure on hospitals in various Italian regions, recording an even higher mortality rate of COVID patients than the first (Istat ISS, 2021).

In this situation, palliative care teams provided support in many COVID wards, trying not only to manage the end of life of dying patients, but also to help colleagues by providing them with professional and psychological support (Singh et al., 2021).

Humanitarian crises and health emergencies, events generally characterized by high mortality rates, have excluded the involvement of palliative care (Nouvet et al., 2018). This paradox, however, has been highlighted recently in literature, pointing out the importance of including palliative care also in these cases (Wynne et al., 2020). In 2018, the WHO also formulated a guide on the topic, emphasizing the need to integrate palliative care in contexts where the humanization of care and patient treatment often tends to fail due to scarcity of resources, high number of deaths and the inability of health services and health professionals to provide adequate care to save the patient (WHO, 2018). Although palliative care teams showed to possess consistent skills and training for responding to health emergencies, there are still not many investigations on their real contribution in emergency departments and intensive care units, particularly during the most critical phases of the COVID pandemic.

Starting from this premise, this work aims to explore the experience and point of view of health professionals and physicians specialized in palliative care, who were deployed (or reported to have played a supportive role) in emergency departments during COVID pandemic in Italy. Specifically, this work will aim to have palliative care team perspectives on the management of end-of-life care in the emergency department.

A brief presentation of the main sociological literature on end-of-life management in hospital contexts will be firstly presented and discussed to offer a theoretical frame. Subsequently, some of the most significant results that emerged from our research will be illustrated in relation to the role played by palliative care professionals during the pandemic and their perception of the relevance of the palliative care approach in emergency contexts.

Sociological contributions to the management of the end of life in hospital contexts

Interdisciplinary research and, in particular, sociological research, have considered a series of questions around the end of life of a patient and the health organization of death and dying.

First studies, in the early 60s, dealt with the orchestration of dying within organizational structures in hospital settings (e.g., Glaser and Strauss, 1965, 1968; Sudnow, 1967).

In *Awareness of Dying*, Glaser and Strauss (1965) observed how in the hospital setting US doctors were reluctant to reveal impending death to their patients, while nurses were not authorized to give information about it without the doctors' consent. This was due to a generalized attitude in the American culture of the time, which did not allow speaking openly about death, even when this event was personal. The behavior of the hospital staff, analyzed by Glaser and Strauss, was defined by the authors as characterized by different levels of awareness of dying: a *close awareness*, a *suspicion awareness*, a *mutual pretense of awareness* and an *open awareness*. The prevalence in hospitals observed by Glaser and Strauss was to maintain a close awareness of the patient, which meant to deny him knowledge of his true state of dying. At the most, there was an awareness of reciprocal pretense between doctor and patient on his actual end-of-life conditions but, less frequently, there was an *open awareness*, through a mutually and explicitly recognized imminence of death.

Although this research was set in the hospital context of the 1960s in the US, it is still considered very topical. In fact, in the most recent practice we can observe how nurses and doctors continue to check the information given to the patient about his dying state, by delaying, modifying or avoiding the moment of open awareness as much as possible (Andrews and Nathaniel, 2015). Therefore, Glaser and Strauss findings are still very relevant today and continue to highlight problematic aspects of care in health organizations, especially in the contexts of intensive care units (Bandini, 2020).

In the same period, Sudnow (1967), in the ethnomethodological study *"passing on"*, observed that medical and nursing staff organized a set of practices and routine interactions resulting in the so-called patient's "social death". This situation consisted in healthcare staff considering a dying patient as essentially already a corpse, although still biologically and clinically alive; therefore, the person wasn't involved in his/her care and very limited interactions were

planned or happened. Such a situation also influences and determines the medical choices regarding resuscitation attempts to be adopted on the patient.

In the following years, sociologists interested in death and dying in healthcare settings continued their research on several aspects like the ethical issues of medicine and intensive care (Timmermans, 1999), the end-of-life decision-making process (Anspach, 1993; Jenkins, 2015; Bandini, 2020), the medical management of death (Kaufman, 2005; Timmermans, 2005) and the non-ordinary treatments for dying patients (Kaufman, 2015).

Kaufman's (2005) anthropological work on the time of death in hospitals, for example, provides a complete picture of the complexity surrounding decision-making on end-of-life care. In his more recent work, Kaufman (2015) focuses on the boundaries between too many and too few treatments and on the healthcare system' ethical, cultural and political issues that make it difficult to understand such boundaries. His concept of "ordinary" medicine explains how new and advanced screening and treatments become normal in current medicine and how these represent a "standard of care" around which doctors determine what is considered as an excessive or insufficient treatment for the patient care (Kaufman, 2015).

Timmermans (2005), on the other hand, notes that the medical profession can exercise a sort of professional authority in dealing with certain types of death. In an era of advanced therapies and medical technologies, there are different levels of alternative "good deaths" that doctors use to propose family members when they have to decide about the end of life of their relative. However, although technological advances help in saving the lives of critically ill patients, have reinforced dilemmas over decisions regarding end-of-life management, recovery and resuscitation interventions, because they lead physicians to offer patients and their families different options about possible treatment through an increasing shared decision-making process (Seymour, 2001). This kind of behavior, though, has produced as a result an attempt to "normalize" and make end-of-life management as non-conflictual as possible, especially in the hospital setting. In fact, advanced treatments, which were once considered new and not very widespread (such as intubation, oxygenation of extra corporal membranes or dialysis in intensive care), have become ordinary medical practices, constituting a sort of "buffet of choices" or "à la carte menu" submitted to family members, especially when doctors find difficult to decide on the type of treatment to be reserved for their dying relative (Bandini, 2020). This has progressively shifted the "onus" of the end-of-life decision from solely the medical profession into a shared decision making process. However, according to some authors, the metaphor of the "buffet of choices" can reduce burn-out and moral distress experienced by healthcare professionals in the contexts of patients in dying conditions (Hamric and Blackhall, 2007). In fact, several studies have highlighted a variety of situations that can generate ethical and moral conflicts in the management of the dying patient, especially in intensive care and emergency units (Fossum-Taylor et al., 2020). Other authors highlighted problems of communication and disagreement between doctors and nurses over decisions to maintain or discontinue life support treatments for dying patients or the lack of time to provide quality care (Ferrand et al., 2003).

One of the prevailing explanations on the difficulty of managing the process of accompanying death in many clinical contexts is linked to the fact that the final result of end-of-life care is "by definition" the patient's death, that is, according to the principles of medicine, essentially perceived as the "failure" of the cure by clinicians (Bishop, 2011; Gawande, 2014). This conception derives in part from the "clinical mentality" mentioned by Freidson (1988) which consists of an active and pragmatic medical orientation, aimed at making immediate decisions that can always allow a concrete improvement of the health conditions of the patient or a continuous recovery of his vital functions. This mentality implies to put aside any sort of scepticisms, fears and uncertainties about the possibility that the patient may not survive. When such decisions are no longer possible, because medicine is not able any more to cure and heal the patient, different strategies begin to take over to get away from the "problem" of having to manage the end of life; thus, medical profession perceived this instance as cessation or abandonment of power over the patient.

This process, therefore, highlights the cultural authority of medical professionalism, which tries to distinguish the line between to cure and to let die, pursuing the "good death" for the patient and avoiding bad deaths, determining the lifestyles to be promoted and therapeutic changes to make the patient survive as long as possible. In this sense, the end-of-life management can be seen as a professional result (Abbott, 1988) that is subject to incursions from *competitors*, such as palliative care specialists, and to redefinitions of different domains established by the involved health professionals. Not surprisingly, the role of the palliativist professionals still seems to be poorly considered and often subjected to a series of prejudices, not yet demystified by literature and clinical practice. This is due in part to the medical treatment of end-of-life, which implies palliative care for the dying patient, and therefore, it is only initiated when medicine can no longer intervene to save him/her (Masel and Kreye, 2018; Shen and Wellman, 2019). On the contrary, at the basis of the palliative approach there is not only the value of life, which must be lived in the best possible way until the end, but also the value of death, considered as a natural and inevitable event and which, therefore, must not be accelerated, nor postponed unnecessarily, but accompanied to the end.

Palliative care management is a very complex practice in healthcare services; it involves different professionals, ethical and moral choices, minimizing pain, maintaining the dignity of the dying person, facilitating patient and their relative's preferences. For these reasons, palliative care requires very

TABLE 1 Participants' characteristics.

Age: mean (SD)	47.04 years (11.9)
Gender: female *n* (%)	19 (79.1)
Professional experience in PC:	
Mean (SD)	15.45 years (10.1)
Range	2–35 years
Healthcare setting/sector (%)	
Hospice	(29.2)
Community services	(29.2)
PC units and/or PC team actively working in hospitals	(41.6)
Professional role *N* (%)	
Nurse	7 (29.2)
Nurse PC specialist	1 (4.2)
PC Physician	6 (25)
PC anesthetist	1 (4.2)
Psychologist	6 (25)
Physiotherapist	1 (4.2)
Spiritual support counselor	1 (4.2)

specific and specially trained medical-health figures, who are able to apply a holistic approach, for the best interest and the good of the patient, which includes knowledge and experience in non-traditional areas of medicine (Aldridge et al., 2016). Therefore, a palliative model of care will unequivocally strive (more than other approaches) to provide person centered care and support optimal end-of-life management (Schofield et al., 2021). Having said that, palliative care professionals are strongly suggesting that end-of-life care must be a broad activity in which all medical specialties and professions should be involved at any level (Masel and Kreye, 2018). Thus, an important palliative care team role is related to encouraging and educating other health professionals to manage end-of-life care effectively with an integrated perspective (Kim, 2020).

The results of the research

Method

The goal of this research is to explore the perspective and experience of palliative care professionals during pandemic and their role in supporting doctors and nurses in COVID wards.

The study was conducted through a qualitative study design aimed at examining the perspective and experience of different professionals specialized in palliative care, who were deployed and worked in COVID wards during the first two waves of the pandemic.

Qualitative data was collected through 24 semi-structured in-depth interviews. The interview's questions were focused on four thematic areas concerning different aspects of the role and functions of the palliative care specialist (physician and healthcare professional); thus, trying to capture and analyse participants' experience during critical phases of the pandemic.

The interviews were carried out online (through zoom or meet) and recorded, and they were conducted in two different periods: after the first wave of COVID infection (May–July 2020) and after the second wave (May–July 2021).

The participants, a convenience sample, were recruited through personal contact and networks, like the Italian palliative care society (SICP) and two post-graduate courses in palliative care for health professionals (see Table 1).

The study inclusion criteria were:

a) to be a healthcare professional or physician involved in a palliative care team;
b) to have worked in palliative care contexts in the regions most affected by the first wave of the virus (Lombardy, Piedmont, Veneto, and Tuscany).

The interviews were video-recorded and transcribed *verbatim*. The textual material was analyzed through the thematic analysis approach (Braun and Clarke, 2006). Following Braun and Clarke's six-phase framework, before starting coding, each member of the research team became familiar with the data reading independently through all the interview transcripts. Particularly, the interviews were analyzed by the research team to identify the full description of the participants' perspectives and experiences across all data. Initial codes were generated dividing the transcript texts into meaning units, describing and interpreting the most significant.

Then, they were selected and condensed into relevant themes, focused on the palliative role in COVID patient's management, especially in emergency and ICU departments:

- *Theme 1: The support of palliativists to doctors and health professionals;*
- *Theme 2: The experience of COVID for the reorganization of palliative and end-of-life care.*

Rigor and research validity were achieved by frequent discussing and sharing results in researchers' inter-analysis meetings and realizing an ordered and traceable series of cognitive actions (Rolfe, 2006).

Below are reported some results emerged from the interviews analysis, in particular in relation to the issue of end-of-life management in emergency contexts.

The support of palliativists to doctors and health professionals

One of the critical issues that clearly emerged from the analysis of interviews concerned the support of palliative care

specialists to doctors and health professionals in COVID wards. Their experience of support elicited several aspects. The first aspect concerns the management of the moment of death.

In many cases, the interviewees highlighted how their preparation for the management of the dying patient was more effective than other doctors and professionals deployed from other wards and even doctors from intensive care units. This aspect confirmed the specific expertise of the palliativist team, based on the logic of adaptation and resilience to death, and on the ability to balance personal and professional dimensions. These professional qualities unfortunately are often not a priority for medical professions who work in other areas and settings, as they are generally still anchored to the idea of resuscitation at all costs and the tendency of refusing the failure of medical interventions in end-of-life (McNamara et al., 1994).

> "While I was working at the COVID High-Dependency ward, I realized the important contribution that palliative care can make in the emergency room and intensive care wards. This is because the colleagues from these areas who came to work with us on a team were immediately stressed especially when they saw patients die as happened during the first wave! We have had all these people coming in with severe dyspnea asking you 'Help me! Help me!' They held tight to the sides of the bed and could not breathe! People died like this and these colleagues were so upset that they could not do anything to help them survive. Because all they knew was to resuscitate patients, while it was clear from the signs and symptoms, that the people who came to us were dying and that there was nothing we could do. In these situations, we (=the palliative care team) endeavored to provide sedation for the patients' unpleasant symptoms, while they (=the emergency team) have always tried to rescue these patients; but it was like wanting to bring patients back to life at any cost [...]. However, the collaboration between the two different teams has helped to understand how some conditions need less aggressive support and only an accompaniment to die. Moreover, we helped our colleagues in the emergency room to ascertain in which situations a more intense support is needed and in which it was important to let go instead". (Nurse, int.16 - 2021)

Especially in the first wave, there were no guidelines and doctors operating in the emergency and COVID intensive care units had to change their approach quickly, often by trial and error. The burden of decisions and doubts about intubation or other resuscitation treatments have also given rise to psychological trauma for the professionals involved, not used to sharing their decisions within a multidisciplinary team.

> "(…) But whether you think about the problem of intubating a patient or not. Having an expert there, for these decisions, (= a palliative care doctor) would clearly have made things faster and, how can I tell? There is that process of shared responsibility that makes the difference. However, I believe that resuscitators and anesthetists have no idea what this concept means. Therefore, they think these decisions are unnecessary (= shared end-of-life responsibility)". (Psychologist, int.8 - 2020)

A second aspect concerns the communication with the dying patient. The literature has shown this issue still to be difficult to manage for doctors and healthcare professionals not accustomed to death and that, in some way, it still represents a problem in the management of end of life in intensive care (Glaser and Strauss, 1965; Bandini, 2020).

> "I have always been used by them (= emergency ward) to report worsening patients' conditions to families. 'I'm so lucky!' I told myself. However, while for me, it was very normal because I understood that it was a difficulty that I have overcome previously and that I have experienced this situation before. Therefore, during the emergency, the burden was on me and I had to take that responsibility (=in deployment)". (PC Physician, int. 9 - 2020)

Finally, a third aspect, linked with specific skills of the palliative care team, consisted in the ability to relate to patients that were, for the emergency COVID situation, left alone because family and relatives weren't allowed to enter the wards. These patients had completely individual needs, depending on the physical state, age, disorders caused by COVID.

> "[…]Dyspnea management is a situation that requires specific skills. It is an indescribable sensation that must be managed with the right medications and the right actions. And, from a relational point of view, being closer to the person, means establishing a relationship. It also means knowing how to ask and identify his needs, to support them to get in touch with other people. Knowing how to communicate and choose together what is most appropriate for them, showing what we can and cannot do. These are all skills that must be carried out by professionals who have undergone a specific learning path and who are basically palliativists". (PC Physician, int.2 - 2020)

In some cases, palliativists have also managed to treat and heal some COVID patients in critical conditions, despite a prejudice against them by the intensive care staff, showing how this approach is not only able to alleviate suffering, but also to support treatment therapies (Masel and Kreye, 2018).

> "Our goal was to go and provide palliative care. Instead, those who hosted us (=emergency COVID wards) expected us to somehow take away the workload, a job that would fail. Let's say that they could not spend energy on these sick people, because they were so sick and lost. Interesting, however, if one could reason with the statistics and if the period would have been a little longer, it could have emerged that the palliative care team, at some point, have cured and pulled out of the situation at least two or three people, who remain a little in the history now. No? They were able to give essential care to people who had somehow been abandoned therapeutically". (Nurse PC Specialist, int.5 - 2020)

> "Some dying patients admitted to hospice have come out of it (=COVID) simply because they have been treated effectively with palliative care. We have managed their shortness of breath, fever, cough, pain, and then all these aspects of the cure (=of COVID symptoms)". (PC Physician, int.1 - 2020)

In a context of continuous and immediate deaths, lack of resources, exhausted and shocked personnel, the role of palliativists was the opposite of the principle of "social death" (Sudnow, 1967), even in those COVID patients who were already considered juts "bodies" by medical staff. Palliative care team tried to bring the treatments back to their "humanized" and personalized dimension, regardless of the patient's condition and the outcome of the therapeutic intervention.

> "You cannot think of dealing with the end of life without having in mind the principles of ethics and bioethics. This implies that if you don't consider the human being, then you go back of being a technician. And, you will stop doing the palliative care professional at that point. To cut it short, it is essential. The identification of what the patient's choices are, what is their relational context, what is his/her idea of health, his/her idea of wellbeing, what are his/her decisions for their self-determination. You cannot ignore them. Otherwise, you would do another job. I would have applied to become an orthopedist. With all due respect to the orthopedic colleagues, right?" (PC Physician, int. 20 - 2021)

The experience of COVID for the reorganization of palliative and end-of-life care

The COVID experience has certainly represented a challenge for the palliative culture and the management of the end of life even in emergency contexts (Fadul et al., 2021).

On this aspect, interviewees tried to reflect on the lessons learned and on some areas of intervention that can improve the management of the end of life in different healthcare contexts and situations. In particular, some have observed how palliative care should have undertaken before the patient's end of life and how both staff and patients in the emergency and intensive care wards could benefit from this.

> "From this experience, it would have been right to untie anesthesiologists or operators in the critical area from having to assist people who would inevitably have died. I think this should have been done, precisely to avoid the extreme frustration that many of them have had in having to assist these people who, despite the care, attention, and everything, would not have made it. Palliative care teams were available from the start to care for these patients. Moreover, palliative care could have been recruited specifically to assist these patients, that is, these patients whose outcome was known to be unsuccessful". (Physiotherapist, int.3 - 2020)

During the emergency there was substantially more action and less reflection on ethical, moral and practical implications of relevance of palliative approach also in the management COVID Patients.

> "We did not have any studies that told us that if you intubate, some get along/through or not. What are the prognostic factors that tell you it will be good or bad? So it was all done in a hurry". (Physician, int. 7, 2020)

> "(…) there was no senior doctor, so they were junior anesthetists. (...) they didn't want to make decisions of a certain type. This was a problem. (...) The thing is (…) we treat people, and we do not treat objects so (...) you cannot leave certain responsibilities to trainees. (...) And, when in doubt I have always seen action and no stopping and trying to reflect for a moment". (Nurse, int. 3, 2020)

On the other hand, thinking back to what they experienced during the critical phases of the pandemic, some interviewees highlighted the need to change the approach with respect to the "long time" of the end of life, mainly intended for dying patients.

> "In my opinion, we had extraordinary expertise to spend. It is clear that it was a question of thinking about a new way of providing palliative care, that is, we could not think that it was always the same way. And, in my opinion, that was the interesting challenge, wasn't it? Because patients died even in two hours (=in COVID Wards). So, we didn't have the time for (=traditional) palliative care. However, it

> was a way to start thinking differently about end of life care. And, we missed this opportunity, so I really have this great regret". (Psychologist, int. 8 - 2020)

Several interviewees reiterated that palliative care should be activated early in patients, to manage pain and suffering, despite the adverse prognosis outcome. This aspect is consistent with the palliative care scopes and aims, which are clearly not just for the last moments of the life of the person but that it must be an ongoing process from the diagnosis and before the insurgence of symptoms (Zagonel et al., 2017). Palliative care societies and associations are striving to support national health organizations to build a culture of palliation for long-term or chronic lethal diseases. In fact, most recent international guidelines suggest contemplating early the integration of palliative care in the path of anticancer treatments for all patients with advanced disease diagnoses (Armento et al., 2016). Therefore, palliative care could have an early activation and so act "simultaneously" with other treatments, health professionals, and care pathways that the person is undergoing, and this process can even last all life to maintain a balance and support the person with symptom control with a holistic perspective.

> "It was understood that palliative care can act on several fronts, not only on the cancer patient, but also on other pathologies, and also on the territory. The family doctor recognized the value of palliative care in end-of-life care, and today we see palliative care activated for different patients than in the past, not just for oncology anymore". (Nurse, int. 13 - 2021)

Lastly, some interviewees expressed their displeasure for having seen so many patients dying in solitude, without the presence of family and relatives around them. This principle goes against the palliative ethic, which considers the role of the family as an integral part of end-of-life care (Bakar et al., 2020).

> "COVID has brought out the suffering of loneliness, isolation and lack of relationship, which are instead necessary to cure. People who died of COVID disease, who could not live the relationship and were left alone". (Psychologist, int. 14 - 2021)

Discussion

This work highlighted the complexity of end-of-life management and the need to rethink palliative care as a longitudinal competence integrated in various clinical-care areas, beyond the specific medical area (Julià-Torras et al., 2021).

The strategies highlighted by the sociological literature regarding the decision-making process of dying, as well as the practices for managing patient awareness or the buffet of options on advanced therapies to be shared with family members to accompany death, have proved in fact to be inapplicable during the acute phases of the pandemic. They showed how doctors, anesthetists and other professionals of intensive care or from other departments were all substantially unprepared to so many and unexpected patient's death in emergency conditions and with limited available health and clinical resources.

The management of so many COVID patients, often incurable or who have already entered the hospital in desperate conditions has indirectly shown how death still represents a conflicting and not yet resolved aspect of medicine, which marks a cultural and, in some cases, jurisdictional border between the expertise of the physician and that of the palliative care specialist. This expertise is based on the logic of adaptation and resilience to death and on the ability to balance personal and professional reflections (Singh et al., 2021).

The choice between keeping alive or letting die COVID patients has clashed with attempts, often useless, to recover patients who should have been only accompanied to death in a dignified, but also morally and ethically, acceptable way. In this situation, the role of palliative care specialists (when they were present) seemed to consist in providing not only the support for the management of pain and symptoms of COVID. They also showed to relate, in an individualized way, with dying patients, highlighting their needs, and, at the same time, to psychologically support doctors and health professionals, who were inevitably frustrated by having to continuously and rapidly manage so many deaths. The lack of interprofessional and shared decision-making practices among different health professionals and, particularly, palliative care professionals seems to have aggravated the "burden" of managing so many deaths during the critical phases of the pandemic and increased the sense of inadequacy in front of dying patients for many doctors and professionals not used to operating in emergency and terminal departments. This raises the question of greater reflection not only on the need to develop inter-professional teams also in emergency wards (Dreher-Hummel et al., 2021), but also on the relevance of palliative care experts in these sectors (Lamba et al., 2014).

In this study emerged how in emergency contexts, such as those that managed COVID patients during the acute phases of the pandemic, the action of healthcare professionals is often not accompanied by ethical reflection on what the initiated medical interventions implied (Falcó-Pegueroles et al., 2021). The speed of action and the desire to "do at any cost" is opposed to the assessment on the real needs of the dying patient and the necessity, as well as to heal, to bring medical personnel back to the acceptance of the inevitability of death. Consequently, the study also implicitly points out how the education and training on bioethical aspects and on palliative approaches is fundamental and how they could have supported many COVID staff in the decision-making process, avoiding the subsequent psychological traumas reported by many doctors and health professionals (Rosa et al., 2020; Donkers et al., 2021). What

emerged by interviews is also a sort of "moral need" by palliative care professionals to educate e support their colleagues who work in other disciplines and especially in ICU and emergencies wards to manage end-of-life (Fadul et al., 2021; Hanna et al., 2021). This issue underlines the necessity to introduce end-of-life training and fundamental palliative care competencies into all the medical school and nursing curricula (Kim, 2020).

Therefore, this research aimed to point out that palliative care does not only manage patients' pain, but it can contribute significantly in supporting doctors and health professionals, from every healthcare setting, in dealing with different clinical and social situations emerging in terminal diseases scenarios. Besides, such scenarios represented all the palliative care spectrum of interventions, from the effective management of breathing and other symptoms to supporting doctors in choosing the "buffet" of options, without having to improperly delegate family members.

Nevertheless, the traditional biomedical vision of the holistic approach to palliative care as a medical failure (Bishop, 2011; Gawande, 2014) remains perhaps a significant aspect to reflect on, in order to overcome the medical perception of social death of dying patients and to give ethical relevance and quality of care to end-of life management. In our research, this cultural gap seems to be a critical point for the development of a more human, personalized and centered interprofessional approach on dying patients in healthcare settings such as emergencies and intensive care (McConnell et al., 2016).

Conclusion

In conclusion, this brief analysis suggests the need to deepen and, probably, redefine the professional, ethical and clinical role of palliative care teams, not only in the management of COVID patients, but also in the healthcare system as a whole. This also requires a reflection on current clinical-care practices and on how to include an early integration of palliative care team knowledge and expertise at the service of collective and individual health (Zaborowski et al., 2022).

During the pandemic, perhaps looking at and facing the topic of death have certainly become everyone's business, but especially for doctors and health professionals. The palliative care model could help fill a gap in end-of-life care, which has persisted for years, by building a bridge between the ethics of care and the ethics of dying. Could this be one of the many lessons we could have learnt from the experience of this health emergency?

Data availability statement

The datasets presented in this article are not readily available because they are part of a research that is in progress. Requests to access the datasets should be directed to barbara.sena@unitelmasapienza.it.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication. However, for formal attribution reasons the Introduction, the paragraph on Sociological contributions on end of life care and the Discussion can be attributed to BS, the Results and the Conclusion to EDL.

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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frontiers | Frontiers in Sociology

TYPE Review
PUBLISHED 16 November 2022
DOI 10.3389/fsoc.2022.1017077

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Sociological Theory, a section of the journal Frontiers in Sociology

RECEIVED 11 August 2022
ACCEPTED 20 September 2022
PUBLISHED 16 November 2022

CITATION
Di Rosa RT (2022) "Without social there is no health": Social work perspectives in multidisciplinary healthcare. *Front. Sociol.* 7:1017077. doi: 10.3389/fsoc.2022.1017077

"Without social there is no health": Social work perspectives in multidisciplinary healthcare

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The pandemic has not just affected the health sphere: strong social effects of the emergency have added to the health risk, stressing on social relations and the deterioration of people's living conditions, and making those who are already fragile more fragile. Notwithstanding, during the emergency following the COVID-19 pandemic the attention was focused, indeed understandably, on the health aspects, widening the already existing misalignment between the health interventions and the social ones. Emergency oriented efforts and resources more toward a clinical care approach (cure) than toward support for the social and the inclusion aspects (care). Reflecting on the specific area of health care that interacts with social care (and vice versa), shows how the medicalization in managing the emergency have undermined or, at least, weakened the global approach to the person and to vulnerability profiles that should inspire the socio-healthcare integration. The aim of this review is describing the relationship between the health and social systems and the effects of the COVID-19 pandemic on it: a review of studies on the role played by social work in the health sector before and during COVID-19 pandemic emergency shows how much potential there is still to be developed for social work in the health sector that acts together with the personal health services; a care that looks at the person within his or her relationships, community resources and environmental aspects requires an investment toward integration between hospital care, social services and local communities.

KEYWORDS

social work, hospitalization, reintegration processes, community work, interprofessional recognition

Introduction

In a pandemic situation, the urgency of medical care is compounded by the need for social care, i.e., specific attention to personal, family, and neighborhood relations—despite social distancing—, careful and in-depth monitoring of the population's needs, facilitation of access to home care and specialist services, and a thorough social epidemiology study that integrates with the health one. Emergency affects an entire community, as well as the many personal and family life stories that

result in individual emergencies, and require an immediate, or at least timely, social work intervention. The pandemic has not just affected the health sphere: as it is enshrined in the very definition given by the WHO, an all-encompassing conception of health is also extended to the social dimension. The risk of neglecting the social aspects should not be underestimated: suffice it to think of the needs related to support in daily life and the problems arising from social isolation and loneliness. Every hospitalized patient, in addition to being ill, suddenly found himself alone, without being able to count on family members who were strictly banned from the wards or simply from the same room. And into that void the social workers intervened, stemming the loneliness of patients, and helping their families (CNOAS, 2020). Moreover, social workers act as a link between health services, local authority services and the private social sector. They take care of people's connections, and (they) can be a bridge between the inside and the outside of the Intensive care, knowing how to work in difficult conditions, involving all spheres of a person's life (Allegri and Di Rosa, 2020).

The aim of this review is describing the relationship between the health and social systems, through a literature search on the current state of the relationship between social and health care, and to say that the pandemic has forced the hand with respect to the need for integration that until recently was little considered, making the urgency of its implementation evident today. "Hospitals are ground zero for pandemic" (Muskat et al., 2022, p. 129) and an important setting for social work practice, where during pandemic, social workers have been called upon to response to change and challenges in health care, to respond to increases in patient medical complexity.

Furthermore, it is proposed to interweave looked at integration prospects from the perspective of a community-based approach. The continuity of care requires an intervention that goes beyond the focus on the individual and his or her close circle of life. Various studies show that the more effective and sustainable pathways are over time insofar as social intervention on specific cases is combined with a broad-based commitment to the community (Cook, 1994). Wishing to explore the implications of professional methods connected with the commitment to "continuity of care," it appears necessary to frame the appropriate type of intervention within the framework of actions defined in the literature as a "community development". Studies by Reynolds (1982), Spergel (1987), Christenson and Robinson (1989), Twelvetrees (1991), Biggs (1999), and Driu (2014) can be recalled in this direction. Community development is a concept that currently has wide appeal in public health policy, as central element of population-based health promotion strategies that purport to involve community groups in determining the form and purpose of resources for advancing the community's health (Petersen, 1994). As Reynolds (1982) suggest, the survival of the community depends on its ability to meet the social development and social welfare needs of its residents. That's the reason because social work in community development acts as "a deliberate intervention into the social network or structure of relations among people and organizations in a local area or interest community to facilitate social problem solving and improve patterns of service delivery and sociopolitical functioning" (Spergel, 1987, p. 300).

Studies and research about social work in COVID time: An overview

The COVID-19 pandemic impacted the knowledge production. Researchers and scholars wanted to make their contribution through scientific action, and from the very beginning of the pandemic they set in motion pathways to analyze the response to the emergency, seeking both to understand what the most relevant critical issues were for the present (Banks et al., 2020), and what could then be the significant elements to be recorded for future professional developments (Ben-Ezra and Hamama-Raz, 2020; Sanfelici et al., 2020; Ravalier et al., 2021; Fronek and Rotabi-Casares, 2022).

The contemporary academic debate is concentrated in observing and analyzing on pandemic experience to integrate social work knowledge at many levels. A high attention has been paid to innovative practices of support people, helping them deal with failing health systems and aftermath of widespread disease on families and communities (López Peláez et al., 2020; Mishna et al., 2021). Also, the discussion focuses on the need to work to change systems at the macrolevel and to value social work as an essential contributor to health emergency plans (Jen et al., 2021).

Focusing on the complex and difficult work conditions social workers faced during pandemic, an interesting line of research was that which revisited existing studies on social work in disasters and emergencies, reworking them by considering the specific (and absolutely new) case of a global pandemic (Harms et al., 2020; Biddle et al., 2021; Borenstein et al., 2021). The extraordinariness of the situation reflected on which strategies and methodologies were most effective; the results of more than one research converged on highlighting the importance of modifying social work job demands in disaster work, by learning from case examples of earlier disasters to prepare guidelines/recommendations for such events. A positive work environment with the re-assurance of personal safety during the COVID-19 pandemic were the main factors that were the key to encourage medical staff to continue working during the epidemic (Campisi et al., 2022).

Different directions of innovation were identified: among them, one considers the internal need of organizations and services, relating to the dynamics between professionals. Levin-Dagan and Strenfeld-Hever (2020) explored the experiences and strategies of hospital social work in Israel in responding that accompanied distanced social support for patients and

families, taking in count the increase in mental health and grief support, as well as mediating heightened feelings of loss of control were adapted through virtual modalities. Muskat et al. (2022) explored the role changes, the availability of resources needed for the new job duties, emergent training needs with a survey conducted in December 2020 in Ontario. They developed interesting recommendations for pandemic social work practices in hospitals through the reorganization of hospital social service. In particular, they underline the centrality that emerges with respect to the need on the one hand for recognition for social service as "essential hospital staff" on par with other hospital professions, and on the other hand for collaboration between hospital administrators and social workers in building "clear protocols to ensure seamless transitions during future pandemic" (Muskat et al., 2022, p. 136) that take into account both social and medical assessments toward a shared readiness and flexibility.

This includes also adapting practice through innovative solutions (e.g., available technology), to determine which cases can be supported remotely and which require in-person visits, and how to ensure social worker workforce safety from contracting the virus (Cadell et al., 2022). The intersection between the social and health spheres, in the COVID-19 pandemic era, was represented using digital technologies as a privileged means to build and maintain a relationship among professionals, patients and families, despite distance, and/or isolation. In the post-hospitalization phase, psycho-social counseling "at a distance" (Sanfelici, 2020) was fundamental to guarantee guidance and information on the help available, psycho-social support and listening to the experiences of uncertainty, anguish and sometimes pain and suffering linked to the impact of the illness, interviews to support the elaboration of mourning, to people in isolation and quarantine, and to families called upon to reorganize care management after hospitalization.

Another strand of innovation is that of investment in the dynamics between services and the community in the direction of ensure meaningful collaboration and co-production with people with lived experience in health and social care (Biddle et al., 2021). While, the health system perspective is mainly focused on understanding COVID-19 pandemic physiological aspects, the different ways in which patient have re-integrated society and the support they have received from medical professionals after intensive care. Borenstein et al. (2021) stressed how the chosen critical and participatory approach helped them to create nuanced knowledge on the complexities related to the experiences of formal kinship care—something required and longed for by people who use services and practitioners alike.

Other authors, focusing the role of social work in health care at the intersection of these two directions of innovation—call for a spreading awareness of the relevance of the link between social and health care intervention (Fronek and Rotabi-Casares, 2022). With respect to the recognition issue, it had been highlighted yet before the pandemic (Wong, 2018) that gaining a place at the hospitals does not mean that gaining professional recognition. Moreover, literature shows that interdisciplinary approach has many barriers to overcome (Hua, 2004). Some notable ones include turf protection, different values and perceptions regarding problems and needs of patients, self-promotion, prestige, and status discrepancies that prevents open communications, skills and knowledge areas, and differences in problem solving processes (Cowles, 2003). To win recognition from medical, nursing, and allied health disciplines for contribution of social workers on the bedsides of patients requires a pathway that starts with formal and legislative recognition but needs to turn into cultural change and an appreciation of the relevance of the role and profession and its complementarity to health care pathways (Sen et al., 2020). Dealing with the changes taking place in pandemic time in the paths of recognition and enhancement of social service in health care, permits to observe that—even if recognition of government toward the importance of healthcare social work is often more formal than substantive—pandemic called social work upon to be the bridge between the inside and the outside of health care settings.

In this direction, then, it is appropriate for social workers to operate by activating and supporting community members to identify and take collective awareness, empowering, and resourcing the community members to create stronger and more connected communities (Twelvetrees, 1991). The social worker, in order to act as a liaison agent between the hospital and the territory must invest his or her cognitive effort and professional action both internally and externally, to ensure the activation of resources for each individual patient in connection with the "uniqueness of the community" (Driu, 2014) of reference. The concrete benefits of community development (…) came through local people changing attitudes, mobilizing existing skills, improving networks, thinking differently about problems, and using community assets in a new way (Tan, 2009).

Italian debates and experiences

With respect to the social work response in Italy, there has been no shortage of studies that have stressed, since the first lockdown period in 2020, the impact of emergency in social work practices and had have given attention to the operational processes at work, analyzing their characteristics and developments throughout the pandemic period (Allegri and Di Rosa, 2020; Binkin et al., 2020; Dellavalle and Cellini, 2020; Sanfelici et al., 2020; Terraneo, 2020; Cabiati, 2021; Fargion et al., 2020). In the Italian debate, much emphasis has been given precisely to the need for a paradigm shift in the management of public health emergencies: to combat the epidemic effectively, a community-based approach appears as the model that can best address the social and health needs

related to the pandemic, while being aware of the difficulties of this profound transformation of the health system (Dente, 2020). The reference to a community-based approach finds its meaning in the reaffirmation of social capital as a community resource, in the paths of rediscovering "solidarity." A solidarity-based response is the only one that can quickly address the effects of inequality amplified by the pandemic: "Building socially and individually acceptable systems of solidarity will be the great challenge of the coming times. (…) Solidarity, then, is the only 'social' response, easily achievable for all" (Lo Verde, 2022, p. 83).

Italian authors (Giarelli and Vicarelli, 2020; Terraneo, 2020; Pirrone, 2022) have been immediately reading the pandemic experience in the broader context of the already existing vulnerability of healthcare system (Gori, 2017; Smorto, 2020). Italy's response has been characterized by some rapid measures to tackle the health crisis, but few plans in the mitigation stage and a lack of community involvement. The impact on society, in terms of pre- and post-hospitalization social vulnerability, has made the absence of a national policy capable of building an adequate system of long-term care, the shortcomings of home care, the imbalance on monetary transfers, the scarce support and valorization of caregivers, the marginal role attributed to social services, often understood as mere providers of benefits. The model centered on hospital care did not prove to be the most suitable to manage the effects of a pandemic, if it was not adequately supported by territorial health services and prevention activities on the ground (Nacoti et al., 2020).

Although in Italy the role of the social worker as a connector of the clinical and care pathways should be better enhanced—particularly for the continuity of care between the hospital and the territory—, the pandemic stimulated the official recognition of the centrality of sociomedical intervention. The community dimension of Social Work in Health System was stated in 2010 by the Italian Ministry of Health, where it was stressed the objective of integration between hospitals and territories, to be achieved through specific actions as networking all the resources in the territory, ensuring integrated and synergistic interventions, acting as a promoter of strategies for rationalization and integration between the health and social system. It enables the implementation of an intervention model based on a multidimensional and integrated concept of health, thanks to the professional specificity inherent in the training of the Social Worker and the profession's own ability to connect all areas of welfare (Italian Ministry of Health, 2010).

The public health measures issued in Italy during 2020 and 2021 focused on the more specifically health-related aspect, even if a willingness emerged to manage the emergency with specific attention to the social dimensions connected to the health ones, thus broadening the concept of emergency and intervention from the clinical to the social sphere. The measures enacted took this potential into account and introduced innovations in terms of professional recognition and inclusion in care settings, therefore constituting the start of a significant reform of services integration, e.g., with the institution of special units of "continuity of care" (named USCA) for the purposes of the multidimensional assessment of patients' needs and of the integration with the territorial social and socio-health services, that were brought into the system of integrated social and health services.

Some specific elements should be emphasized with respect to the Italian reality with a view to strengthening the role of social service within hospital care pathways. Social listening and helping relationship complement the action of doctors in filtering access to services, especially those with limited availability, and explaining why this is necessary, as well as directing people to other social, health and welfare services; as well as explaining and interpreting government policies, so that these are accessible to all segments of the population. Pandemics do not know about class differences, but they have an impact, accentuating even more inequalities and social injustices (Mazzola, 2022). The professional tasks assigned to social workers are, firstly, the assessment of emerging needs, the information on rights and orientation to services, and the listening and psycho-social support. Not less important, they work for guarantee to patients support and guide of their natural support networks, activating social capital (Putnam, 2000) both in sense of "bonding" and "bridging." In the first one, organizing and coordinating the timely response to basic needs (distribution of food, drugs, finding safe housing, restoring safety conditions for health) and to relational needs, through the activation of formal network services (services for the elderly, for minors, for addictions, for victims of violence, for mental health) and informal network services (activation and networking of voluntary organizations that intervene to satisfy basic needs (home delivery). In the second one, building bridges between patients and their communities, through an involvement of the community in the analysis of emerging needs (with particular attention to less visible or less empowered groups), in the identification of resources to respond to these needs, in awareness-raising and information projects about health emergencies. In the case of the pandemic emergency, the activation of community resilience becomes an essential condition for the resilience of individuals, for the recovery and reintegration of post-COVID patients into a community that must rethink itself and the rules of coexistence and solidarity (Christenson and Robinson, 1989).

The presence of social workers can also make it possible to promote public health by mobilizing communities with respect to prevention, with a community education action, offering help to people in identifying how to keep themselves safe and how to practically live out the social distancing indications, even if it has been observed that the applicability of the community approach may be limited to countries where public health and curative services are integrated (Binkin et al., 2020). In addition to participating in efforts to strengthen health and social services as essential protection against the

virus, social care also requires special attention to be paid to existing social services and a re-organization of work to enable services to remain open and proactive in supporting vulnerable communities and populations.

These lines of social action are intertwined with other essential functions: data collection on emerging needs with particular reference to groups or to the most vulnerable communities, constant updating of the map of the network of formal and informal social and health services present in the community of reference useful for dealing with the emergency; advocacy actions to give voice to the rights of the most vulnerable and most difficult to access people; experimentation with innovative solutions (use of digital technologies) to respond in a timely manner to emerging needs, ensuring an exchange through the national network.

Finally, the COVID-19 pandemic has confirmed how social and health integration is essential for the definition of integrated pathways for taking charge of citizens on the health and social fronts, even in emergency situations such as the one that occurred in the current context or on other occasions (post-earthquake or other similar events) and how the role of the social worker is strategic in guaranteeing an important function of connection, integration, and support. The action of the social worker proves to be indispensable, complementary and strategic to the transition from a condition of "extraordinary" to one of "everyday;" acting as a "ferryman" of the patient toward the achievement of a new equilibrium, aimed at favoring and facilitating the course of therapeutic and care continuity also at the Health and Social Services of the Territory after the exit or the overall needs with integrated projects shared, as was recently recognized in Ministerial Decree No. 77/2022 on models and standards for the development of territorial care in the national health service.

Perspectives

This contribution stresses the importance of a cultural shift in health care system toward a stronger professional integration with social work, particularly with a community social development approach to build concrete actions of collaborative (Craig et al., 2020) and integrated practices in care settings (Sanfelici, 2020). As emerged clearly, the support of professional social workers can improve the capacity of the health system to respond adequately in terms of long-term community wellbeing, integrating health services with a broader range of information, prevention, and support activities for the population (Maglajlic and Ioakimidis, 2022). Social workers are the link between health services, local authority services and the private social sector. They take care of people's connections, as bridges between the inside and the outside the health system; never before integration between social work and health care have been as fundamental as they are now, in making care projects that cover all spheres of a person's life. The intervention on individuals cannot disregard an overall intervention on the social fabric to which the individual belongs, if one wants to work toward the restoration of lifestyles, the satisfaction of needs and the activation of resources and potential—necessary to enable people to regain confidence in social life and to be able to cope with difficulties, contributing to the redefinition of everyday life. As stated in the main global policy frameworks to guide disaster management (Pyles, 2007; Dominelli, 2015), the effort to achieve integration through project sharing in multi-professional teams and the implementation of effective interventions may overcome sectorial fragmentation and promote an ecological vision of the person and the living environment.

In conclusion, the outcome of the review presented is offered for the future consideration of scholars and professionals, with the aim of highlighting how the role of the social worker as a connector of the clinical and care pathways implemented in response to the COVID-19 pandemic emergency needs to be better defined and enhanced, for the continuity of care between hospital and territory. It is more necessary than ever to devise, together with hospital and territorial social and health professionals, new integrated procedures for the continuity of care pathways of protected discharge in the post-acute phase. As well, the review shows that there is potential to invest in, in the direction of strengthen cooperation between health and social services, paying a special attention to a re-organization of procedures in both fields, so that they serve, in a coherent and coordinated way, as open and proactive resources in supporting vulnerable communities and populations.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 06 December 2022
DOI 10.3389/fmed.2022.1017371

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 11 August 2022
ACCEPTED 17 November 2022
PUBLISHED 06 December 2022

CITATION
Zulbaran-Rojas A, Mishra R, Rodriguez N, Bara RO, Lee M, Bagheri AB, Herlihy JP, Siddique M and Najafi B (2022) Safety and efficacy of electrical stimulation for lower-extremity muscle weakness in intensive care unit 2019 Novel Coronavirus patients: A phase I double-blinded randomized controlled trial.
Front. Med. 9:1017371.
doi: 10.3389/fmed.2022.1017371

Safety and efficacy of electrical stimulation for lower-extremity muscle weakness in intensive care unit 2019 Novel Coronavirus patients: A phase I double-blinded randomized controlled trial

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Background: Intensive care unit (ICU) prolonged immobilization may lead to lower-extremity muscle deconditioning among critically ill patients, particularly more accentuated in those with 2019 Novel Coronavirus (COVID-19) infection. Electrical stimulation (E-Stim) is known to improve musculoskeletal outcomes. This phase I double-blinded randomized controlled trial examined the safety and efficacy of lower-extremity E-Stim to prevent muscle deconditioning.

Methods: Critically ill COVID-19 patients admitted to the ICU were randomly assigned to control (CG) or intervention (IG) groups. Both groups received daily E-Stim (1 h) for up to 14 days on both gastrocnemius muscles (GNMs). The device was functional in the IG and non-functional in the CG. Primary outcomes included ankle strength ($Ankle_s$) measured by an ankle-dynamometer, and GNM endurance (GNM_e) in response to E-Stim assessed with surface electromyography (sEMG). Outcomes were measured at baseline, 3 and 9 days.

Results: Thirty-two (IG = 16, CG = 16) lower extremities in 16 patients were independently assessed. The mean time between ICU admission and E-Stim therapy delivery was 1.8 ± 1.9 days (p = 0.29). At 3 days, the IG showed an improvement compared to the CG with medium effect sizes for $Ankle_s$ (p = 0.06, Cohen's d = 0.77) and GNM_e (p = 0.06, d = 0.69). At 9 days, the IG GNM_e was significantly higher than the CG (p = 0.04, d = 0.97) with a 6.3% improvement from baseline (p = 0.029). E-Stim did not alter vital signs

(i.e., heart/respiratory rate, blood saturation of oxygen), showed no adverse events (i.e., pain, skin damage, discomfort), nor interfere with ICU standard of care procedures (i.e., mechanical ventilation, prone rotation).

Conclusion: This study supports the safety and efficacy of early E-Stim therapy to potentially prevent deterioration of lower-extremity muscle conditions in critically ill COVID-19 patients recently admitted to the ICU. If confirmed in a larger sample, E-Stim may be used as a practical adjunctive therapy.

Clinical trial registration: [https://clinicaltrials.gov/], identifier [NCT04685213].

KEYWORDS

COVID-19, critically ill patients, lower extremity weakness, electrical stimulation, intensive care unit

Introduction

Bed rest and immobilization are time-honored treatments for managing trauma and acute or chronic illnesses. Problems arising from this treatment modality can complicate a primary disease, worsening the initial cause of admission (1). For instance, critically ill patients who require prolonged immobilization due to intensive care unit (ICU) stay often suffer from muscle weakness (2). Particularly, this condition may originate from neuro-myogenic disturbances in lower extremities (3, 4) that, when immobilized, major pathways involving inflammation, impaired oxygen delivery, and hyperglycemia arise (5, 6). These consequences are highly prevalent among hospitalized patients with 2019 Novel Coronavirus (COVID-19) in need of intensive care (7, 8). Particularly, this population receive concomitant standard therapy of paralytics and glucocorticoids that leads to inhibition of acetylcholine receptors in the neuromuscular junctions (9); ultimately, causing deleterious effects on the musculoskeletal metabolism (10).

