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On the cusp of the silent wave of the long COVID pandemic: why, what and how should we tackle this emerging syndrome in the clinic and population?

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On the cusp of the silent wave of the long COVID pandemic: why, what and how should we tackle this emerging syndrome in the clinic and population?

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Editorial: On the cusp of the silent wave of the long COVID pandemic: why, what and how should we tackle this emerging syndrome in the clinic and population?

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Editorial on the Research Topic
On the cusp of the silent wave of the long COVID pandemic: why, what and how should we tackle this emerging syndrome in the clinic and population?

1 Context

There is an urgent public health problem due to the rising number of individuals who remain with their health and daily functions impaired for months and even years after a SARS-CoV-2 infection (1). This impairment is encapsulated by a new medical condition known as post COVID-19 syndrome, post-acute COVID-19 syndrome, post-acute sequelae of SARS-CoV-2 infection, and persistent post-COVID-19 syndrome. The general public knows this condition as long COVID (LC), a coined termed by patients at the beginning of the pandemic (1).

Individuals with LC report experiencing many symptoms, including fatigue, post-exertional malaise (PEM), and sleep disturbances (2). Coincidently, these specific symptoms are the heart of the most consensual case definitions of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), a "older" disease often triggered by an infection (e.g., infectious mononucleosis) and also causing high levels of physical and mental distress (3). It is then no surprise that individuals with LC can also receive an ME/CFS diagnosis (4, 5). This diagnostic overlap is the main reason for the growing interest in understanding the medical relationship between LC and ME/CFS in order to accelerate the development of efficacious pharmacological and non-pharmacological interventions for the benefit of the patients (6–8).

The present Research Topic aimed then at gathering new data on the public health and medicine of LC and ME/CFS. The Research Topic compiled 11 papers of which nine were original research. Seven papers concerned LC directly or indirectly. The remaining four papers focused on ME/CFS specifically or together with LC. Below the reader can find a brief account of the research conducted.

2 Contributions to current knowledge on the public health impact of LC

Four large-scale studies on LC surveyed more than 1,000 individuals. These studies evaluated different health-related metrics after a SARS-CoV-2 infection using retrospective data or convenient cross-sectional surveys.

From the United States of America, Sandoval et al. reported a retrospective study on 91,007 adult patients from Southeast Texas. The study aimed at evaluating the chance of hospital readmission after a SARS-CoV-2 infection. The main finding is that 21% of the individuals were readmitted to the hospital within 90 days after infection. The chance of hospital admission seemed to be dependent on different factors, including a dose-response relationship with area deprivation index.

From 16 countries in Latin America, with the special focus on Ecuador, Mexico, Argentina, Colombia, Peru, and Chile, Angarita-Fonseca et al. estimated the prevalence of individuals with LC using an online survey of 2,466 people. In this survey, 1,178 individuals (47.8%) reported experiencing symptoms after 3 months of a SARS-CoV-2 infection. This survey also suggested several risk factors for LC, including a COVID-19 episode earlier in the pandemic, old age, no vaccination against SARS-CoV-2, and a high number of pre-existing co-morbidities.

From Brazil, Malheiro et al. conducted a telephone-based survey in the city of São Paulo on 291 hospitalized and 1,118 non-hospitalized patients with COVID-19. The study also aimed at estimating the prevalence of LC at least 3 months after infection and to determine the respective risk factors. The study estimated the LC prevalence at 47.1 and 49.5% for these two populations, respectively. These estimates were in almost perfect agreement with the ones reported by Angarita-Fonseca et al.. Again, pre-existing co-morbidities such as hypertension are possible risk factors for LC manifestations.

From Italy, Gagliotti et al. estimated the incidence and determined the factors affecting the access to specific healthcare services up to a year after the acute phase of a SARS-CoV-2 infection. The study was conducted in a large number of healthy individuals ($n = 35{,}128$ and 88,881 from Emilia-Romagna and Veneto, respectively). This study found that more than 20% of the surveyed individuals accessed a health service, mostly outpatient care more than drug prescription as follow-up of their SARS-CoV-2 infection. Whether this access was a direct cause of LC specifically remained an open question from this study.