Recent studies have explored the physiopathology of muscle wasting in critically ill COVID-19 patients (11). Cytokine storms, C-reactive protein, and pro-inflammatory molecules are thought to be part of the biological mechanism (12). These factors may induce endothelial damage and mitochondrial autophagy leading to myofibrillar breakdown (13). In the lower extremities, these consequences can contribute to muscle atrophy, weakness, functional impairment, and persistent symptoms that can last for up to 1 year following ICU discharge (14). Eventually these symptoms can increase fall risk, lack of independence, and quality of life deterioration (15, 16). Therefore, there is a need to implement a practical solution to prevent muscle deterioration of bedbound patients, particularly those with severe COVID-19 infection.

Physical therapy (PT) greatly benefits neuromuscular outcomes in patients with muscle deconditioning and weakness (17). However, reduced personnel and resources can be a limitation for ICU COVID-19 patients. Additionally, the rapid loss of muscle mass within hours after ICU admission (5) requires an immediate approach, making this condition time-dependent. One practical solution is the use of electrical stimulation (E-Stim) therapy. This modality prevents muscle deconditioning (18), improves muscle strength, and restores functionality in ICU patients (19). While it may be a suitable treatment to facilitate the rehabilitation pathways for COVID-19 patients (20), empirical evidence is needed (11). Today, this technology has been demonstrated to improve muscle strength in ICU COVID-19 patients (21). However, there is still a lack of randomized studies (22) to confirm its efficacy. Thus, it is unclear whether this adjunctive therapy prevents lower-extremity muscle deconditioning in ICU COVID-19 patients.

This study examines the potential safety and efficacy of lower-extremity E-Stim therapy to prevent lower-extremity muscle deconditioning in ICU COVID-19 patients. We hypothesized that patients receiving short-term E-Stim therapy will show significant improvement in lower-extremity outcomes [i.e., muscle endurance, ankle strength ($Ankle_s$), risk of fall] compared to those who do not receive it.

Materials and methods

Study design and settings

Critically ill COVID-19 patients admitted to the ICU due to acute respiratory failure at Baylor St. Luke's Medical Center (BSLMC, Houston, TX, USA) were recruited in a phase I double-blinded randomized controlled trial. Recruitment was performed from December 2020 to March 2021 by research assistants (AZ-R and NR). The protocol of the study was registered on clinicaltrials.gov, Identifier: NCT04685213. This

study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized clinical trials.

Participants

To be eligible, patients must have been admitted to the ICU due to COVID-19 infection within 3 days prior to initiating E-Stim therapy, received assisted ventilation therapy, and indicated bed rest for at least 7 days. These conditions were based on the judgment of clinical intensivist investigators (MS and JPH). Patients were excluded if they were medically paralyzed (i.e., rocuronium, cisatracurium) or under vasopressor therapy (i.e., norepinephrine, epinephrine, vasopressin) at the moment of enrollment; expected to be discharged from critical care in the next 24 h; had below the knee amputations or lower-extremity wounds; demand-type cardiac pacemaker, implanted defibrillator, or other implanted electronic devices; and any conditions that may interfere with outcomes or increase the risk of the use E-Stim based on the judgment of clinicians.

Intervention

Patients were randomized (ratio: 1:1) to either control (CG) or intervention (IG) groups through a computer-generated list followed by sequential allocation. Participants and care providers were blinded to the group allocation. The IG received E-Stim through two electrode adhesive pads (2 cm × 2 cm, Conductive electrode pads, Avazzia Inc., Dallas, TX, USA) placed on proximal gastrocnemius muscle (GNM) (23) and Achilles tendon of each leg using a bio-electric stimulation technology (BEST®, Dallas, TX, USA) microcurrent platform [Tennant Biomodulator device (R), Dallas, TX, USA, **Figure 1**] for 1 h daily for up to 14 days. The CG was provided with an identical but non-functional device (placebo) for the same period. Therapy was delivered in supine position placing the

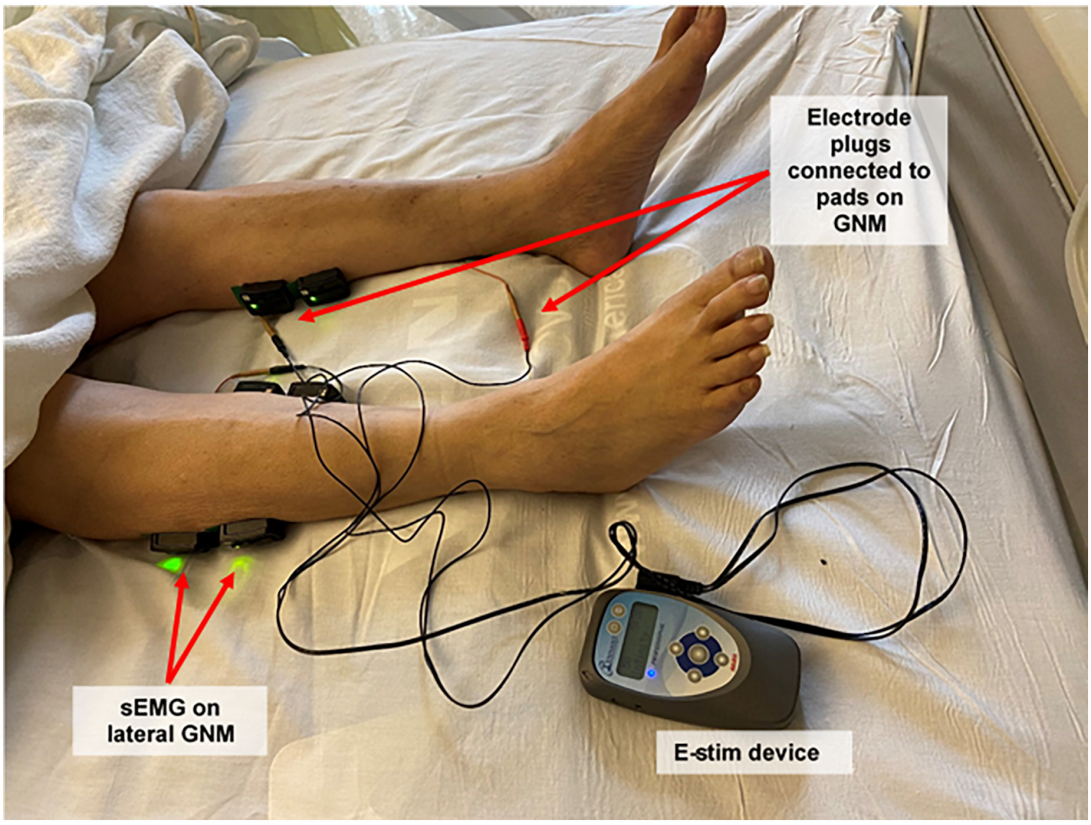

FIGURE 1
Study setup: electrical stimulation device, plugs and pads, and surface electromyography sensors. Participants received electrical stimulation through electrode adhesive pads placed on both proximal and distal gastrocnemius muscles using a bio-electric stimulation technology® (BEST) micro-current platform (Tennant Biomodulator®). Electrical stimulation (E-Stim) was active in the intervention group and non-functional in the control group. Two surface electromyography (Delsys Trigno Wireless EMG System, MA, USA) sensors were placed on the proximal lateral gastrocnemius of each lower extremity to evaluate muscular outcomes. Proximal medial gastrocnemius signal was also recorded, but not included for analysis. sEMG, surface electromyogram; GNM, gastrocnemius muscle; E-Stim, electrical stimulation.

head of the patient's ICU bed between 30–45 degrees. In cases of prone positioning, E-Stim therapy was delivered placing the head of the patient's ICU bed within 20° (24).

The E-Stim application was set at 50 V with an interactive high voltage pulsed alternative current (HVPAC) in the shape of an asymmetrical damped sinusoidal biphasic pulsed waveform (25), which allows for muscle relaxation and avoids fatigue during therapy (26). An intensity level from 50 to 250 V has been previously FDA-cleared for the use of pain relief (25). The pulse duration was between 400 and 1400 microseconds (μs), and pulse frequency between 20 and 121 hertz (Hz). These same intensity level and pulse characteristics were shown to be harmless in a previously published clinical trial for lower-extremity ischemic lesions (27). E-Stim was discontinued if the patient presented rapid deterioration [i.e., arterial blood oxygen desaturation < 93% under ventilation assistance, hemodynamic instability, septic shock, thigh extracorporeal membrane oxygenation (ECMO) placement, or generalized gross edema] despite intensive care treatment. Intubation was not an indication for E-Stim discontinuation.

Equipment for muscular assessment and data analysis

Surface Electromyography (sEMG, Delsys Trigno Wireless EMG System, MA, USA) was recorded bilaterally from the proximal lateral GNM (**Figure 1**) according to the Surface Electromyography for a Non-Invasive Assessment of Muscles (SENIAM) guidelines (28). Prior to electrode placement, the skin was cleaned with alcohol and prep gel (Nuprep, CO, USA) to minimize impedance. The raw sEMG signal was recorded at 2,000 Hz and filtered using a 4th order Butterworth band-pass filter with cutoff frequencies of 20 and 400 Hz (29, 30). The filtered sEMG data was full-wave rectified and smoothed using a moving average to estimate the sEMG linear envelope (29, 30). Furthermore, the area under the envelope was calculated to estimate the integrated EMG (iEMG) to quantify the level of muscular activity (31, 32). EMG analysis was performed using custom-made software programmed in MATLAB (The MathWorks Inc., Natick, MA, USA).

Efficacy outcomes

Lower-extremity muscle outcomes included voluntary and involuntary contraction metrics. First, in a standardized supine position (33), $Ankle_s$ was determined by the average of three 5 s dorsiflexion maximum voluntary isometric contractions (MVIC) per 30 s of relaxation in-between (**Figure 2**) assessed with a dynamometer (RoMech Digital Hanging Scale). Second, GNM endurance [GNM_e, defined as sustained muscle involuntary contraction (34)] in response to 5 min of E-Stim therapy was assessed with iEMG analysis.

Lower-extremity perfusion outcomes included plantar tissue oxygen saturation (SatO2), a surrogate of muscle oxygen consumption in response to E-Stim (35). SatO2 was measured using a validated Near Infra-red Spectroscopy (NIRS) camera (Snapshot NIR, KENT Imaging Inc., Calgary, AB, Canada) that detects an approximate value of real-time SatO2 level in superficial tissue. SatO2 levels were examined in the metatarsal area, including the five toes. Muscular and perfusion outcomes of the lower extremity were assessed at baseline, 3 and 9 days.

Lower-extremity functional outcome was the likelihood of falling assessment *via* Morse Fall Scale (MFS) (36). This scale is a standardized assessment performed by hospitalists at BSLMC that assesses functional aspects of the lower extremity such as ambulatory aid, gait, and transferring, among other features related to risk of falling. As the score increases, it indicates proportionally worse outcomes (low risk < 24; moderate risk 25–44; high risk > 45). The functional outcome was collected from the electronic medical records at baseline, and at the time of ICU discharge (i.e., home, hospital floor, or patient expiration) to assess overall impact of intervention on subjects. Electronic medical records were also reviewed to differentiate whether outcomes were associated with any demographic characteristics or comorbidities.

Safety and feasibility outcomes

Safety outcomes included monitoring of vital signs (i.e., heart/respiratory rate, blood pressure, blood saturation of oxygen), and study-related adverse events (i.e., pain, skin damage, discomfort, non-compliance). Feasibility outcomes included average of patient E-Stim therapy completion, average of measured outcomes at each time point (i.e., 3 and 9 days) excluding non-study-related adverse events (i.e., death, intubation, deep vein thrombosis, rapid deterioration) (37, 38). Acceptability outcomes included interference with ongoing COVID-19 standard of care procedures (i.e., mechanical ventilation, prone rotation, PT, other clinical trials), and interaction with the ICU staff (i.e., nurses, respiratory and occupational therapists, nutritional specialists, machinery technicians).

Sample size justification and power analysis

The sample size was estimated based on a Najafi et al. study (39), in which the effectiveness of daily lower-extremity E-Stim demonstrated a significant improvement in motor performance (Cohen effect size, $d = 1.35$). To observe the benefit of functional E-Stim (IG) to prevent or improve lower-extremity muscle outcomes compared to non-functional (CG), we conducted a power analysis following a (1) Conservative effect size (Cohen's

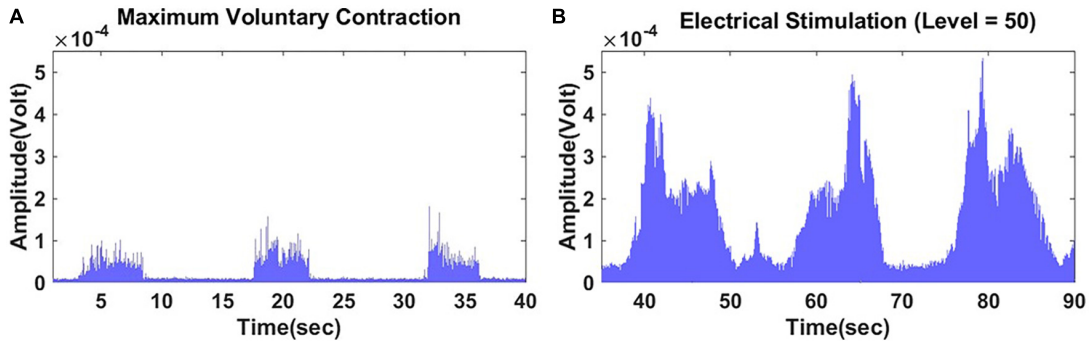

FIGURE 2
A typical case comparison between a maximum voluntary contraction and involuntary contraction of the gastrocnemius muscle assessed *via* surface electromyogram. **(A)** Three 5–10 s dorsiflexion maximum voluntary contractions. **(B)** Three 5–10 s intervals of electrical stimulation set at 50 V. Both panels having a 5–10 s relaxation period between contractions.

d = 0.6); (2) 80% generated power; (3) Alpha of 5%; (4) two number of groups; and (5) two repeated measurements, utilizing G *Power software (version of 3.1.6) (40). Each lower extremity was considered as an independent sample due to the variability in muscular and vascular status (41, 42).

Statistical analysis

Shapiro–Wilk test ($p > 0.05$) was used to assess the normality of the data. Independent t-test was used for group comparison at baseline on normally distributed continuous demographics, clinical data, and sEMG parameters. Mann–Whitney U test was used if the assumption of normal distribution was not satisfied. For categorical variables, Chi-square test was used to compare between-group differences at baseline. The effect size for baseline continuous and categorical data were measured using Cohen's d and Cramer's V, respectively. Values ranging from 0.20 to 0.49 indicate small effects, and values between 0.50 and 0.79 indicate medium effects. Values ranging from 0.80 to 1.29 indicate large effects, and values above 1.30 indicate very large effects. Generalized estimating equations (GEE) was used to test the main effect of group (two levels: CG and IG), time [two levels: baseline, 3/9 days (muscle and perfusion outcomes), or discharge time (MFS Score)], and their interaction on the outcome measures. For all tests, an alpha level of < 0.05 was considered statistically significant. All calculations were made using IBM SPSS Statistics 27 (IBM, IL, USA).

Ethical consideration

This study was approved by the local Institutional Review Board (IRB) at Baylor College of Medicine (Houston, TX, USA) in accordance with the Declaration of Helsinki (approval number H-47781). All participants read and signed the IRB-approved informed consent forms before initiating assessments or data collection. If the participant was cognitively impaired, consenting was performed *via* telephone call with a legal representative. The informed consent was obtained from all participants and/or their legal guardians.

Results

Clinical characteristics

The progress through the phases of screening, allocation, follow-up, and data analysis is shown in **Figure 3**. The vast majority of patients were excluded from initial screening due to anticipated discharge from critical care within 24 h. Nineteen participants satisfied the inclusion and exclusion criteria. From these, three were withdrawn due to rapid deterioration before the mid-point (3 days), leaving a total of 16 participants (Age = 64.8 ± 9.5, p = 0.43, d = 0.40) for analysis. Therefore, eight participants (n = 16 lower extremities) were allocated to the CG and eight participants (n = 16 lower extremities) to the IG. Baseline characteristics showed the IG group had significantly higher fasting glucose ($p < 0.01$, d = 1.767) than the CG. All other baseline characteristics were not significantly different between the groups (**Table 1**). The mean time between ICU admission and delivery of E-Stim therapy was 1.8 ± 1.9 days (p = 0.61, d = 0.25). At the study enrollment, the mean body SatO2 (SpO2) was 80.53 ± 13.38% (p = 0.27, d = 0.56) in the complete cohort with all the participants (100%) undergoing corticosteroid therapy. Limited or null mobility persisted for a mean of 3.3 ± 3.5 days (p = 0.54, d = 0.38) and after 7.5 ± 5.7 days (p = 0.93, d = 0.05), 68.7% (p = 0.59, V = 0.13) of the participants began vigorous activity involvement (i.e., physical/occupational therapy, standing up,

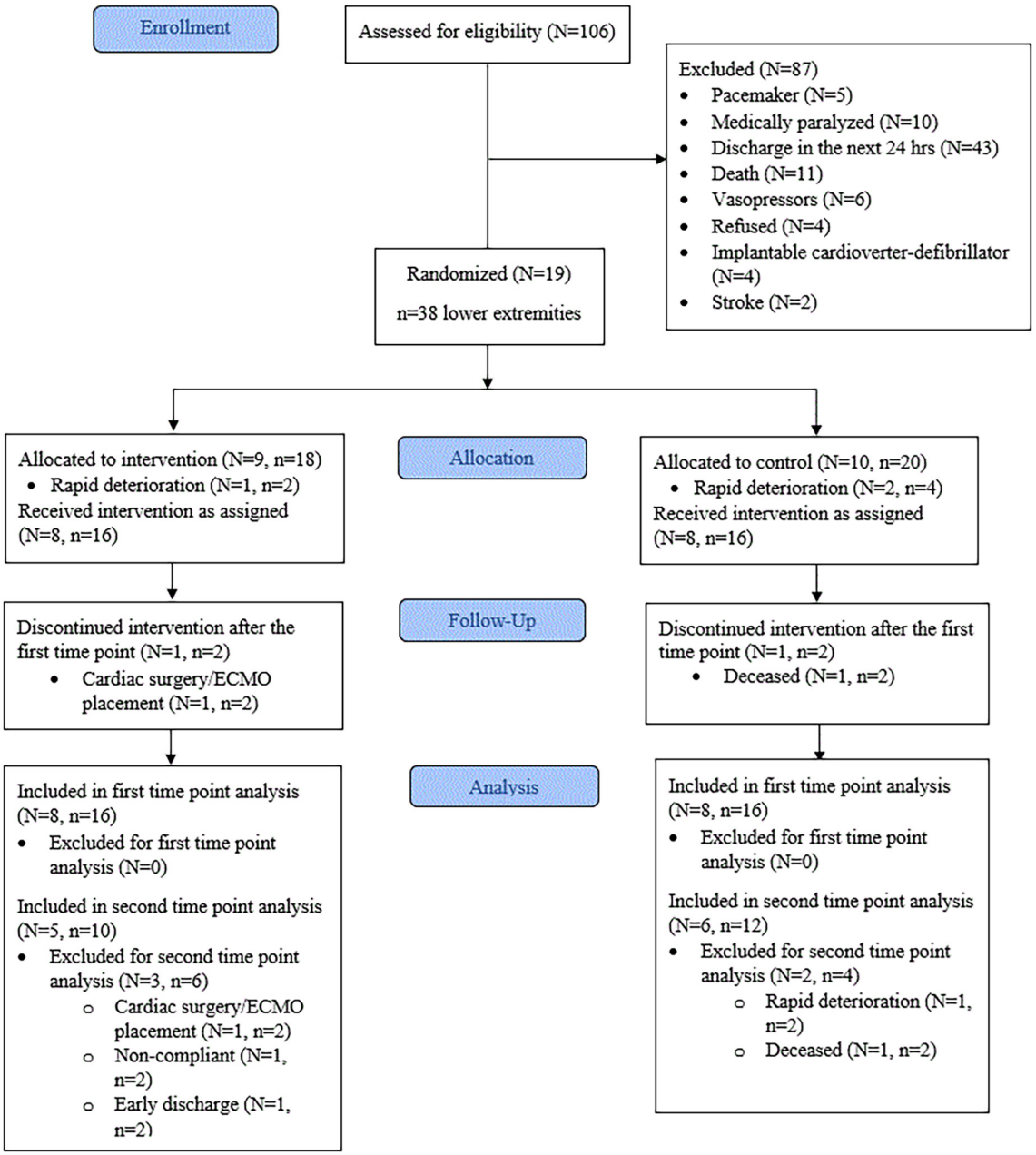

FIGURE 3
Consort flow diagram. N, number of patients. n, number of lower extremities. ECMO, extracorporeal membrane oxygenation. First time point = 3 days. Second time point = 9 days.

walking to chair). All others (31.3%) remained immobile during their ICU stay.

Efficacy outcomes and longitudinal analysis

At 3 days, the IG showed a non-significant improvement compared to the CG with medium effect sizes for $Ankle_s$ (p = 0.06, d = 0.77, Figure 4A) and GNM_e (p = 0.06, d = 0.69, Figure 4B), whereas the CG showed a non-significant deterioration for GNM_e in comparison to baseline (−3.9%, p = 0.08). At 9 days, the IG showed a significant improvement compared to the CG with large effect size for GNM_e (p = 0.04, d = 0.97, Figure 4C). In comparison to baseline, the IG's GNM_e showed a significant improvement (+6.3%, p = 0.029). Lower-extremity oxygen consumption (SatO2) values remained stable between and within groups

TABLE 1 Demographic and clinical characteristics.

	Intervention group ($N = 8$, $n = 16$)	Control group ($N = 8$, $n = 16$)	*P*-value	Effect size
Baseline characteristics				
Female, no.	5 (62.5)	2 (25)	0.31	2.28
Male	3 (37.5)	6 (75)		
Age, years	66.75 ± 9.81	62.88 ± 9.51	0.43	0.40
Ethnicity, no.				
Caucasian	1 (6.25)	1 (12.5)	0.31	0.26
African American	5 (31.3)	2 (25)		
Hispanic	9 (56.3)	5 (62.5)		
Asian	1 (6.25)	0 (0)		
BMI, kg/m^2	28.49 ± 7.17	32.45 ± 8.04	0.31	0.52
Diabetes mellitus, no.	3 (37.5)	6 (75)	0.13	0.37
Hypertension	5 (62.5)	6 (75)	0.59	0.13
Hyperlipidemia	4 (50)	2 (25)	0.30	0.25
Acute kidney injury	1 (12.5)	1 (12.5)	1.00	0.00
Chronic kidney disease	1 (12.5)	2 (25)	0.52	0.16
Coronary artery disease	1 (12.5)	1 (12.5)	1.00	0.00
Anemia	8 (100)	6 (75)	0.13	0.37
Pneumonia	7 (87.5)	8 (100)	0.30	0.25
biPAP/CPAP use	3 (37.5)	4 (50)	0.31	0.25
Vapotherm use	3 (37.5)	5 (62.5)	0.31	0.25
Hypercoagulable state	7 (87.5)	6 (75)	0.52	0.16
Immunosuppressed status	3 (37.5)	4 (50)	0.61	0.12
Time between admission and E-Stim therapy, days	2.13 ± 1.25	1.63 ± 2.45	0.61	0.25
Total E-Stim therapy duration, days	7.00 ± 3.02	8.75 ± 3.45	0.29	0.53
Physical therapy no.	5 (62.5)	6 (75)	0.59	0.13
Deceased after study end-point, no.	4 (50%)	5 (62.5)	0.61	0.12
Laboratory values				
SpO2, %	78.75 ± 16.35	82.57 ± 9.82	0.27	0.56
Hb, g/Dl	11.20 ± 2.34	12.56 ± 2.37	0.26	0.57
Platelets, K/CU MM	253.00 ± 94.80	247.50 ± 146.55	0.93	0.04
WBC, K/μL	13.01 ± 3.91	9.36 ± 3.23	0.06	1.01
Glucose, mg/Dl	104.88 ± 28.08	167.38 ± 41.39	< 0.01	1.76
Creatinine, mg/Dl	1.92 ± 1.21	1.58 ± 1.23	0.58	0.27
D-dimer, MG/L FEU	4.15 ± 5.42	4.32 ± 7.11	0.96	0.02
Ferritin, ng/Ml	1360.38 ± 1345.60	2303.31 ± 1707.55	0.29	0.60
Fibrinogen, mg/Dl	528.21 ± 237.50	521.02 ± 264.60	0.95	0.02
Lactase dehydrogenase, mg/Dl	579.43 ± 138.17	907.67 ± 660.90	0.22	0.71

N, number of patients; *n*, number of extremities. Values are presented as mean ± standard deviation or *n* (%); BMI, body max index; biPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; SpO2, body oxygen saturation without ventilatory assistance; Hb, hemoglobin; WBC, white blood cells. Immunosuppressed status included patients with renal or lung transplant, cancer, or autoimmune disease. The effect sizes were calculated by Cohen's *d* (continuous) and Cramer's *V* (categorical), respectively.

through time ($p > 0.05$, Table 2). At the time of ICU discharge, the IG showed a significant improvement compared to the CG with small effect size for MFS score ($p = 0.05$, $d = 0.36$, Figure 4D). In comparison to baseline, the IG's MFS score showed a significant improvement (−12.7%, $p = 0.05$), opposite to the CG, which showed a significant worsening score (48.1%, $p = 0.04$). All other parameter comparison are shown in Table 2.

Safety and feasibility outcomes

Electrical stimulation therapy did not alter vital signs nor result in adverse events during the study period. The device did not interfere with the ongoing standard of care procedures for COVID-19 ICU patients, nor cause a burden to the ICU staff. Protocol delivery showed 14/16 patients (87.5%, $n = 28$ lower extremities) were able to complete

TABLE 2 Outcome comparison across time between both groups.

Outcomes	CG (n = 16)		Time effect P-value	Δ%	IG (n = 16)	Time effect P-value	Δ%	Time × group P-value (Cohen's d)
3 days								
$Ankle_s$, kg	Baseline	2.5 ± 1.2	0.15	−8	2.7 ± 1.7	0.26	42	0.06 (0.77)
	3 days	2.1 ± 0.7			3.0 ± 1.6			
GNM_e, iEMG	Baseline	327 ± 12	0.08	−3.9	331 ± 10	0.37	1.8	0.06 (0.69)
	3 days	314 ± 27			338 ± 36			
Plantar SatO2, %	Baseline	64.9 ± 9.6	0.13	4.6	68.9 ± 6.2	0.33	2.7	0.7 (0.14)
	3 days	67.9 ± 8.0			71.3 ± 6.7			
9 days								
GNM_e, iEMG	Baseline	327 ± 12	0.52	−1.5	331 ± 10	0.029	6.3	0.04 (0.97)
	9 days	323 ± 18			352 ± 37			
Plantar SatO2, %	Baseline	64.9 ± 9.6	0.92	0.4	68.9 ± 6.2	0.89	0.3	0.86 (0.06)
	9 days	67.2 ± 9.5			69.2 ± 8.9			
Discharge								
MFS score	Baseline	31.2 ± 7.4	0.04	48.1	43.7 ± 17	0.05	−12.7	0.05 (0.36)
	Discharge	46.2 ± 11.8			39.3 ± 11			

N, number of patients; n, number of extremities; kg, kilograms; iEMG, integrated electromyography unit. Values are presented as mean ± standard deviation Values of time effect are presented as p-values from generalized estimating equation models. $Ankle_s$, ankle strength; GNM_e, gastrocnemius muscle endurance; SatO2, tissue oxygen saturation; MFS, Morse Fall Risk Scale; MFS high score is proportional to severity; discharge time = 18.00 ± 10.19 days.

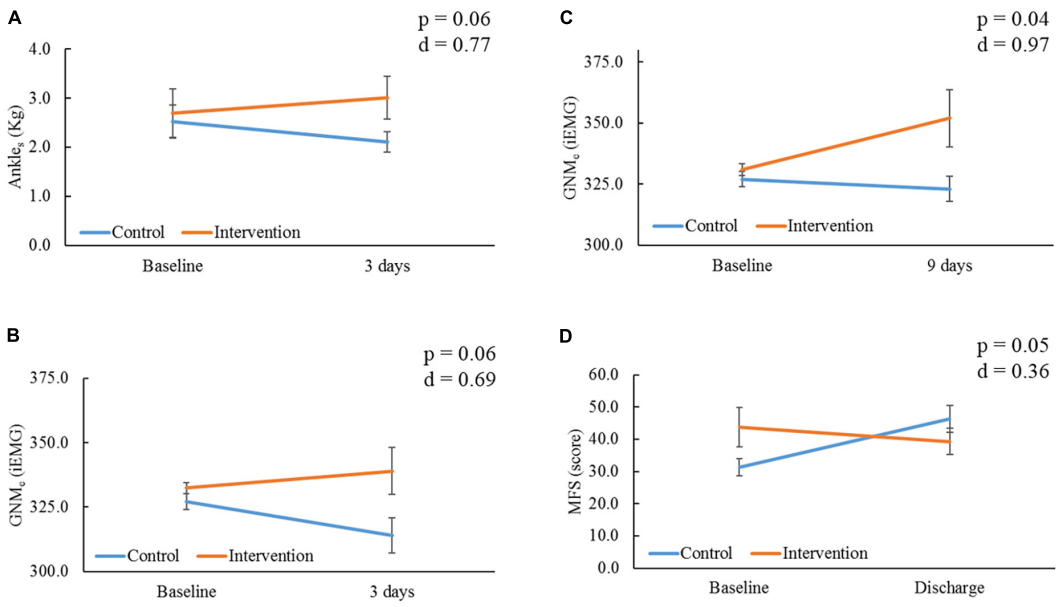

FIGURE 4
Comparison of outcomes within and between groups through time. $Ankle_s$, ankle strength; kg, kilograms; GNM_e, gastrocnemius muscle endurance; iEMG, integrated electromyography unit; MFS, Morse Fall Risk Scale. **(A)** Comparison of $Ankle_s$, and **(B)** GNM_e within and between groups at 3 days from baseline. **(C)** Comparison of GNM_e within and between groups at 9 days from baseline. **(D)** Comparison of MFS within and between groups at the time of intensive care unit (ICU) discharge (18.00 ± 10.19 days) from baseline; severity is proportional to high score. P-value and Cohen's d effect size are noted from time group interaction at each determined time point.

E-Stim therapy during the established study period (9 days). At the first time point (3 days), the average of measured outcomes from independent lower-extremity voluntary metrics ($Ankle_s$) data excluding non-study-related adverse events (i.e., rapid deterioration = 6) was 100% (n = 26/26 samples), and the average for involuntary metrics (muscle endurance and SatO2) was 100% (32/32 samples). At the second time point (9 days), the average of measured outcomes from independent lower-extremity voluntary metrics ($Ankle_s$) data excluding non-study-related adverse events (i.e., intubation = 10, early

discharge = 2, death = 2, deep vein thrombosis = 1) was 94.1% (16/17 samples), and the average for involuntary metrics (muscle endurance and SatO2) excluding non-study-related adverse events (i.e., intubated = 4, early discharge = 2, death = 2) was 91.6% (22/24 samples). Data for MFS functional assessment at the time of ICU discharge (18.0 ± 10.2 days, $p = 0.81$, $d = 0.11$) was collected in 100% (32/32 samples) of the participants.

Discussion

This study examined the safety and efficacy of lower-extremity E-Stim adjunctive therapy to prevent muscle deconditioning. Our main goal was to determine whether this system can improve musculoskeletal outcomes at the earliest application from ICU admission. Results suggest that patients undergoing active E-Stim to the GNM had an improvement in $Ankle_S$ and muscle endurance after 3 days compared to those that utilized sham devices. Comparison at 9 days showed there was significantly higher muscle endurance in patients undergoing active stimulation compared to those that did not. We believe these findings are due to the prompt activation of muscle fibers which may deaccelerate the rapid atrophy, myofilament damage, protein synthesis, and wasting found within the first week of ICU length of stay (43). E-Stim induces non-selective recruitment and activation of both type I and type II muscle fibers which conform the GNM (44), ultimately enhancing strength and cross-sectional area (45) in immobilized patients (46). Despite wide evidence which supports the feasibility and safety of E-Stim in the ICU setting (47, 48), further exploration is needed to confirm its efficacy at improving lower-extremity musculoskeletal outcomes, particularly in patients with severe hypoxia (i.e., ICU COVID-19).

Electrical stimulation is known to excite motor units that are used for greater levels of force production (49), aiding lower-extremity muscle strength preservation for voluntary activation (50). In a recent prospective cohort study in ($n = 5$) ICU COVID-19 patients, Righetti et al. stated daily E-Stim to the quadricep muscles in mechanical ventilated patients is feasible at improving strength at 5 and 8 days per interrupted sedation assessment (21). Similar non-COVID population studies utilizing E-Stim to the peroneus longus ($n = 24$) (51) and anterior tibialis ($n = 11$) (52) found a significant improvement in ankle dorsiflexion strength. Moreover, a randomized control trial (RCT) (53) delivering E-Stim to the GNM of ICU patients ($n = 36$) showed an improvement in strength at 9 days. The present RCT in ICU COVID-19 patients undergoing active E-Stim to the GNM showed an improvement in ankle dorsiflexion strength compared to controls with a medium effect size ($p = 0.06$, $d = 0.77$, **Figure 4A**) after 3 days of starting therapy. Unfortunately, results at 9 days were limited due to the high morbimortality status (i.e., deep vein thrombosis, intubation, death) impeding patients from performing voluntary tests, and limiting further assessment post-sedation.

2019 Novel Coronavirus reviews have also claimed E-Stim therapy may improve muscle endurance (18); however, evidence is supported by different types of immobilized populations (54). Hence, Veldman et al. suggested that E-Stim may result in a fast-to-slow muscle fiber type transition, which could potentially enhance endurance in patients with severe weakness unable to perform voluntary contractions (i.e., cardiorespiratory, critically illness) (55). However, due to the challenging objective assessment of muscle endurance in patients with severe illness, these outcomes were functionally assessed (i.e., waking distance movement) after recovery. In our study, we assessed real-time muscle endurance in the ICU setting utilizing electromyography (56). This test is optimal for assessment of muscle endurance and weakness as it offers a way to study the myoelectric features of neuromuscular activation associated with E-Stim (57). That said, the present study showed the IG had a higher improvement in GNM_e with medium effect size at 3 days ($p = 0.06$, $d = 0.69$, **Figure 4B**) than the CG, yet a significant improvement with a large effect size at 9 days ($p = 0.04$, $d = 0.97$, **Figure 4C**) by increasing 6.3% ($p = 0.029$) from baseline (**Table 2**). This was especially noteworthy since all patients had null mobility over the first ∼3 days from ICU admission, avoiding any confounding effect of physical or nutritional therapy. This suggest that daily E-Stim may gradually improve GNM_e in ICU COVID-19 patients.

Multiple studies (58) have suggested applying E-Stim therapy immediately after ICU admission to prevent lower-extremity neuromuscular damage in ICU patients (59–61). The physiology behind this suggestion relies on the fact that early introduction to E-Stim can ensure early activation/contraction of the motor unit (15). This is important because there is an abrupt decline in amplitude of nerve action potential and motor depolarization within 24 h from ICU admission (62). In ICU COVID-19 patients, there is an additional degenerative transformation and shrinkage of skeletal muscle due to sarcopenia, oxidative stress, and hyper-catabolism induced by cytokine storms and malnutrition (11, 63). In the present study, E-Stim was provided within ∼1.8 days from ICU admission; thus, an early involuntary contraction of motor units may have led the IG muscle outcomes to improve as early as 3 days. However, we believe therapy should be provided for prolonged periods, even after ICU discharge. Further studies are needed to explore musculoskeletal outcomes with the continuous use of E-Stim after hospital discharge.

Another consequence of immobile status, loss of voluntary contraction, and weakness acquired from the ICU is physical function impairment (64–66). A recent systematic review about post-ICU syndrome (67) reported significant functional disability due to lower-extremity problems during the first year following critical illness. The present study utilized the

MFS (36) that evaluates ambulatory aid, gait, and transferring, among other functional aspects. Despite some patients losing consciousness during the study period (N = 6) and high-risk morbimortality, E-Stim was safely and continuously delivered in 87.5% (n = 28 lower extremities) of the cohort for a 9 days period without interfering with the responsibilities of the hospital staff. The short-time therapy effect was reflected in the significantly lower likelihood of falling in the IG compared to the CG (p = 0.05, **Figure 4D**) at the time of ICU discharge. Nonetheless, a longer follow-up period with larger sample sizes targeting functional objective measurements is warranted to assess limb functionality in critically ill COVID-19 patients undergoing E-Stim therapy.

Under E-Stim therapy, oxygen consumption of the lower extremity increases to supply energy to the lower-extremity muscles and thus maintain isometric muscle contraction (35, 68). At hypoxic levels, glycogen substitutes oxygen for energy supplementation *via* the anaerobic metabolism pathway (69) that, when depleted, may result in muscle fatigue and subsequent injury (70). Although no study has explored the effect of E-Stim on the tissue perfusion in the lower extremities of ICU COVID-19 patients (71), Gerovasili et al. examined it the thenar muscle of (n = 29) ICU patients. With a provoked vascular occlusion, they found that mean SatO2 assessed with Near Infra-red Spectroscopy (NIRS) did not differ before and after E-Stim therapy. With the severe hypoxia and blood oxyhemoglobin disassociation that critically ill COVID-19 patients present (72), one could expect this population may be more susceptible to muscle perfusion deterioration after undergoing stress (73). In the present RCT, the IG's lower-extremity distal perfusion showed a similar pattern to the CG by remaining stable during the study period, meaning that daily E-Stim did not alter the level of muscle oxygen consumption in patients with severe hypoxia. However, studies evaluating SatO2 before and after 1 h E-Stim are needed to explore the real-time effects of COVID-19 in lower-extremity muscle perfusion.

We acknowledge the main limitation of this study is the small sample size, which may be underpowered for some of the outcomes. However, from the feasibility standpoint, we successfully collected all outcomes (i.e., $Ankle_S$, muscle endurance, and muscle perfusion), excluding those who underwent non-study-related adverse events, in 100% of the available samples at the 3 days time point, and 91.6% at the 9 days time point. Based on the observed effect sizes (d = 0.69–0.77, **Table 2**) at the 3 days time point, the available 26 samples (lower extremities) resulted in a generated power in range of 92–96% for $Ankle_S$, whereas for muscle endurance, the available 32 samples (lower extremities) resulted in a generated power in range of 97–99%. At the 9 days time point, the generated power for muscle endurance was greater than 80% (available samples = 22, d = 0.97, **Table 2**). However, the power was insufficient for $Ankle_S$ (less than 80%) because of the reduced available samples (n = 15) in patients with deep vein thrombosis, intubation, or death due to COVID-19; thus, were not reported. This study was preventative; therefore, patient selection focused on those at high risk of muscle deconditioning but not clinically diagnosed with established guidelines for myopathy or neuropathy. COVID-19 variants were not reported. Creatinine phosphokinase, serum lactate, nor blood indicators for muscle damage were measured. SatO2 was not directly measured from the GNM. There were no other muscles stimulated or assessed. The duration of follow-up was short due to the high mortality rate in this particular population. Despite these limitations, the observed medium effects for benefit of E-Stim, ease of administration without overwhelming the nursing staff, and high acceptability encourage future studies to confirm the observed effects in preventing muscle deconditioning among clinically ill patients who require prolonged bed rest.

Conclusion

Our study supports the safety and efficacy of E-Stim in the ICU setting to prevent deterioration of lower-extremity muscle weakness in critically ill COVID-19 patients. This adjunctive therapy may provide a potential benefit for gastrocnemius muscle endurance and $Ankle_S$, thus, possibly aid on the prevention of functional sequelae in critically ill bedbound patients or those with similar characteristics of severe hypoxia or low SpO2. This is also true given the fact the benefit was observed in those intubated patients who continued to receive E-Stim therapy during their hospital length of stay. The benefits of E-Stim rely on the rapid involvement of therapy at the time of ICU admission. However, E-Stim does not replace PT, but rather enhances gastrocnemius muscle endurance and $Ankle_S$ as an adjunctive treatment. Moreover, a portable and practical system that is easy to use does not interfere with the daily duties of the ICU staff. In addition, E-Stim did not alter vital signs or lower-extremity oxygen consumption, nor did it show adverse events during the study period. Further studies with larger sample sizes and longer follow-ups are warranted to examine the effectiveness of E-Stim to prevent muscle deconditioning in critically ill COVID-19 patients.

Data availability statement

The data that support the findings of this study are not publicly available but are available from the corresponding author BN, najafi.bijan@gmail.com upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review

Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals (BCM IRB). The patients/participants provided their written informed consent to participate in this study. If the participant was cognitively impaired, consenting was performed via telephone call with a legal representative. The informed consent was obtained from all participants and/or their legal guardians.

Author contributions

BN, AZ-R, NR, MS, and JPH: concept and study design. AZ-R, NR, RM, RB, ML, and AB: acquisition, analysis, and interpretation of the data. AZ-R, RM, RB, ML, and AB: drafting the manuscript. BN, MS, and JPH: critical revision of the manuscript for important intellectual context. RM: statistical analysis. BN: obtained the funding. AZ-R, NR, and RB: administrative, technical, or material support. BN, MS, and JPH: supervision. All authors contributed to the article and approved the submitted version.

Funding

This study received funding from Avazzia Inc. (Dallas, TX, USA). The funder was not involved in the study design, collection, analysis, interpretation of data, and the writing of this article or the decision to submit it for publication.

Acknowledgments

We thank Michele Loor, Andrea Braun, and the ICU Staff from BSLMC for assisting with the data collection and coordination of this research study between involved key investigators.

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.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 04 January 2023
DOI 10.3389/fmed.2022.1061955

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 05 October 2022
ACCEPTED 05 December 2022
PUBLISHED 04 January 2023

CITATION
Naorungroj T, Viarasilpa T, Tongyoo S, Detkaew A, Pinpak T, Wimolwattanaphan R, Ratanarat R, Promsin P, Thamrongpiroj P, Phumpichet A and Permpikul C (2023) Characteristics, outcomes, and risk factors for in-hospital mortality of COVID-19 patients: A retrospective study in Thailand.
Front. Med. 9:1061955.
doi: 10.3389/fmed.2022.1061955

Characteristics, outcomes, and risk factors for in-hospital mortality of COVID-19 patients: A retrospective study in Thailand

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Introduction: Data on the characteristics and outcomes of patients hospitalized for Coronavirus Disease 2019 (COVID-19) in Thailand are limited.

Objective: To determine characteristics and outcomes and identify risk factors for hospital mortality for hospitalized patients with COVID-19.

Methods: We retrospectively reviewed the medical records of patients who had COVID-19 infection and were admitted to the cohort ward or ICUs at Siriraj Hospital between January 2020 and December 2021.

Results: Of the 2,430 patients included in this study, 229 (9.4%) died; the mean age was 54 years, 40% were men, 81% had at least one comorbidity, and 13% required intensive care unit (ICU). Favipiravir (86%) was the main antiviral treatment. Corticosteroids and rescue anti-inflammatory therapy were used in 74 and 6%, respectively. Admission to the ICU was the only factor associated with reduced mortality [odds ratio (OR) 0.01, 95% confidence interval (CI) 0.01–0.05, $P < 0.001$], whereas older age (OR 14.3, 95%CI 5.76–35.54, $P < 0.001$), high flow nasal cannula (HFNC; OR 9.2, 95% CI 3.9–21.6, $P < 0.001$), mechanical ventilation (OR 269.39, 95%CI 3.6–2173.63, $P < 0.001$), septic shock (OR 7.79, 95%CI, 2.01–30.18, $P = 0.003$), and hydrocortisone treatment (OR 27.01, 95%CI 5.29–138.31, $P < 0.001$) were factors associated with in-hospital mortality.

Conclusion: The overall mortality of hospitalized patients with COVID-19 was 9%. The only factor associated with reduced mortality was admission to

the ICU. Therefore, appropriate selection of patients for admission to the ICU, strategies to limit disease progression and prevent intubation, and early detection and prompt treatment of nosocomial infection can improve survival in these patients.

KEYWORDS

mortality, coronavirus, COVID-19, SARS-CoV-2, risk factor, Thailand, developing country

Introduction

COVID-19 (Corona virus disease 2019) is an emerging disease declared by the WHO (World Health Organization) as a Public Health Emergency of International Concern in January 2020. Since the first case reported from China in December 2019, more than 500 million people have been infected worldwide, with an overall mortality rate of 1.14% (1), a mortality rate 17–28% for hospitalized patients, and 49–60% for mechanically ventilated patients (2–10). Risk factors for increased mortality from previous studies included older age, pre-existing medical illnesses, high Sequential Organ Failure Assessment (SOFA) score, receipt of IMV, acute respiratory distress syndrome (ARDS), and elevated D-dimer (2, 6, 9, 11, 12). However, most data were reported from China and developed countries, while the epidemiological data for COVID-19 diseases from low- and middle-income countries are lacking. The limitation of healthcare resources and treatment capacity may impact patient outcomes. This study aimed to determine the characteristics and outcomes and identify risk factors for in-hospital mortality for hospitalized COVID-19 patients in Thailand.

Materials and methods

Study design and population

This is a retrospective cohort study conducted at Siriraj Hospital, a tertiary care academic hospital in Bangkok, Thailand. The study protocol was approved by the Human Research Protection Unit of Siriraj Hospital Faculty of Medicine, Mahidol University. The requirement for written informed consent was waived.

In Thailand, the COVID-19 pandemic has occurred since January 2020. All COVID-19 patients who require admission to our hospital are treated in cohort wards and intensive care units (ICU) with modified airborne infection isolation rooms (AIIR). The patients requiring vasopressors, high flow nasal cannula (HFNC), non-invasive ventilation (NIV), or invasive mechanical ventilation (IMV) were admitted to the ICUs when beds were available. Guideline for critical care management of severe COVID-19 patients in our hospital has been previously published (13–15). Moreover, the recommendation for antiviral and anti-inflammatory therapies for COVID-19 patients in Thailand have been changed regularly according to the updated published data (16, 17). Since the publication of the preliminary report of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial (18), dexamethasone has been recommended for all patients with a resting oxygen saturation of $< 96\%$ or a reduction in oxygen saturation of $\geq 3\%$ after exercise-induced desaturation or those requiring respiratory support. However, before the publication of the RECOVERY study, some critically ill patients who had rapidly worsening respiratory symptoms with evidence of hyperinflammation and were less likely to have superimposed bacterial infections received corticosteroid therapy as previously described (13).

In this study, we investigated all adult patients aged $\geq$ 18 years diagnosed with COVID-19 and admitted to the cohort wards and ICUs at Siriraj Hospital from January 2020 to December 2021. The diagnosis of COVID-19 disease was confirmed by detecting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from any respiratory specimens by reverse transcription-polymerase chain reaction (RT-PCR). Patients who were readmitted due to diagnoses other than reinfection of COVID-19 were excluded.

Data collection

We initially obtained data from electronic medical records (EMRs) in collaboration with Siriraj Informatics and Data Innovation Center (SiData +) and then manually reviewed

Abbreviations: COVID-19, corona virus disease 2019; SOFA, sequential organ failure assessment; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; AIIR, airborne infection isolation rooms; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; RT-PCR, reverse transcription-polymerase chain reaction; EMR, electronic medical records; SiData+, Siriraj Informatics and Data Innovation Center; RRT, renal replacement therapy; HFNC, high flow nasal cannula; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; ROX, respiratory rate oxygenation index; SpO_2/FiO_2, pulse oxygen saturation/fractional inspired oxygen; SD, standard deviation; OR, odds ratios; CI, confidence intervals; BMI, body mass index; MAP, mean arterial pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; AKI, acute kidney injury.

the EMRs of all patients to verify the diagnosis of COVID-19 infections and recorded the data that could not be collected electronically.

The data collected included demographic data of the patient, comorbidities, vital signs, and laboratory results at admission, antiviral and anti-inflammatory medications used for the treatment of COVID-19 disease, admission to the ICU, the requirement for renal replacement therapy (RRT) and respiratory support, including oxygen therapy, HFNC, NIV, IMV. The respiratory rate oxygenation index (ROX), the ratio of oxygen saturation measured by pulse oximetry (SpO_2)/FiO_2 to respiratory rate, was also calculated in all patients (19).

Patient outcomes included survival at hospital discharge, ICU and hospital length of stay, complications during admission, including ARDS according to the Berlin Definition (20), nosocomial infections, septic shock, venous thromboembolism, and bleeding complications.

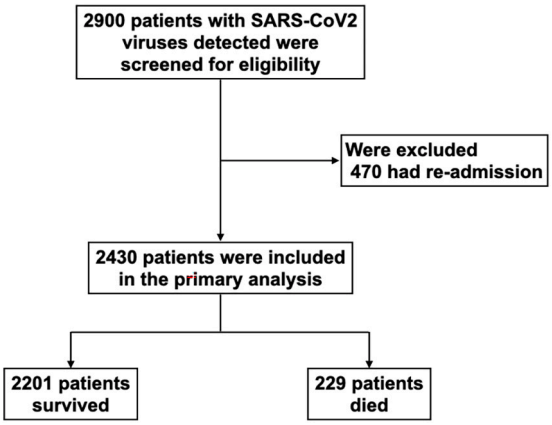

FIGURE 1
Study population. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Statistical analysis

Categorical variables were presented as numbers and column percentages, while continuous variables were presented as mean with standard deviation (SD), or median with 25th and 75th quartiles, as appropriate. Categorical variables were compared using Chi-square or Fisher exact tests, while continuous variables were compared using the *t*-test or Mann-Whitney *U*-test, as appropriate. A multivariate logistic regression model with a stepwise forward method was used to identify independent clinical risk factors associated with in-hospital mortality. We report risk factors with odds ratios (OR) and 95% confidence intervals (CI). All *p*-values < 0.05 were considered statistical significance. All statistical analyses were performed using IBM SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA) (21).

Results

Study patients

From January 2020 to December 2021, 2,900 patients with SARS-CoV2 viruses detected by RT-PCR were admitted to the cohort wards and ICUs of Siriraj hospital. Of these patients, 470 were excluded due to readmission for diagnoses other than COVID-19 reinfections; the remaining 2,430 patients were included in the final analysis (**Figure 1**); 2,201 (91%) survived and 229 (9%) died. In Thailand, the first case of the delta variant was reported in December 2020, and the first case of the omicron variant was found in December 2021. In our cohort, most patients (n = 2,329) were admitted from December 2020 to December 2021. The mortality rates changed over time; the highest mortality (14%) occurred at the same time as the highest admission rate (1,204 hospitalized patients) in July–September 2021 (**Figure 2**). Only 101 patients were admitted between January and April 2020; no mortality was observed in that period, and no COVID-19 patient was hospitalized from May to November 2020.

Baseline characteristics and laboratory results

The mean age of the hospitalized patients was 54 years, 40% were men and 19% had a body mass index (BMI) > 30 kg/m^2. Most of the patients (81%) had at least one comorbid disease; 44% had hypertension, 26% had diabetes mellitus, 9% had chronic kidney disease, and 2% had chronic heart disease. The mean duration from the onset of symptoms to hospital admission was 5 days, and only 2% of the patients had hypotension [mean arterial pressure (MAP) < 65 mmHg] at admission. For patients receiving HFNC, the mean ROX index was 17.8. In the univariate analysis, non-survived patients were older [74 (13) vs. 52 (19) years, $P < 0.001$], and were more often men (58% vs. 37%, $P < 0.001$) and had hypertension (74% vs. 41%, $P < 0.001$), diabetes mellitus (32% vs. 25%, $P = 0.045$), chronic kidney disease (28% vs. 7%, $P < 0.001$), and chronic heart disease (5% vs. 1%, $P < 0.001$), required a higher FiO2 [0.5 (0.3) vs. 0.3 (0.2), $P < 0.001$], and had a lower ROX index [10.4 (6.7) vs. 18.5 (6.4), $P < 0.001$] compared to patients who were discharged alive. The BMI and duration from the onset of the symptoms to admission were not significantly different between the survived and non-survived patients (**Table 1**).

For baseline laboratory results, patients who did not survive had slightly lower hemoglobin [12 (2) vs. 13 (2) g/dl, $P < 0.001$], platelet counts [206 (97) vs. 243 (92) $\times 10^3$/mm^3, $P < 0.001$], and serum sodium [136 (6) vs. 137 (2) mEq/L, $P < 0.001$],

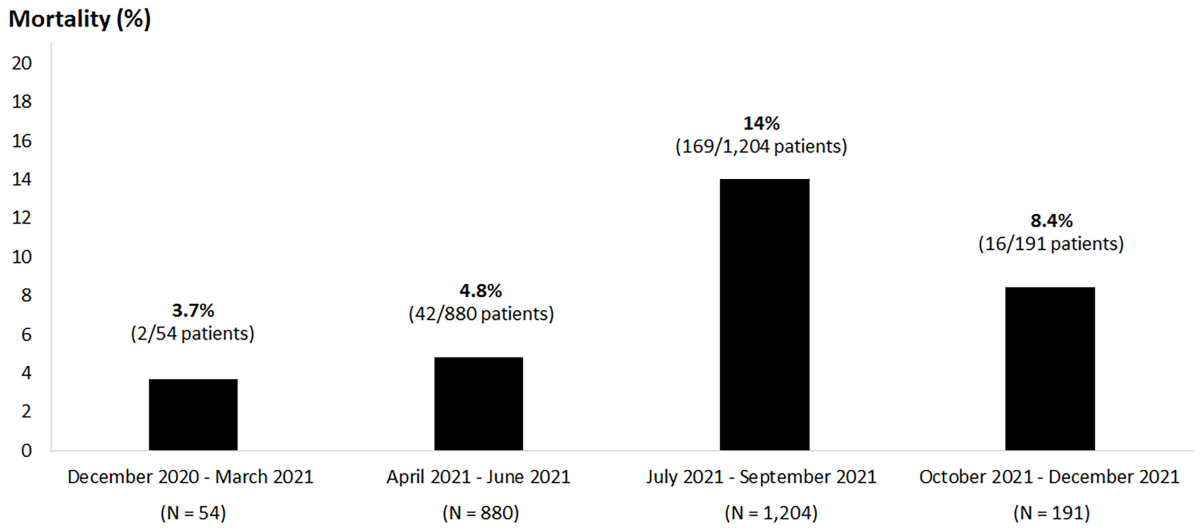

FIGURE 2
Trends in mortality from December 2020 to December 2021. Most cases (n = 2,329) were admitted from December 2020 to December 2021. The mortality rates changed over time; the highest mortality (14%) occurred at the same time as the highest admission rate (1,204 hospitalized patients) in July–September 2021. Only 101 patients were admitted between January and April 2020; no mortality was observed in that period, and no COVID-19 patient was hospitalized from May to November 2020.

bicarbonate [21 (4) vs. 22 (3) mEq/L, $P < 0.001$] and albumin level [3.1 (0.6) vs. 3.7 (0.6) g/dl, $P < 0.001$], but higher white blood cells [8.2 (4.8) vs. 6.8 (3.4) $\times 10^3$ cells/mm^3, $P < 0.001$], serum creatinine [Cr; 1.9 (2.3) vs. 1.2 (1.8) mg/dl, $P < 0.001$], potassium [4.2 (0.7) vs. 3.9 (0.6) mEq/L, $P < 0.001$], total bilirubin [0.8 (1.3) vs. 0.5 (0.5) mg/dl, $P = 0.024$], aspartate aminotransferase [AST; 75 (130) vs. 41 (49) U/L, $P = 0.002$], alanine aminotransferase [ALT; 52 (95) vs. 37 (55) U/L, $P = 0.003$], C-reactive protein [CRP; 75 (64) vs. 35 (46) mg/L, $P < 0.001$], and procalcitonin level [3.3 (9.8) vs. 1.2 (3.6) mg/mL, $P < 0.001$]. There were no significant differences in hemoglobin A1c, serum chloride, and alkaline phosphatase levels (Table 2).

Treatments and outcomes

Eighty-one percent of patients received respiratory support; 49% required low flow oxygen via nasal cannula or non-rebreathing mask with a reservoir bag, 25% required HFNC or NIV, and 7% required IMV. However, admission to the ICU was available for only 307 patients (13%). RRT was used in 90 patients (4%). Favipiravir (86%) was the most common antiviral medication, followed by remdesivir (9%) and lopinavir boosted with ritonavir (2%). Corticosteroids were administered to 1,799 patients (74%); dexamethasone (67%) was the most common type of corticosteroids used in patients with COVID-19, followed by methylprednisolone (3%) and hydrocortisone (3%). Rescue anti-inflammatory therapies with tocilizumab (4%) or baricitinib (2%) were required in 149 patients (6%). Of these patients, 113 survived (76%), and 36 died (24%; Table 3).

Overall in-hospital mortality was 9%; the mortality rate increased to 31% (187 of 605) in patients requiring HFNC or NIV, and 56% (99 of 178) in patients requiring IMV. The mortality rate for patients admitted to the ICU was 24% (74 of 307). Deceased patients were admitted more frequently to the ICU and received antiviral and anti-inflammatory medications, respiratory support, and RRT than survived patients (Table 3). Nosocomial infections (6.4%) were the most common hospital complications, followed by ARDS (4.7%), septic shock (4.1%), pulmonary embolism (1.4%), and bleeding complications (0.6%). All complications occurred more frequently in patients who did not survive than in those who survived.

Factors associated with hospital mortality

In a multivariate logistic regression analysis, the only factor related to mortality reduction in mortality was admission to the ICU (OR 0.01, 95%CI 0.01–0.05, $P < 0.001$). Factors associated with increased mortality included age > 65 years (OR 14.3, 95%CI 5.8–35.5, $P < 0.001$), thrombocytopenia (platelet $< 150 \times 10^3$/mm^3; OR 2.4, 95%CI 1.1–5.5, $P = 0.034$), renal dysfunction (Cr > 2 mg/dL; OR 6.2, 95%CI 2.3–16.6, $P < 0.001$), ROX index < 12 (OR 2.32, 95%CI 1.0–5.0, $P = 0.033$), MAP < 90 mmHg (OR 4.8, 95%CI 2.3–4.9, $P < 0.001$), the use of respiratory support with low flow O_2 through a non-rebreathing mask with a reservoir bag (OR 4.5, 95%CI 1.7–12.0, $P < 0.001$), non-invasive respiratory support (HFNC or NIV, OR 9.2, 95%CI 3.9–21.6, $P < 0.001$), and

TABLE 1 Baseline characteristic within 24 h of hospital admission according to hospital mortality.

	Overall population	Survived	Deceased	*P*-value
Demographics	2,430	2,201	229	
Age, year	54.2 ± 19.8	52.1 ± 19.2	74.3 ± 13.1	<0.001
Male gender (%)	982 (40.4)	850 (38.6)	132 (57.6)	<0.001
Weight, kg	66.4 ± 17.4	66.1 ± 17.5	63.3 ± 15.1	0.006
Height, cm	160.7 ± 9.0	160.8 ± 9.1	160.5 ± 8.5	0.697
BMI, kg/m^2	25.6 ± 6.0	25.7 ± 6.0	24.6 ± 5.9	0.007
BMI > 30 kg/m^2	471 (19)	431 (20)	40 (18.1)	0.502
Comorbidities				
Diabetes (%)	640 (26.3)	567 (25.3)	73 (31.9)	0.045
Hypertension (%)	1,070 (44.2)	904 (41.1)	170 (74.2)	<0.001
Heart disease (%)	37 (1.5)	26 (1.2)	11 (4.8)	<0.001
CKD overall (%)	223 (9.2)	160 (7.3)	63 (27.5)	<0.001
Stage 3 (%)		79 (3.6)	35 (15.3)	<0.001
Stage 4 (%)		16 (0.7)	12 (5.2)	<0.001
Stage 5 (%)		65 (3)	16 (7)	0.001
Day onset of symptom, days	4.9 ± 3.8	4.9 ± 3.7	4.8 ± 4.2	0.126
Respiratory rate, per minute	22.2 ± 4.1	21.9 ± 3.4	25.2 ± 5.1	<0.001
Oxygen saturation, %	97.2 ± 2.8	97.3 ± 2.6	95.7 ± 4.2	<0.001
FiO2, %	0.32 ± 0.19	0.29 ± 0.16	0.53 ± 0.28	<0.001
ROX index	17.8 ± 6.9	18.51 ± 6.43	10.43 ± 6.67	<0.001
MAP, mmHg	96.1 ± 11.8	96.6 ± 11.5	91.1 ± 13.6	<0.001
MAP < 65 mmHg (n = 2,419)		0 (0%)	5 (2.2%)	<0.001

BMI, body mass index; CKD, chronic kidney disease; FiO2, fraction inspired oxygen; MAP, mean arterial pressure; ROX index, the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate.

IMV (OR 269.4, 95%CI 33.6–2173.6, $P < 0.001$), receiving hydrocortisone (OR 27.0, 95%CI 5.3–138.3, $P < 0.001$) and occurrence of septic shock (OR 7.8, 95%CI 2.0–30.2, $P < 0.001$; Table 4).

A predictive model including only baseline parameters was shown in Supplementary Table 1. Similar baseline parameters including age > 65 years, platelet < 150 × 10^3/mm^3, Cr > 2 mg/dL, ROX index < 12, and MAP < 90 mmHg were persistently associated with increased mortality. Moreover, abnormal liver test namely serum albumin < 3 g/dL, AST > 40 IU/mL, and total bilirubin > 3 mg/dL were independently associated with greater mortality.

Discussion

In this large cohort of patients hospitalized for COVID-19 infections in Thailand, the overall mortality rate was 9%; the rate was higher in patients requiring admission to the ICU (24%) and IMV (56%). In multivariate analysis, admission to the ICU was the only factor associated with a reduction in mortality. Patients who were elderly, required high-level respiratory support, especially those with a lower ROX index, had renal dysfunction and thrombocytopenia at admission, were complicated by septic shock, and received hydrocortisone were at high risk of mortality in hospital.

The overall mortality of 9% in our cohort was lower than previously reported during the early stage of the pandemic (2, 3), but the mortality in patients who required admission to the ICU (24%) and IMV (56%) was comparable (3–5, 7–9). In previous studies, the mortality rate of hospitalized patients with COVID-19 ranged from 17 to 28% (2–4, 6, 18), and the mortality for ICU patients was 24–62% and for mechanically ventilated patients was 49–62% (3–5, 7–11).

A better understanding of the natural history of the disease and the availability of antiviral and anti-inflammatory therapies can lead to a reduction in mortality over time. Prior studies were carried out during the early stage of the pandemic, January–April 2020, in which information on the natural course and effective treatment strategies for emerging diseases was limited (3, 4, 6), while our study period was longer (January 2020–December 2021) and included the later stage of the pandemic

TABLE 2 Baseline laboratory data within 24 h of admission according to hospital mortality.

Variables	Overall (2,430)	Survived (2,201)	Deceased (229)	*P*-value
Hemoglobin, g/dl	12.7 ± 2.0	12.74 ± 1.97	11.90 ± 2.45	<0.001
Hematocrit, %	38.5 ± 5.7	38.7 ± 5.5	36.4 ± 7.0	<0.001
Hematocrit < 36% (*n* = 2,259)	662 (29.3%)	571 (27.6%)	91 (44.6%)	<0.001
WBC,/mm^3	6,880 ± 3,567	6,770 ± 3,431	8,240 ± 4,833	<0.001
WBC > 12,000 (*n* = 1,931)	155 (8.0%)	124 (69%)	31 (22.6%)	<0.001
Platelet, mm^3	240,060 ± 93,241	243,450 ± 92,250	205,910 ± 97,017	<0.001
Platelet < 150,000 (*n* = 2,259)	307 (13.6%)	240 (11.7%)	67 (32.8%)	<0.001
HbA1c	7.0 ± 1.9	7.02 ± 1.92	7.04 ± 1.85	0.926
BUN, mg/dL	18.8 ± 18.1	17.0 ± 15.4	36.3 ± 29.4	<0.001
Cr, mg/Dl	1.24 ± 1.83	1.17 ± 1.77	1.91 ± 2.26	<0.001
Cr > 2 mg/dL (*n* = 2,174)	150 (6.9%)	110 (5.6%)	40 (20.2%)	<0.001
Sodium, mEq/L (*n* = 2,218)	137.1 ± 4.3	137.1 ± 1.77	136.1 ± 6.3	0.001
Sodium > 145 mEq/L	28 (1.3%)	14 (0.7%)	14 (6.5%)	<0.001
Sodium < 135 mEq/L	476 (21.3%)	397 (19.8%)	79 (35.3%)	<0.001
Potassium, mEq/L (*n* = 2,217)	3.9 ± 0.6	3.9 ± 0.6	4.2 ± 0.7	<0.001
Potassium > 5 mmol/L	73 (3.3%)	56 (2.8%)	17 (7.9%)	<0.001
Potassium < 3 mmol/L	33 (1.5%)	30 (1.5%)	3 (1.4%)	0.906
Chloride, mEq/L	100.6 ± 4.9	100.6 ± 4.7	100.2 ± 6.7	0.227
HCO_3, mEq/L	22.4 ± 3.4	22.6 ± 3.3	20.6 ± 4.2	<0.001
HCO_3 < 20 mEq/L (*n* = 2,214)	380 (17.2%)	299 (15%)	81 (37.7%)	<0.001
CRP	38.4 ± 49.2	35.1 ± 46.3	74.9 ± 63.6	<0.001
Procalcitonin	1.46 ± 5.02	1.16 ± 3.59	3.26 ± 9.84	<0.001
AST, IU/mL	43.5 ± 59.2	40.9 ± 48.5	75.2 ± 130.0	0.002
ALT, IU/mL	37.7 ± 58.9	36.6 ± 54.9	51.5 ± 94.5	0.003
ALP, IU/mL	90.9 ± 61.9	89.8 ± 61.8	99.3 ± 62.9	0.58
Albumin, g/dL	3.6 ± 0.6	3.72 ± 0.59	3.12 ± 0.61	<0.001
Albumin < 3 g/dL (*n* = 917)	122 (13.3%)	81 (10.4%)	41 (36%)	<0.001
Total bilirubin, mg/dL	0.57 ± 0.62	0.53 ± 0.45	0.84 ± 1.33	0.024
Total bilirubin > 3 mg/dL (*n* = 804)	8 (0.9%)	5 (0.7%)	3 (3.1%)	0.06
Direct bilirubin, mg/dL	0.31 ± 0.54	0.27 ± 0.34	0.61 ± 1.22	0.008

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; WBC, white blood cell.

when more scientific knowledge about COVID-19 was available (18, 22–27). The difference in mortality of hypoxemic COVID-19 who did not require mechanical ventilation at admission was also found in two randomized controlled trials conducted in different periods. The RECOVERY trial revealed the effectiveness of dexamethasone in COVID-19 and was carried out between March and June 2020. That trial reported that the mortality at 28 days was 23% in the dexamethasone group and 26% in the usual care group (18). The Adaptive COVID-19 Treatment Trial 4 (ACTT-4) compared baricitinib and dexamethasone in combination with remdesivir for the treatment of hospitalized patients with COVID-19 was carried out from December 2020 to April 2021. ACTT-4 reported that mortality at 60 days was only 7 and 8% in the baricitinib and dexamethasone groups, respectively (28).

The different variants of the virus and the availability of COVID-19 vaccines may be the other important reasons for the decreased mortality in our cohort (29). A prior study also reported a lower fatality of COVID-19 patients during the outbreak of the omicron variant compared to that of the delta and beta variants (30). At the end of 2021, 63% of the Thai population had already received at least two doses of

TABLE 3 Treatment and clinical outcomes of according to hospital mortality.

Variables	Overall (2,430)	Survived (2,201)	Deceased (229)	*P*-value
ICU admission, %	307 (13%)	233 (10.6%)	74 (31.6%)	<0.001
ICU LOS, days	9.0 ± 7.4	7.5 ± 6.6	14.1 ± 7.6	<0.001
Hospital LOS, days	8.6 ± 6.2	8.1 ± 5.8	12.8 ± 8.0	<0.001
Respiratory support				
Cannula, %	1,060 (44%)	912 (41.4%)	148 (64.6%)	<0.001
Mask with bag, %	133 (5%)	90 (4.1%)	43 (18.8%)	<0.001
HFNC, %	605 (25%)	418 (19%)	187 (81.7%)	<0.001
Mechanical ventilation, %	178 (7%)	79 (36%)	99 (43.2%)	<0.001
Renal replacement therapy	90 (4%)	63 (2.8%)	27 (11.8%)	<0.0001
Antiviral therapy				
Favipiravir, %	2,095 (86.2%)	1,883 (84.2%)	212 (92.6)	0.001
Remdesivir, %	230 (9.5%)	169 (7.7%)	61 (26.6%)	<0.001
Lopinavir/ritonavir, %	60 (2.5%)	58 (2.6%)	2 (2.9%)	0.102
Anti-inflammatory therapy				
Tocilizumab, %	103 (4%)	75 (3.4%)	28 (12.2%)	<0.001
Baricitinib, %	46 (2%)	38 (1.7%)	8 (3.5%)	0.06
Dexamethasone, %	1,639 (67%)	1,421 (64.8%)	218 (95.2%)	<0.001
Methylprednisolone, %	78 (3%)	54 (2.5%)	24 (10.5%)	<0.001
Hydrocortisone, %	82 (3%)	12 (0.5%)	70 (30.6%)	<0.001
Complications				
Acute respiratory distress syndrome, %	114 (4.7%)	51 (2.34%)	63 (22.5%)	<0.001
Septic shock, %	100 (4.1%)	21 (1%)	79 (34.5%)	<0.001
Nosocomial infection, %	155 (6.4%)	78 (3.5%)	77 (33.6%)	<0.001
Pulmonary embolism, %	34 (1.4%)	21 (1%)	13 (5.7%)	<0.001
Bleeding, %	15 (0.6%)	9 (0.4%)	6 (2.6%)	<0.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; WBC, white blood cell.

vaccines (31), and all types of COVID-19 vaccines are proven to reduce the risk of developing severe disease and death (32–36). Unfortunately, information on COVID-19 vaccination status for our individual patients was not available, so the influence of the vaccination status on hospital mortality could not be determined.

This study also revealed the survival benefit of admission to the ICU for patients with severe COVID-19 (**Table 4**). Of the 307 patients admitted to the ICU, 76% were discharged alive. According to our results, patients who needed high-level respiratory support, HFNC or IMV, and who had septic shock and renal failure were at the highest risk of death; these patients should be the main priority for admission to the ICU. However, we also demonstrated the shortage of cohort ICU beds in our hospital, since almost one-third of our patients received HFNC or IMV, but only 13% of all patients were treated in the ICU. Therefore, increasing the capacity of the ICU with AIIR is an essential plan to prepare for the next pandemic.

Previous studies have reported an association between the degree of hypoxemia and increased mortality; our results supported this finding (4, 9, 11, 37). The lower ROX index and use of respiratory supports represented more severe hypoxemia in our patients. Since the risk of death was much higher in patients requiring IMV than in those requiring HFNC and low-flow O_2 therapy (**Table 4**), strategies to limit disease progression and prevent intubation, including early antiviral treatment for patients at high risk of disease progression, and rescue anti-inflammatory therapy with tocilizumab or baricitinib for those who had rapid worsening despite corticosteroid treatment, appear reasonable (25–27, 38).

Hydrocortisone is the only type of corticosteroid found to be associated with mortality in this study (**Table 4**). In contrast to dexamethasone, no prior research has demonstrated

TABLE 4 Univariate and multivariate analysis to predict hospital mortality.

Variables	Univariate		Multivariate	
	Odd (95%CI)	*P*-value	Odd (95%CI)	*P*-value
Baseline parameters				
Age > 65 years	8.41 (6.12–11.58)	<0.001	14.30 (5.76–35.54)	<0.001
Male gender	2.16 (1.64–2.85)	<0.001	–	–
Diabetes mellitus	1.35 (1.01–1.81)	0.045	–	–
Hypertension	4.13 (3.04–5.63)	<0.001	–	–
Heart disease	4.22 (2.06–8.66)	<0.001	–	–
Chronic kidney disease stage 3–5	4.84 (3.48–6.75)	<0.001	–	–
Hematocrit < 36%	2.09 (1.56–2.80)	<0.001	–	–
Platelet < 150,000/mm^3	3.70 (3.68–5.10)	<0.001	2.43 (1.07–5.53)	0.034
WBC > 12,000/mm^3	3.94 (2.54–6.11)	<0.001	–	–
Creatinine > 2 mg/dL	4.30 (2.89–6.39)	<0.001	6.22 (2.33–16.60)	<0.001
Sodium > 145 mEq/L	9.90 (4.65–21.05)	<0.001	–	–
Sodium < 135 mEq/L	2.21 (1.64–2.99)	<0.001	–	–
Potassium > 5 mEq/L	2.98 (1.70–5.23)	<0.001	–	–
Bicarbonate < 20 mEq/L	3.44 (2.54–4.65)	<0.001	–	–
Albumin < 3 g/dL	5.01 (3.20–7.82)	<0.001	–	–
AST > 40 IU/mL	3.56 (2.51–5.04)	<0.001	–	–
Total bilirubin > 3 mg/dL	4.74 (1.12–20.16)	0.020	–	–
Respiratory rate > 20/min	5.12 (3.72–7.06)	<0.001	–	–
Pulse oximetry < 95%	3.66 (2.67–5.01)	<0.001	–	–
ROX index < 12	8.69 (6.45–11.69)	<0.001	2.32 (1.01–5.01)	0.033
MAP < 90 mmHg	2.26 (1.72–2.98)	<0.001	4.75 (2.28–4.88)	<0.001
Treatment parameters				
ICU admission	3.95 (2.90–5.39)	<0.001	0.01 (0.01–0.05)	<0.001
Mask with bag	5.42 (3.66–8.03)	<0.001	4.51 (1.70–11.97)	<0.001
High flow nasal cannula	18.97 (13.35–26.70)	<0.001	9.23 (3.94–21.60)	<0.001
Mechanical ventilation	20.46 (14.49–28.87)	<0.001	269.39 (33.6–2173.63)	<0.001
Renal replacement therapy	4.54 (2.83–1.28)	<0.001	–	–
Favipiravir	2.34 (1.41–3.89)	<0.001	–	–
Remdesivir	4.37 (3.13–6.09)	<0.001	–	–
Tocilizumab	3.95 (2.50–6.24)	<0.001	–	–
Baricitinib	2.06 (0.95–4.76)	0.06	–	–
Dexamethasone	10.45 (5.83–19.82)	<0.001	–	–
Methylprednisolone	4.66 (2.82–7.69)	<0.001	–	–
Hydrocortisone	80.31 (42.64–151.27)	<0.01	27.04 (5.29–138.31)	<0.001
Complications				
ARDS	16.00 (10.71–23.91)	<0.001	–	–
Septic shock	54.67 (32.87–90.94)	<0.001	7.79 (2.01–30.18)	0.003
Nosocomial infection	13.79 (9.67–16.67)	<0.001	–	–
Pulmonary embolism	6.25 (3.09–12.65)	<0.001	–	–
Bleeding	6.55 (2.31–18.58)	<0.001	–	–

the benefit of hydrocortisone in patients with COVID-19 (39, 40). We found that septic shock was associated with high mortality in the multivariate model. This association between hydrocortisone and mortality could be explained by the fact that in our hospital hydrocortisone was used primarily in patients with septic shock who received high-dose vasopressor treatment. An observational study in Argentina also found that septic shock and refractory hypoxemia were the major causes of death in patients with COVID-19 requiring IMV, and the use of vasopressors on admission was an independent predictor of hospital mortality (10), the rate of nosocomial infection in our cohort was 6% (155 of 2,430) and 65% (100 of 155) of these patients developed septic shock (**Table 3**). Therefore, early detection and treatment of superimposed bacterial infections are essential to improve patient outcomes.

The associations between increased mortality and older age, thrombocytopenia, and renal dysfunction on admission in patients with COVID-19 have been reported in previous studies (2, 4, 8, 11, 41–43), but older age is not modifiable, and thrombocytopenia and renal dysfunction appear to be attributable to the severity of the disease (44–47). Thrombocytopenia, defined as platelet counts $< 150 \times 10^3/mm^3$, is common in COVID-19 disease. The proposed pathophysiological mechanisms include reducing platelet synthesis from the bone marrow due to direct viral infection or cytokine storm, increasing platelet destruction by the immune system, and increased platelet consumption resulting from aggregation and formation of microthrombi in damaged lung parenchyma and pulmonary endothelial cells (48). The possible pathophysiology of acute kidney injury (AKI) in COVID-19 consists of direct effects of the virus that causes endothelial and tubular epithelial damage and indirect impact from volume depletion, nephrotoxic drugs, sepsis-associated AKI from superimposed bacterial infection, increased renal venous pressure complicated from mechanical ventilation with high intrathoracic pressure, organ crosstalk from lung injury or cardiorenal syndrome, and rhabdomyolysis (46, 47). Patients with any of these factors need close observation for severe disease.

The strengths of our study are that we reported the characteristics and outcomes of a relatively large cohort of hospitalized patients with COVID-19 and performed a multivariate analysis to determine the independent factors associated with in-hospital mortality. We also performed manual searches on the EMR to verify the diagnosis of COVID-19 infection in all patients and to obtain the data that could not be collected electronically. We also acknowledge several limitations of this study. First, this is a single-center study, which may limit the generalizability of our findings. Second, we did not have data on underlying chronic lung disease, SOFA score, and D-dimer level, which increased mortality risks in previous studies. Third, concurrent life-threatening medical or surgical diseases necessitating urgent treatment were not recorded; these conditions may impact patient outcomes. Fourth, we were unable to obtain clinical outcomes after hospital discharge. Finally, similar to other observational and retrospective studies, unmeasured confounders may affect the results.

Conclusion

The overall mortality of hospitalized COVID-19 patients in Thailand was 9%. Admission to the ICU was the only protective factor. Patients who received invasive or non-invasive respiratory support and were complicated by septic shock had the highest risk of death. Therefore, appropriate patient selection for admission to the ICU, strategies to limit disease progression and prevent intubation, and early detection and prompt treatment of nosocomial infection may improve survival. Although unmodifiable, elderly patients and those with thrombocytopenia and renal dysfunction need close observation for the development of severe disease.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Human Research Protection Unit of Siriraj Hospital Faculty of Medicine, Mahidol University (Certificate of Approval no. Si 335/2020). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

TN had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, designed the study, performed manual searches for additional data collection and interpretation, drafted and revised the manuscript. TV designed the study, reviewed, interpreted the data, drafted, and revised the manuscript. ST designed the study, performed the statistical analysis, drafted, and revised the manuscript. AD, TP, RW, RR, PP, PT, AP, and CP assisted in data collection, data interpretation, and critically reviewed the manuscript. All authors have read and approved the final manuscript and agreed to be responsible for all aspects of the work.

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/fmed.2022.1061955/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Study Protocol
PUBLISHED 04 January 2023
DOI 10.3389/fmed.2022.990639

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 10 July 2022
ACCEPTED 28 November 2022
PUBLISHED 04 January 2023

CITATION
Sum CH, Ching JYL, Song T, Cheong PK, Lo CW, Lai MK, Chia CP, Chan KL, Mak WY, Leung KC, Leung SB, Zhang H and Lin Z (2023) Chinese medicine for residual symptoms of COVID-19 recovered patients (long COVID)—A double-blind, randomized, and placebo-controlled clinical trial protocol.
Front. Med. 9:990639.
doi: 10.3389/fmed.2022.990639

Chinese medicine for residual symptoms of COVID-19 recovered patients (long COVID)—A double-blind, randomized, and placebo-controlled clinical trial protocol

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Introduction: Coronavirus disease 2019 (COVID-19) is the current global pandemic of which residual symptoms exhibited by post-acute, rehabilitating patients include fatigue, dyspnoea, and insomnia. Chinese medicine (CM) has been widely used in China to treat different stages of COVID-19. While there are a significant number of clinical studies suggesting its efficacy and safety in its use during acute stage, there are very few randomized controlled trials focusing on the rehabilitation stage. Liujunzhi Decoction and Shashen Maidong Decoction are frequently recommended by official clinical guidelines in China to treat COVID-19 patients in rehabilitation stage. This double-blind, randomized, placebo controlled study aims to evaluate the efficacy and safety of the combination of the two formulae [named "COVID-19 Rehab Formula (CRF)"] in treating COVID-19 residual symptoms (long COVID).

Methods: Eligible subjects will be randomly divided into treatment group and control group in 1:1 ratio. Treatment group will receive CRF along with certain pre-defined CM according to symptoms for 8 weeks, while control group will receive equivalent packs of placebo for 8 weeks. Data in terms of Fatigue

Severity Score (FSS), self-reported COVID-19 long term symptom assessment, the modified British Medical Research Council (mMRC) Dyspnoea Scale, EuroQol Five-Dimension Five-Level (EQ-5D-5L) Questionnaire, pulmonary function test and adverse events will be collected and analyzed by SPSS 24. Blood test on liver and renal functions will also be conducted as safety measures.

Conclusion: This study will evaluate the efficacy and safety of CRF in the treatment COVID-19 residual symptoms in a scientifically rigorous design.

Clinical trial registration: [ClinicalTrials.gov], identifier [NCT04924881].

KEYWORDS

Chinese medicine, alternative and complementary medicine, long COVID-19, randomized controlled trial, protocol

1. Background

The first identification in patients with severe pneumonia was in Wuhan province, China in November 2019. A novel coronavirus was identified as the cause by Chinese authorities on 7 January 2020 and was temporarily named "2019-nCoV." Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases. A novel coronavirus (nCoV) is a new strain that has not been previously identified in humans. The new virus was subsequently named the "COVID-19 virus." COVID-19 has spread rapidly and now affects all over the world. This is the greatest pandemic of modern times and has been declared a Public Health Emergency of International Concern by the WHO Director-General (1). On 11 March 2020, coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO). As of 5 June 2022, over 529 million COVID-19 confirmed cases were reported worldwide, with more than 6 million related death (2).

Most of the infected people will develop mild to moderate illness, for example fever, cough, tiredness and joint pain etc. For some older people, and those with comorbidities like cardiovascular disease, diabetes, chronic respiratory disease, and malignancy are more likely to develop serious illness (2).

Up to now, most frequently used therapies are corticosteroids, antiviral agents, antiviral/immunomodulatory drugs, serotherapy, anticoagulant and inflammation inhibitors (3). The medium and long-term problems experienced by survivors of COVID-19 after discharge from hospital include fatigue, breathlessness and joint pain (4). Studies reported that different kinds of residual symptoms were left after patient discharged from the hospital. More than eight-seven percent reported a persistence of at least one symptom, particularly fatigue and dyspnoea 4 weeks after post-discharge (5). Overall, more than fifty four percent of all female patients reported moderate or severe fatigue, compared to 30 percent of male patients. Moderate or severe dyspnoea was also more often reported by females than males when they were under intensive care (53.8 vs. 21.1%) but the proportions were similar in those who stayed in ordinary ward (24.2 and 20.0%) (4). Besides, thirteen percent of patients had gastrointestinal symptoms such as diarrhea, vomiting, loss of appetite, etc. A cohort study showed that some COVID-19 recovered patients suffered from the above symptom up to 6 months or more (6). In Hong Kong, our data showed that 26.7 suffered fatigue, 20% suffered dyspnoea and 23.3% insomnia which are residual symptoms 6 months after discharged from the hospital of our COVID-19 recovered patients (unpublished data).

Traditional Chinese Medicine (TCM) has a long history and played an important role in the prevention and treatment of several epidemic diseases. During SARS epidemic in 2003, the treatment of TCM has achieved remarkable therapeutic effect. Some recent studies have demonstrated that among the limited therapeutics, TCM plays an important role in halting the progress of the disease and promoting the recovery of patients in the absence of vaccines or targeted drugs (7). As early as of 17 February 2020, total number of confirmed COVID-19 cases treated by TCM had already reached 60,107 in China (8).

Many different types of TCM have been proposed to treat COVID-19, of which the most famous are "three medicines and three formulae": Jinhua Qinggan Granule, Lianhua Qingwen Capsule/Granule, Xuebijing Injection; Lung Cleansing and Detoxifying Decoction, HuaShiBaiDu Formula and XuanFeiBaiDu Formula, which are mainly used for active COVID cases of different severity. Clinical and pharmacological studies have suggested their efficacy, safety, and possible mechanisms in treating different stages of COVID-19, either used along with conventional treatment or independently (9–14).

For residual symptoms seen in COVID recovered patients, such as fatigue, dyspnoea and insomnia, there are also studies suggesting that TCM may be helpful. For example, a meta-analysis of 11 studies has shown that using Chinese medicine interventions together with conventional treatment is more effective than using the conventional treatment alone in treating chronic fatigue syndrome (15). There are also meta-analyses that have shown similar conclusions for idiopathic pulmonary fibrosis (16) and insomnia (17).

Liujunzhi Decoction (LJZD) and Shashen Maidong Decoction (SSMDD) are classic Chinese medicine formulae that have been used in China for hundreds of years. LJZD is composed of six herbs, namely, Ginseng Radix Et Rhizoma, Atractylodis Macrocephalae Rhizoma, Poria, Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle, Pinelliae Rhizoma Praeparatum and Citri Reticulatae Pericarpium, while SSMDD of seven: Adenophorae Radix, Polygonati Odorati Rhizoma, Glycyrrhizae Radix Et Rhizoma, Mori Folium, Ophiopogonis Radix, Lablab Semen Album, and Trichosanthis Radix. Their combination is proposed as the intervention of this trial because, from the perspective of Chinese medicine, the residual symptoms of COVID-19 can often be seen as the manifestation of "lung-spleen qi deficiency" or "dual deficiency of qi and yin" (18, 19). LJZD and SSMDD are two of the classic formulae used to treat these two pathologies, respectively. In fact, among the 33 official COVID-19 clinical guidelines published in mainland China, 10 have recommended the use of LJZD, and 6 recommended SSMDD (or their modified versions) in the recovery stage of COVID-19. Modified LJZD and SSMDD are the two most frequently recommended formulae (20).

To date, there are very few clinical studies of using TCM to treat the residual symptoms of COVID-19 recovered patients. A multi-center observational study in Hong Kong has shown that individualized TCM treatments could facilitate resolution of clinical symptoms (including fatigue, cough, shortness of breath, post-meal fullness, and loose stool), improve lung functions, and lead to healthier CM body constitutions in COVID recovered patients (21). A randomized controlled trial comparing a Chinese medicine (Qingjin Yiqi granules) combined with standard rehabilitation treatments (SRTs) against SRTs alone has also shown that the CM granules could assist reduction in fatigue and breathlessness (22). However, there is still a lack of double-blind, placebo-controlled randomized controlled trials on the subject—a void this study aims to fill.

2. Hypothesis

The residual symptoms of COVID-19 recovered patients can be improved after taking Chinese medicine.

3. Objectives

To evaluate the efficacy of using COVID Rehab Formula "CRF" (LJZD and SSMDD with variations) on the residual symptoms of COVID-19 recovered subjects.

4. Study outcomes

4.1. Primary outcome

Improvement of residual COVID-19 symptoms of fatigue using Fatigue Severity Score (FSS) at week 8.

4.2. Secondary outcomes

1. Self-reported COVID-19 Long Term Symptom Assessment at week 8.
2. Improvement of fatigue using Fatigue Severity Score (FSS) at week 12.
3. Change of modified British Medical Research Council (mMRC) dyspnoea scale to measure the improvement of dyspnoea at week 8 and 12.
4. Change of EuroQol five-dimension five-level (EQ-5D-5L) questionnaire and it's Visual Analogue Scale (VAS) to measure the quality of life at week 8 and 12.
5. Improvement of pulmonary function FEV1, FVC, and FEV1/FVC ratio at week 8.
6. Adverse events related to study treatment.

5. Study design

This is a double-blind, randomized, placebo-controlled superiority trial. Eligible subjects will receive either "CRF" granules or placebo granules for 8 weeks followed by a post-treatment visits at week 12.

6. Study population

COVID-19 recovered patient with a confirmed diagnosis of SARS-Cov-2 infection using the PCR or rapid antigen test according to the standard of Center for Health Protection, Department of Health, Hong Kong and released from isolation[1] will be screened for the following eligibility criteria. Study subjects will be recruited from the following clinics/Chinese medicine centers: (1) The CUHK Chinese Medicine Specialty

1 https://www.chp.gov.hk/en/resources/346/index.html

Clinic and Teaching and Research Center on CUHK campus (CUHK-CMSCTRC); (2) The two Integrative Medical Centers, Hong Kong Institute of Integrative Medicine at Shatin and Wan Chai. Moreover, patients following up for residual symptoms at the medical clinics at Prince of Wales Hospital will be provided our study information; interested patients can go to our Integrative Medical Center located at the same hospital. Advertisements in the poster on the clinic and internet platforms, such as Facebook, emails, and website will be made to facilitate community recruitment. Besides, we will publish articles in local newspapers and magazines as well as organize health promotion talks to augment the subject recruitment process.

6.1. Inclusion criteria

- Aged above 18.
- Have fatigue and one more residual symptoms (e.g., dyspnoea, sleep disturbance, cough, loose stool, abdominal distension, loss of appetite, dizziness, etc.) at least 5 weeks after discharge.
- Patients are diagnosed with "lung-spleen qi deficiency" and/or"dual deficiency of qi and yin" by a Chinese Medicine Practitioner.
- Voluntary written consent.

6.2. Exclusion criteria

- Still being SARS-CoV-2 positive.
- Known severe medical conditions, such as cardiovascular, liver or renal dysfunction, diabetes mellitus, cancers, cerebrovascular diseases, and blood system diseases.
- Impaired hematological profile and liver/renal function.
- No concomitant non-steroidal anti-inflammatory drugs (NSAIDs), steroids, antibiotics, prebiotics, and probiotics within 4 weeks.
- Known allergic history to any Chinese herbal medicines;
- Known pregnancy or lactating.

7. Patient visit

7.1. Screening visit

Subjects will be invited to come for screening. Information about the study will be explained and subject will sign the informed consent form before screening. Symptom assessment will be done to confirm if the subjects still have residual symptoms of fatigue and more such as dyspnoea and insomnia. Less than 10 ml blood for hematology, liver and renal function tests will be done as safety measures. A deep throat saliva/professional-administered combined nasal and throat swab test for SARS-CoV-2 will be arranged by using the accredited laboratory or Government service.

7.2. Baseline randomization visit

At randomization visit, eligible subjects will have medical consultation and assessment by registered Chinese medicine practitioners (CMPs) investigators. Vital sign will be assessed, medical history and concomitant medications will also be recorded. If the subject has a result of not detected or negative result of SARS-Cov-2 RT-PCR test of deep throat saliva/professional-administered combined nasal and throat swab, and negative medical and travel history related to COVID-19 within 72 h, subjects will be instructed to do a pulmonary function test using a designated spirometer and complete the questionnaires; however, performing deep throat saliva/professional-administered combined nasal and throat swab test and pulmonary function test are not mandatory. Subjects will be randomly assigned (in a 1:1 ratio) to receive 8 weeks of either "CRF" granules 23–42 g daily or placebo granules 23–42 g daily. CMP investigators will prescribe and dispense the study treatment accordingly.

7.3. Follow-up visit

Subjects will return for follow-up at week 8 (±4 days), and followed by a post-treatment visit at week 12 (**Table 1**). Symptom assessment and other questionnaires will be done. Blood tests will be repeated as safety measures at week 8. Subjects will be arranged to have another SARS-Cov-2 RT-PCR test of deep throat saliva/professional-administered combined nasal and throat swab, and confirmed to have negative medical and travel history related to COVID-19 within 72 h before the pulmonary function test at week 8. Performing deep throat saliva/professional-administered combined nasal and throat swab test and pulmonary function test are not mandatory. Treatment compliance will be recorded and adverse events will be captured on a patient diary. A direct telephone line will be provided so that subjects can report any adverse events during office hours between scheduled visits. The subjects will be recommended to attend Emergency Department at the nearest hospital beyond office hours if deemed necessary. To monitor compliance, subjects will be asked to bring back all remaining packs of granules for counting. One time free consultation with 1 month Chinese herbal treatment will be provided to all subjects after completion of study to ensure the follow up visit compliance.

TABLE 1 Study schedule.

Items	Screening	Treatment period		Post-treatment follow up
	≤7 days to 0 day	Day 0 (baseline)	Week 8 (±4 days)	Week 12 (±4 days)
Informed consent	X			
Eligibility	X	X		
Medical consultation and assessment		X	X	X
Medical history		X		
Concomitant medication		X	X	X
Blood for safety measures	X		X	
Deep throat saliva or nasopharyngeal swab for SARS-Cov-2 RT-PCR test	*X		*X	
AE/SAE assessment			X	X
Questionnaires		X	X	X
Pulmonary function test		#X	#X	
Administration of study drug		X	X	

*Subjects will have deep throat saliva or nasopharyngeal swab for SARS-Cov-2 RT-PCR test within 72 h before follow up visit but it is not mandatory.
#Pulmonary function test will be skipped if no deep throat saliva has been done and showed not detected or negative within 72 h.

7.4. Study assessments

7.4.1. Fatigue severity score (FSS)

Fatigue severity score is a 9-item scale which measures the severity of fatigue and its effect on a person's activities and lifestyle in patients with a variety of disorders. Scores range from 9–63; the higher the score, the greater fatigue severity (23).

7.4.2. Self-reported COVID-19 long term symptom assessment

For the symptom questionnaire, participants will be asked to report newly occurring and persistent symptoms, or any symptoms worse than before COVID-19 development. The symptom assessment has 5 scale, from none to very severe.

7.4.3. The modified British medical research council (mMRC) dyspnoea scale

The mMRC scale is a five-category scale to characterize the level of dyspnoea with physical activity in which higher scores correspond with increased dyspnoea (6).