The three remaining studies on LC contemplated a moderate number of surveyed individuals. From Castellón in Spain, Pérez Catalán et al. provided evidence that the quality of life of 486 Spanish patients tended to remain affected after 1 year of their COVID-19-related hospitalization. This particular study was already criticized due to its reliance on telephone interviews (9). From Vancouver in Canada, Magel et al. followed up 88 patients previously hospitalized due to COVID-19 complications. This study focused on how the levels of fatigue evolved over time. The study that 67% ($n = 58$) of individuals experienced fatigue at 3 months post-infection, but this percentage dropped to 60% ($n = 47$) after 6 months. The same drop was observed in patients experiencing substantial fatigue (16–6% after 3 and 6 months after infection, respectively). Accordingly to other studies published in this Research Topic, the study also provided evidence for a positive association between the number of pre-existing comorbidities and fatigue. From Bari in Italy, Resta et al. reported the single study conducted in a clinical setting. The study focused post-COVID exertion dyspnoea in 318 patients at 3 months after SARS-CoV-2 infection. In this study, the study participants performed a 6-min walking test after which 59.7% showed evidence of dyspnoea. This finding showed that exertion dyspnea might be part of the PEM spectrum in LC.

3 Research on ME/CFS with possible implications to LC

Four papers concentrated their attention on ME/CFS with possible implications to LC. For example, the new study of Hannestad et al. provided evidence for an increase of IgG antibodies against human adenovirus after a SARS-CoV-2 infection in a Swedish cohort of patients with ME/CFS. This finding suggested that a SARS-CoV-2 infection could prompt the reactivation of the human adenovirus. Such a reactivation might explain the worsening of symptoms in some patients with ME/CFS after a SARS-CoV-2 infection, as suggested elsewhere (10). Another example is the perspective paper of Scheibenbogen et al. who compiled and discussed a list of candidate drugs that could treat both ME/CFS and LC patients. This perspective paper also provided an important concept for developing clinical trial networks in this era of LC and ME/CFS. In turn, Grabowska et al. discussed the concept of extending current large-scale prevalence studies of LC to ME/CFS, a disease whose incidence and prevalence remain largely elusive (11). According to these authors, estimating ME/CFS prevalence comes at a minimal cost in such studies, but requires the recognition of PEM as one of the cardinal symptoms for ME/CFS diagnosis. The recognition of PEM in medical care is also important, as demonstrated by a new study of Wormgoor and Rodenburg on a cohort of Norwegian ME/CFS patients. However, data from this new study suggested that PEM remains a neglected symptom by specialized medical staff and healthcare providers.

4 Two final remarks

Most of the new contributions published in this Research Topic were based on the evaluation of simple metrics aiming at capturing different sequelae facets of a SARS-CoV-2 infection. These metrics are fundamental to understand the impact of the problem on public

health and society, as reviewed elsewhere (1). At the same time, the abundance of descriptive studies suggested that we are still at the early stage of addressing the LC problem. In this scenario, the great benefit of this Research Topic seemed to come from an integrated collection of papers where LC and ME/CFS are somehow put side-by-side. This is the case of Scheibenbogen et al. who aimed at leveraging pre-existing knowledge on ME/CFS pathogenesis and treatment with a potential impact on the healthcare of LC patients.

All the original research articles published in this Research Topic had the curiosity of coming from studying European, North American, and South American populations. This illustrates the wide extension of the LC challenge across the world. However, no papers from Asia and Africa were published in this Research Topic. In the case of Asia, it was a simple coincidence with several papers being submitted, but subsequently rejected for one reason or another. This contrasted with Africa from which no submission was received. Interestingly, the current prevalence estimates of LC in Africa (12) are similar to the ones found by Malheiro et al. in São Paulo Brazil and Angarita-Fonseca et al. across Latin America. Given this statistical coincidence, we had the expectation to collect some research studies on LC from this continent. Does this mean that the interest on LC is fading away in Africa even if there is evidence for an accumulation of cases elsewhere? Perhaps this is the right time for revitalizing the LC research in Africa to determine whether this continent is an exception in the global burden of this new post-pandemic condition.

Author contributions

FW: Conceptualization, Writing – original draft, Writing – review & editing. NS: Conceptualization, Writing – original draft, Writing – review & editing.

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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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Exploring long COVID condition in Latin America: Its impact on patients' activities and associated healthcare use

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Background: Studies exploring long COVID condition (LCC) in low- and middle-income countries are scarce. Further characterization of LCC patients experiencing activity limitations and their associated healthcare use is needed. This study aimed to describe LCC patients' characteristics, its impact on activities, and associated healthcare use in Latin America (LATAM).