7.4.4. EuroQol five-dimension five-level (EQ-5D-5L)

The EQ-5D-5L is a validated questionnaire to evaluate patient quality of life by assessment of the following five domains: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Categorization within each factor is divided into five-levels that range from no problems to extreme problems (6). EuroQol Visual Analogue Scale (EQ-VAS) is a patient's subjective assessment of generic health ranging from 0 (worst imaginable health) to 100 (best imaginable health) before COVID-19 and at the time of the visit, with higher scores representing better subjective health experience. A difference of 10 points defined worsened quality of life (6).

7.4.5. Pulmonary function test device

FEV1, FVC, and FEV1/FVC ratio will be measured with the Air Next Spirometer (NuvoAir, Sweden) in combination with the mobile coaching system. Air Next is a novel spirometer that connects *via* bluetooth to a smartphone application, permitting patients to monitoring lung function at home. It has a turbine mechanism (Flow Mir) to perform measurements inside the disposable single use nozzles. To perform spirometry, the user exhales air into the turbine. This air turns a motor, and the device registers the speed of the rotor, adapts it, and transfers the data to the smartphone application (24). The higher of FEV1/FVC ratio, the healthier of subjects.

7.4.6. Blood test

Venous blood samples will be collected from all participants for hematology, liver and renal function tests as safety measures.

7.4.7. Subject withdrawal

A subject must be withdrawn from the study if he/she withdraws consent. Subjects who (1) experience adverse events, or (2) have pre-existing violation of entry criteria may remain in the study unless the investigator determines that it is not in the subject's best interest to continue. The specific reason for withdrawal should be indicated.

Subjects who have withdrawn from the study will be invited to follow up at the last study visit i.e., 8 weeks

after the randomization visit to detect any delayed clinical events.

8. Study intervention

8.1. Study treatments

The core study treatment, COVID Rehab Formula "CRF" is prepared in the form of mixed LJZD and SSMDD concentrated herbal granules with variations.

Essentially, the "CRF" consists of Ginseng Radix Et Rhizoma (renshen) 8 g, Atractylodis Macrocephalae (baizhu) 7.2 g, Rhizoma Poria (fuling) 7.2 g, Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle (zhigancao) 4.8 g, Glycyrrhizae Radix Et Rhizoma (gancao) 4 g, Pinelliae Rhizoma Praeparatum (fabanxia) 9.6 g, Citri Reticulatae Pericarpium (chenpi)7.2 g, Adenophorae Radix (nanshashen) 8 g, Polygonati Odorati Rhizoma (yuzhu) 8 g, Mori Folium (sangye) 4.8 g, Ophiopogonis Radix (maidong) 8 g, Lablab Semen Album (baibiandou) 8 g, and Radix Trichosanthis Radix (tianhuafen) 8 g.

For study subjects with the following symptoms, specified Chinese medicine will be added; fatigue: Astragali Radix (huangqi) 15 g; dyspnea or cough with sputum: Trichosanthis Pericarpium (gualoupi) 10 g, Fritillariae Thunbergii Bulbus (zhebeimu) 10 g, Armeniacae Semen Amarum (kuxingren) 10 g; sleep disturbance: Ziziphi Spinosae Semen (suanzaoren) 10 g, Indian Bread with Pine (fushen) 10 g and Margaritifera Concha (zhenzhumu) 10 g; loose stool: Plantaginis Semen (cheqianzi) 10 g, Artemisiae Scopariae Herba (mianyinchen) 15 g, and Coicis Semen (yiyiren) 10 g.

Granules will be used with the dosage equivalent to the raw herbs according to the manufacturer. One daily dose of which (weight 23–42 g) will be dissolved in hot water and administered while it is lukewarm. Study subjects will take 2 times daily, 1–2 packs in the morning and the other in the evening after meal. The placebo granules, made of starch and caramel with similar appearance, smell and taste to the CRF but contain no active constituents, will be taken by the patients in the placebo group in the same way as those in the treatment group.

Both treatment herbal and placebo granules will be produced by a manufacturer with a Good Manufacturing Practice (GMP) certificate.

8.2. Prohibited drugs

Non-steroidal anti-inflammatory drugs (NSAIDs), steroids and antibiotics are prohibited. Chinese medical treatments which are used to treat those residual symptoms are prohibited during the study period.

8.3. Treatment compliance

Treatment compliance is assessed by the number of doses taken during study period by subjects' self-report and research personnel's counting of returned packs of granules.

8.4. Randomization and blinding

A computer-generated randomization schedule is used to assign subjects to the treatment sequences. Concealment of allocation will be ascertained by an independent research staff member, and identically designed treatment packs will be used for study drugs.

This is a double-blind randomized controlled trial. The random allocations will be put into opaque envelops with sequential study numbers. Two sets of the envelope will be prepared, with one set for randomization at the site, and another set for storage in the investigator's office for emergency unblinding.

9. Possible risks and adverse event reporting

9.1. Possible risks and discomfort

In general, there will be minimal discomfort in blood taking and the risk include bleeding, infection, bruising, and feeling lightheaded. Besides, no serious adverse event has been reported in both decoction (25, 26) and their variations such as Indian Bread with Pine, Ziziphi Spinosae Semen and Margaritifera Conch (27).

There is mild discomfort of taking Shashen Maidong Decoction, Plantaginis Semen and Artemisiae Scopariae Herba including feeling of abdominal discomfort, diarrhea, abdominal distension, nausea, and vomiting as well as loss of appetite (28, 29). On the other hand, studies show that Fritillariae Thunbergii Bulbus may cause toothache, hand numbness and induce allergy reaction, but those can be relieved after treatment (30). Astragali Radix are found to induce allergy reaction, painful sensation on limbs, headache, insomnia and abdominal discomfort, but those may due to overdose usage (over 30 g) and using injection dosage form (31), while Trichosanthis Pericarpium are found to cause allergy reaction and abdominal discomfort, those are possibly by using injection dosage form (32). However, there is no documented evidences about possible risks and discomfort for Coicis Semen and Armeniacae Semen Amarum. Moreover, according to reports of interaction of CM and Herbal Medicine(s) with Anti-cancer Drugs forms, published by The University of Hong Kong, Department of Pharmacology and Pharmacy, there is no evidence for AE or harmful

interaction between COVID-19 Rehabilitation Formula (CRF) and western medicine.

9.2. Adverse events

An adverse event is any undesirable medical event occurring in the subject within the trial period, whether or not it is related to the study intervention. No serious adverse event has been reported of taking COVID-19 Rehabilitation Formula (CRF). The adverse reaction will be recorded and the treatment will be suspended when severe adverse reaction occurs. The assessment of adverse event will be recorded according to CTCAE 4.0 which is a standard assessment tool.

9.3. Serious adverse events

A serious adverse event is an adverse event that results in one of the following outcomes:

- Death.
- Life-threatening.
- In-patient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability or incapacity.
- A congenital anomaly or birth defect.

The definitions of causal relationship to study intervention are the same as those for adverse events. A standard serious adverse event form will be used (provided by The Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee [Joint CUHK-NTEC CREC] at)[2] to report the events within 24 h after acknowledgement.

10. Sample size and statistical methods

10.1. Sample size calculation

The primary outcome is Fatigue Severity Score (FSS). There is no any previous study on the Chinese medicine treatment of COVID-19 measured by FSS. The clinically meaningful improvement in FSS was assumed to be a drop of 9 out of 63 based on previous studies (33, 34). Based on the standard deviation of symptom score of residual fatigue in this study on COVID-19 recovered patients (33, 35), we assumed standard deviation estimates of 12. To detect a clinically meaningful difference of 9 points in FSS, sample size of 58 was estimated based on standard deviation estimates of 12 at an alpha of 0.05 and power of 0.8. It should be noted that these estimates are considered vague approximations, and 58 participants is a conservative estimate to detect a statistically significant result of change in FSS. To compensate a possible drop-out rate of 15%, totally 68 patients will be needed, with 34 in each group.

10.2. Statistical analysis

Baseline data (gender, age, and vital signs) will be descriptively summarized. Differences of measurement data between the groups will be assessed using *t*-test for normally distributed continuous variables and Wilcoxon signed rank test for non-normally distributed variables. Measurement data of different groups in each visit will be reported as mean ± standard deviation (SD). Intra-group comparisons between baseline and each visit will be conducted by using paired *t*-test (or Wilcoxon signed rank test). Comparisons between groups will be conducted by using an analysis of variance (ANOVA), with other confounding factors like multicenter character conducting the covariate analysis. Statistical analysis for the data which do not meet above conditions (e.g., non-normal) will be conducted with the use of non-parametric test. For laboratory parameters, Spearman's coefficient correlation has been used for comparison with different parameters and one way ANOVA test for significant correlation between groups. Study flow chart and graphs will be presented over different study times.

All *p*-values and 95 percent confidence intervals are two-sided, and $p < 0.05$ is considered statistically significant. Statistical analyses will be carried out exclusively by an independent statistician. All analyses will be performed by using SPSS, version 24 (SPSS).

11. Ethics consideration

Application for ethical approval have been sought from Joint CUHK-NTEC CREC before the initiation of this study. All important protocol modifications are approved by the said CREC before implementation (except in emergency situations where immediate hazards to the subjects have to be eliminated) and communicated to investigators, research personnel and trial participants. Participants are informed of our measures to ensure the confidentiality of all information and that data are maintained anonymous. Investigators/research personnel obtain informed consents from subjects and consent forms are signed by the subjects before the study. All information are encrypted and only the involved investigators can access. Password is required to access the data. Participants are free to withdraw at any time without giving a reason or punishment. The personal data of the subjects will only be kept for 10 years and will be destroyed afterward.

2 https://www.crec.cuhk.edu.hk/wp-content/uploads/2022/09/Standard-SAE-Report-Form_Version-2-dated-09-May-2017.pdf

12. Clinical trial insurance

Clinical trial insurance will be purchased according to the university policy.

13. Quality assurance

13.1. Data management

Only the study team and the PI have access right to the database using their login user names and passwords. Subjects' information is kept anonymous. They are identified by their study numbers to maintain subjects' confidentiality. The final dataset of the study will be available from the corresponding author on reasonable request.

13.2. Auditing and inspection

The Clinical Research Management Office at The Chinese University of Hong Kong or an external auditor will perform auditing or inspection to determine whether research activities are conducted according to the protocol, Good Clinical Practice (GCP) and guidelines of the International Conference on Harmonization (ICH).

14. Dissemination policy

We will communicate the results mainly through scientific publications and/or press conferences. No publication restrictions are planned. Authorship will be determined based on the criteria adopted by the International Committee of Medical Journal Editors.

Ethics statement

Approval (reference number: 2021.125-T) has been obtained from The Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee. Informed consent will be signed before subject enrolment. The results will be submitted to peer-reviewed journals and presented at academic conferences.

Author contributions

ZL: conceptualization and funding acquisition. JC, CL, TS, PC, CS, and ML: methodology. CS, WM, KL, and SL: investigation. CL, CS, CC, and KC: project administration. ZL, JC, and KC: supervision. CL, TS, PC, CS, and ML: writing — original draft. ZL, CS, TS, and HZ: writing — review and editing. All authors contributed to the article and approved the submitted version.

Funding

This project was funded by the Chinese Medicine Development Fund of the Hong Kong Special Administrative Region Government (application number: 21B2/009A_R1).

Conflict of interest

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

The study will be conducted in compliance with the Declaration of Helsinki and ICH-GCP guidelines.

Publisher's note

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frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 20 March 2023
DOI 10.3389/fpsyg.2023.1113269

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

RECEIVED 03 December 2022
ACCEPTED 27 February 2023
PUBLISHED 20 March 2023

CITATION
Yoo GE, Na S, Kim SJ and Kim J (2023) Benefits of personal music listening for family caregivers of critically ill patients during the post-COVID era.
Front. Psychol. 14:1113269.
doi: 10.3389/fpsyg.2023.1113269

Benefits of personal music listening for family caregivers of critically ill patients during the post-COVID era

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Objective: This descriptive study surveyed family caregivers of patients in intensive care units (ICUs) during the COVID-19 pandemic to examine the impact of musical listening on their psychological well-being.

Method: The data collected in this study compared with collected from similar research conducted before the COVID-19 pandemic in 2017. The previous study had 195 participants, and the current study had 92. To measure the participants' psychological well-being, the Korean version of the Center for Epidemiologic Studies Depression Scale and the World Health Organization Quality of Life Scale were administered. An investigator-constructed questionnaire was also used to collect information related to participants' engagement in music activities including music listening in their everyday lives and their perceptions of music's benefits.

Results: A two-way ANOVA showed significant effects for time (e.g., before vs. during COVID-19) and involvement in personal music listening (yes vs. no) on current emotional state, with family caregivers reporting significantly greater negative emotions during COVID-19 than before and personal music listening having a positive effect on perceived emotions. For quality of life there was no significant time effect, while the listening effect was statistically significant, indicating a significantly higher quality of life in the group who engaged in music listening in their everyday lives compared to the group who did not. There were no significant time or listening effects for perceived level of depression.

Conclusion: Given the COVID-19 situation and the need to transition to a post-pandemic era, this study suggests that music listening can be an effective option for family caregivers to implement as a resource for attenuating emotional distress and enhancing self-care.

KEYWORDS

family caregivers, COVID-19 pandemic, intensive care unit, music listening, quality of life, emotional support

1. Introduction

Since the first outbreak of COVID-19 in 2020, the number of cases increased dramatically with an average of over 1,000 positive COVID-19 cases identified daily during the third wave of the pandemic from November 2020 to February 2021 in Korea (Choi, 2020; Korea Disease Control and Prevention Agency, 2021). The pandemic severely impeded the ability of family caregivers to care their critically ill family members in health care facilities (Irani et al., 2021).

Strict intensive care unit (ICU) visitation policies were implemented in 2020. These policies sometimes prohibited all visitors (Suh et al., 2023). These measures remained in place for 3 years until late 2022.

Family caregivers reported feeling increasingly burdened due to the pandemic. In addition to restrictive visitation policies, the high rate of infection, unpredictable symptom development, and widespread anxiety in the community all negatively impacted family caregiver well-being (Rahimi et al., 2021). As a result, restrictive visitation policies it was more challenging for family caregivers to tend to their ill family members in ICUs (Andrist et al., 2020; Valley et al., 2020), and this resulted in increased frustration and anger (Hamilton et al., 2020; Morley, 2020). Access to social support from medical and community sources also became more difficult (Azoulay et al., 2020; Beach et al., 2021; Hwang et al., 2021). The COVID-19 pandemic has had multiple impacts on family caregivers, including exacerbating physical, psychological, emotional, and social stressors (Azoulay et al., 2020). However, different emotional distress-related symptoms need to be understood and addressed independently, such as anxiety or fear as a proactive response to uncertainty or situational threats and depression as an internalized reaction to lack of control or loss (Gruber et al., 2021). Research has found that anxious responses are accompanied by heightened arousal to emotional stimuli, regardless of the specific emotion, while depressive responses are associated with a failure to sustain a positive response to pleasant stimuli (Larson et al., 2007). These findings emphasize the importance of considering multiple factors as affecting the psychological health of family caregivers.

Previous studies have shown the potential benefits of incorporating music-related activities including music therapy, in addressing the impact of COVID-19 on family caregivers. Research has demonstrated the effectiveness of music in alleviating emotional distress and empowering family caregivers through enhanced self-care (Jung and Na, 2019; Yoo et al., 2021). The COVID-19 pandemic has highlighted the need for additional support strategies, especially during times of crisis when traditional sources of support may be inaccessible. Music can be an easily accessible and affordable means for self-regulation when access to other activities is limited due to lockdowns or social distancing (Cabedo-Mas et al., 2020; Ziv and Hollander-Shabtai, 2022). Personal music activity, which can be performed independently by an individual in their home, holds particular promise for promoting psychological and emotional stability (e.g., decreased depression and improved quality of life) and has been documented as positively impacting diverse populations in various countries (Cabedo-Mas et al., 2020; Krause et al., 2020; Roese and Merrill, 2021). With COVID-19 interfering with people's ability to engage in music activities that require social contact (e.g., singing together or attending concerts), personal use of music at home, and especially listening to music, has increased with the greater availability of music through various online platforms (Fink et al., 2021; Ziv and Hollander-Shabtai, 2022).

Given the potential benefits of music activities for family caregivers of ICU patients, our previous study (Yoo et al., 2021) investigated family caregivers' engagement in music activities prior to the COVID-19 pandemic and found that active involvement in singing alleviated their emotional distress and served as a self-care strategy for emotional regulation. The current study aimed to extend the previous research by comparing data from both studies (before the pandemic and during the pandemic) to investigate the impact of the pandemic on the psychological and emotional well-being of family caregivers of ICU patients and the impact of personal music engagement on their persistent feelings such as depression and quality of life, as well as their current emotional reactions (e.g., happiness, sadness, anger, fear, and comfort) before and after the emergence of COVID-19. Therefore, the purpose of this study was to investigate whether personal engagement in music activities differentially impacted psychological and emotional states of family caregivers of ICU patients before and during the pandemic.

2. Materials and methods

2.1. Study design and participants

This study is a descriptive study that surveyed family caregivers of ICU patients. The study examined the psychological and emotional states of these caregivers, including their level of depression, quality of life, and current emotional states, and investigated whether they engaged in personal music activities. Furthermore, this study compared the measured variables with data from before the COVID-19 pandemic to investigate differences in family caregivers' psychological and emotional states before and during COVID-19, and to examine how these states varied depending on whether the caregivers engaged in personal music activities. The pre-pandemic data used in this study were collected from January 2017 to July 2017 as part of our previous study (Yoo et al., 2021). For data during the COVID-19 pandemic, new participants were surveyed in 2021.

All procedures were approved by the Institutional Review Board of Severance Hospital (4-2020-1,460) in Seoul, Korea. Inclusion and exclusion criteria for participants were consistent across both studies. A detailed description of the pre-pandemic recruitment procedures and sample can be found in our previous study (Yoo et al., 2021). In both the pre-pandemic and pandemic studies, the participants were adults aged 18 years or older who had a family member admitted to a surgical ICU (SICU). Among family caregivers, only direct family members (i.e., spouse, parent, adult child) who were responsible for providing primary care (e.g., providing day-to-day care and making first-line medical decisions about treatment) for the patient were included. Caregivers who were not direct members (e.g., siblings) or those who did not provide primary care were excluded. The sample size for this study was calculated using G power*3.1 (Faul et al., 2007) based on the effect size from a previous study (Yoo et al., 2021), with a desired power of 0,95, and an alpha level of 0.05. The minimum sample of 285 participants for two groups was determined to be sufficient for this study.

2.2. Measures

In this study, measures of psychological and emotional well-being such as depression, quality of life, and current emotional states, as well as engagement in personal music activity were used. To measure depression, the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1991) was administered. The Korean version of the CES-D (Shin et al., 1991) consists of 20 items rated on a 4-point Likert scale corresponding to how often the participant felt the way presented

in each item over the past week. The Korean version of the CES-D has been validated and the cutoff for the scale is 16 with a score greater than 16 indicating risk for depression. To assess quality of life in caregivers of ICU patients, the abbreviated World Health Organization Quality of Life Scale [WHOQOL-BREF; 25 (World Health Organization, 1998)] was administered. The Korean version of the WHOQOL-BREF (Min et al., 2002) consists of 26 items rated on a 5-point Likert scale based on evaluations of four domains: physical health, psychological health, social relationships, and environment. The Korean version was validated with a total raw score ranging from 26 to 130, and the score for each domain ranges from 4 to 20, with a higher score representing a higher level of perceived quality of life.

Furthermore, an investigator-constructed questionnaire was used to collect information about each participant's demographics, their engagement in personal music activities, and their perceptions on the benefits of music use. The items included whether each participant had engaged in each of three music activities (i.e., music listening, singing, and instrument playing) in their everyday lives after their family member became sick and what benefits they believed this involvement with music brought to their lives (e.g., physically, cognitively, emotionally, socially, and environmentally). Participants self-administered the questionnaire to provide personal information. In the questionnaire, a 100 mm visual analogue scale was incorporated for the participants to self-rate their current emotional states. Participants were instructed to rate the degree to which they experienced the presented emotion (i.e., happiness, sadness, anger, fear, and comfort) in the past week on a straight line anchored at the ends by "feeling the presented emotion not at all" and "feeling the emotion very much."

2.3. Procedures

Data collection was conducted between February 2021 and July 2021 during a period of highly restrictive hospital visitation policies. Participants were recruited through posters placed in the waiting areas of the SICU units and eligible participants were those who approached the research team after reading the poster. Each participant provided written informed consent prior to their participation in the study. Participants then completed a self-administered questionnaire in a private and quiet area of the hospital typically used for counseling.

2.4. Data analysis

The data collected in 2017 were compared with the data collected in 2021. An independent t test was conducted to assess differences in psychological and emotional measures as well as demographic information (i.e., participant's age, patient's age, days on mechanical ventilation, and number of ICU stays) between the two groups. A chi-square test was used to investigate if the two groups differed in terms of whether they engaged in music activities after they became a family caregiver. Furthermore, a two-way ANOVA was conducted to determine if there were significant differences in the measured assessment (i.e., WHOQOL-BREF and CES-D) depending on the time point (before COVID-19 sample and during COVID-19 sample) and engagement in music listening (i.e., yes and no). Finally, among the participants who perceived music as beneficial, the percentage who were currently engaging in music listening at the time of data collection versus the percentage who were not was compared by conducting a chi-square test.

3. Results

For this study conducted in 2021, a total of 104 family caregivers were initially surveyed. Five surveys were excluded due to incomplete responses, and additional seven participants were excluded because they did not meet the inclusion criteria of being a direct family member. The final sample included 92 caregivers with a mean age of 47.3 years. The comparison data from 2017 had a sample of 195 caregivers with a mean age of 51.2 years (Krause et al., 2020) was also analyzed. Detailed information about the 2017 sample can be found in our previous study (Krause et al., 2020). The 2021 sample included 38 (41.3%) spouses, 43 (46.7%) adult children, and 11 (12.0%) parents of ICU patients. The participants' ill family members (i.e., ICU patients) had been in the ICU for 3.8 days on average. Demographic information about the participants from the study conducted before COVID-19 and the study conducted during COVID-19 is summarized in Table 1. When the two groups were compared, significant differences were found in terms of the patient's age ($p < 0.001$), duration of mechanical ventilation ($p < 0.001$), and length of ICU stay ($p < 0.001$). The sample from 2021 showed a significantly younger patient age, longer duration of mechanical ventilation and longer ICU stays compared to the sample from 2017.

3.1. Differences in psychological and emotional measures between 2017 and 2021 samples

The descriptive statistics for the psychological measures of the participants are displayed in Table 2. To control for the effects of the aforementioned differences between the two sample, a one-way ANCOVA was conducted, while controlling for the participant's age, the patient's Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the patient's length of mechanical ventilation, and length of ICU stay. Perceived level of depression and quality of life were not significantly different depending on the time point. When examining the effects of the covariates, it was found that age was a significant factor in the effect of the time point on the measured quality of life, $F(1, 286) = 21.175$, $p < 0.001$, while both the age of participants and the number of ICU days experienced by patients were significant factors in the effect of the time point on perceived depression, $F(1, 286) = 4.072$, $p = 0.045$ (for the effect of age) and $F(1, 286) = 10.140$, $p = 0.002$ (for the effect of ICU days). In addition, all emotions except for anger were significantly different between the two groups, with those during COVID-19 reporting significantly higher levels of sadness and fear and significantly lower levels of happiness and comfort. For controlled covariates, the participant's age was found to significantly affect the difference in their happiness levels between the two time points, $F(1, 286) = 7.223$, $p = 0.008$, and anger, $F(1, 286) = 9.226$, $p = 0.003$, and the length of patient's ICU stay significantly affected the effect of the time point on the sadness felt by caregivers, $F(1, 286) = 4.051$, $p = 0.045$.

TABLE 1 Participants' demographic information.

Variable	Before COVID-19 (2017 sample) (*N*=195)	During COVID-19 (2021 sample) (*N*=92)	t/χ^2	*p*
Sex (male: female)	69: 126	38: 54	0.94	0.361
Age (years), $M \pm SD$	51.2 ± 13.9	47.2 ± 13.9	2.24	0.026*
Relationship to patient			6.24	0.056
Spouse	86 (44.1%)	38 (41.3%)		
Adult child	98 (50.3%)	43 (46.7%)		
Parent	11 (5.6%)	11 (12.0%)		
Patient information, $M \pm SD$				
Age of patient (years)	65.3 ± 13.3	57.6 ± 15.5	4.39	<0.001***
Duration since onset of diagnosis (months)	28.1 ± 72.6	25.4 ± 40.0	0.34	0.733
Diagnosis at ICU admission			244.62	<0.001***
Elective surgery	170 (87.2%)	75 (81.5%)		
Emergent surgery	15 (7.7%)	6 (6.5%)		
Respiratory failure	4 (2.1%)	1 (1.1%)		
Cardiac failure	2 (1.0%)	1 (1.1%)		
Sepsis	3 (1.5%)	7 (7.6%)		
Acute bleeding	0 (0.0%)	2 (2.2%)		
Acute kidney injury	1 (0.5%)	0 (0.0%)		
APACHE II score (0–75)	17.7 ± 7.2	17.2 ± 7.6	0.51	0.607
Length of mechanical ventilation (days)	1.0 ± 2.3	2.1 ± 2.9	−3.33	<0.001***
Length of ICU stay (days)	2.2 ± 1.1	3.8 ± 4.1	−5.22	<0.001***

APACHE, Acute Physiology and Chronic Health Evaluation. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

3.2. Differences in levels of personal music engagement between 2017 and 2021 samples

In the 2021 sample, 60.9% of participants were currently engaging in music listening, 12.0% in singing, and 4.3% in instrument playing. The percentage of these participants who engaged in music listening was higher (51.3% in the 2017 sample) and their engagement in other types of music activities (i.e., singing and instrument playing) was lower (11.3% for singing and 5.1% for instrument playing in the 2017 sample) when compared with 2017 sample. The percentage of participants who reported that they continued to sing and play an instrument after their family member became ill was similar in both samples (11.3% in the 2017 sample and 11.0% in the 2021 sample for singing; 5.1% in the 2017 sample and 4.4% in the 2021 sample for instrument playing). While 51.3% of participants maintained their engagement in music listening after their family member became ill in the 2017 sample, a greater percentage of participants (60.9%) reported continuing to engage in music listening in the 2021 sample.

When asked if music use benefits their health, 72.8% of the participants in the 2021 sample reported yes, while 88.2% of the 2017 sample reported yes. A chi-square test indicated that the percentage of participants who perceived music as beneficial significantly decreased during COVID-19 compared to before COVID-19 ($\chi^2 = 21.230$, $p = 0.020$). When asked about the area in which engagement in music activities would have a beneficial impact, the emotional domain was reported the most frequently at both time points (78.5% in the 2017 sample and 88.2% in the 2021 sample). A chi-square test showed no significant relationship between when data were collected (i.e., before and during COVID-19) and the domain in which music was perceived to be beneficial ($\chi^2 = 8.412$, $p = 0.999$).

TABLE 2 Subjective measures of mood and well-being by family caregivers of ICU patients.

Variable	Before COVID-19 (2017 sample) (*N*=195)	During COVID-19 (2021 sample) (*N*=92)	*t*	*p*
CES-D	16.7 ± 10.6	15.4 ± 11.8	3.383	0.067
WHOQOL-BREF	88.1 ± 15.1	88.9 ± 13.5	0.171	0.679
Emotional state				
Happiness	51.6 ± 25.3	44.5 ± 24.7	4.860	0.028*
Sadness	44.9 ± 29.5	55.9 ± 29.5	4.745	0.030*
Anger	37.3 ± 26.3	36.8 ± 26.4	0.000	0.999
Anxiety	42.3 ± 53.9	53.8 ± 30.4	5.603	0.019*
Comfort	46.7 ± 26.2	39.1 ± 26.9	4.062	0.045*

A one-way ANCOVA was conducted controlling for the participant's age, the patient's length of ventilation, and length of ICU stay. WHOQOL-BREF, World Health Organization Quality of Life Scale abbreviated version; CES-D, Center for Epidemiologic Studies Depression Scale. *$p < 0.05$. **$p < 0.01$.

Furthermore, it was investigated whether engagement in music activities affected the participants' perceived psychosocial health (i.e., quality of life and level of depression) and what benefits family caregivers of ICU patients identified as resulting from their music

activities. Among the three types of music activities, whether participants currently engaged in music listening was analyzed as a factor for influencing psychosocial health of participants given that only 12.0% of respondents reported having recent singing experience and only 4.4% of respondents reported having recent instrument playing experience. Since these percentages were not suitable for subgroup analysis, further analyses were conducted to identify differences in the psychological measures depending on engagement in music listening.

3.3. Effects of time point and engagement in music listening on psychological and emotional measures between 2017 and 2021 samples

A two-way ANOVA was conducted to compare the psychological health of family caregivers of ICU patients depending on the time point (i.e., before COVID-19 sample and during COVID-19 sample) and current engagement in music listening (i.e., yes and no). At both time points, the listening group reported a lower level of depression and higher level of quality of life compared to the nonlistening group. Also, the listening group at both time points reported a greater degree of happiness and comfort and a lower degree of anger, sadness, and fear than the nonlistening group (see Table 3).

The results of this two-way ANOVA are displayed in Table 4. With regard to perceived level of depression, two-way ANOVA results showed that there were no significant time or listening effects. No significant interaction effect between time and listening was found. For quality of life, there was no significant time effect, while the listening effect was statistically significant, indicating a significantly higher level of quality of life in the listening group compared to the nonlistening group (see Figure 1). Also, no significant interaction effect between time and listening was found. In terms of rated emotional states, significant time and listening effects were found for all the emotions except anger. With regard to the time effect, during COVID-19, a significantly lower degree of happiness and comfort and significantly greater degree of sadness and fear were found compared to before COVID-19. The same trend was found in the listening group compared to the nonlistening group, exhibiting a significantly greater level of positive emotions and significantly lower level of negative emotions except anger (see Figure 1). No significant interaction effects between time point and listening were found for any of the emotions, indicating differences in ratings on the emotional states depended on the emotion type and were similar before and during COVID-19.

Among the participants who perceived music as beneficial, the ratio of participants who were currently listening to music versus those who were not at the time of data collection differed before and during COVID-19. There was a significant relationship between current engagement in music listening and time point ($\chi^2 = 4.091$, $p = 0.043$), and it was found that a greater percentage of participants currently was engaging in music listening during COVID-19 (67.2%) than before COVID-19 (51.2%).

4. Discussion

In this study, we investigated the perceptions of family caregivers of ICU patients who were hospitalized during the COVID-19 pandemic. Family caregivers' level of depression and quality of life were measured, and their engagement in music activities and its benefits were assessed. In addition, we compared the results of this study to data from a similar sample from before the COVID-19 pandemic.

First, before and during COVID-19, the mean score of CES-D for family caregivers of ICU patients was close to or just above the cutoff point for clinical depression. This aligns with the finding that family caregivers experience extensive psychosocial burdens and emotional distress (Pochard et al., 2005; Choi et al., 2012; Alfheim et al., 2019) and gives rise to the need for interventions that target caregivers' psychological well-being. When comparing the caregivers' perceptions on their psychological well-being before and during COVID-19, there were no significant differences between the time points in terms of perceived depression and quality of life, while ratings on current emotional states were significantly different between the two groups. During COVID-19, caregivers reported feeling significantly higher levels of sadness and fear and lower levels of happiness and comfort compared to the sample measured before COVID-19. Interestingly, no significant differences in perceived depression and quality of life were found between the two time points. Although previous studies have demonstrated that the pandemic aggravated people's depression and decreased their quality of life in general (Azoulay et al., 2020; Irani et al., 2021; Rahimi et al., 2021), such an effect was not significant

TABLE 3 Perceived levels of depression and quality of life for the two samples.

Variable	Before COVID-19		During COVID-19	
	Listening (n=100)	Nonlistening (n=95)	Listening (n=56)	Nonlistening (n=36)
CES-D	15.2 (10.1)	18.3 (11.0)	14.8 (10.9)	16.4 (13.3)
WHOQOL	90.7 (15.7)	85.4 (14.0)	90.0 (14.4)	87.3 (11.9)
Emotional state				
Happiness	56.8 (25.2)	46.1 (24.3)	47.1 (25.9)	40.4 (22.3)
Sadness	38.9 (27.1)	51.2 (30.7)	51.5 (29.7)	62.6 (28.2)
Anger	34.1 (25.9)	40.8 (26.4)	34.9 (27.3)	39.8 (25.0)
Fear	37.1 (27.9)	47.7 (29.3)	50.1 (30.2)	59.4 (30.2)
Comfort	50.7 (25.5)	42.4 (26.4)	42.6 (27.7)	33.8 (25.0)

Values in the table are n(%).

TABLE 4 Results of the two-way ANOVA for the effects of time point (before and during COVID-19) and music listening (yes vs. no).

Variable	Time point (before and during COVID-19)		Music listening		Time point * Music listening	
	F	*p*	*F*	*p*	*F*	*p*
CES-D	0.631	0.428	3.331	0.069	0.262	0.609
WHOQOL	0.088	0.767	4.379	0.037*	0.769	0.381
Emotional state						
Happiness	5.008	0.026*	8.009	0.005**	0.442	0.507
Sadness	8.799	0.003**	7.435	0.007**	0.445	0.505
Anger	0.021	0.886	1.721	0.191	0.551	0.458
Fear	11.199	0.001**	6.152	0.014*	0.197	0.658
Comfort	6.782	0.010*	6.595	0.011*	0.000	0.988

*$p < 0.05$. **$p < 0.01$.

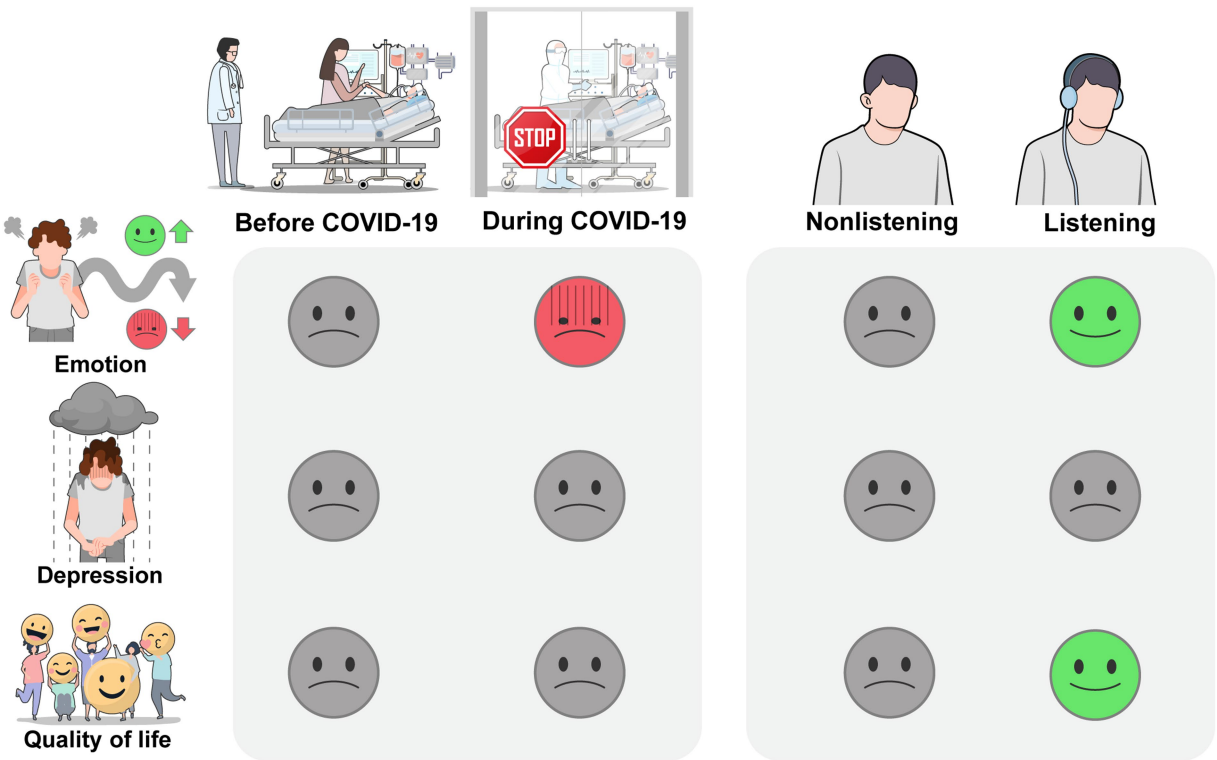

FIGURE 1
Self-reported psychological well-being of family caregivers of ICU patients before and during the COVID-19 pandemic and whether currently engaging in music listening. During COVID-19, the emotional states as an acute response to current stressors were significantly more negative, and current engagement in music listening showed a significant change in the opposite direction. For perceived depression as a more chronic mood state, time point and current engagement in music listening did not result in significant changes. For quality of life, which is a general perception of life influenced by multiple factors, there was no significant difference between the two samples. However, the listening group showed a significantly higher level of quality of life compared to the nonlistening group.

among the family caregivers of ICU patients in this study. This finding may be attributed to the fact that family caregivers of ICU patients already have a high level of depression and a low level of quality of life, and such distress should be understood as a fundamental issue of family caregivers of ICU patients regardless of the other situations that may impact them, such as the COVID-19 pandemic.

Meanwhile, when comparing the reported current emotional states as an immediate reaction to situational stressors, significant differences were found between the two time points. This result can be explained by the fact that mood as a more persistent feeling (e.g., depression) is separate from emotion as a relatively more temporary reaction to current environmental stressors (Larson et al., 2007). The COVID-19 pandemic caused severe disruptions forcaregiving environment for family caregivers of ICU patients, such as limiting access to caregiver resources (e.g., restricting visits with patients and contact with medical staff), and it might have exacerbated family caregivers' acute emotional

distress (Hamilton et al., 2020; Hwang et al., 2021). Given that persistence in negative emotion leads to more chronic mood states and lower perceived quality of life (Gendolla and Brinkmann, 2005), the current study's results support the importance of timely and appropriate interventions targeting such negative emotions.

During COVID-19, the participants frequently engaged in music listening, while participation in more active forms of music activity, such as singing and playing an instrument, declined compared to the sample measured prior to the pandemic. This change in music engagement can be attributed to the widespread accessibility and affordability of music listening, even under environmental restrictions that affect human activities (Roese and Merrill, 2021; Ziv and Hollander-Shabtai, 2022). This also supports that music listening can be an adaptive and protective strategy for promoting psychological health while minimizing the risk of widespread infection (Mas-Herrero et al., 2020). Given the growing need to address the emotional and social stressors faced by caregivers during crises, such as the ongoing pandemic, music listening can be considered a feasible strategy for self-care and self-regulation. However, previous studies identified more active forms of music activity (e.g., singing and instrument playing) as being more effective coping strategies since more active control of their actions during such music activity empowers the family caregivers more effectively (Jung and Na, 2019; Yoo et al., 2021). Future studies will need to investigate how music listening can be incorporated into family-centered care in more diversified ways while requiring more active and creative engagement.

Finally, this study investigated the impact of personal music listening on the perceived psychological and emotional well-being of family caregivers of ICU patients before and during the pandemic (see Figure 1). Results showed that during the pandemic, there were significant increases in negative emotions, such as sadness, and decreases in positive emotions, such as happiness. However, engagement in personal music listening had a positive effect on emotional states and quality of life. These results suggest that while the COVID-19 pandemic may trigger an immediate reaction to environmental stressors, listening to music can help mitigate these impacts. The lack of an effect on depression levels indicates that engagement in music listening, which is a relatively passive activity, may not be sufficient to address the chronic and clinical symptoms of depression. This also corroborates that more active engagement in music, such as singing, or a more structured intervention may be necessary to effectively alleviate depression.

When examining the caregivers' perceptions on the benefits of music, they were less positive during COVID-19 compared to the sample measured before COVID-19; however, among the caregivers who reported that music was beneficial for their health, a higher percentage of respondents were currently engaging in music listening during COVID-19 than before the pandemic. This decrease in the perceived benefits of music may be attributed to the limited options for music activities available to family caregivers during COVID-19. Despite these restrictions, engagement in music listening improved the caregivers' perceptions not only of their psychological and emotional well-being but also of the benefits of music to a greater extent than the nonlistening group. This suggests that utilizing resources for self-regulation, such as music, can effectively mitigate the emotional distress (Shaffer et al., 2016; Ferreri et al., 2021) resulting from caregiving responsibilities and exacerbated by physical and psychological restrictions during the COVID-19 pandemic. Engagement in music listening could also help caregivers identify meaningful and rewarding aspects in their immediate environment as seen in enhanced perception on their quality of life. And for that emotional resource, engagement in music listening can be one readily available, effective, and creative medium for increasing arousal and motivation to a desirable level (Jung and Na, 2019; Yoo et al., 2021) and for empowering family caregivers to better cope with their situation and gain a greater sense of control (Wartella et al., 2009; Ferreri et al., 2021).

Given the COVID-19 situation and the need to transition to a post pandemic era, this study suggests that music listening can be an effective option for family caregivers to implement as a resource for self-care, although its effects would not lead to significant changes in depression, as more chronic and clinical symptoms require a more systematic intervention. Considering the uncontrolled nature of ICU admission, the collection of data from two different groups resulted in differences in terms of patient age and duration of ICU stays. These differences limit the generalizability of the results and constrain their applicability to a generalized population. Perceived changes in the caregiving burden and corresponding emotional distress in family caregivers of critically ill patients with chronic diseases before and after the COVID-19 pandemic should also be further investigated. Furthermore, in this study, engagement in music listening was examined as a mediating factor for influencing the psychological health of caregivers, and the effects of singing and instrument playing were not examined due to the unbalanced percentage of participants who engaged in these music activities. This limits the explanation of differential effects of passive versus active forms of music engagement on family caregivers of ICU patients. Further studies are needed to directly compare engagement in passive and active music activities and to identify how each activity differs in supporting the needs of caregivers during the COVID-19 pandemic and post-COVID era.

5. Conclusion

In conclusion, this study demonstrates the impact of the COVID-pandemic and personal music activities on the psychological and emotional well-being of family caregivers of ICU patients. The results show that family caregivers experienced significant decreases in happiness and comfort and increases in sadness and fear during the pandemic. However, engaging in personal music listening was found to have a reverse effect, increasing positive emotions and decreasing negative emotions, as well as improving quality of life. The measure of depression did not vary significantly between the time points and engagement in music listening.These results indicate the importance of considering the multiple factors that influence persistent emotions, such as depression. It is important to note that personal music engagement may not have significant effects on depression, which requires more intensive and clinical intervention from professionals, such as music therapists. In light of the ongoing impact of the COVID-19 pandemic, self-initiated music engagement, such as personal music listening, should be encouraged as a form of self-care in the post-COVID era. At the same time, it is important to acknowledge the limitations of such approaches and to continue to develop and expand systematic and intensive music therapy interventions to address more complex emotional and clinical issues faced by this population of family caregivers of ICU patients.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Severance Hospital (4-2020-1460). The participants provided their written informed consent to participate in this study.

Author contributions

GY: formal analysis and writing. SN: conceptualization and supervision. SK: supervision and validation. JK: conceptualization and investigation. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors thank Medical Illustration and Design, part of the Medical Research Support Services of Yonsei University College of Medicine, for providing excellent support with medical illustration.

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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frontiers | Frontiers in Sociology

TYPE Original Research
PUBLISHED 16 May 2023
DOI 10.3389/fsoc.2023.1143561

OPEN ACCESS

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RECEIVED 13 January 2023
ACCEPTED 17 April 2023
PUBLISHED 16 May 2023

CITATION
Maslova O, Vladimirova T, Videnin A, Gochhait S and Pyatin V (2023) Comparative study of quality of life 9 months post-COVID-19 infection with SARS-CoV-2 of varying degrees of severity: impact of hospitalization vs. outpatient treatment. *Front. Sociol.* 8:1143561. doi: 10.3389/fsoc.2023.1143561

Comparative study of quality of life 9 months post-COVID-19 infection with SARS-CoV-2 of varying degrees of severity: impact of hospitalization vs. outpatient treatment

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Purpose: This experimental study was conducted during the post-COVID-19 period to investigate the relationship between the quality of life 9 months after and the severity of the SARS-CoV-2 infection in two scenarios: hospitalization (with/without medical oxygen) and outpatient treatment.

Methods: We employed the EQ-5D-5L Quality of Life tests and the PSQI as a survey to evaluate respondents' quality of life 9 months after a previous SARS-CoV-2 infection of varying severity.

Results: We identified a clear difference in the quality of life of respondents, as measured on the 100-point scale of the EQ-5D-5L test, which was significantly lower 9 months after a previous SARS-CoV-2 infection for Group 1 ($n = 14$), respondents who had received medical attention for SARS-CoV-2 infection in a hospital with oxygen treatment, compared to those with the SARS-CoV-2 infection who were treated without oxygen treatment (Group 2) ($n = 12$) and those who were treated on an outpatient basis (Group 3) ($n = 13$) ($H = 7.08$ $p = 0.029$). There were no intergroup differences in quality of life indicators between hospitalized patients (Group 2) and groups 1 and 3. PSQI survey results showed that "mobility," "self-care," "daily activities," "pain/discomfort," and "anxiety/ depression" did not differ significantly between the groups, indicating that these factors were not associated with the severity of the SARS-CoV-2 infection. On the contrary, the respondents demonstrated significant inter-group differences ($H = 7.51$ $p = 0.023$) and the interdependence of respiratory difficulties with the severity of clinically diagnosed SARS-CoV-2 infection. This study also demonstrated significant differences in the values of sleep duration, sleep disorders, and daytime sleepiness indicators between the three groups of respondents, which indicate the influence of the severity of the infection. The PSQI test results revealed significant differences in "bedtime" ($H = 6.00$ $p = 0.050$) and "wake-up time" ($H = 11.17$ $p = 0.004$) between Groups 1 and 3 of respondents. At 9 months after COVID-19, respondents in Group 1 went to bed at a later time ($pp = 0.02727$) and woke up later ($p = 0.003$) than the respondents in Group 3.

Conclusion: This study is the first of its kind in the current literature to report on the quality of life of respondents 9 months after being diagnosed with COVID-19 and to draw comparisons between cohorts of hospitalized patients who were treated with medical oxygen vs. the cohorts of outpatient patients. The study's findings regarding post-COVID-19 quality of life indicators and their correlation with the severity of the SARS-CoV-2 infection can be used to categorize patients for targeted post-COVID-19 rehabilitation programs.

KEYWORDS

post-COVID-19 conditions, patients with post-COVID-19, SARS-CoV-2, health-related quality of life, patient-reported outcome

Introduction

The continuation or persistence of symptoms after the acute phase of SARS-CoV-2 infection is commonly known as long COVID-19 or post-COVID-19. These symptoms can range from general (e.g., fever, myalgia, fatigue, and tiredness) to neurological, psychological, and cognitive symptoms (Amdal et al., 2021; Belopasov et al., 2021; Pazukhina et al., 2022). In most of the published studies, symptoms of post-COVID-19 have been observed in patients for up to 6 months after receiving treatment in a hospital or in an outpatient setting (Lopez-Leon et al., 2021; Michelen et al., 2021; Nasserie et al., 2021). It was found that the prevalence of post-COVID-19 symptoms varies significantly between hospitalized and non-hospitalized patients (Peghin et al., 2021). Thus, post-COVID-19 symptoms were observed in 54% of hospitalized patients and in 34% of non-hospitalized patients (Chen et al., 2022). Prolongation of post-COVID-19 symptoms among hospitalized and non-hospitalized patients has been reported to persist for a long period of time, that is, ranging from up to 3–6 months (Peghin et al., 2021; Sivan M, et al., 2022) to even up to 2 years after the SARS-CoV-2 infection (Fernández-de-las-Peñas et al., 2022). Moreover, Sivan et al. (2022) reported for the first time on the phenotypes of symptom severity in a cohort of people who were mostly not hospitalized. With regard to the clinical symptoms of the disease in the SARS-CoV-2 infection, the presence of post-COVID-19 symptoms was significantly associated with the number of symptoms at the beginning of the disease and the degree of its severity that requires hospitalization in the intensive care unit (ICU) (Del Rio et al., 2020; Carvalho-Schneider et al., 2021; Pérez-González et al., 2022).

In general, it can be stated that there are relatively few direct comparisons of post-COVID-19 symptoms among hospitalized and non-hospitalized respondents in the literature compared to the studies on SARS-CoV-2-infected patients during hospitalization. For example, a recent review provided five references to studies directly comparing the differences and prevalence of post-COVID-19 symptoms between previously hospitalized and non-hospitalized subjects. However, observations were from follow-up of only 3 months post-COVID-19 (Van Kessel et al., 2022).

There are no studies in the literature on the new paradigm of comparisons, namely, differences in the quality of life post-COVID-19 among hospitalized patients who were prescribed medical oxygen during the acute phase of SARS-CoV-2 infection and among hospitalized patients who were treated without oxygen therapy. However, acute hypoxic respiratory failure is the most common complication that occurs in 60–70% of patients, and patients that developed this complication were admitted to the ICU (Phua et al., 2020). Therefore, medical oxygen is a critical element in the treatment of patients with COVID-19 (Saadatmand et al., 2022), as active oxygen therapy to treat hypoxia is important for positive patient outcomes. Moreover, patients who survived hospitalization due to COVID-19 received additional oxygen treatment at home to treat persistent hypoxemia after discharge (Kaul et al., 2022). Consequently, to date, no long-term comparative study on the quality of life in post-COVID-19 subjects with different disease severity at hospital admission has been conducted. In the active phase of SARS-CoV-2 infection, the quality of life of the patients was the object of analysis in publications (Amdal et al., 2021), but it is not clear to what extent the quality of life and health indicators of the active phase of the disease was prolonged in the post-COVID-19 period. Therefore, a comparative study of the quality of life after 6 months of post-COVID-19 of respondents who have experienced SARS-CoV-2 infection with varying degrees of severity during hospitalization and of those who received outpatient treatment is relevant.

This study aimed to investigate the impact of different degrees of severity of the SARS-CoV-2 infection during hospitalization on the quality of life of respondents 9 months post-COVID-19. Specifically, the study examined the quality of life of hospitalized respondents who received medical oxygen treatment vs. those who did not. It is critical to understand that the relevance of the question lies in the consequences of the infection if the person becomes a survivor after completing medical treatment (Pomara et al., 2020). SARS-CoV-2 infection has several consequences (Amdal et al., 2021; Hayes et al., 2021). Moreover, this study examined a new aspect of the management of COVID-19 survivors, namely the post-COVID-19 quality of life of those who were hospitalized due to the COVID-19 condition in the ICU as well as that of those who were hospitalized but were not treated in an intensive care setting.

The COVID-19 pandemic has adversely affected the population's quality of life in all spheres of life, causing a negative impact on their overall wellbeing. In several studies, it has been found that people with a coronavirus infection experience significant physical and emotional impacts on their lives, including

their social functioning, which is markedly affected. Some of these consequences can last for 3 months or more, with varying degrees of severity (Poude et al., 2021). Furthermore, sleep disorders have been associated with patients who have been infected with SARS-CoV-2 as a result of the infection, and it has been documented that these disorders can worsen the severity of the infection, reducing the quality of life of the patient in the process. Tedjasukmana et al. (2023) conducted an online survey of the condition following COVID-19 in different countries, which found that 78.58% of respondents had sleep disorders, including insomnia, sleep breathing disorders, hypersomnolence, sleep-wake circadian rhythm disorders, parasomnia, and sleep-related movements. As a result, several SF-36 quality-of-life parameters were statistically significant positive predictors of moderate to severe insomnia in the SF-36 scale. A statistically significant positive correlation was found between various areas of the SF-36 quality of life questionnaire and the Pittsburgh Sleep Quality Index (PSQI) when assessing the global assessment of conditions after COVID-19 using the PSQI. The relationship between sleep disorders and mental health disorders is closely interconnected, highlighting the urgent need for intervention strategies to prevent mental health disorders, including sleep disorders, and improve rehabilitation and patients' quality of life after COVID-19.

Several questionnaires and scales are commonly used to assess the quality of life of patients (Hawthorne et al., 2001), including the following tools: the 36-item Short Form (SF-36) survey (RAND Corporation, 2022) and the Centers for Disease Control and Prevention's (CDC) 14-item Health Related Quality of Life (CDC HRQOL-14) (CDC HRQOL—14, 2022); in terms of the SF-36, it can be described as a short form questionnaire.

In 2009, the EuroQol Group introduced a five-level EQ-5D [EuroQol Group (EQ-5, 2019)] to improve its psychometric properties and facilitate its widespread use for patients with COVID-19 after discharge worldwide (Feng et al., 2021; Nandasena et al., 2022).

This study aimed to determine whether sleep disturbances and quality of life were significantly improved in patients with COVID-19 9 months after discharge from the hospital.

Materials and methods

The study was conducted between September 2021 and October 2021 with patients aged 18 years and older who were diagnosed with COVID-19 and who were treated at the clinics of Samara State Medical University in 2021 and had successfully recovered. The patients were followed up 9 months after their discharge from the hospital post-recovery. According to the Helsinki Declaration of Ethical Standards, the study was conducted in accordance with Samara State Medical University's ethical standards, as approved by its ethics committee (Protocol No. 196). All survey respondents provided informed consent to participate in the study before they were included in it.

Inclusion criteria

There are a number of inclusion criteria that needed to be met. These criteria included (1) being at least 18 years of age, (2) having been diagnosed with COVID-19 and recovered, (3) having been treated at SamSMU clinics (either as an inpatient or outpatient), and (4) being willing to provide informed consent to participate in the survey. Of 123 discharged patients, 39 of them met these selection criteria and were included in the study, comprising 15 men and 24 women (Table 1).

Patients

A total of 39 adult patients who had acute respiratory failure participated in this study after their treatment while staying in the hospital and after treatment in an outpatient setting. The study was conducted between September and October of 2021, nearly 9 months after the acute phase of coronavirus infection associated with SARS-CoV-2 had ended. Participants were recruited online from a database of patients diagnosed with COVID-19 provided by the Otorhinolaryngology Department of Samara State Medical University. The results of the survey led to the formation of three groups of respondents. The first group consisted of hospitalized respondents who received medical oxygen during the treatment period. The second group of respondents had a history of hospitalization and treatment without medical oxygen. The third group of respondents had a history of outpatient treatment during the acute period of the SARS-CoV-2 infection.

Period of infection

The period of infection was defined as the number of days spent by the respondent in the hospital during the treatment of COVID-19. In Group 1, the average length of stay was 15.1 ± 1.9 days, while in Group 2, it was 13.2 ± 0.9 days (Table 1).

Data collection and measures

To prevent the spread of COVID-19 and comply with the ethical protocol of the ethical board, data collection was conducted online and via a telephone-based survey. Data were collected using a medical database and two questionnaires. The first section comprised demographic questions related to age and gender and to hospitalization status in terms of the start date of staying in the intensive care unit, the discharge date from the intensive care unit, the number of days spent in the intensive care unit, and the first day of hospitalization from the beginning of the illness (Socio-Demographic Questions). These questions were based on the demographics and hospitalization status of a database provided by the Otorhinolaryngology Department of Samara State Medical University.

The second session involved the administration of the official Russian version of the Quality of Life Questionnaire (EQ-5D-5L). In the third session, the participants completed the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989; Luca et al., 2015). The participants were interviewed by three physicians

TABLE 1 Description of groups.

Characteristics	Mean ± standard error of mean			Mann-Whitney *U* Test, p_0	Kruskal-Wallis test
	Gr.1	Gr.2	Gr.3		
Number of respondents	14	12	13	-	-
Age of respondents	60.0 ± 2.1	54.2 ± 1.5	58.5 ± 1.0	Gr.1 and Gr.2–0,076 Gr.1 and Gr.3–0,645 Gr.2 and Gr.3–0,073	H = 5,68 p = 0,058
The number of days spent by the respondent in the hospital during the treatment of COVID-19	15.1 ± 1.9	13.2 ± 0.9	0.0 ± 0.0	Gr.1 and Gr.2–1,000	-
On what day of the COVID-19 disease was the respondent admitted to the hospital	7.6 ± 0.9	8.7 ± 1.7	0.0 ± 0.0	Gr.1 and Gr.2–0,526	-

from the Otorhinolaryngology Department of Samara State Medical University.

The EQ-5D-5L questionnaire consists of two sections: the descriptive system and the visual analog scale (EQ VAS). The EQ-5D-3L collects information on a respondent's quality of life in the form of a health profile described by three levels of problem expression in five components (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-VAS is a visual analog scale that is used to assess a respondent's self-rated health status. The EQ-5D questionnaire also yields an EQ-5D index score, which is a measure of overall health status (Feng et al., 2014; Karimi and Brazier, 2016).

The EQ-5D-5L descriptive system consists of five dimensions as follows: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response levels: Level 1, "no problems;" Level 2, "slight;" Level 3, "moderate;" Level 4, "severe;" and Level 5, "extreme problems".

The respondents were asked to indicate their health state by marking the box that corresponded to the most appropriate statement in each of the five dimensions. The EQ-5D-5L also includes a visual analog scale (EQ-VAS) rated on a scale of 0 to 100 mm, providing a single global rating of self-perceived health. The data collected using the EQ-5D-5L are presented in a descriptive system as a health profile. The results of the EQ VAS are presented as a measure of overall self-rated health status.

The Pittsburgh Sleep Quality Index (PSQI) is a widely used 19-item self-reported questionnaire for measuring sleep disturbances and healthy sleep [Buysse et al., 1989; Luca et al., 2015].

The PSQI includes seven clinically derived domains of sleep difficulties: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Each domain score was calculated based on the participant's response to specific items, most of which were presented on a 0–3 Likert-type scale (with higher scores indicating poorer sleep quality). These sleep domains were combined into a single PSQI sleep quality factor, with a higher score indicating worse sleep quality. In addition to the global PSCI factor, a validated three-factor model of the PSQI was proposed to assess disturbances in three separate factors of subjective sleep reports: sleep efficiency, perceived sleep quality, and daily disturbances.

Statistical analysis

Statistical data processing was performed in the STATISTICA 12 program. The normality of the distribution was checked according to the Shapiro–Wilk, Kolmogorov–Smirnov, and Lilliefors criteria. Most of the studied parameters were characterized by a different distribution from the normal one. The Mann–Whitney test was used to compare individual groups with each other. The Kruskal–Wallis test was used to compare all three groups. Closed-ended questions were visually presented as pie charts with a sector for each answer option. The value corresponded to the number of participants who chose this answer option. Integrative parameters were visually represented in the form of boxplot diagrams, where the upper and lower borders of the shaded rectangle indicate the corresponding quartiles, the horizontal line within the rectangle indicates the median, the cross indicates the arithmetic mean, the outflow lines indicate the maximum and minimum values and the horizontal line between the rectangles indicates the presence of statistically significant differences.

Results

Three groups of patients who survived COVID-19 were included in the study. The first group (Gr. 1, n = 14, age 60.0 ± 2.1) consisted of six men and eight women, with a total of 14 individuals. This group consisted of patients who were treated in hospitals with medical oxygen for the SARS-CoV-2 infection and were included in this study. A total of 42.9% of the participants in the study were men, while 57.1% of them were women. The second group (Gr.2) included 12 patients with an infection of SARS-CoV-2 who were treated without medical oxygen. Men and women were represented equally in the group, with 58.3% of men and 41.7% of women. In the third group (Gr.3, n = 13, average age 58.5 =1.0), two men and 11 women were included among the 13 participants. Those who were treated for COVID-19 as outpatients were included in this study. Among the men and women in the group, the percentages of men and women were 15.4% and 84.6%, respectively. The ages of the group members did not differ significantly from each other.

A sociological survey was conducted via phone 9 months after the respondents were discharged from the hospital and who

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TABLE 2 EQ-5D test results.

Question	Response options	Responses			Mann-Whitney U Test, p_0	Kruskal-Wallis
		Gr.1	Gr.2	Gr.3		
Mobility	I have no difficulty walking	57.1%	75.0%	92.3%	Gr1 and Gr2–0,662 Gr1 and Gr3–0,126 Gr2 and Gr3–0,446	H = 3,83 p = 0,147
	I have some difficulty walking	42.9%	8.3%	7.7%		
	I'm bedridden	0.0%	16.7%	0.0%		
Self-care	I have no difficulty taking care of myself	71.4%	91.7%	100.0%	Gr1 and Gr2–0,382 Gr1 and Gr3–0,216 Gr2 and Gr3–0,744	H = 5,18 p = 0,075
	I have some difficulty washing or dressing	21.4%	8.3%	0.0%		
	I am not able to wash or dress myself	7.1%	0.0%	0.0%		
Daily activities	I am not experiencing difficulties	64.3%	75.0%	100.0%	Gr1 and Gr2–0,758 Gr1 and Gr3–0,120 Gr2 and Gr3–0,301	H = 5,17 p = 0,076
	I'm having some difficulties	35.7%	16.7%	0.0%		
	I am not able to do my usual daily activities	0.0%	8.3%	0.0%		
Pain / Discom-fort	I don't feel any pain or discomfort	78.6%	83.3%	92.3%	Gr1 and Gr2–0,857 Gr1 and Gr3–0,560 Gr2 and Gr3–0,724	H = 0,97 p = 0,615
	I am experiencing moderate pain or discomfort	21.4%	16.7%	7.7%		
	I am experiencing extremely severe pain or discomfort	0.0%	0.0%	0.0%		
Anxiety / Depression	I don't experience anxiety or depression	71.4%	91.7%	100.0%	Gr1 and Gr2–0,368 Gr1 and Gr3–0,216 Gr2 and Gr3–0,744	H = 5,26 p = 0,072
	I am experiencing moderate anxiety or depression	14.3%	8.3%	0.0%		
	I am experiencing extremely severe anxiety or depression	14.3%	0.0%	0.0%		
Condition today: subjective assessment on a 100-point scale, where 0 is disgusting, and 100 is fine	0–25	0.0%	0.0%	0.0%	Gr1 and Gr2–0,537 Gr1 and Gr3–0,011 Gr2 and Gr3–0,073	H = 7,08 p = 0,029
	26–50	57.1%	25.0%	7.7%		
	51–75	35.7%	66.7%	53.8%		
	76–100	7.1%	8.3%	38.5%		
	Mean	49.07	55.83	69.15		

visited the hospital during the post-COVID-19 period for follow-up as outpatients. The EQ-5D-5L questionnaire was used to study respondents' quality of life at the time of their current state, which was 9 months after their recovery from COVID-19. An analysis of respondents ' responses to questions in the EQ-5D-5L questionnaire among the different groups (Table 2) showed that significant differences between the groups (H = 7.08 p = 0.029) occurred only in responses to the question (Figure 1), where the respondents had to describe their subjective state using a number on a 100-point scale.

Moreover, 0 points corresponded to a highly negative assessment of the quality of life 9 months after COVID-19, and 100 points corresponded to a positive assessment of the quality of life after 9 months post-COVID-19. As shown in Figure 1, the subjective state of respondents in Group 1 was significantly (0.011) worse than that of respondents in Group 3: the average score on a 100-point scale was 49.1 ±5.4 in Group 1 and 69.2 ±4.4 in Group 3. Here, 0 points corresponded to a highly negative quality of life score at 9 months post-COVID-19, and 100 points corresponded to a positive quality of life score at 9 months post-COVID-19. As shown

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in Figure 1, the subjective condition of respondents in Group 1 was significantly (0.011) worse than that of respondents in Group 3. The average score on a 100-point scale was 49.1 ±5.4 in Group 1 and 69.2 ±4.4 in Group 3. There was no significant difference in the EQ-VAS rating of respondents in Groups 1 and 2 compared with respondents in Groups 2 and 3 (Figure 1).

Using the Pittsburgh Sleep Quality Questionnaire (PSQI), we designed the study to analyze inter-group differences among respondents at 9 months post-COVID-19. We found that the total score based on the results (Table 3) of the PSQI ($p = 0.042$) differed significantly between the groups (Figure 2). Thus, in Group 1, the total score averaged 3.79 ± 1.18, while in Group 2, it was 3.42 ± 0.87. In Group 3, the average total score was 1.08 ± 0.21.

Consequently, the quality of sleep for the respondents in Groups 1 and 2, who were hospitalized for COVID-19, remained significantly worse than that of the respondents in Group 3, who did not require hospitalization, even 9 months after their recovery. Analysis of the obtained data from the PSQI showed differences in the degree of influence of the severity of the SARS-CoV-2 infection on different components of sleep quality (Table 3).

Thus, the values of sleep duration, sleep disorders, and daytime sleepiness significantly differed between the three groups of respondents, which indicates that they are susceptible to the influence of a previous infection, SARS-CoV-2, affecting these components of sleep quality. The indicators "subjective sleep quality," "time to sleep onset," "sleep efficiency," and "frequency of taking sleeping pills" did not show significant intergroup differences. This indicates that these sleep quality indicators are not affected by the severity of the SARS-CoV-2 infection in the studied respondents. However, analysis of respondents' responses to individual PSQI questions (Table 3) demonstrated the following significant differences.

The indicator "bedtime" (Figure 3) significantly differed between the groups ($H = 6.00$ $p = 0.050$): patients who were treated for SARS-CoV-2 infection in an oxygen-supported hospital (group 1) went to bed at a later time after 9 months ($p = 0.027$) than the respondents in Group 3 who were treated for SARS-CoV-2 infection on an outpatient basis.

The indicator "get up time" (Figure 4) also significantly differed between the groups ($H = 11.17$ $p = 0.004$): the respondents of Group 1 got up later than those of Group 3 ($p = 0.003$). This may indicate that the SARS-CoV-2 infection in its severe form (group 1) causes a long-term violation of circadian biorhythms in such respondents. Answers to the question "How often have you been unable to breathe freely?" (Figure 5) showed significant intergroup differences ($H = 7.51$ $p = 0.023$). In Group 1, 28.6% of respondents experienced similar breathing difficulties on average once a week or more. In Group 2, breathing difficulties occurred in 50% of respondents, and in Group 3, none of the respondents experienced this problem in the last month.

In addition to the data obtained as a result of analyzing the answers to the above questions, there were significant differences between all groups (Kruskal–Wallis test) in the answers to the questions of how often respondents felt that they were experience hot flashes and how often respondents had bad dreams. Moreover, there were no significant differences between individual groups (Mann–Whitney U Test) in these indicators.

The study showed significant differences between groups ($H = 8.69$ $p = 0.013$) in the answers to the question "Do respondents share the same bed with a partner during sleep?" (Figure 6).

All participants in Group 3 responded positively to this question, while in Group 1, this indicator was significantly

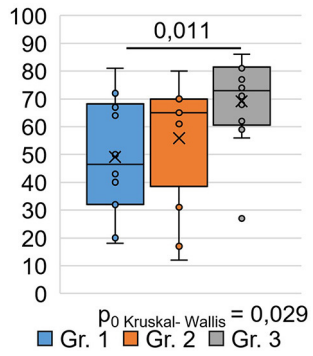

FIGURE 1
EQ-5D-5L, current subjective assessment of the condition.

TABLE 3 Scores of the Pittsburgh Sleep Quality Index (PSQI).

Component	Average score for the group Mean ± standard error of mean			Mann-Whitney *U* Test, p_0			Kruskal-Wallis test	
	Gr.1	Gr.2	Gr.3	Gr1 and Gr2	Gr1 and Gr3	Gr2 and Gr3	H	p_0
Subjective sleep quality	0.79 ± 0.28	0.83 ± 0.17	0.54 ± 0.14	0.471	0.884	0.289	1.45	0.484
Sleep latency	0.36 ± 0.13	0.25 ± 0.18	0.08 ± 0.08	0.504	0.225	0.703	3.05	0.217
Sleep duration	0.57 ± 0.25	0.08 ± 0.08	0.00 ± 0.00	0.227	0.120	0.744	**7.25**	**0.027**
Sleep efficiency	0.43 ± 0.25	0.17 ± 0.11	0.08 ± 0.08	0.777	0.528	0.724	1.17	0.559
Sleep disturbance	0.71 ± 0.19	1.08 ± 0.23	0.31 ± 0.13	0.292	0.182	**0.016**	**7.29**	**0.026**
Use of sleep medication	0.43 ± 0.25	0.42 ± 0.26	0.00 ± 0.00	0.939	0.357	0.301	3.46	0.177
Daytime sleepiness	0.50 ± 0.20	0.58 ± 0.26	0.00 ± 0.00	0.877	0.120	0.082	**6.50**	**0.039**
Composite score	3.79 ± 1.18	3.42 ± 0.87	1.08 ± 0.21	0.857	0.174	**0.006**	**6.33**	**0.042**

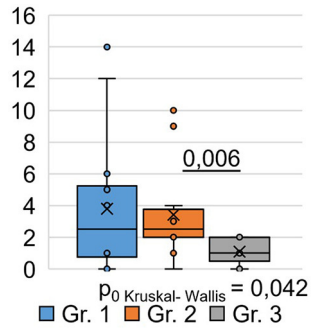

FIGURE 2
PSQI, composite score.

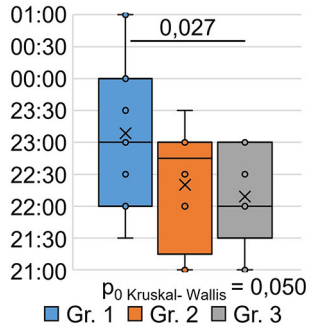

FIGURE 3
PSQI, when do respondents usually go to bed?

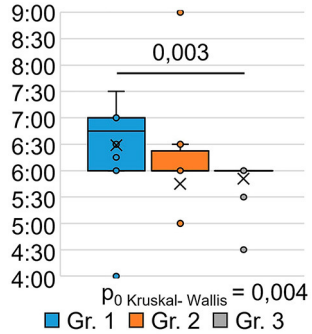

FIGURE 4
PSQI, when respondents usually get up in the morning.

lower (0.029) and reflected 50% of positive responses. In Group 2, this indicator occupied an intermediate value (75% of positive responses) and did not show significant differences with other groups.

Discussion

The current study found that the quality of life in post-COVID-19 patients is influenced by the severity of the SARS-CoV-2 infection, which is associated with hospitalization and oxygen therapy, as well as outpatient treatment for the SARS-CoV-2 infection. This relationship was shown in the three groups of respondents who received different levels of medical care during the period of COVID-19 disease despite having similar age indicators. A systematic review examined during active COVID-19 described several dozen different symptoms and other quality-of-life issues in patients, ranging from general symptoms (e.g., fever, myalgia, fatigue, and tiredness) to symptoms of neurological and psychological problems and cognitive impairment (Amdal et al., 2021; Hayes et al., 2021). To the best of our knowledge, this study is the first to examine inter-group differences in the quality of life in hospitalized post-COVID-19, who received treatment for varying degrees of severity of the SARS-CoV-2 infection, using a sociodemographic questionnaire, the PSQI, and the EQ-5D-5L test. Hospitalization of SARS-CoV-2-infected patients outside the intensive care unit (not ICU) has had an impact on the quality of life of post-COVID-19 patients in Group 2, even 9 months after recovery. However, according to our data, there was no significant difference in the quality of life between the respondents in Groups 1 and 3. Our study also found that, 6 months after the acute phase of SARS-CoV-2 infection, the quality of life indicators such as "mobility," "self-care," "daily activities," "pain/discomfort," and "anxiety/depression" did not show any intergroup differences. Therefore, these factors may not be related to the severity of the SARS-CoV-2 infection in the context of the three post-COVID-19 groups. In addition to physical symptoms, people with a post-COVID-19 condition may experience emotional symptoms such as anxiety and depression, which are prevalent during the acute phase of SARS-CoV-2 infection (Li et al., 2021; Liu et al., 2021] and may persist in the post-COVID-19 period (Shanbehzadeh et al., 2021). According to the authors, the presence of physical and emotional symptoms in patients with post-COVID-19 shows that biological and behavioral factors interact in the context of COVID-19 [Hall et al., 2021]. Recent studies have found that higher levels of depressive symptoms are associated with a higher risk of physical symptoms post-COVID-19, such as pain and shortness of breath (Bottemanne et al., 2021].

Our study found that quality of life indicators such as "mobility," "self-care," "daily activities," "pain/discomfort," and "anxiety/depression" did not show any intergroup differences in the post-COVID-19 period 9 months after the acute phase of SARS-CoV-2 infection and are therefore not related to the severity of the SARS-CoV-2 infection in the context of the three groups of post-COVID-19 conditions considered in our study. However, a subjective assessment of the quality of life on a 100-point scale of the EQ-5D test at 9 months post-COVID-19 revealed significant differences between the respondents who were treated with oxygen therapy during the active phase of the SARS-CoV-2 infection and those who were treated as outpatients. According to Amdal et al. (2021), the number of active COVID-19 publications in the global database of articles was 100 for patients treated in the ICU, 266 for those hospitalized without the ICU, and 49 for those treated in nursing homes, isolation units, or at home. Therefore, we can assume that, after a severe form of infection, SARS-CoV-2-infected patients treated in the ICU at 6 months post-COVID-19 retained the most negative assessment of their quality of life compared

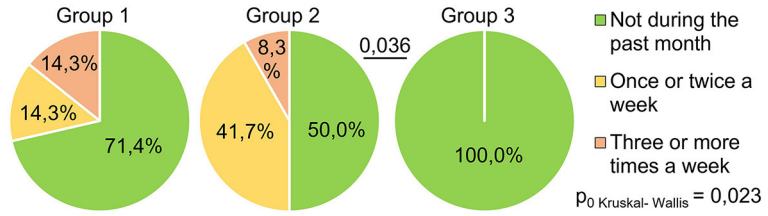

FIGURE 5
PSQI, how often during the past month did respondents have problems sleeping because they could not breathe comfortably?

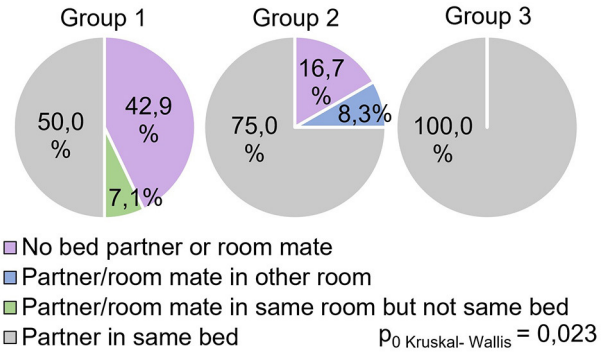

FIGURE 6
PSQI, do respondents have a bed partner or roommate?

to the respondents in Group 2 and Group 3. In a recent study that compared post-COVID-19 symptoms in hospitalized and non-hospitalized patients at 2 years after SARS-CoV-2 infection, no differences in the manifestations of post-COVID-19 were observed (Fernández-de-las-Peñas et al., 2022). According to the authors, this supports the hypothesis that the symptoms post-COVID-19 do not correlate only with the severity of COVID-19. To the best of our knowledge, our study, for the first time, revealed the presence of a relationship at 9 months post-COVID-19 between the quality of life of post-COVID-19 patients and the severity of the SARS-CoV-2 infection in different groups of the hospitalized patients. Previously, other authors suggested that post-COVID-19 affects the daily activity of subjects (Amdal et al., 2021; Pizarro-Pennarolli et al., 2021; Soriano et al., 2022). Our research in the context of analyzing the relationship between the severity of the SARS-CoV-2 infection and the quality of life of post-COVID-19 patients confirms the view that there are more and more data indicating new potential challenges for the health system that long-COVID-19 brings (Menges et al., 2021). It is necessary to emphasize the difference between our study of quality of life indicators at 6 months post-COVID-19 and the abovementioned studies, which examined symptoms detected mainly during the physical examination of respondents, including in conditions of comorbidity. Available evidence suggests that sleep problems are common in people with post-COVID-19 conditions (Iqbal et al., 2021). In a systematic review (Amdal et al., 2021), when describing the symptoms of active COVID-19 function deficits, two reports out of 305 publications showed the problem of insomnia. According to other authors, in the post-COVID-19 phase, sleep quality was disrupted due to the presence of pain symptoms (Pacho-Hernández et al., 2022). In the study by El Sayed et al., it has also been noted that sleep disorders in post-COVID-19 patients are associated with physical and mental aspects of quality of life (El Sayed et al., 2021]. Patients with the post-COVID-19 condition report greater difficulty falling asleep at the desired sleep time and have trouble waking up (Goldstein et al., 2022). Analysis of personal sources on the identified quality problem sleep patterns in the post-COVID-19 period showed that our study is the first comparative study of the sleep quality of respondents with a history of varying severity of the SARS-CoV-2 infection during hospitalization and outpatient treatment at 9 months post-COVID-19. We have established two groups of sleep quality indicators for respondents in three groups. One group of indicators for respondents (sleep duration, sleep disorders, and daytime sleepiness) has a significant relationship with the severity of the SARS-CoV-2 infections. The other group of indicators for sleep quality among respondents ("subjective sleep quality," "time to sleep," "sleep efficiency," and "frequency of taking sleeping pills") did not demonstrate significant intergroup differences. Consequently, these sleep quality problems appear regardless of the severity of the post-COVID-19 SARS-CoV-2 infection in the 9 months following the acute phase of COVID-19. Thus, our study at 9 months post-COVID-19 confirmed the data from other authors (Amdal et al., 2021; El Sayed et al., 2021; Iqbal et al., 2021; Goldstein et al., 2022; Pacho-Hernández et al., 2022) that the SARS-CoV-2 infection negatively affects sleep quality. The negative impact of a SARS-CoV-2 infection on sleep quality may be the result of a disruption in the circadian regulation system. Moreover, a number of authors have identified the interdependence between circadian disturbances, sleep difficulties, and the COVID-19 pandemic as a major consequence of the COVID-19 crisis on the sleep-wake cycle through lifestyle changes studied in the active stage (1 month) of COVID-19 (Salehinejad et al., 2020, 2022). Notably, a number of indicators of sleep quality are interrelated with the severity of the manifestation of the disease, for which medical oxygen was prescribed to maintain vital signs. This is an important step in understanding the post-clinical manifestation of a previous SARS-CoV-2 infection and its long-term effects on neurophysiological mechanisms such as circadian rhythms during long COVID-19 with differences in the severity of a previous SARS-CoV-2 infection and the prognosis of the disease, as well as its impact on health. The presence of circadian system disorders in the active stage of COVID-19 (Salehinejad et al., 2020) and in the post-COVID-19 stage indicates a long-term disruption in

the regulation of circadian biorhythms and the relevance of the rehabilitation of sleep disorders in individuals. It can be assumed that, in the treatment of respondents with post-COVID-19 sleep disorder, circadian technology was not implemented (Pyatin, 2018). In addition, individuals who recovered from COVID-19 had a later chronotype than those without a history of COVID-19 (Han et al., 2023; Tedjasukmana et al., 2023).

Finally, in our context of a comparative study, considering different post-COVID-19 groups by severity of a previous SARS-CoV-2 infection and different medical treatment protocols may be prognostically important, as Rimal et al. (2021) showed in the area of data analysis and visualization, which are essential for exploring and communicating medical research findings, especially when examining COVID-19 records.

Conclusion

In the study, a total of 123 post-COVID-19 patients who visited SamGMU clinics were includedto. However, only 39 patients (15 men, 24 women) met each of the inclusion criteria; thus, their samples were divided between three groups. For the first time in the history of the SARS-CoV-2 infection, 9 months after the severity of the infection, a quality-of-life assessment (socio-demographic questionnaire, EQ-5D-5L, PAQI) was conducted in two hospitalized groups: those who were treated in oxygen intensive care units (ICU) and those who were treated with anti-COVID-19 therapy. The third group of individuals required outpatient care after being exposed to COVID-19. Although SARS-CoV-2 infection severity differed significantly between the hospitalized post-COVID groups, there was no difference in the quality of life (sociodemographic questionnaire, EQ-5D-5L, PAQI). There was a significant difference between those who were hospitalized and those who were outpatient treated 9 months after hospital discharge in terms of quality of life and sleep disturbances, and there was no difference between groups of patients who were hospitalized.

Limitations

There are a few limitations to the results of this study, which should be taken into account when interpreting them. The study was conducted in one tertiary care hospital, and the sample size was relatively small; thus, caution should be exercised when disseminating the study results to the general public. Owing to a lack of data available in hospital records, the variables of SARS-CoV-2 in this study did not differ from those observed in previous studies. Sleep quality was assessed using a questionnaire, contributing to the concept of determining the presence of the subjectivity element and the possibility of systematic memory errors being present in the sleep evaluation. For a more critical assessment of the problem of insomnia during prolonged COVID in the long run, higher-quality data may be required to collect complete information. As a result of the assessment of the quality of life, no information was provided regarding the level of assessment that existed prior to the disease's onset. There was no question concerning the average income of the patients that could be found in the sociodemographic questionnaire used by the researchers. It was therefore not possible to assess the impact of this factor on the recovery process as a result of this factor. As the study was conducted online 9 months after discharge from the hospital, one of the questions asked concerning which genetic variant of COVID-19 was more prevalent among the patients was unable to be answered. This study took into account the need to investigate the quality of life indicators with the use of a broader scale of tests in large hospitalized populations to achieve the goals of this project.

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 Ethics Committee of Samara State Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Software: AV and SG. Supervision: VP and OM. Project administration: VP, OM, and SG. Conceptualization, validation, investigation, resources, writing—original draft preparation, writing—review and editing, visualization, and methodology: All authors. All authors have read and agreed to the published version of the manuscript.

Funding

Grant Strategic Academic Leadership: Priority 2030, Recourse: State Concurs, Moscow 2021–2030.

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.

Publisher's note

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frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 05 June 2023
DOI 10.3389/fpsyg.2023.1132154

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

RECEIVED 26 December 2022
ACCEPTED 30 March 2023
PUBLISHED 05 June 2023

CITATION
Habibi Asgarabad M, Etesam F, Salehi Yegaei P, Vahabi Z, Akbari Saneh N, Fathi F, Ghosi F and Wiium N (2023) Construct validity of the General Health Questionnaire (GHQ-12) in patients with COVID-19 and its demographic and medical correlates.
Front. Psychol. 14:1132154.
doi: 10.3389/fpsyg.2023.1132154

Construct validity of the General Health Questionnaire (GHQ-12) in patients with COVID-19 and its demographic and medical correlates

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Introduction: The present cross sectional study aimed to evaluate the construct and criterion validity, reliability, and gender and age differences of the 12-item General Health Questionnaire (GHQ-12) among hospitalized patients with COVID-19 in 2020. The criterion validity was assessed *via* its link with perceived stress, sleep quality, daily life activities, and demographic and medical characteristics.

Methods: A total of 328 COVID-19 patients (55.8% men; M_{age} =50.49, SD=14.96) completed the GHQ-12, the Perceived Stress Scale (PSS), the Pittsburgh Sleep Quality Index (PSQI), the Activities of Daily Life (ADL)-Katz Scale, and the Lawton Instrumental Activities of Daily Living Scale (IADL).

Results: Among 13 factorial models, the three-factor model (successful coping, self-esteem, and stress) was shown to have the best fit. GHQ-12 was positively associated with PSQI, PSS, Hyperlipidemia, psychiatry disorders, hospitalization duration, the change in sleep time, and use of sleeping pills, and negatively correlated with educational level, and the number of family members. The GHQ-12 also had a negative correlation with ADL and IADL in over 60years of age group. Females scored higher on total GHQ-12 scores, compared to males. Finally, the hospitalization duration was longer for patients over 60 (mean=8.8days, SD=5.9) than patients under 60 (mean=6.35days, SD=5.87).

Discussion: Overall, the findings provided evidence that mental distress in patients with COVID-19 is correlated with high perceived stress, low sleep quality, low ADL and IADL, and a range of demographic features and medical conditions. Designing

psychological interventions for these patients that target the aforementioned correlates of mental distress is warranted.

KEYWORDS

COVID-19, concurrent validity, general health, medical condition, reliability, sleep, activities of daily life, stress

Introduction

New measures of the COVID-19 pandemic (e.g., self-isolation and quarantine) have led to an increase in mental distress, such as anxiety, insomnia, and suicidal attempt (WHO, 2020; Santomauro et al., 2021). Review studies after the COVID-19 pandemic showed high prevalence rate of anxiety (27–41.3%) and depression (27 to 34.1%) in Eastern Europe (Zhang et al., 2022), Southeast Asia (Pappa et al., 2022) and South Asia (Hossain et al., 2021).

To capture changes in mental health in both general and clinical populations, the self-administered General Health Questionnaire (GHQ; Goldberg, 1988) was developed. The 12-item short-form of GHQ (GHQ-12; Goldberg et al., 1997) was derived from the original 60-item questionnaire for fast administration in busy clinical settings. This questionnaire screens those with common psychological problems, such as poor self-esteem, stress, and sleep loss (del Pilar Sánchez-López and Dresch, 2008).

Although GHQ-12 was originally designed as a unidimensional measure (Goldberg, 1972), several exploratory factor analyses indicated that a two-factor (Zhong et al., 2021) or three-factor model (del Pilar Sánchez-López and Dresch, 2008) is the most common model (full information of these factorial models and their reliabilities are presented in Table 1). However, considering the study of Liang et al. (2016) for instance, they failed to find the best fitting model among ten existing factorial models, highlighting that there is a need for further research on the factor structure of GHQ-12.

General mental health: Stress and sleep quality

Mental health is reciprocally linked to sleep quality, specifically in patients with COVID-19 who are commonly susceptible to sleep disturbances (Deng et al., 2021; Marvaldi et al., 2021). Perceived stress, referring to the extent to which a person perceives their daily life situations as stressful, was also found to be positively associated with GHQ-12 in a large cross-national sample of COVID-19 patients (Bonsaksen et al., 2022). Patients infected with COVID-19 experienced the burden of job loss (Crayne, 2020), death anxiety (Korkut, 2022), and may react with heightened stress (Bonsaksen et al., 2022).

General mental health: Medical conditions and demographic characteristics

Coronavirus may severely impair the subsequent physical functioning in some patients, especially the elderly (Carfì et al., 2020; Halpin et al., 2020). The Activities of daily living (ADL) and the Instrumental Activities of Daily Living (IADL; Katz et al., 1970; Lawton, 2000) are basic skills necessary for independently taking care of oneself (Edemekong et al., 2017) and environmental adaptation (Roehrig et al., 2007). Although few in number, some studies have shown the link of mental health to ADL and IADL scores (de Castroe Costa et al., 2008).

Due to the negative effect of COVID-19 on several aspects of people's lives (Santomauro et al., 2021), research should document the association of mental health status in COVID-19 patients with demographics and medical features. Previous studies have suggested the positive link of mental health status with medical features, such as change in sleep time before and after COVID-19 and use of sleeping pills (Becker et al., 2018), hospitalization duration (Liao et al., 2020), psychiatry disorders (Kaufman et al., 2020), hyperlipidemia (HLP; Chang et al., 2021), diabetes (Moradian et al., 2021), cardiovascular disease (CVD; de Paiva Teixeira et al., 2020), substance use history (Czeisler et al., 2020), as well as demographics characteristics, namely, educational level (Dalgard et al., 2007), unemployment (Achdut and Refaeli, 2020), and the number of family members (Hendriksen et al., 2021). COVID-19 pandemic was shown to result in greater mental distress in women (Giorgi et al., 2014; Bucciarelli et al., 2021). As an example, in a study on large data of 49,156 participants, Proto and Quintana-Domeque (2021) found that after the COVID-19 pandemic, women manifested higher elevation in GHQ-12 scores (higher psychological distress) than men. Aging is believed to be associated with decrease in mental distress (Hoeymans et al., 2004), while COVID-19 pandemic have led to greater mental distress in younger patients (Bruine de Bruin, 2021).

The study context

Iran is among the worst-hit countries by Coronavirus, with heavy death tolls (more than 19,000 deaths until August 2020; Shahriarirad et al., 2021). Challenging factors, namely, the shortage of hygiene and medical supplies and equipment (i.e., masks and disinfectants), economic constraints (Zandifar and Badrfam, 2020), and the incapacity of government to formulate and enforce effectual social distancing and lockdown measures have led to the mental distress in the Iranian general population (Moghanibashi-Mansourieh, 2020; Zandifar and

Abbreviations: GHQ, General Health Questionnaire; PSS, Perceived Stress Scale; PSQI, Pittsburgh Sleep Quality Index; ADL, activities of daily life; IADL, instrumental activities of daily living; HTN, high blood pressure; HLP, hyperlipidemia; CVA, cerebrovascular accident; HPA, hypothalamic pituitary adrenal; PD, pulmonary disease; IDD, immune deficiency disease; MI, myocardial infarction; CVD, cardiovascular disease.

TABLE 1 Studies Validating the Psychometric Properties of the GHQ-12 in Different Populations.

Author	Country	Participant characteristics	Factor structure and fit indices	Factors and corresponding items	Reliability
Unidimensional models					
Alaminos-Torres et al. (2021)	Spain	$n = 342$ Age range = 41–50 years	Range of factor loadings (EFA; unidimensional model) = 0.57–0.95	–	Total score = 0.85
Gnambs and Staufenbiel (2018)	Germany	$n_1 = 76{,}473$ $n_2 = 410{,}640$	Fit index (CFA; unidimensional model) = CFI = 0.89, RMSEA = 0.11	–	Total score = 0.85
Hystad and Johnsen (2020)	Norway	$n_1 = 591$ $n_2 = 196$	Fit index (CFA; unidimensional model) = CFI = 0.91, RMSEA = 0.07	–	–
Romppel et al. (2013)	Germany	$n = 2{,}041$ (53% female) M_{age} (SD) = 48.8 (18.1)	Fit indexes (CFA; unidimensional model) = CFI = 0.93, RMSEA = 0.10	–	Total score = 0.89 Positively worded items = 0.79 Negatively worded items = 0.86
Two-factor models					
Hamad (2022)	Saudi Arabia	$n = 473$ (60.81% female)	Fit index (CFA; two-factor model) = CFI = 0.96, RMSEA = 0.05	F1 Personal and Social Dysfunction = 1,3,4,7,8,9,10,11,12 F2 Anxiety = 2,5,6	Total score = 0.85
Kalliath et al. (2004)	New Zealand	$n_1 = 691$ (54% female) $M_{age} = 38$ $n_2 = 415$ (54% female) $M_{age} = 38$	Fit index (CFA; two-factor model) = CFI = 0.98, RMSEA = 0.07	F1Social Dysfunction = 4,7,8,12 F2 Anxiety/ Depression = 6,9,10,11	Total score at $T_1 = 0.91$ Total score at $T_2 = 0.90$
Montazeri et al. (2003)	Iran	$n = 748$ (76% female) M_{age} (SD) = 21.1 (2.1)	Range of factor loadings (EFA; two-factor model) = $F_1 = 0.56$–0.81; $F_2 = 0.46$–0.69	F1 Psychological distress = 1,3,4,7,8,10,11 F2 social dysfunction = 2,5,6,7,9,12	Total score = 0.87
Najarkolaei et al. (2014)	Iran	$n = 428$ (56% female) M_{age} (SD) = 22.83 (3.09)	Range of factor loadings (EFA; two-factor model) = $F_1 = 0.46$–0.73; $F_2 = 0.39$–0.78 Fit indexes (CFA; two-factor model) = GFI = 0.96, RMSEA = 0.04	F1 social dysfunction = 1,2,5,7,9,12 F2 psychological distress = 3,4,6,8,10,11	Total score = 0.85 Social dysfunction = 0.77 Psychological distress = 0.76
Politi et al. (1994)	Italy	$n = 320$ (0% female) M_{age} (SD) = 18	Range of factor loadings (EFA; two-factor model) = $F_1 = 0.31$–0.80; $F_2 = 0.34$–0.72	F1 general dysphoria = 2,5,6,9,10,11,12 F2 social dysfunction = 1,3,4,7,8	Total score = 0.81
Schrnitz et al. (1999)	Germany	$n = 572$ (68.7% female) M_{age} (SD) = 42.7 (15.7)	A principal-components factor analysis = factors' eigenvalues of >1	F1 Anxiety/ Depression = 1,2,6,7,10,11 F2 Social Performance = 4, 5, 8, 9 and 12	Anxiety/ Depression = 0.86 Social Performance = 0.82 Total score = 0.91
Zhong et al. (2021)	China	–	Range of factor loadings (EFA; two-factor model) = $F_1 = 0.62$–0.72; $F_2 = 0.48$–0.79 Fit indexes (CFA; two-factor model) = 0.92, RMSEA = 0.08	F1 = 1,2,5,7,9,12 F2 = 3,4,6,8,10,11	Total score = 0.89
Three-factor models					
Daradkeh et al. (2001)	United Arab Emirates	$n = 157$	Range of factor loadings (EFA; three-factor model) = $F_1 = 0.57$–0.79; $F_2 = 0.44$–0.80; $F_3 = 0.55$–0.87	F1general dysphoria = 10, 5, 9, 11, 6 F2 lack of enjoyment = 7, 12, 1, 8, 2 F3 social dysfunction = 3, 4	Total score = 0.86

(Continued)

TABLE 1 (Continued)

Author	Country	Participant characteristics	Factor structure and fit indices	Factors and corresponding items	Reliability
del Pilar Sánchez-López and Dresch (2008)	Spain	n = 1,001 (60% female) M_{age} (SD) = 41.75 (10.95)	Range of factor loadings (EFA; three-factor model) = F_1 = 0.50–0.71; F_2 = 0.41–0.63; F_3 = 0.63–0.65	F1Successful Coping = 1,3,4,7,8,12 F2 Self-esteem = 6,9,10,11 F3 Stress = 2,5,9	Total score = 0.76
Farrell (1998)	Australia	n = 270 (85% female) M_{age} (SD) = 0.36 (9)	Range of factor loadings (EFA; three-factor model) = F_1 = 0.62–0.81; F_2 = 0.60–0.80; F_3 = 0.70–0.84	F1 Anxiety = 10,12,2,5,11 F2 Depression = 1,9,8,7,6 F3 Social dysfunction = 3,4	Anxiety = 0.84 Depression = 0.81 Social dysfunction = 0.69
Gao et al. (2004)	Singapore	n = 120 (47.5% female) M_{age} (SD) = 43.1 (12.7)	Fit index (CFA; three-factor model model) = CFI = 0.93, RMSEA = 0.10	F1 Anxiety and depression = 2,5,9,6, F2 Social dysfunction = 1,3,4,8,7,12 F3 Loss of confidence = 10,11	–
Graetz (1991)	Australia	n = 8,998 (49% female) Age range = 16–25 years	Range of factor loadings (EFA; three-factor model) at T_1 and T_2 = F_1 = 0.44–0.78; F_2 = 0.44–0.59; F_3 = −0.70 – -0.72 Range of factor loadings (EFA; three-factor model) at T_3 and T_4 = F_1 = 0.38–0.77; F_2 = 0.44–0.64; F_3 = −0.72 – -0.74	F1 Anxiety and depression = 2,5,6,9 F2 Social dysfunction = 1,3,4,7,8,12 F3 loss of confidence = 10,11	–
Lee and Kim (2020)	South Korea	n = 504 (66.8% female) M_{age} (SD) = 20.2 (1.63)	Fit indexes (CFA; three-factor model) = CFI = 0.93, RMSEA = 0.07	F1 Anxiety and depression = 2,5,6,9 F2 Social dysfunction = 1,3,4,7,8,12 F3 loss of confidence = 10,11	Total score = 0.81
Liang et al. (2016)	China	n = 1,051 (38.5% female) Age range = 29–35 years	Three-dimensional model (CFA) = CFI = 0.98, RMSEA = 0.03	F1 = 4,6,9,10,11,12 F2 = 3,5,7,8 F3 = 1,2	Total score = 0.84
Martin (1999)	Australia	n = 169 (61.1% female) M_{age} (SD) = 28 (11)	Range of factor loadings (EFA; three-factor model) = F_1 = 0.46–0.64; F_2 = 0.65–0.70; F_3 = −0.63–0.84	F1 Self-esteem = 1,3,4,8 F2 Stress = 2,5,7 F3 Successful Coping = 6,9,10,11,12	Self-esteem = 0.83 Stress = 0.71 Successful Coping = 0.67

n, sample size; *F*, factor; *T*, study wave; *M*, mean; CFI, comparative fit index; RMSEA, root mean square error of approximation; GFI, goodness of fit index; EFA, exploratory factor analysis; CFA, confirmatory factor analysis. Inconsistency in reporting the demographic characteristics including sample size, percentage of females, $Mean_{age}$ (*SD*) in column "participants" is due to not reporting the relevant data in the papers.