Participants: Individuals who (cared for someone or) had COVID-19 and could read, write, and comprehend Spanish and lived in a LATAM country were invited to complete a virtual survey. Sociodemographic characteristics, COVID-19 and LCC symptoms, activity limitations, and healthcare use.

Results: Data from 2,466 people from 16 countries in LATAM were analyzed (females=65.9%; mean age of 39.5±53.3 years). 1,178 (48%) of the respondents had LCC symptoms (≥3 months). These were more likely to have COVID-19 earlier in the pandemic, were older, had no COVID vaccines, had more comorbidities, needed supplementary oxygen, and reported significantly more COVID-19 symptoms during the infectious period. 33% of the respondents visited a primary care provider, 13% went to the emergency department, 5% were hospitalized, 21% visited a specialist, and 32% consulted ≥1 therapist for LCC symptoms mainly extreme fatigue, sleep difficulties, headaches, muscle or joint pain, and shortness of breath with activity. The most consulted therapists were respiratory therapists (15%) and psychologists (14%), followed by physical therapists (13%), occupational therapists (3%), and speech pathologists (1%). One-third of LCC respondents decreased their regular activities (e.g., work, school) and 8% needed help with activities of daily living (ADLs). LCC respondents who reduced their activities reported more difficulty sleeping, chest pain with activity, depression, and problems with concentration, thinking, and memory, while those who needed help with ADLs were more likely to have difficulty walking, and shortness of breath at rest. Approximately 60% of respondents who experienced activity limitations sought a specialist and 50% consulted therapists.

Conclusions and relevance: Results supported previous findings in terms of the LCC demographics, and provided insight into LCC impact on patients' activities and healthcare services used in LATAM. This information is valuable to inform service planning and resource allocation in alignment with the needs of this population.

KEYWORDS

activity limitations, long COVID, healthcare use, long COVID disability, Latin America

Background

The Coronavirus Disease-2019 (COVID-19) continues its spread worldwide, reaching over 754 million confirmed cases, including 6.8 million deaths as of February 7, 2023 (1). As the pandemic progresses, a large subgroup of people with COVID-19 disease reported a wide range of new, recurring, or ongoing health problems or symptoms months after infection, known as long COVID (2). According to the World Health Organization (WHO), long COVID condition (LCC) "occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" (3, 4). In early reports, the WHO estimated that at least 10–20% of people had one or more symptoms 12 weeks or more after their initial diagnosis (5). A higher prevalence of LCC has recently been described at 90 and 120 days after infection (32 and 49%, respectively) (6). Overall, the prevalence of LCC has not been determined; wide variations have been reported due to differences in follow-up time, the characteristics of the population studied, and the type of data used (7). Despite the global impact of COVID-19, studies reporting LCC have been conducted primarily in high-income countries, and its effect in low- and middle-income regions has not been widely explored (6–8).

COVID-19 is primarily a respiratory disease, but it can also affect other systems, such as musculoskeletal, cardiovascular, or neurological systems, leading to a wide range of symptoms in the short, medium, and long term in COVID-19 survivors (8–10). The most commonly reported LCC symptoms are chronic fatigue, dyspnea, and brain fog, which in many cases affect the patient's activities of daily living (ADL) (11, 12), quality of life and the ability to return to work in the active population (8). Although the impact of LCC on patients' regular activities has been reported, the characteristics of the population more likely to be affected and their healthcare use have not been described. Due to the significant impact of LCC on patients' lives, the demand for care is expected to increase (13, 14). Therefore, healthcare systems and healthcare providers should aim to improve the diagnosis and management of patients with this condition. Further characterization of the patients experiencing difficulties returning to their regular activities will support this objective.

In the Latin American (LATAM) region, failures of health systems to adequately prevent and control chronic diseases are likely to result in a higher proportion of the population at risk of developing complications related to COVID-19 and LCC (15, 16). Additionally, public health emergencies challenge the ability of the healthcare systems to meet the essential needs of the population, increasing gaps in access and quality of care (16). To the best of our knowledge, there are no studies exploring healthcare use among LCC patients in the LATAM region. Therefore, this study aimed to describe LCC patients' characteristics, LCC impact on patients' activities, and associated healthcare use in LATAM.