Badrfam, 2020; Shahriarirad et al., 2021). The Iranian population has been no exception to the global trend of increased mental issues. In a group of 5,328 individuals from the general population of Iran, the prevalence rates of anxiety, depression, and comorbid depression-anxiety were determined to be 30.1, 33.4, and 22.1%, respectively (Nakhostin-Ansari et al., 2020). Moreover, in another recent study by Maroufizadeh et al. (2022), the prevalence of mild-to-severe anxiety and depression in Iranian medical students was found to be 38.1 and 27.6%, showing a significant impact on sleep patterns.

In Iran, two studies have assessed the psychometric properties of GHQ-12. In a study on emerging adults, Montazeri et al. (2003) findings confirmed the two-factor model, comprising "depression" and "social dysfunction." Their study showed the negative association of GHQ-12 with global quality of life, supporting its satisfactory convergent validity. Similarly, the results of Najarkolaei et al. (2014) study supported a two-factor model including "distress" and "social dysfunction" in freshmen university students. Nevertheless, participants of these two studies had limited age range (18–26 years of age) and were recruited from university students, which prevent their results from being generalized to the general or clinical Iranian population.

The present study was first-of-its-kind that aimed to examine the psychometric properties of the GHQ-12 in Iranian patients with COVID-19. In specific, we aimed to examine: (1) the factor structure by conducting Confirmatory Factor Analysis (CFA) based on 13 empirically-derived factorial models, (2) the internal consistency, (3) the criterion validity through the relationship of GHQ with perceived stress, sleep quality, ADL/IADL, and demographic and medical variables, and (4) the comparison of the average GHQ-12 scores among age and gender groups (if any). We hypothesized that higher GHQ-12 score—that reflects lower mental health—has a positive relationship with: (1) poor sleep quality, (2) higher perceived stress, and (3) lower level of ADL/IADL functions.

Materials and methods

Participants

Participants comprised a total of 328 patients with COVID-19 (55.8% men), aged 21 to 92 ($Mean_{age}$ (SD) = 50.49 (14.96); 73.6%

60 years old or younger). As for educational level, 19.8% of participants were illiterate, 22.9% had primary education, 16.5% had secondary education, 23.5% had diploma level, and 17.3% had higher education. Their job status included 15.3% employee, 6.7% skill-worker, 20.7% self-employed, 39.6% unemployed, and 13.1% retired. Most patients (88.6%) were living with their spouse and/or their children, while 10.5% were living alone. A majority of 86.6% had no history of smoking, while 10.1 and 2.4% reported smoking in the past and at the present time. In addition, 93.9 and 96.6% reported no history of alcohol and drug use, respectively. Among participants, 4.6% reported using sleeping pills—mostly Alprazolam, Chlordiazepoxide, and Asentra. Patients under and over 60 reported underlying diseases, including Diabetes (13 and 44.6%), High Blood Pressure (HTN; 15.2 and 28.9%), HLP (11.7 and 31.3%), psychiatry disorders (4.8 and 3.6%), immune deficiency disease (IDD; 1.3 and 4.8%), and Cardiovascular disease (9.1 and 28.9%), each. Finally, the mean of hospitalization duration was 6.35 days (SD = 5.87) for patients under 60 and 8.8 days (SD = 5.9) for patients over 60.

Measurements

General Health Questionnaire

The self-report GHQ-12 was developed to screen global mental state (Goldberg et al., 1997). Among two common scoring methods of the bi-modal (*0–0–1-1*) and *Likert* scoring (*0–1–2-3*) types, the *Likert* method is preferable since it measures the symptom severity on a continuum (Hystad and Johnsen, 2020). In this study, the scoring based on the 4-point *Likert*-scale (*0–1–2-3*) was used, in which: 0 = "*not at all*," 1 = "*no more than usual*," 2 = "*rather more than usual*," and 3 = "*much more than usual*," where a higher score indicated lower mental health (Goldberg et al., 1997).

Pittsburgh Sleep Quality Index

This 19-item self-administered tool (Buysse et al., 1989) was designed for brief assessment of seven components: (1) subjective sleep quality (e.g., "*how would you rate your sleep quality overall?*"), (2) sleep latency (e.g., "*cannot get to sleep within 30 min*"), (3) sleep duration (e.g., "*how many hours of actual sleep do you get at night?*"), (4) sleep efficiency (e.g., "*when have you usually gone to bed?*"), (5) sleep disturbances (e.g., "*wake up in the middle of the night or early morning*"), (6) use of sleeping medication (e.g., "*how often have you taken medicine to help you sleep?*"), and (7) daytime dysfunction (e.g., "*how often have you had trouble staying awake while driving,…*"). Each component was weighted on a *Likert* scale from 0 to 3, with higher scores indicating poorer sleep quality. *Cronbach*'s alpha in the current study was.77 for the total score. The Persian version of PSQI that showed adequate psychometric properties (Farrahi Moghaddam et al., 2012) was used in the current study.

Perceived Stress Scale

PSS is a 10-item unidimensional scale (Cohen et al., 1983) that measures how much patients appraise the situations in their life as stressful during the preceding month. Items were coded based on a 5-point *Likert*-type scale: 0 (*never*), 1 (*almost never*), 2 (*once in a while*), 3 (*often*), and 4 (*very often*). Higher scores indicated higher perceived stress (e.g., *"unable to control the important things in your life"*). *Cronbach*'s α for the Persian version of PSS was.84 for the total score (Maroufizadeh et al., 2018), while an alpha value of.68 was obtained in our study.

ADL-Katz Scale and The Lawton Instrumental Activities of Daily Living Scale

The 6-item ADL-Katz Scale (Katz et al., 1970) assessed the ability of bathing, transferring, dressing and grooming, walking, toileting, and feeding in people over 60 years of age. The Lawton Instrumental Activities of Daily Living Scale (Lawton, 2000) measured instrumental functioning, namely, using the phone, doing housework, doing laundry, managing transportation, shopping, cooking, managing medications, and managing finances. Items for both ADL and IADL were scored based on 0 (*no*) and 1 (*yes*). *Cronbach*'s alphas for the Persian versions of ADL and IADL were 0.80 (Sharifi et al., 2018) and between 0.72 and 0.76 (Mehraban et al., 2014), respectively. In this study, alphas were 0.66 and 0.82 for ADL and IADL, respectively.

Medical conditions and demographic characteristics

In order to evaluate the patients' demographics and medical characteristics, a questionnaire constructed by researchers was used. The medical features included: (a) the history of underlying diseases (Diabetes, HTN, HLP, Myocardial Infarction (MI), Cerebrovascular Accident (CVA), Pulmonary Disease (PD), Kidney failure, Psychiatry disorders, Obesity, IDD, and CVD) (*yes/no*), (b) cigarette, alcohol, and drug history (*yes/no*), (c) hospitalization duration (*days*), (d) use of downer or sleeping pills (*yes/no*), and (e) the change in sleep time before and after COVID-19 (*hours*). The demographic characteristics included: (a) gender (*male/female*), (b) age (*years*), (c) job status (*employed/unemployed*), (d) educational level (*illiterate, primary education, secondary education, diploma level, and higher education*), and (e) the number of family members.

Procedure

The current cross-sectional study was carried out on patients hospitalized due to Coronavirus infection at the Baharloo and Ziaeian Hospitals from March to October 2020 in Tehran, Iran. After being discharged from the hospital, those who accepted to take part in the current study were asked to sign the consent form. The demographic information of those who consented to take part and their contact number was collected in a registration form. Then, three psychologists collected the data (demographic and medical variables, GHQ-12, PSS-10, PSQI, ADL and IADL), using telephone survey. Patients were informed about their optional participation in the current research and that they can leave the research any time they wish. This study received ethic approval from the Review Board of Tehran University of Medical Sciences (Ethical Code: IR.TUMS.VCR.REC.1399.156).

Statistical strategy

Data screening was performed *via* IBM SPSS Statistics (Version 28). CFA tests of the GHQ-12 were conducted using Mplus version 8.8. Evaluating the assumption of normality revealed a mostly positive but non-substantial skewness in all items; thus, transformation was

not required (Gravetter et al., 2020). We applied CFA using the Weighted Least Square Mean and Variance Adjusted (WLSMV) estimator. Statistical strategies were as follows: First, we used the following statistical tests and indices (MacCallum et al., 1996; Hu and Bentler, 1999; Hooper and Coughlan, 2008) to assess the models' "goodness-of-fit" (acceptable values in parenthesis): the Chi-square (χ^2; desired $p > 0.05$), the Comparative Fit Index (CFI > 0.95), the Tucker–Lewis Index (TLI > 0.95), the Standardized Root Mean Square Residual (SRMR <0.08), the Normal Chi-square (χ^2/df < 5), the Root Mean Square Error of Approximation (RMSEA <0.10), and its 90% Confidence Interval (Bentler and Bonett, 1980; MacCallum et al., 1996; Loehlin, 2004; Miles and Shevlin, 2007). The exact fit is defensible when the Chi-square is not significant, regardless of the SRMR value. Approximate fit is tenable when Chi-square is significant, SRMR ≤0.08, and standard residuals are all small ($|r_{res}| < 0.1$), and finally poor fit is concluded if Chi-square is significant, and SRMR >0.08 (Satorra and Bentler, 2010).

Second, for internal consistency—as recommended for ordinal *Likert*-type scales, the equivalents of *Cronbach*'s alpha coefficient (Ordinal *Theta* and *Omega* reliability coefficients) using R version 4.1.2 (Team, R. C, 2013; Revelle, 2017) were conducted, which instead of the Pearson correlation matrix, apply the poly-choric correlation matrix (Zumbo et al., 2007; Gadermann et al., 2012). A reliability coefficient of 0.70 or higher was considered an acceptable level (Cicchetti, 1994).

Third, the criterion validity was evaluated by the Spearman coefficient of rank correlation of GHQ-12 with PSQI, PSS-10, and ADL/IADL, since the data showed evidence of non-normality. Correlation coefficients were interpreted based on the effect size classification of Cohen (1988): 0.10 = small, 0.30 = medium, 0.50 = large, and 0.70 = very large.

Forth, Multivariate Analysis of Variance (MANOVA) and effect size (Hedge's g) were used to compare the mean and standard deviation of the GHQ-12 scores across gender. According to a rule of thumb suggested by Cohen (1988), effect sizes were classified into small (<0.20), medium (0.21–0.50), large (0.51–0.80), and very large (>0.80).

Results

Aim 1: GHQ-12 construct validity

To test the GHQ-12 factor structure, CFA was conducted and the goodness of fit for 13 models was examined (Table 2). Model 1 (M_1) examined a general factor, in which, the total of the 12 items were loaded on a single common factor of general mental health (Goldberg et al., 1997; Romppel et al., 2013; Gnambs and Staufenbiel, 2018; Hystad and Johnsen, 2020; Alaminos-Torres et al., 2021) to test the unidimensional model of assumed latent factor and included just random measurement error and indicator-specific variance (Gustafsson and Åberg-Bengtsson, 2010). If the general factor model fitted the data well, it meant that the assumption of the multidimensionality of the measurement tool was violated. Models two to seven (M_2 to M_7) consisted of a the first-order two-factor oblique models that suggested two subscales measuring two distinct dimensions (Politi et al., 1994; Schrnitz et al., 1999; Montazeri et al., 2003; Kalliath et al., 2004; Najarkolaei et al., 2014; Zhong et al., 2021; Hamad, 2022). Models 8–13 (M_8 to M_{13}) examined first-order three-factor oblique models, resembling the Exploratory Factor Analysis (EFA) according to the literature (Graetz, 1991; Farrell, 1998; Martin, 1999; Daradkeh et al., 2001; Gao et al., 2004; del Pilar Sánchez-López and Dresch, 2008; Liang et al., 2016; Lee and Kim, 2020). Model 8 (M_8) included general dysphoria, lack of enjoyment, and social dysfunction (Daradkeh et al., 2001). Model 9 (M_9) consisted of anxiety, depression,

TABLE 2 Fit indices of the Measurement Models of the GHQ-12.

Model	χ^2	*df*	χ^2/df	CFI	TLI	RMSEA	SRMR	Based Model	$\Delta\chi^2$ (df)
M_1 (Goldberg et al., 1997; Romppel et al., 2013; Gnambs and Staufenbiel, 2018; Hystad and Johnsen, 2020; Alaminos-Torres et al., 2021)	1030.608	54	19.08	0.900	0.878	0.240 (0.227–0.253)	0.172	–	–
M_2 (Politi et al., 1994)†	1016.411	53	19.17	0.902	0.878	0.241 (0.228–0.254)	0.170	M_1	–
M_3 (Kalliath et al., 2004)†	458.688	19	24.14	0.869	0.806	0.271 (0.250–0.293)	0.099	M_1	–
M_4 (Montazeri et al., 2003)†	955.448	52	18.37	0.908	0.883	0.235 (0.222–0.248)	0.165	M_1	–
M_5(Najarkolaei et al., 2014; Zhong et al., 2021)†	1023.869	53	19.31	0.901	0.877	0.242 (0.229–0.255)	0.170	M_1	–
M_6 (Schrnitz et al., 1999)†	951.700	43	22.13	0.825	0.776	0.259 (0.245–0.274)	0.134	M_1	–
M_7 (Hamad, 2022)†	1017.709	53	19.20	0.902	0.878	0.241 (0.228–0.254)	0.172	M_1	–
M_8 (Daradkeh et al., 2001)	672.991	51	13.19	0.938	0.920	0.197 (0.184–0.210)	0.099	M_1	357.62 (3)***
M_9 (Farrell, 1998)†	1016.582	51	19.93	0.904	0.876	0.246 (0.233–0.259)	0.135	M_1	–
M_{10} (Graetz, 1991; Gao et al., 2004; Lee and Kim, 2020)	530.411	51	10.40	0.952	0.938	0.173 (0.160–0.187)	0.087	M_1	500.20 (3)***
M_{11} (Martin, 1999)	751.738	51	14.73	0.930	0.910	0.209 (0.196–0.223)	0.107	M_1	278.87 (3)***
M_{12} (Liang et al., 2016)†	3018.809	50	60.37	0.704	0.610	0.435 (0.422–0.448)	0.287	M_1	–
M_{13} (del Pilar Sánchez-López and Dresch, 2008)††	**502.118**	**50**	**10.04**	**0.955**	**0.941**	**0.170 (0.156–0.183)**	**0.080**	**M_1**	**528.49 (4)*** **

χ^2, Chi-square; df, degrees of freedom; TLI, Tucker–Lewis index; CFI, comparative fit index; ABIC, sample-size adjusted Bayesian information criterion; χ^2/df, normal Chi-square; $\Delta\chi^2$, difference between minus twice log likelihoods between the full and the nested models; SRMR, standardized root mean square residual; RMSEA, root mean square error of approximation; Δ, differences between parameters of two models; † = The problem with the model is that the factors correlate greater than one which makes the model inadmissible, then, model cannot be used. †† = The final selected model. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
The bold values correspond to the final selected model.

and social dysfunction (Farrell, 1998). Model 10 (M_{10}) was loaded by all three first-order factors, which included social dysfunction, anxiety and depression, and loss of confidence (Graetz, 1991; Gao et al., 2004; Lee and Kim, 2020). Model 11 (M_{11}) included cope, stress, and low self-esteem (Martin, 1999). Model 12 (M_{12}) comprised low level of social function, anxiety/depression, and poor self-confidence (Liang et al., 2016). Finally, Model 13 (M_{13}) included successful coping, self-esteem, and stress (del Pilar Sánchez-López and Dresch, 2008).

Model selection

In Table 2, all two-factor models (Politi et al., 1994; Schrnitz et al., 1999; Montazeri et al., 2003; Kalliath et al., 2004; Najarkolaei et al., 2014; Zhong et al., 2021; Hamad, 2022) are inadmissible, due to factors correlate greater than 1.00 between two latent factors. The correlation between the two latent factors in two out of six models for the three-factor model also exceeded 1.00, as shown in Table 2 (M_9 and M_{12}; Farrell, 1998; Liang et al., 2016). The fit indices of the three-factor oblique model for remaining four models (Table 2; M_8, M_{10}, M_{11}, and M_{13}) met some of the specified fit criteria, as prior, and based on the theory-derived models (Graetz, 1991; Martin, 1999; Daradkeh et al., 2001; Gao et al., 2004; del Pilar Sánchez-López and Dresch, 2008; Lee and Kim, 2020). Then, the parsimonious principle (Bollen, 1989) was used to compare the fit indices of the three-factor first-order oblique models (Table 2; M_8 [$\Delta\chi^2$ = 357.62, Δdf = 3, p < 0.001], M_{10}[$\Delta\chi^2$ = 500.20, Δdf = 3, p < 0.001], M_{11}[$\Delta\chi^2$ = 278.87, Δdf = 7, p < 0.001], and M_{13}[$\Delta\chi^2$ = 528.49, Δdf = 4, p < 0.001]) with those of the unidimensional first-order model (M_1) as the baseline/null model. For three-factor models, four out of six models exhibited similar fitness, though with poor goodness-of-fit (Table 2). To determine the most efficient parsimonious model, the nesting and equivalence testing (NET) methodology was implemented *via* Mplus 8.8 (Bentler and Satorra, 2010; Asparouhov and Muthén, 2019). Since all models are non-tested and/or non-equivalent, as was expected (the NET value = 0.0000001), it can be concluded that model 13 showed the best fit, due to its low Chi-square value in comparison with the others (χ^2/df = 10.04; CFI = 0.96; TLI = 0.94; RMSEA = 0.17; 90% CI = 0.16 to 0.18; SRMR = 0.08). More information on confirmatory factor analysis of models 1, 8, 10, 11, and 13 is presented in supporting information file (Supplementary Figures S1–S5).

Aim 2: GHQ-12 reliability

The Ordinal *Theta* and the *Omega* reliability coefficients for the subscales of GHQ-12 are presented in Table 3. The means of inter-item correlation were 0.10, 0.53, 0.48, and 0.58 for the total score, successful coping, self-esteem, and stress, respectively. Almost all items within the three subscales had a moderate positive relationship with each other (based on the corrected item-total correlation for subscale's items), with values ranging from 0.34 to 0.83, 0.23 to 0.78., and 0.53 to 0.66 for successful coping, self-esteem, and stress, respectively.

Aim 3: GHQ-12 and related measures

Table 4 demonstrates that the inter-correlation between GHQ-12 total score and subscales ranged from 0.40 to 0.83 (p < 0.01). Criterion validity was estimated by the correlation of GHQ-12 total score and its subscales with PSQI and PSS (Table 4). PSQI had significant positive correlations with total GHQ-12 (r = 0.28, p < 0.01), successful coping (r = 0.24, p < 0.01), self-esteem (r = 0.21, p < 0.01), and stress (r = 0.20, p < 0.01). Also, PSS had significant positive correlations with the total score of GHQ-12 and its subscales (r = 0.31 to 0.58, p < 0.01). In the over 60 years of age group, negative correlations of the total GHQ-12 score were found with the ADL (r = −0.34, p < 0.01; r = −0.37, p < 0.01) and IADL scores (r = −0.42, p < 0.01, r = −0.46, p < 0.01) before and after the infection of COVID-19, respectively (Table 4).

As depicted in Table 5 for demographic and medical variables, the total score of GHQ-12 was significantly correlated with HLP (r = 0.16, p < 0.01), kidney failure (r = 0.12, p < 0.05), psychiatry disorders (r = 0.18, p < 0.01), the hospitalization duration (r = 0.15, p < 0.01), the change in sleep time (r = 0.31, p < 0.01), use of sleeping pills (r = 0.30, p < 0.01), educational level (r = −0.26, p < 0.01), and the number of family members (r = −0.12, p < 0.05). The correlation of the total score of GHQ-12 with Diabetes, HTN, MI, CVA, PD, obesity, IDD, CVD, and drug, alcohol, and cigarette history were non-significant (p > 0.01). Information for the correlation of GHQ-12 subscales is presented in Table 5.

Aim 4: Gender, age, and GHQ-12

Table 3 presents the mean and Standard Deviations (SD) of the GHQ-12 total score and subscales across gender and age groups. The female patients scored significantly higher than the males on total GHQ-12 scores [t (310) = −4.77, p < 0.001, Cohen's d = −0.65, mean difference bootstrap 95% CI = −4.46 to-1.92]. The patients above 60 also scored slightly higher than patents under 60 on their total GHQ-12 scores [t (312) = −1.45, p = 0.08, Cohen's d = −0.19, mean difference bootstrap 95% CI = −2.94 to 0.55]. A Multivariate Analysis of Variance (MANOVA) showed significant group differences by gender [F (3–308) = 10.80, p < 0.001, η^2 = 0.095] and age groups

TABLE 3 The Descriptive statistics of GHQ-12.

	Mean (SD)					Ordinal *Theta*	*Omega*	α
	Total	Female	Male	Under 60	Over 60			
1. Successful Coping	8.95 (3.42)	8.39 (3.20)	9.39 (3.55)	9.30 (3.31)	7.98 (3.55)	0.90	0.86	0.87
2. Self-esteem	3.91 (2.63)	4.37 (2.61)	3.22 (2.39)	3.86 (2.54)	4.04 (2.88)	0.75	0.77	0.77
3. Stress	3.96 (2.43)	4.72 (2.40)	3.33 (2.27)	4.06 (2.40)	3.67 (2.51)	0.93	0.88	0.80
4. GHQ-12	15.52 (6.19)	16.18 (3.66)	14.87 (3.82)	15.88 (3.80)	14.39 (3.82)	-	-	0.86

Notes. GHQ = General health questionnaire, α = Alpha, SD = Standard deviation. $^{*}p$ < 0.05, $^{**}p$ < 0.01.

TABLE 4 The correlation between GHQ-12 subscales and their correlations with sleep quality, perceived stress, and daily functioning.

	2	3	4	PSQI							PSS	ADL		IADL	
				Total	SSQ	SL	SD	SE	SD	USM	DD		Before	After	Before	After
1. Successful Coping	0.40**	0.45**	0.83**	0.24**	0.41**	0.24**	0.15	0.26**	0.29**	0.25**	0.51**	0.31**	-0.35**	-0.43**	-0.48**	-0.55**
2. Self-esteem		0.73**	0.80**	0.21**	0.43**	0.27**	0.20*	0.22*	0.27**	0.23**	0.23**	0.50**	-0.25*	-0.33*	-0.28**	-0.31**
3. Stress			0.81**	0.20**	0.57**	0.23**	0.38*	0.27**	0.48**	0.23**	0.28**	0.58**	-0.22*	-0.16	-0.19	-0.15
4. GHQ-12				0.28**	0.55**	0.30**	0.28**	0.30**	0.42**	0.30**	0.45**	0.53**	-0.34**	-0.37**	-0.42**	-0.46**

Notes. GHQ = General health questionnaire, PSQI = Pittsburgh sleep quality index, SSQ = Subjective sleep quality, SL = Sleep latency, SD = Sleep duration, SE = Sleep efficiency, SD = Sleep disturbances, USM = Use of sleeping medication, DD = Daytime dysfunction; PSS = Perceived stress scale. *$p < 0.05$, **$p < 0.01$.

[F (3–310) = 7.27, $p < 0.001$, $\eta^2 = 0.066$] on mean scores of the subscales (see Table 3 for Mean scores). Subsequent tests of between-subjects' effects showed that females scored significantly higher on successful coping [F (1–310) = 5.68, $p < 0.05$, $\eta^2 = 0.018$], self-esteem [F (1–310) = 28.11, $p < 0.001$, $\eta^2 = 0.083$], and stress [F (1–310) = 27.38, $p < 0.081$, $\eta^2 = 0.081$] than males. The patients over 60 scored significantly higher on successful coping [F (1–312) = 9.41, $p < 0.01$, ns, $\eta^2 = 0.029$], than patients under 60. However, non-significant differences in mean score were found for self-esteem [F (1–312) = 0.31, $p = 0.58$, ns, $\eta^2 = 0.001$] = and stress [F (1–312) = 1.60, $p = 0.21$, ns, $\eta^2 = 0.005$] across age.

Discussion

The present study aimed to assess the psychometric properties of the General Health Questionnaire-12 in patients hospitalized with a diagnosis of COVID-19. Overall, our results offer support for the construct validity, criterion validity, and internal consistency of GHQ-12. Therefore, this questionnaire demonstrates its applicability in Iranian COVID-19 patients.

Among 13 theoretically and empirically emerged models of the GHQ-12 tested in this study, the current data fitted better with the three-factor model of del Pilar Sánchez-López and Dresch (2008), including successful coping, self-esteem, and stress. The factor loading of all items was adequate (Ford et al., 1986). This result is contrary to Liang et al. (2016) study that showed equal model fit (CFI = 0.98, RMSEA = 0.03) for 11 previously emerged factorial models. The unidimensional model (Goldberg et al., 1997) was not supported in our study, suggesting that GHQ-12 may not be a homogeneous tool that measures only one construct of mental health, or rather, it may cover several constructs instead of concentrating on "narrow aspects" of mental health (Gustafsson and Åberg-Bengtsson, 2010). The established factorial model manifested good reliabilities. Indeed, the overall results of the *Cronbach*'s alpha, *Theta,* and *Omega* coefficients were satisfactory, with the adequate means of inter-item correlations for subscales. These results are in line with a bulk of studies on the psychometric features of GHQ-12 in different contexts (Liang et al., 2016; Elovanio et al., 2020).

To test how accurately the GHQ-12 can correlate the expected outcomes, the criterion validity was conducted as our third objective through the relationship of GHQ with perceived stress, sleep quality, ADL/IADL, and demographic and medical variables. First, GHQ-12 total score and subscales showed significant weak to strong correlations with the sleep quality total score and all subscales, where the subscale of subjective sleep quality had the strongest correlation coefficients. These findings are supported by previous research (Xiong et al., 2019; Aquil et al., 2021; Thielmann et al., 2021). Oh et al. (2019), for instance, found that adults with higher psychological distress had higher difficulty falling asleep. Second, perceived stress showed moderate to high positive correlations with the GHQ-12 total score and three subscales, further supporting the criterion validity of GHQ-12. These findings were consistent with previous studies (Örücü and Demir, 2009; Gajula et al., 2021). It is thought that psychosocial stressors, such as living alone, social restrictions and isolation, financial burden, and loss of family members, that lead to heightened anxiety, fear, and anger, made a significant contribution to the higher level of stress

TABLE 5 The correlations of Mental Health with demographic and medical variables.

	HLP	KF	Psychiatry disorders	Hospitalization duration	Change in sleep time	Use of sleeping pills	Educational level	Family members (n)
1. Successful Coping	0.14*	0.09	0.13*	0.17**	0.10	0.24**	-0.30**	-0.12*
2. Self-esteem	0.15**	0.08	0.14*	0.10	0.29**	0.25**	-0.17**	-0.11*
3. Stress	0.06	0.09	0.17**	0.08	0.44**	0.25**	-0.08	-0.05
4. GHQ-12	0.16**	0.12*	0.18**	0.15**	0.31**	0.30**	-0.26**	-0.12*

Notes. GHQ = General health questionnaire, HLP = Hyperlipidemia, KF = Kidney failure. $^{*}p < 0.05$, $^{**}p < 0.01$.

experienced by patients with COVID-19 (Torales et al., 2020; Matalon et al., 2021; Varman et al., 2022).

The GHQ-12 in patients over 60 demonstrated negative correlations with ADL and IADL-as the third criterion variable. A similar result was found by earlier studies (Albanese et al., 2020). Our finding suggested that lack of autonomy in daily life can seriously damage a person's self-esteem, increase their conflicts with others, and make them more vulnerable to symptoms of anxiety and depression.

The forth variable used to evaluate the criterion validity of GHQ-12 was medical variables, that manifested a set of significant associations. This questionnaire had significant positive correlation with HLP, in line with the study of Wang et al. (2016) that found the GHQ-12 scores was significantly higher in patients with HLP. This association seems bidirectional, given that on the one hand, the empirical evidence suggested that HLP triggers the onset of depression (Chuang et al., 2014), and on the other hand, patients with depression experience a higher incidence of HLP, compared to the general population (Chien et al., 2013). Chang et al. (2021) also showed positive correlation of high blood fat and stress. Kidney failure was shown to be positively correlated with GHQ-12, consistent with two systematic reviews that found a high rate of depression in patients with Kidney failure (Bautovich et al., 2014; Kondo et al., 2020). One explanation for this link might be the impact of difficulties the patients with kidney failure face, such as the psychological and social burden of the disease, comorbid diseases, and the experience of dialysis, which may lead to depression/anxiety (Ozcan et al., 2015). These symptoms are, in turn, associated with negative outcomes including poor quality of life, poor treatment compliance, and elevated mortality rates (Bautovich et al., 2014; Butt et al., 2022). Furthermore, GHQ-12 was significantly correlated with psychiatry disorders. This association is expected because mental illnesses decrease the quality of life and severely impair patients' ability to communicate and form social relationships. Therefore, it is likely that they are more affected by a pandemic than those with no psychiatric conditions (Kaufman et al., 2020). GHQ-12 was positively correlated with the hospitalization duration. This is another expected result, because at hospitals, patients experience a loss of dignity as a result of their physical conditions, elevating their senses of powerlessness, embarrassment, and being violated. Consequently, these debilitating experiences may lead to mental distress (Liao et al., 2020). Finally, GHQ-12 showed positive correlations with change in sleep time and use of sleeping pills. The change in the sleep–wake cycle might be explained by a third mechanism like anxiety symptoms (Becker et al., 2018). Tang et al. (2017) suggested that higher score of GHQ-12 was strongly predicted by the reduced sleep duration and use of sleeping pills, and vice versa. They argued that extremely long or short sleep duration and excessive use of sleeping pills lead to difficulty in daytime function, which result in adverse outcomes. However, it should be noted that all of these correlations in the current study were weak to moderate and should be interpreted cautiously.

Finally, the criterion validity of GHQ-12 was examined *via* its link with demographic characteristics. GHQ-12 showed negative correlations with educational level and the number of family members. Consistent with our finding, Dalgard et al. (2007) study have shown a significant association between lower educational level and

psychological distress in both Norwegian males and female. Additionally, people who live alone may be especially dependent on others for social connection and support, making them more vulnerable to social distancing (Hendriksen et al., 2021). Hence, larger number of family members may be a protective factor against the sense of loneliness and act as a means for social support.

Due to some clues that showed the gender and age differences in the level of GHQ-12, we investigated these group mean differences to be considered in the future use of the questionnaire. In the present study, consistent with previous evidence (Giorgi et al., 2014), lower average of general health in women (higher GHQ-12 total scores and subscales) was observed. Previous evidence have shown that the prevalence of factors thought to be intensified during a pandemic (such as preceding anxiety and depression, chronic environmental exposure, and domestic violence) is higher among women (Bucciarelli et al., 2021). This could increase women's odds of developing mental health issues. As for age differences, higher level of the GHQ-12 total score and successful coping subscale in patients older than 60 years was found in the present study. This result contradicted previous findings that indicated the association of aging with an intrinsic reduction in susceptibility to psychological distress (Hoeymans et al., 2004). However, losing social contacts in the elderly (e.g., the death of family members), becoming prohibited from engagement in common social interactions due to social distancing order, and receiving limited access to social support and services may increase their susceptibility to mental health problems (Stuart et al., 2022).

Limitations, future directions, and clinical implications

The current study results provide insight into the general mental health status in patients with COVID-19. However, this study is not without limitations. First, GHQ-12 is a screening tool and was not designed for diagnosis objectives and distinguishing among mental disorders (Goldberg, 1986; Schrnitz et al., 1999). Researchers in future work can use semi-structured interviews to provide more in-depth information regarding high scored items of GHQ-12 and compare yielded scores of GHQ-12 with the additional probe questions (i.e., regarding symptom severity and duration) to evaluate the accuracy of GHQ-12. Second, the cross-sectional design of the current study has prevented causal inferences. It restricts our knowledge on the direction of the correlation of GHQ-12 with perceived stress and sleep quality. It also prevents us from measuring the stability of mental health scores over time. Longitudinal studies are recommended to explore the predictive role of the abovementioned variables on each other, and evaluate the stability of GHQ-12 scores over time. Finally, the present study did not perform the measurement invariance analyses across gender or age, because the sample sizes would start to become small when we divided the sample into age and gender subgroups. In the age case, sample size would be down to 87 for the younger segment. Such small sample sizes lacked sufficient power to detect any invariance.

Given the positive link of poor mental health with perceived stress, sleep disturbances, and impaired independent daily activities among Iranian COVID-19 patients, an important clinical implication for physicians, psychologists, and psychiatrists is to design psychological interventional courses for COVID-19 hospitalized patients that specifically target these problems. Access to such services *via* social media may be beneficial not only for their mental health, but also for their ability to improve their physical and mental functioning and independency (Shojaei and Masoumi, 2020).

Conclusion

The current study was undertaken to evaluate the psychometric properties of GHQ-12 among Iranian COVID-19 patients. The results of construct validity analyses supported the three-factor model of successful coping, self-esteem, and stress, which showed satisfactory reliability. The criterion validity of GHQ-12 was confirmed through its positive relationship with perceived stress and sleep quality, as well as its negative relationships with activities and instrumental activities of daily living in patients with over 60 years of age. Women and patients above 60 manifested higher GHQ-12 scores, compared to men and patients under 60.

Data availability statement

The raw data supporting the conclusions of this article can be provided by the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Review Board of Tehran University of Medical Sciences (ethical code: IR.TUMS.VCR.REC.1399.156). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MHA, FE, and ZV: conceptualization, design, methodology, and investigation and project administration. FF and FG: data collection. MHA: formal analysis and supervision. PSY, NAS, and MHA: writing the original draft. PSY, NW, and MHA: revising the draft. All authors have contributed to the conception and design of the study, drafted or revised this manuscript, reviewed the final version of this manuscript before submission, and agreed to be accountable for all aspects of the work.

Funding

This research was supported by grant number 99-1-101-47,395 from the Tehran University of Medical sciences.

Acknowledgments

The authors would like to thank all patients who participated in the study and the Baharloo and Ziaeian Hospitals' staff who assisted in data collection.

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/fpsyg.2023.1132154/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 June 2023
DOI 10.3389/fmed.2023.1185479

OPEN ACCESS

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RECEIVED 13 March 2023
ACCEPTED 05 June 2023
PUBLISHED 26 June 2023

CITATION
Lulic-Kuryllo T, Benedini M, Cogliati M, Cudicio A, Guarneri B, Gazzina S, Piva S, Latronico N, Orizio C and Negro F (2023) Sex-differences in the longitudinal recovery of neuromuscular function in COVID-19 associated acute respiratory distress syndrome survivors.
Front. Med. 10:1185479.
doi: 10.3389/fmed.2023.1185479

Sex-differences in the longitudinal recovery of neuromuscular function in COVID-19 associated acute respiratory distress syndrome survivors

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Introduction: Patients admitted to the intensive care unit (ICU) following severe acute respiratory syndrome 2 (SARS-CoV-2) infection may have muscle weakness up to 1 year or more following ICU discharge. However, females show greater muscle weakness than males, indicating greater neuromuscular impairment. The objective of this work was to assess sex differences in longitudinal physical functioning following ICU discharge for SARS-CoV-2 infection.

Methods: We performed longitudinal assessment of physical functioning in two groups: 14 participants (7 males, 7 females) in the 3-to-6 month and 28 participants (14 males, 14 females) in the 6-to-12 month group following ICU discharge and assessed differences between the sexes. We examined self-reported fatigue, physical functioning, compound muscle action potential (CMAP) amplitude, maximal strength, and the neural drive to the tibialis anterior muscle.

Results: We found no sex differences in the assessed parameters in the 3-to-6-month follow-up, indicating significant weakness in both sexes. Sex differences emerged in the 6-to-12-month follow-up. Specifically, females exhibited greater impairments in physical functioning, including lower strength, walking lower distances, and high neural input even 1 year following ICU-discharge.

Discussion: Females infected by SARS-CoV-2 display significant impairments in functional recovery up to 1 year following ICU discharge. The effects of sex should be considered in post-COVID neurorehabilitation.

KEYWORDS

intensive care unit, motor unit, sex differeces, neuromuscular function, COVID-19

1. Introduction

Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) has infected millions of individuals worldwide. SARS-CoV-2 infection negatively affects multiple organ systems, including the neuromuscular system (1, 2), especially in patients admitted to the intensive care unit (ICU). Patients admitted to the ICU due to SARS-CoV-2 infection present with muscle weakness for up to 1 year or more following ICU discharge (3–6), regardless of the disease severity. Sex differences in recovery of muscle function and fatigability were observed following ICU discharge in these patients. Specifically, females exhibit greater muscle weakness and fatigue up to 1 year following hospital discharge compared to males (3, 4). These findings suggest that the progression of recovery between the sexes following ICU discharge may be different, and rehabilitation protocols may need to be sex specific. The cause and mechanisms leading to greater muscle weakness in females are unclear, although muscle weakness may be a consequence of greater neuromuscular dysfunction. No studies to date have examined sex differences in neuromuscular function longitudinally following SARS-CoV-2 infection in patients discharged from the ICU. This knowledge is critical for post-COVID rehabilitation considering sex differences in disease outcome and progression were already established.

Patients infected with SARS-CoV-2 frequently present with neuromuscular dysfunction following infection. Other than muscle weakness, the neurophysiological tests commonly show low compound muscle action potential (CMAP) amplitude, polyphasic motor unit potentials, and spontaneous fibrillations (1). These findings suggest that motor unit neural control may be impaired, and only limited data are currently available (7). Since the increase in muscle force is modulated through the progressive recruitment of motor units and an increase in the motor unit firing rate, dysfunction in motor unit properties may lead to muscle weakness. Moreover, motor unit properties are different between healthy males and females in several leg muscles (8). For the tibialis anterior, a primary muscle involved in ankle dorsiflexion, healthy older females typically have lower motor unit firing rates than age-matched healthy males (9, 10), while overall leg strength is greater in males compared to females (10). Considering greater muscle weakness was demonstrated in females following ICU discharge for SARS-CoV-2 infection, it is likely that females have greater neuromuscular dysfunction than males following ICU discharge, possibly related to alteration in motor unit firing rate modulation. Furthermore, the literature lacks studies on the use of electromyographic (EMG), signal decomposition to monitor the progress of patients over time.

Therefore, the present study aimed to assess sex differences in longitudinal physical functioning following ICU discharge for SARS-CoV-2 infection. We hypothesized that females would display lower motor unit firing rates than males if no abnormalities in motor unit firing properties were present following ICU discharge. Further, we hypothesized that females would have greater muscle weakness than males post-ICU discharge. Lastly, we hypothesized that females would have lower CMAP amplitudes and greater physical impairment than males.

2. Materials and methods

2.1. Participants

This study was conducted on critically ill adult patients with confirmed SARS-CoV-2 infection admitted to the ICU at the Spedali Civili University Hospital in Brescia, Italy, from February 2020 to December 2021. All patients admitted to the ICU tested positive for SARS-CoV-2 infection on a C-reactive Protein test. The data presented in this study is part of a larger longitudinal study. The sample consisted of two groups of patients who were assessed longitudinally at either three- and six-months or six- and 12 months following ICU discharge. Specifically, seven females (64 ± 9.4 years) and seven males (64 ± 8.5 years) were assessed 3- and 6- months following ICU discharge, while 14 females (62 ± 8.8 years) and 14 males (62 ± 8.4 years) were assessed 6- and 12-months following ICU discharge. Patients were diagnosed with acute respiratory distress syndrome (ARDS) according to the Berlin criteria. Patients were invited to attend a post-ICU clinic, where the assessment was performed. Demographic information, including age, weight, and height of the participant was collected. This study was reviewed and received ethics approval from the Brescia Ethics Committee (NP3369) and conformed to the Declaration of Helsinki. Written informed consent was obtained from each participant prior to data collection.

2.2. Experimental design

Patients visited the post-ICU clinic on three occasions, where they performed several tests to examine their physical functioning, fatigue, peripheral nerve and muscle function, strength, and muscle activation. The experimental session started with an assessment of fatigue. Patients were asked to self-report activity limitations by filling out a short questionnaire that required patients to rate their fatigue level. This questionnaire provided a fatigue severity scale (FSS), with a higher score indicating greater fatigue. Following this, physical functioning was examined using the six-minute walking test (6MWT). The 6MWT is a standardized, objective assessment of physical performance, which tests both cardiopulmonary and skeletal muscle function. 6MWT was performed in accordance with the American Thoracic Society recommendations. The absolute distance walked in 6 min was measured.

Following 6MWT, patients were lying in bed, and the CMAP was used to assess the peroneal nerve function. CMAP was recorded using a novel technique with Nicolet Viking EDX (Natus Medical incorporated Middleton, WI). CMAP was obtained from the tibialis anterior muscle of the dominant leg using surface electrodes (Figure 1). The negative and positive electrodes were placed on the tibialis anterior muscle belly and distally on the tendon, respectively, with the ground electrode placed on the ankle of the same leg. The foot was strapped to a custom-made dynamometer equipped with a load cell (model SM-500 N). The knee was fully extended (180°), with the ankle in neutral position (110°) (11, 12). The common peroneal nerve was stimulated under the peroneal head with a bar electrode (BARR0026 - Spes Medica) with an interelectrode distance of 2.5 centimeters while patients remained fully relaxed. The stimulation started at 0 and automatically increased its intensity until the minimum stimulation intensity needed to elicit a maximal response

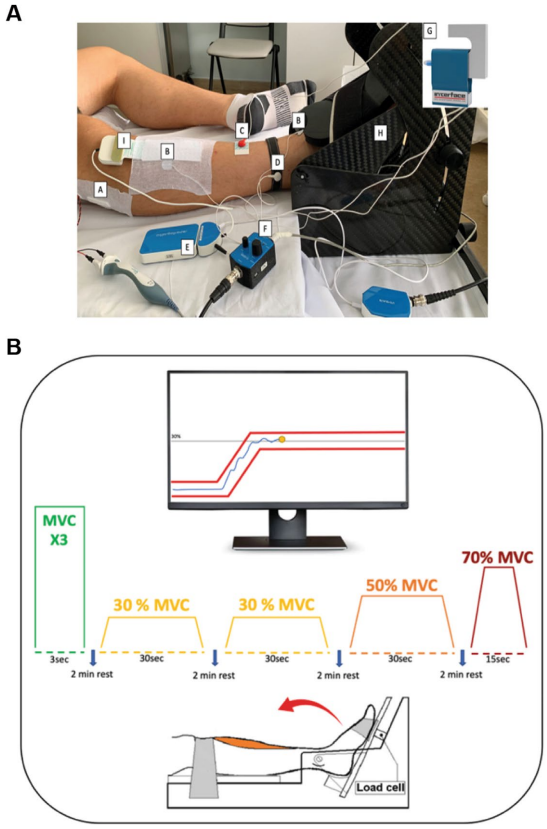

FIGURE 1
A: Protocol set-up: **(A)** Stimulator bar placed over the common peroneal nerve. **(B)** Surface electrodes for the identification of the CMAP-TA. **(C)** Stimulator ground electrode and **(D)** Ground electrode for the **(E)** EMG amplifier to prevent interference with biopotential signals. **(F)** Analog force amplifier to amplify the force signal detected by the **(G)** Load cell. The foot of the patient was strapped in a **(H)** carbon ankle-ergometer. **(I)** 64 Electrode Matrix was placed over the belly of the tibialis anterior muscle. **B**: Experimental protocol: With the help of the visual feedback, patients were asked to perform three maximal voluntary contractions (MVC) involving ankle dorsiflexion followed by submaximal trials at 30, 50 and 70% MVC. During the tasks at different MVC levels, the patients were required to keep the yellow dot between the red lines through ankle dorsiflexion.

from the tibialis anterior was identified. CMAP was defined as the action potential obtained at the maximal stimulation amplitude.

Following CMAP acquisition, patients performed maximal isometric ankle dorsiflexion with their dominant leg. Maximal voluntary contractions (MVC) were performed three times and involved maximal foot dorsiflexion with a 1.5-min rest between each trial. Each trial lasted 3 s to reach the MVC and 3 s of isometric contraction. Patients were verbally encouraged by the researchers throughout MVC performance. The peak force of three trials was used as a measure of MVC (11, 12). The load cell signals were amplified with an analog force amplifier (OT Bioelecttronica, Turin, Italy) connected to a portable bioelectrical signal amplifier (Sessantaquattro; OT Bioelettronica, Turin, Italy).

Following MVC performance, high-density surface electromyography (HD-sEMG) was applied to the tibialis anterior muscle (Figure 1). HD-sEMG signals were recorded in monopolar mode with an adhesive 64 electrodes matrix (GR08MM1305:13 rows by 5 columns, 8 mm IED; OT Bioelettronica, Turin, Italy). The matrix was placed following the guidelines of Barbero et al. (13) over the muscle belly thanks to a double-sided foam covered with conductive paste (NEURGEL250V–Spes Medica). Prior to applying the matrix, the skin was shaved and cleaned with abrasive paste (EVERI160SPE–Spes Medica) and water. Reference electrodes were positioned proximally over malleoli of the dominant leg. HD-sEMG signals were band-pass filtered (10–500 Hz), and sampled at 2000 Hz with a 16-bit A/D resolution.

Following rest, patients performed several submaximal isometric ramp-and-hold trials (Figure 1B). This task involved following a trapezoidal trajectory displayed on a computer monitor by contracting the tibialis anterior to generate torque using ankle dorsiflexion. Real-time visual feedback was provided to the patients throughout the trial. Patients performed submaximal trials at three levels: 30, 50, and 70% MVC randomly, with a 2-min rest between each trial. The 30% MVC trapezoid was repeated twice, and it was 36 s in duration, consisting of a 3-s ramp-up phase from baseline, a 30 s hold phase at 30% MVC, and a 3 s ramp-down phase. The 50% MVC trapezoid was 40 s in duration, consisting of a 5 s ramp-up phase from baseline, 30 s hold phase at 50% MVC, and a 5 s ramp-down phase. Lastly, the 70% MVC trapezoid was 29 s in duration, consisting of a 7 s ramp-up phase from baseline, 15 s hold phase at 70% MVC, and a 7 s ramp-down phase. All participants were familiarized with the experimental protocol prior to data collection.

2.3. Data analysis: motor unit decomposition

Monopolar HD-sEMG signals were decomposed into individual motor unit spike trains using a convolutive blind source separation algorithm previously validated (14). The EMG signals were band-pass filtered (3rd order Butterworth, 20–500 Hz). The decomposition outputs were inspected by highly trained operators, and erroneous discharges were corrected. Only motor units with a silhouette value greater than 0.90 were used in further analyzes (14).

2.4. Data analysis: motor unit properties

Several motor unit properties were quantified from the decomposed data. First, mean firing rates and coefficient of variation for inter-spike-intervals were quantified from the hold phase of the trapezoidal submaximal contractions. For the 30% MVC, we analyzed the motor unit properties of low-threshold motor units, while for the 50% and 70% MVC, we examined only the high-threshold motor units. Recruitment and derecruitment thresholds (%MVC) were estimated from the generated torque of the first and last firing of the identified motor units. Firing rates at recruitment and derecruitment were quantified as the average of the first and last six firings of the identified motor units.

2.5. Statistical analyzes

All statistical analyzes were performed in SPSS (IBM, version 21). Data were checked for normality using the Shapiro–Wilk test. An

independent two-sample t-test was used to assess age, weight, and height differences between groups. Most of the variables included in this study satisfied this condition. For the data that were normally distributed, a two-way repeated measures ANOVA was performed with a within-subject factor follow-up visit (Group 1: 3 and 6 months; Group 2: 6 and 12 months) and between-subject factor sex (Male, Female). Non-parametric statistical tests were used if data were not normally distributed. Specifically, to test group differences, the Mann–Whitney U test was used, while within-subject factor differences were tested using a Wilcoxon Signed Rank test. Significance was set to $p < 0.05$, and post-hoc tests were Bonferroni corrected.

2.6. Data availability

The data associated with the paper are available from the corresponding author upon request.

3. Results

Thirty-three patients were selected from a large number of subjects who took part in this study. Nine patients (4 females and 5 males) were assessed at 3-, 6- and 12- months and were allocated to both groups analyzed by the study, five patients (3 females and 2 males) were evaluated only at 3- and 6- months while 19 patients (10 females and 9 males) were evaluated at 6- and 12- months. It was not possible to assess all these patients in all three follow-ups due to the lockdown, which forcibly interrupted research activity in hospitals.

3.1. Patient demographics and physical functioning

Patient demographics and treatment details are presented in Table 1. There were no age differences between the sexes in patients assessed at 3- and 6-months (two samples t-test, $p = 0.88$) or 6- and 12-month follow-ups (two samples t-test, $p = 0.82$). There were no sex differences in the duration of hospitalization in our 3-to-6-month group ($p = 0.93$) nor 6-to-12-month group ($p = 0.41$). Similarly, no sex differences existed in the duration of mechanical ventilation in our 3-to-6-month group ($p = 0.18$) or 6-to-12-month group ($p = 0.14$). Additional data regarding corticosteroids and other drugs administered in ICU can be found in Table 1.

3.2. Fatigue

No sex differences existed in fatigue scores at 3 or 6 months (3 months: $p = 0.62$; 6 months: $p = 0.90$; Table 2), nor at 6 or 12 months (6 months: $p = 0.54$; 12 months: $p = 0.76$; Table 3). However, in 3-to-6-month follow-up group, 2 out of 7 females and 3 out of 7 males had fatigue at 3 months, while 4 out of 7 females and 2 out of 7 males had fatigue at 6 months. Further, in 6-to-12-month follow-up group, 8 out of 14 females and 4 out of 14 males had fatigue at 6 months, while 6 out of 14 females and 3 out of 14 males had fatigue at 12 months.

3.3. Physical functioning

Patients assessed at 3- and 6-month follow-ups walked a 30% greater distance at 6 months ($F1,12 = 14.2$, $p = 0.003$, $\eta p^2 = 0.5$; Table 2). No sex differences ($p = 0.17$) and no interaction effects between sex and follow-up month ($p = 0.90$) were observed in this group. Males walked a greater distance than females in the 6- to 12-month follow-up group ($F_{1,24} = 6.8$, $p = 0.01$, $\eta_p^2 = 0.22$; Table 3). No differences in follow-up month ($p = 0.55$), and no interaction between sex and follow-up month ($p = 0.98$) existed.

3.4. Maximal torque

Maximal torque produced by the patients was similar between the sexes and follow-up visits in patients assessed at 3-to-6-month

TABLE 1 Participant demographics with standard deviations.

	Group 1 (3–6 months)		Group 2 (6–12 months)	
	Female (*N*=7)	Male (*N*=7)	Female (*N*=14)	Male (*N*=14)
Age (years)	64 ± 9.4	64 ± 8.5	62 ± 8.8	62 ± 8.4
Height (cm)	163.1 ± 7	174.1 ± 9.3	161 ± 6.7	174.9 ± 8.1
Weight (kg)	84 ± 12.3	82.8 ± 13.4	77.7 ± 14.8	83.9 ± 12.3
Duration of Hospitalization Stay, days–Mean (SD)	28.7 ± 15.2	28 ± 16.1	34.1 ± 16.4	29.1 ± 15.4
Duration of ICU Stay, days–Mean (SD)	8.1 ± 5.7	9.4 ± 6.3	13.4 ± 10	9.9 ± 6.5
Intubation–*N* (%)	7 (100%)	5 (71.4%)	14 (100%)	13 (92.8%)
Duration of Intubation, days–Mean (SD)	8.4 ± 9	3.4 ± 2.7	12.4 ± 10.2	7.2 ± 5.9
ICU Catecholamine–*N* (%)	4 (57%)	1 (14.2%)	6 (42.9%)	6 (42.9%)
ICU Tocilizumab – N (%)	1 (14.2%)	0 (0%)	1 (7.1%)	3 (21.4%)
Steroids in ICU – N (%)	7 (100%)	6 (71.4%)	12 (86%)	13 (92.8%)
ECMO – N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tracheosotomy–*N*	1 (14.2%)	1 (14.2%)	4 (28.6%)	4 (28.6%)

ICU, Intensive Care Unit; ECMO, Extracorporeal Membrane Oxygenation.

follow-up ($p = 0.54$; Figure 2A). In contrast, a significant interaction existed between follow-up month and sex for patients assessed at 6-to-12-month follow-up ($F_{1,26} = 4.7$, $p = 0.03$, $\eta_p^2 = 0.15$; Figure 2B). Specifically, at 12-months males had greater maximal torque than females ($p = 0.013$), but not at 6-months ($p = 0.11$). Maximal torque did not change in females ($p = 0.059$) but increased in males ($p < 0.001$) between 6 and 12-month follow-up visits.

TABLE 2 Summary of fatigue severity scale score, six-minute walking test score, and CMAP amplitude with standard deviations for participants tested at 3- and 6-months following ICU discharge.

	3 months		6 months	
	Female	Male	Female	Male
FSS	26.7 ± 18.1	30.1 ± 17.8	32.6 ± 20.6	30.5 ± 17.2
6MWT (m)	318.5 ± 95.9	381.4 ± 128.1	420 ± 99.4	490 ± 72.8
CMAP	6.3 ± 2.2	5.6 ± 1.3	7.4 ± 1.9	6.6 ± 1.3

FSS, fatigue severity scale; 6MWT, six-minute walking test; CMAP, compound muscle action potential.

TABLE 3 Summary of fatigue severity scale score, six-minute walking test score, and CMAP amplitude with standard deviations for participants tested at 6- and 12-months following ICU discharge.

	6 months		12 months	
	Female	Male	Female	Male
FSS	35.2 ± 18	30.5 ± 18.8	31.6 ± 20.1	27 ± 19.7
6MWT (m)	418.4 ± 132.7	506.4 ± 74.99	418.5 ± 115.6	510 ± 84.8
CMAP	7.3 ± 1.8	6.8 ± 1.4	7.9 ± 2	7.2 ± 1.9

FSS, fatigue severity scale; 6MWT, six-minute walking test; CMAP, compound muscle action potential.

3.5. Compound muscle action potential amplitude

CMAP amplitude was 17% greater at 6- compared to 3-months ($F_{1,12} = 11.2$, $p = 0.006$, $\eta_p^2 = 0.48$; Table 2) and 7% greater at 12- compared to 6-months ($F_{1,26} = 5.06$, $p = 0.03$, $\eta_p^2 = 0.16$; Table 3) irrespective of the sex. No sex differences existed in CMAP amplitude in 3-to-6-month follow-up ($p = 0.41$) or 6-to-12-month follow-up group ($p = 0.42$), and no interaction effects between sex and follow-up month were observed in either group (3-to-6-month follow-up: $p = 0.76$; 6-to-12-month follow-up: $p = 0.61$).

3.6. Motor unit properties

Due to technical difficulties, we were unable to decompose HD-sEMG signals in one female at 50% MVC and 70% MVC in our 3-to-6-month group and at 70% MVC in our 6-to-12-month group. Therefore, this data and their age-matched male data were not included in the analyzes.

3.7. Number of motor units decomposed

In our 3-to-6-month group, we decomposed a total of 202 and 209 motor units in females and 279 and 302 motor units in males at 30% MVC at 3 and 6 months, respectively. At 50% MVC, we decomposed a total of 31 and 43 motor units in females and 52 and 40 motor units in males at 3 and 6 months, respectively. Lastly, at 70% MVC, we decomposed a total of 44 and 48 motor units in females and 51 and 63 motor units in males at 3 and 6 months, respectively.

In our 6-to-12-month group, we decomposed 413 and 376 motor units in females and 611 and 532 motor units in males at 30% MVC at 6 and 12 months, respectively. At 50% MVC, we decomposed a total

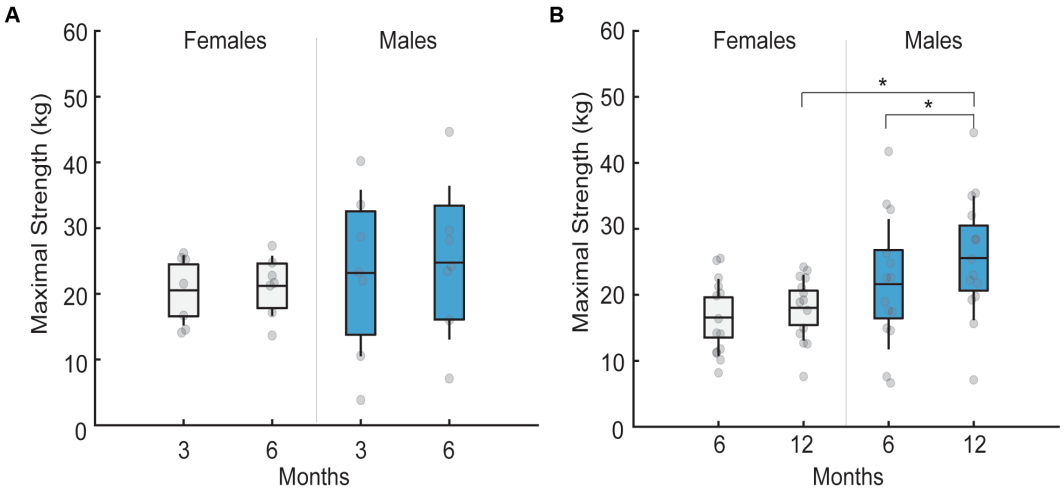

FIGURE 2
Mean maximal strength in males and females across different follow-up months. Black lines in the bar graphs denote means. Colored bars with lines denote 95% confidence intervals with standard errors. Scatter dots represent individual participant data. Brackets with stars denote significant differences between sexes or months. **(A)** Mean maximal strength for females (white) and males (blue) at 3 and 6 month follow-up. No sex differences existed across follow-up months. **(B)** Mean maximal strength for females (white) and males (blue) at 6 and 12 month follow-up. Males had greater maximal strength at 12 compared to 6 months. Males also had greater maximal strength than females at 12 months, but not at 6month follow-up.

of 86 and 101 motor units in females and 124 and 166 motor units in males at 6 and 12 months, respectively. Lastly, at 70% MVC, we decomposed a total of 91 and 86 motor units in females and 151 and 163 motor units in males at 6 and 12 months, respectively.

3.8. Mean motor unit firing rates

In 3-to-6-month follow-up, no interaction effects between sex and follow-up month were observed in mean motor unit firing rate when patients performed isometric ramp-and-hold trials at 30% MVC ($p = 0.79$; Figure 3A), 50% MVC ($p = 0.58$; Figure 3B), and 70% MVC ($p = 0.18$; Figure 3C). Further, no sex differences were observed in the mean motor unit firing rate in this group at 30% MVC ($p = 0.95$), 50% MVC ($p = 0.066$), or 70% MVC ($p = 0.18$).

An interaction effect between sex and follow-up month was observed in mean motor unit firing rates in 6-to-12-month follow-up group. Specifically, at 30% MVC, a significant month by sex interaction existed ($F_{1,26} = 4.70$, $p = 0.03$, $\eta_p^2 = 0.15$; Figure 3D). At 6-month follow-up, no sex differences in low-threshold motor unit firing rates existed ($p = 0.20$), but at a 12-month follow-up, low-threshold motor unit firing rates were 2.01 pps greater in females than males ($p < 0.001$). Further, males had 0.89 pps lower low-threshold motor unit firing rates at 12- compared to 6-months ($p = 0.006$), while low-threshold motor unit firing rates in females did not differ between the two visits ($p = 0.59$). At 50% MVC, females had greater high-threshold motor unit firing rates than males, irrespective of the follow-up month ($F_{1,26} = 9.5$, $p = 0.005$, $\eta_p^2 = 0.26$; Figure 3E). Lastly, no differences in high-threshold motor unit firing rates between follow-up months and sexes existed at 70% MVC (all $p > 0.05$; Figure 3F).

3.9. Motor unit firing rate at recruitment

No month-by-sex interaction or main effects of sex existed in our 3- to 6-month follow-up or 6- to 12-month follow-up groups in firing rate at recruitment at any submaximal task level (all $p > 0.05$).

3.10. Motor unit recruitment threshold

No month-by-sex interaction or main effects of sex existed in our 3-to-6-month follow-up group in the recruitment threshold at any submaximal task level (all $p > 0.05$). In contrast, the recruitment threshold was greater at 12- compared to 6-month follow-up irrespective of the sex at 30% MVC ($F_{1,26} = 5.6$, $p = 0.02$, $\eta_p^2 = 0.17$), 50% MVC ($F_{1,26} = 8.6$, $p = 0.007$, $\eta_p^2 = 0.24$), and 70% MVC (Mann–Whitney U: $p = 0.014$).

3.11. Motor unit derecruitment threshold

Derecruitment threshold was not different between the sexes in 3- to 6-month follow-up at 30% MVC (Mann–Whitney U: all $p > 0.05$), 50% MVC ($p = 0.47$), or 70% MVC ($p = 0.28$). Similarly, no interactions between sex and follow-up month existed in the derecruitment threshold in 6- to 12-month follow-up group at 30% MVC ($p = 0.97$), 50% MVC ($p = 0.95$), or 70% MVC ($p = 0.12$).

4. Discussion

To our knowledge, this is the first study to objectively investigate sex differences in the longitudinal effects of SARS-CoV-2 hospitalization on physical functioning and neural drive to the muscle. Our findings revealed no sex differences in physical functioning, maximal torque, fatigue, CMAP amplitude, or motor unit properties in the 3-to-6-month follow-up group. In contrast, sex differences existed in physical functioning, maximal torque, and motor unit firing characteristics but not fatigue or CMAP amplitude in our 6-to-12-month follow-up group. Our findings demonstrate that neuromuscular function is impaired in both males and females, up to 6 months following ICU-discharge for SARS-CoV-2 following which recovery at 1 year is only observed in males. Additionally, to our knowledge, this is also the first study to longitudinally evaluate changes in neural drive to muscles in a disease state.

4.1. Impairments in physical functioning

Physical impairment was present in our 3-to-6-month follow-up group in both, males and females. In healthy adults, males typically walk a greater distance than females when not corrected for height (15). However, we did not observe these differences in our data. Both, males and females, had impairments in physical functioning at 3-months following ICU discharge as their mean scores for the 6MWT fell well below the typical scores for healthy older adults (15, 16). Moreover, the 6-min walking distance at 3 months in females was lower compared to patients who had the classic ARDS (females: 318 meters vs. ARDS: ~360 meters) (17) and SARS-CoV-2 patients assessed at 3 months (382 meters) (18). These findings align with previous observations that female ARDS patients typically have lower 6MWT results (17). In contrast, male six-minute walking distance at 3 months was slightly less impaired than that of ARDS patients (males: 381 meters vs. ARDS: ~360 meters), similar to that of SARS-CoV-2 patients tested at 3-months following infection (382 meters) (18), but below those values achieved in healthy older males (healthy older males: ~690 meters) (16). These results indicate that males affected by and hospitalized for SARS-CoV-2 may be less impaired than classic ARDS patients, but still have substantial physical impairments compared to healthy older males. By 6-months, both sexes exhibit substantial increases in six-minute walking distance and have less impairment than classic ARDS patients [for reference values, see Parry et al. (17)] although the values for both sexes still fall below those of healthy older adults.

In our 6-to-12-month follow-up group, males walked a greater distance than females irrespective of the follow-up month, which aligns with what is typically observed in healthy adults (15, 16, 19). However, female results still fell below those reported in classic ARDS patients (17) and were significantly below those documented in healthy older females (16). In contrast, males showed less impairment than classic ARDS patients, but their results still fell below those observed in healthy older males. Moreover, observed sex differences in healthy older adults are typically between 30 to 62 meters (16, 19). However, in our study, this difference was ~88 meters at 6 months and 91 meters at 12 months, indicating that female recovery in physical functioning is lagging. Females admitted to the ICU usually have greater illness severity (20), which may contribute to reductions in

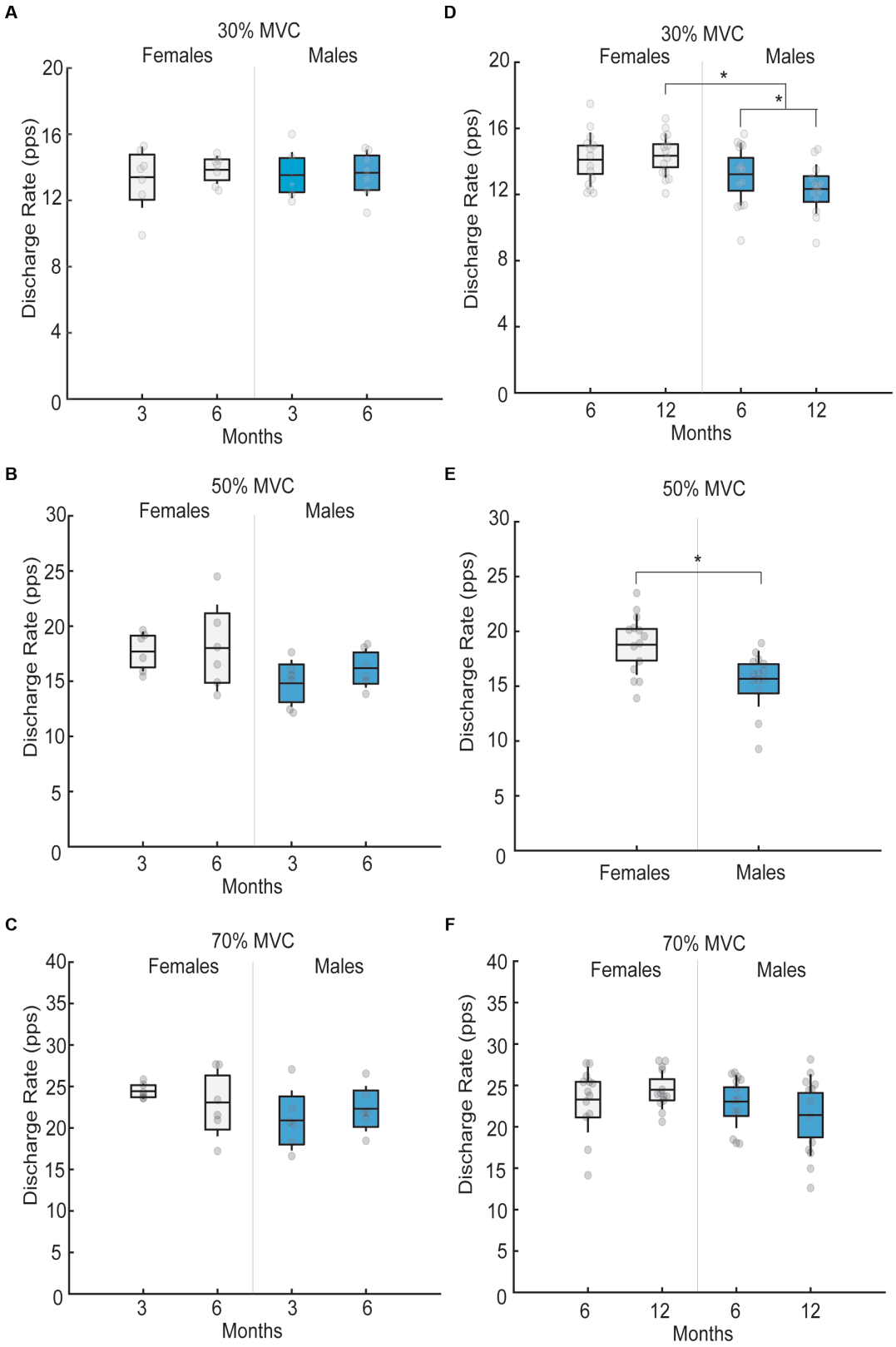

FIGURE 3
Mean motor unit firing rates in males and females across different follow-up months for 30, 50 and 70% submaximal tasks. Black lines in the bar graphs denote means. Colored bars with lines denote 95% confidence intervals with standard errors. Scatter dots represent individual participant data. Brackets with stars denote significant differences between sexes or months. **(A)** Mean motor unit firing rate for females (white) and males (blue) for 30% MVC at 3 and 6month follow-up. No differences in mean motor unit firing rates were observed across months or sex. **(B)** Mean motor unit firing rate for females (white) and males (blue) for 50% MVC at 3 and 6month follow-up. No differences in mean motor unit firing rates were observed across months or sex. **(C)** Mean motor unit firing rate for females (white) and males (blue) for 70% MVC at 3 and 6month follow-up. No differences in mean

(Continued)

FIGURE 3 (Continued)
motor unit firing rates were observed across months or sex. **(D)** Mean motor unit firing rate for females (white) and males (blue) for 30% MVC at 6 and 12 month follow-up. At 6-month follow-up, no sex differences in mean motor unit firing rates existed, but at a 12-month follow-up, mean motor unit firing rates were greater in females than males. Males also had lower mean motor unit firing rates at 12- compared to 6-months, while mean motor unit firing rates in females did not differ between the two visits. **(E)** Mean motor unit firing rate for females (white) and males (blue) for 50% MVC. Females had greater motor unit firing rates than males irrespective of the follow-up month (6 versus 12). **(F)** Mean motor unit firing rate for females (white) and males (blue) for 70% MVC at 6 and 12 month follow-up. No differences in mean motor unit firing rates were observed across months or sex.

peak exercise aerobic capacity (21). This is partly due to the deconditioning and muscular limitation. Therefore, greater impairments in the cardiopulmonary or muscular system may be the contributing factor to the impairments in physical functioning observed in females.

4.2. Strength impairments

Healthy older males have greater strength than females in ankle dorsiflexion (10). The absence of sex differences in strength in our 3-to-6-month follow-up group and at 6-months in our 6-to-12-month follow-up group indicates the presence of muscle weakness in males, although muscle weakness in females cannot be ruled out. By 12-months, sex differences in maximal strength are observed and the differences can be primarily attributed to the increase in muscle strength in males, which reaches similar values to that reported in healthy older adults (11). These findings indicate that males recover their maximal strength by 12-months following ICU-discharge. Considering that muscle strength does not change in females from 3 to 6 months nor 6 to 12 months, these data suggest that females continue to exhibit muscle weakness up to 1 year following ICU discharge. These findings support those of Huang et al. (4), which found greater muscle weakness in females 6- and 12-months post ICU-discharge compared to males. Patients requiring hospitalization and ICU stay are at greater risk of muscle atrophy, sensory-motor axonal polyneuropathy (critical illness polyneuropathy) and myopathy (22) due to pathological changes such as increased inflammation, mitochondrial dysfunction, and reduced physical activity. Females have a more than four fold greater risk of developing ICU acquired weakness during the ICU stay than males (23, 24) and thus, longitudinal muscle weakness in females may be a consequence of multiple factors including polyneuropathy, myopathy, and/or greater muscle atrophy (22, 23). Additionally, corticosteroid therapy during ICU was also shown to be associated with greater muscle weakness at 12 months (4).

4.3. Altered motor unit firing

The central nervous system controls muscle force production by modulating the number of recruited motor units and their firing rate. In healthy older adults, sex differences exist in tibialis anterior motor unit firing rates, such that females have lower motor unit firing rates than males when submaximal isometric torques are generated at minimal [25% MVC (10)] to high force levels [100% MVC (9)]. Despite this, we found no sex differences in motor unit firing rates in our 3-to-6-month follow-up group. Moreover, we found no sex differences in low-threshold motor unit firing rates at 6 months post-ICU discharge in our 6-to-12-month follow-up group. These findings indicate that patients discharged from the ICU following SARS-CoV-2 infection have impaired low-threshold motor unit firing rates up to 6 months following ICU discharge. Further, sex differences in low-threshold motor unit firing rates were present at 12-months following ICU discharge. These differences were due to a decrease in motor unit firing rate in males from 6 to 12-month follow-up. In contrast, female low-threshold motor unit firing rates remained the same across follow-up months. Moreover, we also observed greater high-threshold motor unit firing rates in females in our 6-to-12-month follow-up group, irrespective of the follow-up month. These findings indicate that motor unit firing rates in males are elevated up to 6 months following ICU discharge and decrease with recovery by 1 year. Decrease in motor unit firing rates in our patients occurred concurrently with improvements in strength, physical functioning, and CMAP amplitude in males.

These findings demonstrate that patients hospitalized for SARS-CoV-2 infection require increased neural input to optimize muscle force production in the first 6-months following ICU discharge and agree with previous observations in patients with myopathic disease (25). As the muscle recovers, there is less requirement for increased neural input to the muscle. Thus, neuromuscular system becomes more efficient at force production 1 year following ICU discharge in males, signifying neuromuscular recovery. In contrast, females do not recover in terms of physical functioning and strength, and thus, the neural input to the muscle remains high even 1 year following ICU-discharge. The exact mechanisms associated with the lack of recovery in motor unit firing rates in females are unclear but may be due to structural changes in the muscle fiber, which consequently affect motor unit firing rates. Considering that females tend to lose significantly more muscle mass than males in the ICU, it is likely that some motor unit denervation occurs as a consequence of concurrent critical illness polyneuropathy. Due to motor unit loss, motor units must fire at higher rates to produce a desired force at low force levels. Moreover, patients with myopathy commonly exhibit high motor unit firing rates (26), which may explain the current findings in females.

4.4. Lack of sex differences in CMAP amplitude, fatigue, and other motor unit characteristics

Our study demonstrates that there is a significant recovery of CMAP amplitudes at 1 year following ICU discharge for SARS-CoV-2 infection, irrespective of sex. A previous study did not find reductions in peroneal nerve CMAP amplitude in SARS-CoV-2 patients (27).

However, none of their patients required ICU treatment, and half did not require hospitalization, which may have resulted in differences between our findings and theirs. Reduced peroneal and tibial nerve CMAP amplitude in ICU admitted SARS-CoV-2 patients were documented previously in case studies (28, 29). Reduced CMAP amplitudes are observed in patients who have critical illness myopathy and critical illness polyneuropathy (30), which cannot be discounted in our patient group.

We observed no differences in fatigue scores between the sexes in either group, although a larger proportion of females reported fatigue compared to males. Fatigue is a commonly reported symptom in SARS-CoV-2 patients (31), and it is more prominent in females (32).

Lastly, we observed an increase in recruitment threshold of low and high-threshold motor units between 6- and 12-months following ICU discharge irrespective of the sex while no differences in recruitment threshold between months or sexes were observed in our 3-to-6-month follow-up group. This increase in recruitment threshold force indicates that the identified motor units were recruited later during the isometric contraction. In general, due to the bias of the surface decomposition algorithms toward higher threshold units (33, 34), it is not straightforward to link this result to an underlying neurophysiological mechanism. Probably, due to tendency to have higher MVC and, therefore, likely, higher motor unit recruitment after 6 months, the complexity of the EMG signal was increasing during the follow-up resulting in the tendency for the decomposition algorithm to identify higher threshold units.

4.5. Limitations

Our study has several limitations. First, the sample size in our 3-to-6-month follow-up group is small and should be considered when interpreting the findings. In general, females are less likely to be admitted to the ICU (20) and ARDS is more frequent in males than females (35), making the recruitment of female patients challenging. Assessment at all time points for all patients in this study was not possible due to patient's unwillingness to participate longer than 6 months or late recruitment of the patients at 6 months. Second, we did not recruit a control group for this study as the likelihood of asymptomatic SARS-CoV-2 infection is high in the general population, making it difficult to control for the lack or history of infection. Even mild SARS-CoV-2 infection was shown to negatively affect the neuromuscular system in individuals who were not hospitalized (27). We did not examine structural adaptations to the muscle, including atrophy, which may have contributed to muscle weakness.

5. Conclusion

In conclusion, we demonstrated sex differences in longitudinal neuromuscular function in patients infected with SARS-CoV-2 following ICU discharge, specifically in physical functioning, maximal strength, and motor unit firing rates. Our data demonstrated that females display significant impairments in functional recovery up to 1 year following ICU discharge for SARS-CoV-2. Therefore, the effects of sex should be considered in post-COVID neurorehabilitation.

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 Brescia Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TL-K, MB, and MC: conceptualization, methodology, investigation, formal analysis, writing original draft, writing review and editing, and visualization. AC: conceptualization, methodology, investigation, writing original draft, writing review and editing, and visualization. BG and SG: investigation, visualization, and writing review and editing. SP, NL, CO, and FN: conceptualization, methodology, writing original draft, writing review and editing, visualization. All authors contributed to the article and approved the submitted version.

Funding

The study was funded by the Italian Ministry of University and Research, project COVI19-FATIGUE, Ref. FISR 2020 COVID: FISR2020IP_01339. Marco Benedini's PhD scholarship was partially funded by Rotary Club Brescia Nord.

Acknowledgments

The authors thank doctors, nurses and collaborators of the LOng-Term Outcome (LOTO) Research Center of the Hospital Spedali Civili di Brescia for the recruitment and the follow-up visits of the patients involved in this study.

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.

Publisher's note

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frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 26 June 2023
DOI 10.3389/fpsyg.2023.1204824

OPEN ACCESS

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RECEIVED 12 April 2023
ACCEPTED 22 May 2023
PUBLISHED 26 June 2023

CITATION
Hajkova D, Sandora J, Žídková R, Malinakova K and Novak L (2023) Effects of the COVID-19 pandemic on Czech citizens: how do depression and anxiety symptoms influence cognitive, behavioral, and emotional changes? *Front. Psychol.* 14:1204824. doi: 10.3389/fpsyg.2023.1204824

Effects of the COVID-19 pandemic on Czech citizens: how do depression and anxiety symptoms influence cognitive, behavioral, and emotional changes?

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Background: This study examined the impact of anxiety and depression symptoms during the first stage of the COVID-19 pandemic on the behavioral, cognitive, and emotional changes of the Czech population.

Methods: The research sample (n = 2363; 48.83 ± 16.53 years; 50.15% men) was obtained using an online survey. Depression and anxiety symptoms were measured using the Overall Depression Severity and Impairment Scale (ODSIS) and the Overall Anxiety Severity and Impairment Scale (OASIS) and associations were adjusted for age, gender, and economic status.

Results: The results showed that increased symptoms of anxiety and depression were significantly linked to feelings of loneliness, helplessness, reduced quality of relationship with a partner, higher probabilities of alcohol abuse, food consumption, and contemplation of existential questions. Higher symptoms of anxiety were associated with feelings of being threatened. Higher symptoms of depression symptoms increased tobacco abuse.

Conclusion: During the first stage of the COVID-19 pandemic, higher symptoms of anxiety and depression among Czech citizens were associated with behavioral, cognitive, and emotional changes.

KEYWORDS

depression, anxiety, alcohol, tobacco, food consumer behavior

Introduction

During the first stage of the COVID-19 pandemic, the prevalence of depression and anxiety significantly increased worldwide (Xiong et al., 2020; Pieh et al., 2021; Fairlamb, 2022; Yu et al., 2022). The United Nations has issued a warning regarding the emergence of mental health crisis related to COVID-19 (Xiong et al., 2020). It is essential to highlight that this crisis continues to persist even after the pandemic (Ren and Guo, 2020). Several researchers have documented the deleterious impact of the pandemic on mental health, particularly in terms of the psychological distress caused by fear of infection, social isolation, and uncertainty about the future (Tudehope et al., 2022; Diotaiuti et al., 2023). For example, research conducted in China revealed a higher incidence of depression and

anxiety symptoms among the general population during the first stage of the pandemic (Wang et al., 2020). Similarly, a study in the United States reported a significant increase in the prevalence of depression and anxiety in response to the pandemic (McGinty et al., 2020). Moreover, in Italy, a country that experienced a severe outbreak of COVID-19, high levels of depression and anxiety symptoms were reported among the population (Diotaiuti et al., 2021, 2023). During the first wave of the COVID-19 pandemic, the Czech Republic was among the countries in Europe which was most influenced and a significant increase in anxiety and depressive symptoms was observed among the general population, with a prevalence of 15.5% and 12.5% (Trnka and Lorencova, 2020).

Individuals experiencing symptoms of depression and anxiety often report experiencing a range of emotional, behavioral, and cognitive changes that can significantly impact their daily lives. The first stage of the pandemic was marked by a variety of emotional changes, including feelings of fear, anger, and hopelessness (Trnka and Lorencova, 2020; Zidkova et al., 2021), which can lead to depression and anxiety symptoms. Behavioral changes related to depression and anxiety symptoms have been correlated with a higher incidence of alcohol and tobacco abuse (Clay and Parker, 2020; Xiong et al., 2020; Bountress et al., 2022). Furthermore, other studies have shown that certain individuals who have not modified their lifestyle habits during the pandemic, such as physical activity during the lockdown, may be at an elevated risk of developing emotional eating patterns or engaging in more frequent food consumption (D'Oliveira et al., 2022; Ferrara et al., 2022; Galli et al., 2022; Pak et al., 2022). Cognitive changes involving contemplation of existential questions, prayer, and matters of religion emerged among individuals during the COVID-19 pandemic (Killgore et al., 2020; Tomaszek and Muchacka-Cymerman, 2020).

Taken together, there are many pieces of research on the topic COVID-19 pandemic related to behavioral changes (Chan et al., 2021; Fu et al., 2021; Lee et al., 2021), emotional changes (Fu et al., 2021; Chen et al., 2022; Dominte et al., 2022), and cognitive changes (Thagard, 2021), but none of the research examines all three types of changes at once relating to anxiety and depression symptoms in the Czech Republic. The finding emphasizes an urgent need to scale up to more researchers in this area. This article aims to find out how the first stage of the COVID-19 pandemic manifested behavioral, emotional, and cognitive changes relating to depression and anxiety symptoms.

Methods

Participants and procedure

We collected data in two stages on a national sample of the Czech population aged between 18 and 97 years. The dataset was collected between April 2020 and June 2020. The first sample is from the first stage of COVID-19 among adults ($n = 1393$) between April 2020 and the beginning of May 2020. The second sample is also from the first stage of COVID-19 among adults ($n = 972$) from the end of May 2020 to June 2020; an online survey was used for both models. Researchers from Olomouc University Social Health Institute designed the study, and the survey was distributed by a professional agency, which also collected the data. Thanks to this process, the sample is balanced in terms of gender, age, and education and has almost representative characteristics.

The dataset from two samples included 2,365 participants, and 2 were excluded because of low-quality data (short response time and a unified pattern of responses). This led to the final sample of 2,363 participants (mean age = 48.83, SD = 16.53, 50.15% men). Participation in the survey was anonymous and voluntary. Participants were allowed to leave the study at any time without stating a reason for their decision.

Measures

Emotional changes focused on anxiety and depression symptoms were measured by questionnaires, including the Overall Anxiety Severity and Impairment Scale (OASIS) for anxiety symptoms and the Overall Depression Severity and Impairment Scale (ODSIS) for depression symptoms.

Overall anxiety severity and impairment scale

The Overall Anxiety Severity and Impairment Scale (OASIS) is a self-report questionnaire used to measure the severity and functional impact of anxiety symptoms. It consists of five items that assess the frequency, intensity, and interference of anxiety symptoms with daily life activities, such as work and social interaction. Participants chose one of five responses, ranging from 0 (never) to 4 (all time), which best illustrated their experience of the symptoms over the past week. The final score ranges from 0 to 20; higher scores mean more significant problems with anxiety. The OASIS has been shown to have good internal consistency, test–retest reliability, and convergent validity with other measures of anxiety. It is a widely used measure in both clinical and research settings for assessing anxiety symptoms severity and treatment outcome (Norman et al., 2006; Campbell-Sills et al., 2009). We used the Czech version of the abbreviated Overall Anxiety Severity and Impairment Scale (OASIS) validated by Sandora et al. (2021). The cutoff score in the Czech version of OASIS was identified as 15 (Sandora et al., 2021).

Overall depression severity and impairment scale

The Overall Depression Severity and Impairment Scale (ODSIS) is a self-reported questionnaire used to assess the severity of depression and its impact on daily functioning. The ODSIS measures both the cognitive and affective aspects of depression, including symptoms such as sadness, guilt, and hopelessness, as well as functional impairment in areas such as work, school, and relationships (Kotov et al., 2010). The questionnaire consists of nine items with responses rated on a 5-point scale. The ODSIS is a reliable and valid measure of depression severity and impairment in both clinical and non-clinical populations (Kotov et al., 2010). We used the Czech version of the abbreviated Overall Depression

Severity and Impairment Scale (ODSIS) validated by Sandora et al. (2021). The final score ranges from 0 to 20; higher scores mean more significant problems with depression. The cutoff score for the original version was defined as ≥8. Different countries, cultures, and samples of participants have other cutoff values, ranging from 5 to 12. The cutoff score in the Czech version of ODSIS was identified as 12 (Sandora et al., 2021).

Behavioral and cognitive changes

The study also measured behavioral and cognitive changes by asking participants whether there were any changes in their daily activities in various areas. These areas were measured by the question: "Has anything changed in your life in the following areas?" with possible answers: (1) "I do this activity less often", (2) "Unchanged", and (3) "I do this activity more often". The researched areas concerned the following: (1) "Thinking about existential questions", (2) "Thinking about religion", (3) "Prayer", (4) "Drinking alcohol", (5) "Eating food", (6) "Smoking or chewing tobacco", (7) "Shopping for new things", and others. Participants were asked to choose from three possible responses: doing the activity less often, unchanged, or more often. The responses were later dichotomized into two groups for further analysis: "less often/unchanged" and "more often". The full list of areas and their corresponding responses can be found in Table 4. This method provided insight into how individuals coped with the pandemic and any associated stressors in the first stage of COVID-19.

Statistical analysis

First, we determined the sociodemographic characteristics of the background characteristics of the sample and examined the data distribution using Mardia's test of skewness and kurtosis, which suggested slight heteroscedasticity. Our data were not normally distributed. As a result, we used Spearman rank correlation and non-parametric group comparison tests to explore relationships between variables of interest. The effect size for the non-parametric group comparison was monitored by the Dunn and Gamas–Howell tests. Furthermore, we used the Bonferroni correction.

Second, we assessed the association of anxiety and depression in COVID-19 pandemic-related changes in emotions and relationships using two logistic regression models,

TABLE 1 Sociodemographic results of the two samples.

Variable	Sample 1	Sample 2	OASIS differences	ODSIS differences
Gender				
1. Male	483 (50%)	702 (50%)		
2. Female	487 (50%)	691 (50%)		
Family status				
1. No relationship	496 (51%)	476 (34%)		
2. In the relationship	474 (49%)	917 (66%)		
Education				
1. Elementary school	86 (8.9%)	113 (8.1%)		
2. Secondary vocational school	367 (38%)	636 (46%)		
3. Secondary school with graduation	354 (37%)	467 (34%)		
4. College/University	124 (13%)	177 (13%)		
Economic status				
1. Employed/Entrepreneur	526 (54.4%)	754 (54%)		
2. In household/without work	88 (9.1%)	114 (8.9%)		
3. Pensioner	300 (31%)	438 (31%)	5 > 4 ($p = 0.008$, Â = 0.35)	5 > 4 ($p = 0.010$, Â = 0.35)
4. Student	52 (5.4%)	77 (5.5%)	5 > 6 ($p = 0.008$, Â = 0.36)	5 > 6 ($p = 0.011$, Â = 0.36)
Religiosity				
1. Convinced atheist		179 (13%)	1 < 4 ($p = 0.014$; Â = 0.4), 1 < 3 ($p = 0.031$; Â =0.57),	
2. Non-believer		731 (52%)	3 > 2 ($p = 0.001$, Â = 0.43)	3 > 2 ($p = 0.006$, Â = 0.42)
3. Believer outside the church		362 (26%)	5 > 6 ($p = 0.002$, Â = 0.4)	
4. Believer, member of the church		121 (8.7%)		

A, Vargha and Delaney's A effect size, sociodemographic differences among more than two groups were calculated using the Dunn test, and two group comparison was conducted using the Wilcoxon rank-sum test; r, Wilcoxon rank-sum test effect size; HSPS.T, Highly Sensitive Person Scale–total score; AES, esthetic sensitivity subscale; EOE, ease of excitation subscale.

TABLE 2 Relationship (in odds ratios) between anxiety symptoms and the COVID-19 pandemic-related changes in emotions and relationships.

			Deterioration						
	Relationship with the partner	Relationship with the children	Rel. with others in the household	Loneliness	Feelings of threat	Fear and anxiety	Helplessness	Hope	Day structure
Crude	1.17*** [1.11, 1.23]	1.12*** [1.05, 1.19]	1.11*** [1.04, 1.18]	1.18*** [1.14, 1.22]	1.18*** [1.15, 1.22]	1.29*** [1.25, 1.34]	1.22*** [1.18, 1.27]	1.16*** [1.12, 1.21]	1.05*** [1.02, 1.08]
Adjusted	1.19*** [1.13, 1.25]	1.11*** [1.05, 1.18]	1.13*** [1.07, 1.20]	1.20*** [1.16, 1.24]	1.18*** [1.14, 1.21]	1.30*** [1.25, 1.35]	1.23*** [1.19, 1.27]	1.17*** [1.12, 1.22]	1.06*** [1.03, 1.09]

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The adjusted effect was calculated using the following variables as covariates: age, gender, socioeconomic status, education, religiosity, and neuroticism. After the Bonferroni correction, only results with $p < 0.001$ remained significant (except the adjusted effect on food consumption). Values in brackets refer to the 95% confidence interval of odds ratios.

TABLE 3 Relationship (in odds ratios) between depression symptoms and the COVID-19 pandemic-related changes in emotions and relationships.

			Deterioration						
	Relationship with the partner	Relationship with the children	Rel. with others in the household	Loneliness	Feelings of threat	Fear and anxiety	Helplessness	Hope	Day structure
Crude	1.16*** [1.10, 1.22]	1.12*** [1.06, 1.19]	1.11*** [1.05, 1.17]	1.18*** [1.14, 1.22]	1.18*** [1.15, 1.22]	1.29*** [1.25, 1.34]	1.22*** [1.18, 1.27]	1.16*** [1.12, 1.21]	1.05*** [1.02, 1.08]
Adjusted	1.18*** [1.12, 1.23]	1.12*** [1.06, 1.19]	1.13*** [1.07, 1.20]	1.20*** [1.16, 1.24]	1.18*** [1.14, 1.21]	1.30*** [1.25, 1.35]	1.23*** [1.19, 1.27]	1.17*** [1.12, 1.22]	1.06*** [1.03, 1.09]

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The adjusted effect was calculated using the following variables as covariates: age, gender, socioeconomic status, education, religiosity, and neuroticism. After the Bonferroni correction, only results with $p < 0.001$ remained significant (except the adjusted effect on food consumption). Values in brackets refer to the 95% confidence interval of odds ratios.

10.3389/fpsyg.2023.1204824

one for anxiety (measured by OASIS) and the second for depression (measured by ODSIS) adjusted for gender, age, and socioeconomic status. Each independent variable was assessed in a separate model.

In the same way, we assessed the associations of behavioral and cognitive changes related to the COVID-19 pandemic with OASIS and ODSIS using a binary logistic model.

Results

The sociodemographic characteristics of the sample are presented in Table 1. The sample of 2363 (mean age = 48.83, SD = 16.53, 50.15% men) was relatively balanced in terms of gender. Higher anxiety measured by OASIS was observed in students than in employed/entrepreneurs and pensioners. Higher anxiety was also noted in religious participants than in non-religious participants. Furthermore, atheists were found to have a significantly lower level of anxiety than religious participants. Higher depression measured by ODSIS was also observed in students than in employed/entrepreneurs and pensioners. Higher depression was also reported in participants who were religious but not members of a church than non-religious.

In Table 2, logistic regression indicated that with increasing depression (measured by OASIS) during the current COVID-19 pandemic, there was a general decline in the quality of relationships, especially in relationships with a partner, by 16.82% ($p < 0.001$). A significant association between the deterioration of emotions during the COVID-19 pandemic and OASIS has also been found: with one-unit increase in the OASIS score, the probability of relapse of loneliness increased by 18.1%, threat by 18.15%, and helplessness by 22.38%.

Similar associations were found in ODSIS in Table 3: a one-unit increase in the ODSIS score was associated with a higher probability of deterioration of relationship quality with a partner by 15.89%, a higher probability of relapse of loneliness by 16.77%, and helplessness by 17.95%. These results are adjusted for age, gender, and economic status.

Behavioral and cognitive changes related to the COVID-19 pandemic were significantly associated with OASIS and ODSIS. Specifically, a one-unit increase in the OASIS score resulted in a higher probability of alcohol drinking by 7.84% and increased food consumption by 8.27%. ODSIS was associated with an even higher number of health-linked behaviors: with an increasing score on ODSIS, the probability of more frequent food consumption increased by 7.77%, alcohol drinking by 7.67%, and smoking or chewing tobacco by 8.64%. These results are adjusted for age, gender, and economic status in Table 4.

Discussion

This study is the first attempt to investigate the impact of anxiety and depression symptoms on the behavioral, cognitive, and emotional changes experienced by the Czech population during the first stage of the COVID-19 pandemic. Our findings reveal that negative emotions such as loneliness and helplessness were significantly associated with higher levels of anxiety and depression symptoms. Furthermore, perceiving a sense of threat was related to increased levels of anxiety symptoms. We also found that the deterioration of a relationship with a partner was linked to higher levels of anxiety and depression symptoms. Additionally, we discovered that levels of anxiety and depression were significantly related to a greater probability of alcohol abuse and heightened food consumption. Moreover, individuals with higher levels of depression symptoms were also more likely to engage in smoking or chewing tobacco. Interestingly, we observed that individuals with higher levels of depression symptoms were more likely to engage in prayer and contemplate existential questions related to religion.

We found that individuals with depression and anxiety symptoms experienced emotional changes such as feelings of loneliness and helplessness, while those with just anxiety symptoms reported a sense of threat. These emotional changes due to COVID-19 occurred all over the world (Wang et al., 2020; Xiong et al., 2020), for example, research conducted in Spain found that the lockdown had significant emotional changes for individuals with depression and anxiety symptoms and stress, which were observed in 20% to 30% of participants. Psychological stress was found in 47.5% of participants (Odriozola-González et al., 2022). The restriction of physical activity and disruption of daily routines may have disrupted people's ability to cope with stressors, further exacerbating symptoms of depression and anxiety. For instance, findings from Italy have demonstrated the effectiveness of a 4-week-based physical exercise protocol for older people in social isolation in improving psychological variables such as anxiety, mood, depression, and stress. This intervention proved to help reduce anxiety and depression symptoms (D'Oliveira et al., 2022). Predictors of physical activity are autonomous motivation and intention. The direct effect of autonomous motivation on physical activity is stronger in participants with low anxiety (Galli et al., 2022). Furthermore, we found out that feeling threatened is linked to anxiety symptoms. Individuals with anxiety tend to experience a heightened sense of threat, which may manifest as a preoccupation with potential danger and an exaggerated fear response. The pandemic situation in the first stage of COVID-19 triggered anxiety symptoms much more than fear (Coelho et al., 2020). In contrast, individuals with depression symptoms may be too exhausted or demotivated to perceive threats in their environment.

According to our study, individuals who suffer from both symptoms of anxiety and depression are prone to alcohol abuse and higher food consumption. The Czech Republic ranks among Europe's nations with the highest alcohol consumption (Svačinová et al., 2022). There is a significant association between perceived stress and changes in alcohol consumption (Tudehope et al., 2022) and also a relationship between reward sensitivity and coping in determining alcohol use (Feil and Hasking, 2008). In the context of our research, increased alcohol consumption associated with anxiety and depression symptoms probably occurred precisely because of overwhelming stress in the first stage of COVID-19, high isolation, and forced public avoidance. However, alcohol was not the only avoidance strategy. For instance, a study conducted on Italian adolescents during the first COVID-19 lockdown found that impulsivity and depressive brooding were predictive factors for

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TABLE 4 Associations of behavioral and cognitive changes related to the COVID-19 pandemic and their relationship with anxiety and depression.

	OR OASIS	OR OASIS na	OR ODSIS	OR ODSIS na
Thinking about existential questions	1.13*** [1.09, 1.16]	1.12*** [1.09, 1.16]	1.10*** [1.07, 1.13]	1.10*** [1.07, 1.13]
Thinking about religion	1.10*** [1.04, 1.16]	1.11*** [1.05, 1.16]	1.10*** [1.04, 1.15]	1.10*** [1.05, 1.15]
Prayer	1.09*** [1.04, 1.15]	1.10*** [1.05, 1.15]	1.09*** [1.04, 1.14]	1.09*** [1.04, 1.14]
Smoking or chewing tobacco	1.07** [1.02, 1.12]	1.08*** [1.04, 1.13]	1.09*** [1.04, 1.13]	1.11*** [1.06, 1.15]
Alcohol drinking	1.08*** [1.03, 1.13]	1.10*** [1.06, 1.15]	1.08*** [1.03, 1.12]	1.11*** [1.06, 1.15]
Buying new things	1.05 [0.98, 1.11]	1.07* [1.01, 1.14]	1.03 [0.97, 1.09]	1.06 [1.00, 1.12]
Food consumption	1.08*** [1.05, 1.12]	1.11*** [1.07, 1.14]	1.08*** [1.04, 1.11]	1.10*** [1.07, 1.14]
Sex	1.01 [0.96, 1.06]	1.04 [0.99, 1.09]	1.02 [0.97, 1.07]	1.06* [1.01, 1.10]
Physical activity	0.98 [0.94, 1.01]	1.00 [0.97, 1.04]	0.99 [0.95, 1.02]	1.01 [0.98, 1.05]
Reading	1.02 [0.99, 1.05]	1.03* [1.00, 1.06]	1.01 [0.98, 1.04]	1.02 [0.99, 1.05]
Self-education	1.01 [0.97, 1.05]	1.03 [0.99, 1.07]	1.00 [0.96, 1.04]	1.02 [0.99, 1.06]
Work	1.02 [0.99, 1.06]	1.04* [1.00, 1.08]	1.01 [0.98, 1.05]	1.03 [1.00, 1.07]
Calls	1.03* [1.00, 1.06]	1.04** [1.02, 1.07]	1.02 [0.99, 1.05]	1.02 [1.00, 1.05]
Other forms of online communication	1.06*** [1.03, 1.09]	1.08*** [1.05, 1.11]	1.04** [1.02, 1.07]	1.06*** [1.04, 1.09]

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. OR, adjusted odds ratios for age, gender, and economical status; na, non-adjusted odds ratios. Only results with $p < 0.001$ survived Bonferroni correction, values in squared brackets refer to the 95% confidence interval of odds ratios.

internet addiction, with 28% of participants in the full dependency range and 34.7% demonstrating internet abuse behavior (Diotaiuti et al., 2022). Higher food consumption has been suggested as another potential underlying mechanism of coronavirus-related stress and may be utilized as a coping strategy for emotional regulation (Wang et al., 2020). Conversely, those individuals who maintain a balanced, positive mindset and focused on the past and future were found to be less likely to exhibit symptoms of food addiction (Bracale and Vaccaro, 2020; Borisenkov et al., n.d.).

Additionally, we found that individuals with depression symptoms tend to make behavioral changes toward tobacco abuse. This result is consistent with previous research that has demonstrated a positive association between depression and smoking (Rigotti et al., 2021; Chen et al., 2022). Our study contributes to the growing body of evidence that suggests a potential link between coping strategies for individuals with depression symptoms and behavior changes in tobacco abuse.

Finally, the study showed cognitive changes such as interest in more frequent prayer, thinking about religion, and existential questions. It is interesting because the Czech Republic is one of the most atheist countries in the Christian world (Furstova et al., 2021). The global outbreak of COVID-19 has set new challenges for every human being, and it can be compared to a profound existential crisis or a traumatic experience (Tomaszek and Muchacka-Cymerman, 2020). The experience of existential anxiety during the pandemic has led many individuals to become more cognizant of their mortality and to increase their frequency of prayer (Killgore et al., 2020; Tomaszek and Muchacka-Cymerman, 2020). People's sources of meaning in life help to achieve psychological adaptation (Chen et al., 2022). Further research findings suggest that heightened existential questions may be a neglected factor in increasing depression during the pandemic (Fairlamb, 2022). Our findings of cognitive changes can be challenging for the atheist state of the Czech Republic.

We found that symptoms of depression and anxiety contributed to the deterioration of relationships with a partner during the first stage of the COVID-19 pandemic. Behavioral, emotional, and cognitive changes may have led to more conflicts and decreased communication between partners.

Limitations and strengths

While our study provides valuable insights, it is important to acknowledge its limitations. First, the data collection was conducted during the COVID-19 pandemic, which could have affected the number of responses and the willingness of participants to take part in the study, potentially influencing the results. Second, the use of self-reported measures and short questionnaires may introduce information bias, as participants' responses can be influenced by their current mood.

The study has several important strengths; the most essential is the large study sample of Czech adults during the first stage of COVID-19, which at the time of the survey was the worst-affected country in Europe and the third-worst affected country in the world. It is the first research that examined behavioral, emotional, and cognitive changes related to depression and anxiety during this period in the Czech Republic. The model was close to the

nationally representative sample because of its characteristics. It was well-balanced regarding the gender and age of the respondents. Moreover, the data used in the study were cross-sectional. The study showed the situation during the first stage of COVID-19 in the Czech environment.

Implications of the study

Our study reveals that the initial phase of the COVID-19 pandemic had a profound impact on the Czech population, as evidenced by a surge in emotional, cognitive, and behavioral changes due to symptoms of depression and anxiety. Higher symptoms of depression and anxiety were associated with behavioral changes such as higher levels of food consumption, alcohol abuse, and the deterioration of relationships with a partner. In addition, our findings indicate that symptoms of depression were significantly linked to tobacco abuse. Notably, the pandemic also brought about cognitive changes, with an increased interest in prayer, religion, and existential questions. All these changes pose new challenges for the Czech citizenry.

These findings show a greater need for primary and selective mental health prevention focused on healthy stress-coping strategies related to depression and anxiety instead of alcohol abuse, tobacco abuse, and increased food consumption. One option provides prevention programs on positive stress-coping strategies and self-care.

Future studies can focus more on cognitive, behavioral, and emotional changes after COVID-19 related to anxiety and depression symptoms to find out how the situation continues in the Czech Republic.

Conclusion

During the first stage of COVID-19 and the subsequent implementation of restrictive measures such as lockdowns, symptoms of depression and anxiety increased among residents of the Czech Republic. These symptoms were associated with various emotional, behavioral, and cognitive changes. Individuals with depression and anxiety symptoms experienced emotional changes, such as feelings of hopelessness and loneliness, while those with anxiety symptoms reported a heightened sense of threat. Behaviorally, individuals with depression and anxiety symptoms exhibited higher levels of alcohol consumption and increased food intake, leading to strain in their relationships with partners. Conversely, those with depressive symptoms alone exhibited tobacco abuse. Cognitively, participants reported an increased interest in existential questions, faith, and prayer, which is noteworthy given the Czech Republic's status as one of the most atheistic countries in the world.

Considering the great influence that symptoms of depression and anxiety appeared to have on Czech citizens' behavioral, emotional, and cognitive changes, the primary and selective mental health prevention focus on healthy stress-coping strategies among people to achieve common goals should be promoted and supported.

To decrease the impact of the pandemic, individuals must take personal responsibility for detecting early symptoms of depression and anxiety and addressing them with positive coping strategies, thus affecting emotional, behavioral, and cognitive changes. To encourage individuals to take responsibility, an effective and accessible tool is necessary to help them detect symptoms, such as the short questionnaires OASIS and ODSIS.

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 Ethics Committee of the Faculty of Theology of Palacky University in Olomouc, Czech Republic (No. 2020/06). 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

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

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.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Clinical Trial
PUBLISHED 11 July 2023
DOI 10.3389/fmed.2023.1219222

OPEN ACCESS

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RECEIVED 08 May 2023
ACCEPTED 29 June 2023
PUBLISHED 11 July 2023

CITATION
Chi W, Pang P, Luo Z, Liu X, Cai W, Li W and Hao J (2023) Risk factors for hypoxaemia following hip fracture surgery in elderly patients who recovered from COVID-19: a multicentre retrospective study.
Front. Med. 10:1219222.
doi: 10.3389/fmed.2023.1219222

Risk factors for hypoxaemia following hip fracture surgery in elderly patients who recovered from COVID-19: a multicentre retrospective study

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Objectives: To explore the risk factors associated with postoperative hypoxaemia in elderly patients who have recovered from coronavirus disease (COVID-19) and underwent hip fracture surgery in the short term.

Design: Multicentre retrospective study.

Setting: The study was performed in three first 3A-grade hospitals in China.

Participants: A sequential sampling method was applied to select study participants. Medical records of 392 patients aged ≥65 years who had recovered from COVID-19 and underwent hip fracture surgery at three hospitals in China between 1 November, 2022, and 15 February, 2023, were reviewed.

Interventions: Patients were assigned to hypoxaemia or non-hypoxaemia groups, according to whether hypoxaemia occurred after surgery. Univariate and multivariate logistic regression analyses were used to identify independent risk factors for postoperative hypoxaemia.

Results: The incidence of postoperative hypoxaemia was 38.01%. Statistically significant differences were found between the two groups in terms of age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, presence of expectoration symptoms, preoperative hypoxaemia, chronic obstructive pulmonary disease, pulmonary inflammation, time between recovery from COVID-19 and surgery, anaesthetic mode, surgical procedure, intraoperative blood loss, intraoperative infusion, duration of surgery, and length of hospital stay ($p < 0.05$). Furthermore, patients with BMI ≥28.0 kg/m^2, expectoration symptoms, presence of preoperative hypoxaemia, ASA classification III, time between recovery from COVID-19 and surgery ≤2 weeks, and general anaesthesia were potential risk factors for postoperative hypoxaemia.

Conclusion: Obesity, expectoration symptoms, preoperative hypoxaemia, ASA classification III, time between recovery from COVID-19 and surgery ≤2 weeks, and general anaesthesia were potential risk factors for postoperative hypoxaemia in elderly patients who recovered from COVID-19 and underwent hip fracture surgery in the short term.

KEYWORDS

COVID-19, hypoxia, hip fractures, aged, risk

1. Introduction

Currently, the global coronavirus disease (COVID-19) pandemic is ongoing (1). However, compared to the early days of the pandemic, most patients with COVID-19 exhibit mild symptoms and recover after 2 weeks. The effect of COVID-19 on perioperative management remains a major concern (2). Research has shown that patients with COVID-19 are at a higher risk of postoperative respiratory failure (3–5). Despite a growing body of literature on COVID-19, there is limited research on identifying perioperative risk factors in recently recovered patients who undergo surgery in a short term, especially, in elderly patients with multiple comorbidities; these patients are at a higher risk of perioperative complications.

Hip fractures are a common occurrence in elderly patients, and surgical intervention is often required. With the aging of the Chinese population, the number of patients undergoing hip fracture surgery is increasing (6, 7). Postoperative hypoxaemia is common in patients with hip fractures and is associated with prolonged hospital stays, high costs, and increased mortality (8). At present, research on postoperative hypoxaemia in elderly patients with hip fracture mainly focuses on patients with or without COVID-19, and research on postoperative hypoxaemia in elderly patients with hip fracture who have recovered from COVID-19 is lacking (9, 10). We hypothesized that factors such as basic characteristics of patients, COVID-19-related sequelae, and changes in blood indicators would affect the development of postoperative hypoxaemia in elderly patients who have recovered from COVID-19 and underwent hip fracture surgery. To test this hypothesis, we conducted a multicentre retrospective study to collect and analyse the relevant risk factors associated with postoperative hypoxaemia in elderly patients who have recovered from COVID-19 and underwent hip fracture surgery in the short term.

2. Materials and methods

2.1. Design, sample, and criteria for participation

This study was approved by our institutional review board. In this retrospective study, only medical records and case information were analysed, no patients were directly involved in setting the research questions or the outcome measures, and patient information was anonymized; therefore, written inform consent was waived by ethic committee.

This multicentre retrospective study included 392 patients who underwent hip fracture surgery at three hospitals (HongHui Hospital, Xi'an JiaoTong University, Xi'an, Shaanxi Province; Binzhou Medical College Affiliated Hospital, Binzhou, Shandong Province; and Linfen Hospital Affiliated to Shanxi Medical University, Linfen, Shanxi Province) in China between 1 November, 2022, and 10 February, 2023.

The sample size was determined based on the following assumptions. According to a previous study in Shanghai, China (9), we used a sample proportion of 30.23, 95% confidence interval, and margin of error of 0.05. The sample size was calculated using the following formula:

$$N = z^2 p(1-p)/d^2 n$$
$$= (1.96)^2 \times (0.3023)(1-0.3023)/(0.05)^2 = 325.$$

where, n = sample size; p = 30.23% of proportion; $q = 1-p$; d = desired degree of precision; and Z = the standard normal value at 95% confidence level. Considering a non-response rate of 5%, we increased the sample size to 342: $n = (325+17) = 342$. To obtain more convincing results, we further expanded the sample size by 50, for a total of 392 samples.

Inclusion criteria were as follows: (1) patients aged ≥65 years who recovered from COVID-19 after formal treatment; and (2) patients who had fractures of the femoral neck or intertrochanteric fracture within 3 months after recovery from COVID-19 and were scheduled for total hip replacement (THR), hemiarthroplasty (HA), or proximal femoral nail antirotation (PFNA). The exclusion criteria were as follows: (1) combined injuries and multiple fractures; (2) pathological fractures; (3) space-occupying lesions in the lungs; (4) liver and kidney insufficiency before COVID-19 diagnosis; and (5) patients with incomplete clinical data. The selection process is illustrated in Figure 1.

2.2. Data collection

Data were collected using a structured checklist adapted from different studies (9, 11, 12). The tool was prepared in English, and data were extracted through a review of patients' medical charts by trained data collectors. The data extracted included age, sex, height, weight, symptoms including cough, expectoration, chest tightness, and hypoxaemia; American Society of Anesthesiologists (ASA) classification; comorbidities including hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease (COPD), stroke, smoking status, chest computed tomography (CT) scans, time between recovery from COVID-19 and surgery, time from admission to surgery, fracture site (fracture of femoral neck or intertrochanteric fracture), surgical procedure (THR, HA, and PFNA), anaesthetic mode (general anaesthesia or intraspinal anaesthesia), intraoperative variables including blood loss, infusion, and duration of surgical time; length of hospital stay; and laboratory parameters including leukocytes, neutrophils, lymphocytes, haemoglobin, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, urea, creatinine, and lactic dehydrogenase. To ensure data quality, chart review was done on 5% (n = 20) of the study population to test the checklist's structure and completeness, and essential modifications were made at HongHui Hospital, Xi'an JiaoTong University. Preoperative hypoxaemia was defined as an arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio of ≤300. Postoperative hypoxaemia was defined as a pulse oxygen saturation <94% on room air (13–15). Patients were sequentially assigned to hypoxaemia or non-hypoxaemia groups, according to whether hypoxaemia occurred after surgery. Chest-CT scans were used to determine the presence of pulmonary inflammation (Figure 2).

Abbreviations: ASA, American Society of Anesthesiologists; BMI, Body Mass Index; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus Disease; CT, Computed Tomography; HA, Hemiarthroplasty; ICU, Intensive Care Unit; OR, Odds Ratio; PFNA, Proximal Femoral Nail Antirotation; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus; SD, Standard Deviation; THR, Total Hip Replacement.

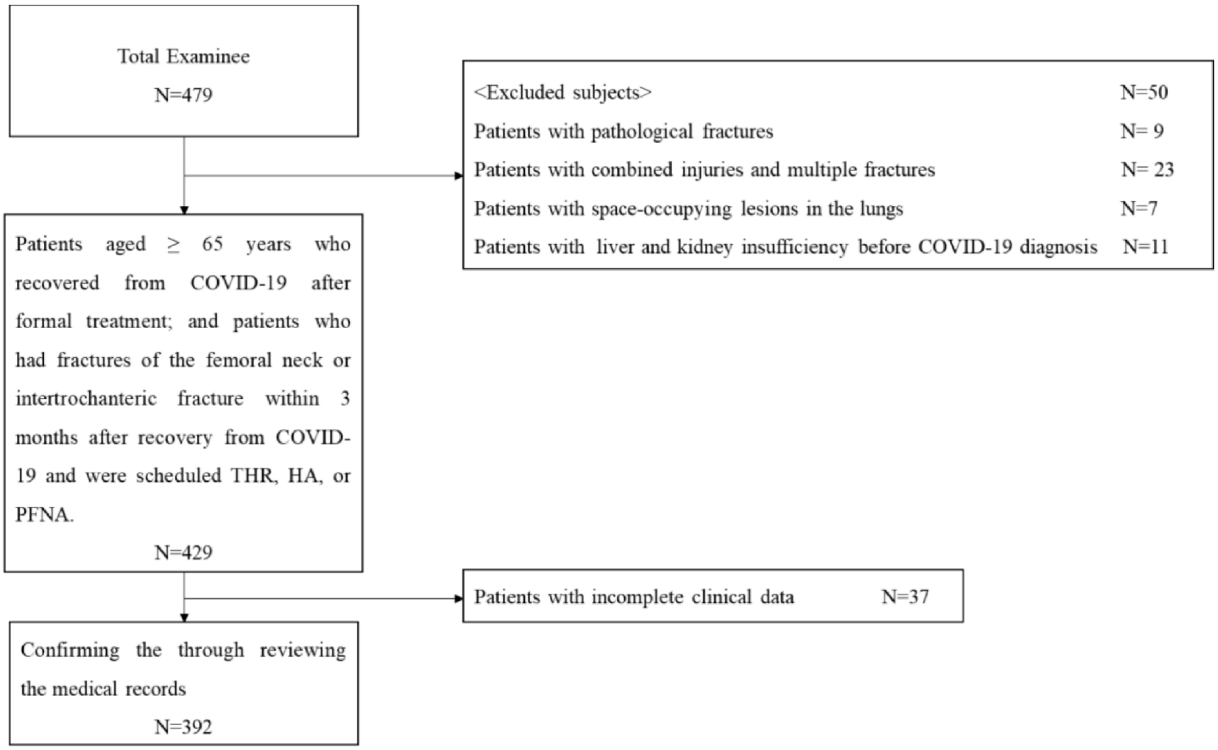

FIGURE 1
Process of selecting the study subjects.

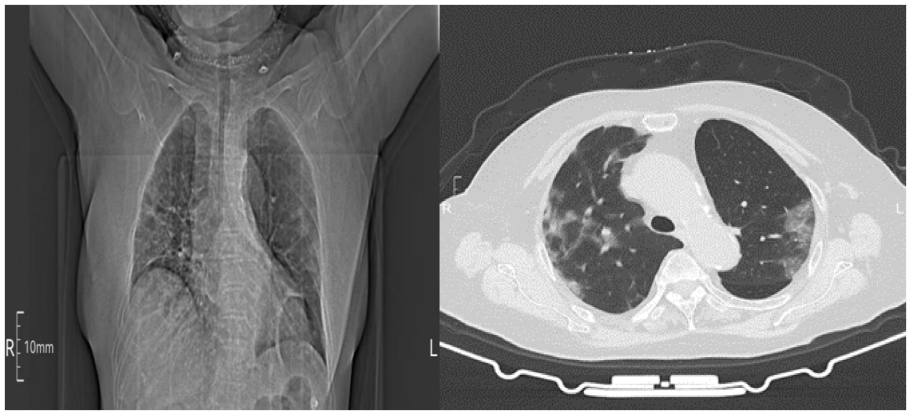

FIGURE 2
Chest computed tomography (CT) indicated non-regional ground-glass opacities in the lungs and infiltrative shadows.

2.3. Statistical analysis

All data were analysed using SPSS® for Windows (version 18; SPSS Inc., Chicago, IL, United States). The measurement data of clinical indices are expressed as the mean ± standard deviation (SD) and analysed using independent sample *t*-tests or the Wilcoxon rank-sum test. Count data are expressed as numbers (percentages) and analysed using either the chi-square test or Fisher's exact test, depending on the sample size and distribution of data. Factors with a $p < 0.05$ in the univariate analysis were selected for logistic multivariate regression analysis. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patients' demographic, clinical, and laboratory characteristics

A total of 392 patients were included, including 301 (76.78%) women and 91 (23.22%) men, with an average age of 79.32 years (SD, 7.97; range, 65–95) and an average body mass index (BMI) of 23.43 kg/m^2 (SD, 3.59; range, 14.17–39.52). Of the 392 patients, 208 had femoral neck fractures, and 184 had intertrochanteric fractures.

Regarding symptoms, 18.62% experienced cough, 7.90% expectoration, 6.12% chest tightness, and 15.56% hypoxaemia. Among 392 patients, 17.09% experienced pulmonary inflammation (Table 1). A high proportion of patients experienced cough, expectoration, hypoxaemia, and pulmonary inflammation within 2 weeks of recovery from COVID-19 (Figure 3).

Regarding laboratory parameters for the 392 patients, leukocytes count, neutrophil count, glutamic-pyruvic transaminase level, glutamic-oxaloacetic transaminase level, blood urea level, serum creatinine level, and lactic dehydrogenase level were above the upper limit of normal in 5.35%, 2.80%, 3.06%, 5.61%, 5.86%, 7.65%, and 7.90% of patients, respectively. The lymphocyte count was below the lower limit of normal in 10.96% of the patients.

3.2. Incidence of postoperative hypoxaemia

The incidence of postoperative hypoxaemia was 38.01% (Table 1). Of all postoperative hypoxaemia cases, 92.62% (138 of 149) presented with an oxygen saturation of 85%–93% on room air; these patients returned to the ward after surgery for supplemental oxygen therapy, and 7.38% (11 of 149) presented with an oxygen saturation of <85% on room air. After surgery, all patients were administered general anaesthesia, kept intubated with an endotracheal tube, and were subsequently admitted to the intensive care unit (ICU) for further treatment. In the ICU, one patient died on postoperative day 17 due to respiratory failure. In the ward, one patient without postoperative hypoxaemia died on postoperative day 2, likely due to pulmonary embolism. All the other patients recovered and were discharged.

3.3. Risk factors for postoperative hypoxaemia

Based on age, patients were divided into three groups: (1) 65 years ≤ age ≤ 74 years, (2) 75 years ≤ age ≤ 4 years, and (3) age ≥85 years. The average time between recovery from COVID-19 and surgery was 4.04 weeks (SD, 0.46; range, 1.00–11.00; median, 4.00). Therefore, patients were divided into three groups according to the time between recovery from COVID-19 and surgery: (1) ≤2 weeks, (2) >2 weeks and ≤4 weeks, and (3) >4 weeks. Statistically significant differences were found in terms of age, BMI, ASA classification, time between recovery from COVID-19 and surgery, surgical procedure, and anaesthetic mode between patients with and without postoperative hypoxaemia ($p < 0.05$). Patients with postoperative hypoxaemia had a higher prevalence of expectoration (12.75% vs. 4.93%, $p = 0.011$), preoperative hypoxaemia (32.21% vs. 5.34%, $p < 0.001$), COPD (18.79% vs. 12.34%, $p = 0.048$), and pulmonary inflammation (26.84% vs. 11.11%, $p = 0.011$) than those without postoperative hypoxaemia (Table 1).

No statistically significant differences were found in sex, cough, chest tightness, hypertension, diabetes, coronary heart disease, stroke, smoking status, time from admission to surgery, fracture site, or laboratory parameters ($p > 0.05$) (Tables 1, 2).

Moreover, patients with postoperative hypoxaemia exhibited a lower amount of bleeding (271.80 ± 42.55 vs. 314.80 ± 37.95, $p = 0.031$), fluid infusion volume (1690.70 ± 249.60 vs. 1909.50 ± 245.80, $p = 0.012$) and duration of surgical time (74.65 ± 3.84 vs. 94.52 ± 3.63, $p = 0.044$) than patients without postoperative hypoxaemia. Patients with postoperative hypoxaemia had a longer hospital stay (11.32 ± 1.14 vs. 8.56 ± 2.87, $p = 0.011$) than patients without postoperative hypoxaemia (Table 1).

3.4. Multivariate analysis of risk factors for postoperative hypoxaemia

Multivariate analysis showed that a BMI ≥ 28.0 kg/m^2 [odds ratio (OR) = 1.501, 95% confidence interval (CI) 1.098–3.421, $p = 0.012$], expectoration symptoms (OR = 1.345, 95% CI 1.127–2.908, $p = 0.001$), preoperative hypoxaemia (OR = 2.345, 95% CI 1.442–3.815, $p < 0.001$), ASA classification III (OR = 1.434, 95% CI 1.023–2.010, $p = 0.037$), time between recovery from COVID-19 and surgery ≤2 weeks (OR = 1.695, 95% CI 1.319–2.817, $p = 0.001$), and general anaesthesia (OR = 2.516, 95% CI 1.902–3.897, $p = 0.018$) were independent risk factors for postoperative hypoxaemia (Table 3).

4. Discussion

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) mainly invades respiratory epithelial cells, and patients infected with SARS-CoV-2 can develop an inflammatory response and acute lung injury (16). The symptomatic phase manifests as fever, cough, myalgia, and severe respiratory failure (17). Changes in laboratory parameters include decreased lymphocyte count, increased neutrophil and leukocyte counts, and elevated glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, creatinine, and lactic dehydrogenase level (18). Chest CT scans show non-regional ground-glass opacities in the lungs and infiltrative shadows (19). In this study, we found that a certain proportion of elderly patients who had recovered from COVID-19 within 3 months experienced persistent respiratory symptoms, including cough, expectoration, chest tightness, hypoxaemia, abnormal laboratory parameters, and chest CT scan changes, which is consistent with the results of Taquet et al. (20) and Cares-Marambio et al. (21). Taquet et al. (20) reported that, among COVID-19 survivors, 7.90% still exhibited abnormal breathing symptoms and serological indicator changes in the 1 to 180-day period after SARS-CoV-2 infection. Cares-Marambio et al. (21) reported that fatigue, breathlessness, chest pain, and cough were the most common respiratory symptoms of COVID-19 survivors between 3 weeks and 3 months after hospital discharge. However, it is worth noting that respiratory symptoms, such as cough, expectoration, chest tightness, hypoxaemia, and serological indicator changes are not specific to COVID-19 (22). Some patients may develop upper respiratory tract infection and systemic inflammatory response caused by other viruses after recovery from COVID-19 and discharge, which can also cause the above respiratory symptoms and serological changes, leading to an overestimation of the incidence of COVID-19 sequelae.

4.1. Incidence of postoperative hypoxaemia

In elderly patients who recovered from COVID-19 and underwent hip fracture surgery in the short term, the incidence

TABLE 1 Demographic and clinical characteristics of the patients.

Variables	Hypoxaemia	Non-hypoxaemia	Overall	*p*
Number	149 (38.01)	243	392	
Age (years)				<0.001*
65–74	31 (20.81)	88 (36.21)	119 (30.36)	
75–84	52 (34.90)	109 (44.86)	161 (41.07)	
≥85	66 (44.29)	46 (18.93)	112 (28.57)	
Sex				0.055
Women	99 (66.44)	202 (83.13)	301 (76.78)	
Men	50 (33.56)	41 (16.87)	91 (23.22)	
BMI (kg/m^2)				0.022*
18.5–23.9	59 (39.60)	136 (55.97)	195 (49.74)	
<18.5	17 (11.41)	21 (8.64)	38 (9.69)	
24.0–27.9	49 (32.89)	72 (29.63)	121 (30.88)	
≥28.0	24 (16.10)	14 (5.76)	38 (9.69)	
Symptoms				
Cough	21 (14.09)	52 (21.39)	73 (18.62)	0.431
Expectoration	19 (12.75)	12 (4.93)	31 (7.90)	0.011*
Chest tightness	11 (7.38)	13 (5.34)	24 (6.12)	0.227
Hypoxaemia	48 (32.21)	13 (5.34)	61 (15.56)	<0.001*
ASA classification				<0.001*
I	18 (12.08)	52 (21.40)	70 (17.86)	
II	43 (28.86)	76 (31.28)	119 (30.36)	
III	88 (59.06)	115 (47.32)	203 (51.78)	
Comorbidities				
Hypertension	31 (20.80)	48 (19.75)	79 (20.15)	0.802
Diabetes	30 (20.13)	54 (22.22)	84 (21.42)	0.501
Coronary heart disease	33 (22.14)	60 (24.69)	93 (23.72)	0.683
Stroke	22 (14.76)	31 (12.75)	53 (13.52)	0.241
COPD	28 (18.79)	30 (12.34)	58 (14.79)	0.048*
Smoking status	16 (10.73.)	28 (11.52)	44 (11.22)	0.148
Pulmonary inflammation	40 (26.84)	27 (11.11)	67 (17.09)	0.011*
Time between recovery from COVID-19 and surgery (weeks)				<0.001*
≤2	47 (31.54)	30 (12.35)	77 (19.64)	
2–4	31 (20.81)	57 (23.46)	88 (22.45)	
>4	71 (47.65)	156 (64.19)	227 (57.91)	
Time from admission to surgery (hours)	39.81 ± 3.78	41.49 ± 4.58	40.73 ± 5.08	0.725
Fracture site				0.071
Fracture of femoral neck	74 (49.66)	134 (55.14)	208 (53.06)	
Intertrochanteric fracture	75 (50.34)	109 (44.86)	184 (46.94)	
Surgical procedure				<0.001*
THR	23 (15.44)	59 (24.28)	82 (20.92)	
HA	85 (57.05)	124 (51.03)	209 (53.32)	
PFNA	41 (27.51)	60 (24.69)	101 (25.76)	
Anesthetic mode				
General anesthesia	96 (64.43)	105 (43.21)	201 (51.28)	<0.001*
Intraspinal anesthesia	53 (35.57)	138 (56.79)	191 (48.72)	
Variables of intra-operation				
Blood loss (mL)	271.80 ± 42.55	314.80 ± 37.95	301 ± 33.91	0.031*
Infusion (mL)	1690.70 ± 249.60	1909.50 ± 245.80	1879 ± 225.31	0.012*
Duration of surgical time (min)	74.65 ± 3.84	87.52 ± 3.63	82.79 ± 2.41	0.044*
Length of hospital stay, days	11.32 ± 1.14	8.56 ± 2.87	10.71 ± 1.97	0.011*

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; COVID-19, novel coronavirus disease 2019; THR, total hip replacement; HA, hemiarthroplasty; PFNA, proximal femoral nail antirotation. *$p < 0.05$.

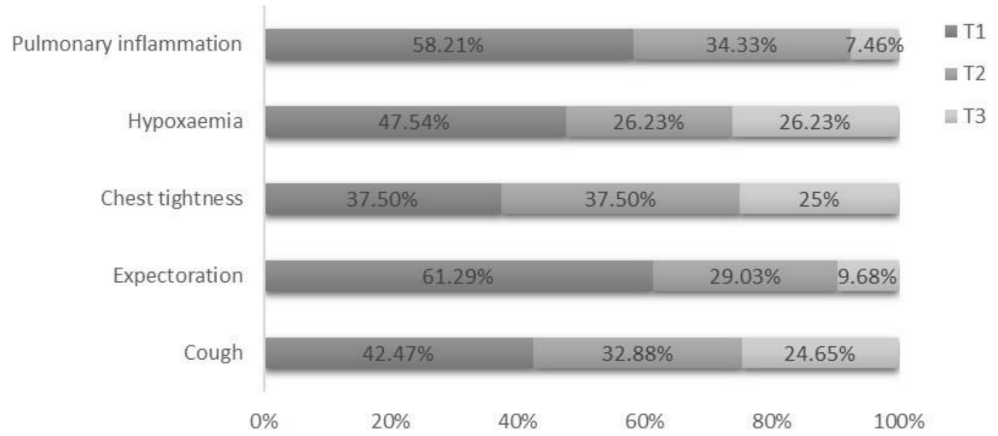

FIGURE 3
Proportion of patients experiencing cough, expectoration, chest tightness, hypoxaemia, and pulmonary inflammation at different time intervals. T1: time between recovery from COVID-19 and surgery ≤2 weeks; T2: 2 weeks < time between recovery from COVID-19 and surgery ≤4 weeks; T3: time between recovery from COVID-19 and surgery >4 weeks.

TABLE 2 Laboratory parameters of the patients.

	Normal range	Mean ± SD (min, max)		Overall (*N* = 392)	*p*
		Hypoxemia (*N* = 149)	Non-hypoxemia (*N* = 243)		
Leucocytes, $\times10^9$ /L	3.5–9.5	5.81 ± 2.44 (2.51–11.17)	5.93 ± 2.12 (2.67–12.11)	5.88 ± 1.99 (2.51–12.11)	0.210
Neutrophils, $\times10^9$ /L	2–7.7	4.52 ± 2.75 (1.62–12.93)	4.77 ± 2.34 (1.69–11.99)	4.60 ± 2.21 (1.62–12.93)	0.334
Lymphocytes, $\times10^9$ /L	0.80–4.00	0.95 ± 0.55 (0.26–2.27)	0.91 ± 0.33 (0.30–2.16)	0.93 ± 0.39 (0.26–2.27)	0.679
Hemoglobin, g/L	130–175	116.24 ± 12.05 (91–131)	121.01 ± 9.79 (90–147)	119.17 ± 9.98 (90–147)	0.553
Glutamic-pyruvic transaminase, U/L	9–50	26.65 ± 15.98 (8.6–56.4)	27.23 ± 14.76 (9.1–55.9)	27.00 ± 13.99 (8.6–56.4)	0.578
Glutamic-oxalacetic transaminase, U/L	15–40	33.43 ± 24.80 (12.1–94)	32.98 ± 23.16 (12.5–101)	33.17 ± 21.58 (12.1–101)	0.467
Blood urea, mmol/L	3.1–8.0	6.84 ± 4.60 (3.4–18.7)	7.11 ± 4.44 (4.0–15.6)	6.99 ± 3.09 (3.4–18.7)	0.456
Serum creatinine, umol/L	57–97	82.83 ± 23.18 (45.8–136.9)	71.01 ± 24.81 (39.9–141.8)	77.80 ± 15.46 (39.9–141.8)	0.337
Lactic dehydrogenase, U/L	120–250	219.56 ± 34.71 (131–392)	227.34 ± 28.57 (108–338)	222.07 ± 41.21 (108–392)	0.462

of postoperative hypoxaemia was 38.01%, which was higher than the incidence of 30.23% reported in previous studies among non-infected patients and lower than the incidence of 50.00% among patients with COVID-19 (9, 10). In addition, of all postoperative hypoxaemia cases, 92.62% only required mask oxygen inhalation after surgery and 7.38% required mechanical ventilation. Of all the subjects in this study, one patient died due to respiratory failure, one patient died due to pulmonary embolism, and all other patients recovered and were discharged. The mortality rate in this study was much lower than that in previous reports among patients with COVID-19. A study by Catellani et al. (23) reported 13 COVID-positive patients with proximal femoral fractures who underwent surgery in northern Italy, of whom 4 (30.8%) died within 1 week after surgery. Another study by Maniscalco et al. (24), conducted in Italy, reported a mortality rate of 43.8% (14/32) within 21 days after surgery in COVID-positive hip fracture patients. This suggests that elderly patients with hip fractures who have recovered from COVID-19 may have temporarily increased oxygen demands postoperatively, but can safely undergo early surgical intervention after appropriate medical optimisation.

4.2. Risk factors for postoperative hypoxaemia

Several studies have shown that obesity is an independent risk factor for postoperative hypoxaemia. Labaste et al. (25) reported that BMI >30 kg/m^2 was an independent risk factor for hypoxaemia during transfers to PACU in all postoperative patients. Aizawa et al. (26) found that obesity was associated with increased risk of postoperative hypoxaemia, as well as prolonged intubation time and ICU length of stay. In this study, we also found that obesity was an independent risk factor for postoperative hypoxaemia in elderly patients who recovered from COVID-19 and underwent hip fracture surgery. There are two main theories to explain this result: first, in patients with obesity, the decrease in lung compliance is evident, and the work of breathing and respiratory resistance is increased (27); second, obesity is often accompanied by several complications, including obstructive sleep apnoea and hypopnea syndrome, which are related to hypoxia (28).

The incidence of preoperative hypoxaemia is high in patients with hip fracture (13.8–23.8%), and can persist throughout the perioperative period (11, 29). Lung lesions, post-traumatic pulmonary micro thromboembolism, fat embolism syndrome, and

TABLE 3 Multivariate logistic regression analysis for risk factors associated with postoperative hypoxaemia.

Risk factors	Adjusted odds ratio (95%CI)	*p*
BMI (kg/m^2)		
18.5–23.9	1.0 (reference)	
<18.5	1.718 (0.699–4.223)	0.239
24.0–27.9	1.260 (0.565–5.279)	0.437
≥28.0	1.501 (1.098–3.421)	0.012*
Expectoration symptoms	1.345 (1.127–2.908)	0.001*
Preoperative hypoxaemia	2.335 (1.442–3.815)	<0.001*
ASA classification		
I	1.0 (reference)	
II	1.021 (0.655–1.991)	0.079
III	1.434 (1.023–2.010)	0.037*
Time between recovery from COVID-19 and surgery (weeks)		
>4	1.0 (reference)	
2–4	1.776 (0.472–1.977)	0.218
≤2	1.695 (1.319–2.817)	0.001*
Anesthetic mode		
Intraspinal anesthesia	1.0 (reference)	
General anesthesia	2.516 (1.902–3.897)	0.018*

BMI, body mass index; ASA, American Society of Anesthesiologists; COVID-19, novel coronavirus disease 2019. *$p < 0.05$.

damage-associated molecular patterns may contribute to preoperative hypoxaemia (11). In this study, we found that preoperative hypoxaemia was an independent risk factor for postoperative hypoxaemia, which was consistent with the findings of Luna et al. (30). In their study, preoperative hypoxaemia significantly increased the risk of postoperative hypoxaemic events during the first week in patients undergoing joint replacement.

ASA classification system is designed to provide perioperative clinicians with a simple classification of patient physiological status to help predict surgical risk (31). It is used to evaluate the tolerance of elderly patients to anaesthesia before surgery and to accurately predict postoperative cardiopulmonary events (32). In this study, we found that ASA classification III was an independent risk factor for postoperative hypoxaemia. Luna et al. (30) reported that ASA classification had a significant correlation not only with the occurrence of postoperative hypoxemia but also with the occurrence of hypoxemia after discharge.

We also found that general anaesthesia was an independent risk factor for postoperative hypoxaemia, which may be related to postoperative pain, opioid administration, and postoperative muscular strength. A study has shown that for hip surgery, compared with general anaesthesia, patients who received intrathecal anaesthesia had lower pain scores at all evaluated time points and required less postoperative oral morphine (33). Postoperative pain was associated with postoperative hypoxaemia. Compared to patients with severe pain, patients with mild and no pain were 82% and 88% less likely to experience postoperative hypoxaemia, respectively (34). Peripheral tissue oxygen saturation was reduced in response to pain, which may account for the association between severe pain and hypoxemia (35). In addition, general anaesthesia requires muscle relaxants and more opioids than intrathecal anaesthesia. Previous studies have shown that opioids are highly correlated with postoperative hypoxaemia, which is related to the respiratory depression effect of opioids, and that residual neuromuscular blockade is an independent risk factor for critical respiratory events in the PACU (36).

In addition to the above independent risk factors, we found that expectoration symptoms and a time between recovery from COVID-19 and surgery ≤2 weeks were risk factors for postoperative hypoxaemia in elderly patients who recovered from COVID-19 and underwent hip fracture surgery in the short term. Expectoration symptoms can cause hypoxia in patients by blocking the respiratory tract with viscous mucus and sputum (37). In particular, sputum increase during mechanical ventilation under general anaesthesia can further cause airway obstruction (38). Therefore, sputum aspiration should be performed in patients with more sputum during the operation. Moreover, some studies have suggested that the use of a humidifier may be effective if a patient exhibits viscous sputum (39). Lateral position ventilation combined with vibration sputum drainage is more effective in promoting expectoration and improving respiratory function (40). Wirén et al. (41) reported that patients with respiratory disease symptoms had an increased risk of hypoxaemia following surgery. In our study, we found that a high proportion of patients experienced cough, expectoration, hypoxaemia, and pulmonary inflammation within 2 weeks after recovery from COVID-19. This resulted in a higher incidence of postoperative hypoxaemia in elderly patients who have recovered from COVID-19 and underwent hip fracture surgery within 2 weeks.

Univariate analysis showed significant differences in age, COPD, pulmonary inflammation, and surgical procedures between patients with and without postoperative hypoxaemia. However, the logistic multivariate analysis showed that they were not independent risk factors for postoperative hypoxaemia. This may be related to the ASA classification and preoperative hypoxaemia. Patients with advanced age and multiple comorbidities, had a higher ASA classification (42). Unlike THR, HA and

PFNA are typically used in elderly and infirm patients with a higher ASA classification (43, 44). Patients with COPD and pulmonary inflammation have a higher risk of developing preoperative hypoxaemia (45).

In addition, we found that patients with postoperative hypoxaemia had a lower amount of bleeding, fluid infusion volume, and duration of surgery than those without postoperative hypoxaemia. This was because a higher proportion of patients in the non-hypoxaemia group underwent THA than those in the hypoxaemia group. Compared with hemiarthroplasty, total HA is complicated, takes a long time, has a large amount of blood loss, and requires a large amount of fluid infusion (46).

Based on the analysis of the above risk factors, we suggest that, it is not advisable to reduce the risk of postoperative hypoxaemia by completely improving respiratory symptoms or by postponing surgery. Research shows that surgical treatment should be performed within the first 24 h, beyond which the odds of perioperative complications increase, and there is a significant increase in mortality when surgery is delayed for more than 48 h (47). Second, in the absence of contraindications, spinal anaesthesia should be administered. General anaesthesia is a risk factor for postoperative hypoxaemia, and all patients who experience severe postoperative hypoxemia received general anaesthesia. Third, for patients who must be administered general anaesthesia, pulmonary function exercise, vibration sputum excretion, and atomisation inhalation can be used to improve pulmonary function, and supplemental oxygen therapy was administered immediately after the operation.

4.3. Limitations of this study

This study has two limitations. First, postoperative hypoxaemia was defined as a pulse oxygen saturation of <94% on room air. A variety of factors can interfere with the accuracy of pulse oxygen saturation detection, such as finger cuff displacement, cold fingertip skin, abnormal fingertip skin or colour, and monitoring limb blood oxygen disorders, resulting in low pulse oxygen saturation readings (48). Second, no patients underwent regional block anaesthesia in the study sample. Studies have shown that lumbar plexus block anaesthesia has less impact on circulation and breathing than general anaesthesia and spinal anaesthesia in patients with hip fractures (49–51). Lumbar plexus block anaesthesia may provide greater benefits for older patients who have recently recovered from COVID-19 and undergone hip fracture surgery.

5. Conclusion

A certain proportion of elderly patients who recovered from COVID-19 within 3 months still exhibited persistent respiratory symptoms, abnormal laboratory parameters, and chest CT scan changes. In these patients, the incidence of hypoxaemia after hip fracture surgery was 38.01%. Obesity, expectoration symptoms, preoperative hypoxaemia, ASA classification III, time between recovery from COVID-19 and surgery ≤2 weeks, and general anaesthesia were potential risk factors for postoperative hypoxaemia. Our findings suggest that elderly patients with hip fractures who recovered from COVID-19 may have temporarily increased oxygen demands postoperatively but can safely undergo early surgical intervention after appropriate medical optimisation.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the datasets used and analysed during the current study are available from the corresponding author on reasonable request. Requests to access these datasets should be directed to JH, haojianhong722@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Coard of HongHui Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JH, WC, and ZL conceived and designed the study, and helped to draft and revise the manuscript. PP, WL, and XL performed data collection. WBC helped to analyse the data and conduct the analysis software. All authors contributed to the article and approved the submitted version.

Funding

This work was funded by the Key Research and Development Project of Shaanxi Province (No. 2023-YBSF-069) and Xi'an Innovation Capability Strengthening Foundation Program (22YXYJ0019).

Acknowledgments

All the authors of the manuscript are immensely grateful to their respective universities and hospitals for their technical assistance and valuable support in the completion of this research project.

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.

Publisher's note

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