Methodology

Study design

This study used data collected between 1 November and 1 December 2022, through an online open survey completed by a convenience sample from countries of LATAM. We included individuals residing in any country in LATAM, who reported having COVID-19 and/or cared for someone (e.g., child, parent, etc.) who had COVID-19, and could read, write, and comprehend Spanish. This study was approved by the University of Manitoba ethics committee (HS25587/H2022:230). It followed the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (17).

Recruitment

An electronic questionnaire was widely distributed on multiple sites accessed by a heterogeneous population on social networks (Facebook, LinkedIn, Twitter, WhatsApp, and Instagram) and was sent directly by email to other healthcare providers who were also asked to share it (snowball effect) within their personal and professional networks. The questionnaire was completely anonymous, and no personal identifiers such as names or emails, or IP addresses were collected. Participation was voluntary and non-monetary compensation was offered. Before completing the survey, the participants were informed about the aim of the study, the length of time of the survey, and the voluntary nature of their participation. It was also mentioned that by clicking next and advancing to the next page, they gave their consent to participate in the study.

Questionnaire and variables

A survey (25 questions) was developed by the research group based on the lists of main LCC symptoms assessed in the C19-YRS screening tool (18). The usability and technical functionality of the Google forms® (Online survey services) questionnaire were tested by all the co-authors before beginning public distribution of the survey. The online form had 10 pages, and all items on the current page had to be filled to move to the next page. However, "prefer not to answer" was one of the options. Unfortunately, Google Forms does not have a feature to track incomplete surveys. The items were not randomized as the survey had a logical order.

Respondents were able to review and change their answers using the back and forward buttons before submitting the final responses. After the form was submitted, the participant could not make any changes to their answers. However, the survey was immediately available again so that the respondent could fill it out for another family member.

Sociodemographic variables, such as country of residency, age, sex, income, and education, were collected. Questions related to the episode of COVID-19 infection included: date of diagnosis (first episode), COVID-19 confirmed with a test, number of COVID-19 vaccines received, smoking status, comorbidities diagnosed at that time of having COVID-19 (high blood pressure or other circulatory problems, breathing problems, heart problems, diabetes, obesity, kidney problems, others), presence and severity of 18 symptoms, and an open-ended question for other symptoms. Participants were also asked if they or the person they care for had COVID symptoms for ≥3 months after infection (LCC), and further items related to LCC were only displayed based on the affirmative response. People with LCC were asked about the presence and severity of the 18 symptoms and an open-ended question for other symptoms, whether LCC symptoms made them reduce the time spent on their usual activities (e.g., work, study, etc.) or have limited their ADLs (e.g., walking, bathing, showering, dressing, etc.). Participants with self-reported LCC were asked how poor or good they rated their health on that day (0 worst to 10 best possible health). Information about the use of health services due to COVID-19 or LCC was also collected, including visits to a primary care provider (PCP), emergency department (ED), and/or hospital, need for oxygen or other respiratory support, and visits to specialists or therapists.

Statistical analysis

Participants' characteristics, symptoms, and healthcare use were presented using mean (standard deviations) and percentages. Comparisons between groups were completed with Chi-Squared or independent t-tests as appropriate. Crude and adjusted logistic regression models were used to explore the characteristics of the participants in relation to reporting LCC, and limitations in their regular activities or ADLs. Statistical significance was accepted at p values below 0.05. All analyses were performed using SPSS software, version 28 (IBM Corp., Armonk, NY, USA).

Results

Responders of the survey

A total of 3,454 responses were collected. Of these, 2,466 people reported having COVID-19 (Figure 1). Responders with COVID-19 were mainly females (65.9%) from 16 countries in LATAM, but the majority (97%) reported Ecuador, Mexico, Argentina, Colombia, Peru and Chile as their place of residence (Supplementary Figure 1). 1,178 (48%) of the responders had COVID-19 or cared for someone that had COVID-19 symptoms ≥3 months after infection. The main symptoms reported during the COVID-19 infection included extreme fatigue, headaches, and issues with pain or discomfort; while extreme fatigue and headaches were also the main symptoms reported in participants with LCC, the third most common complaint in this group being issues with concentration, thinking, and memory (Supplementary Table 1).

Characteristics of the participants with LCC

Participants with LCC were more likely ($p < 0.001$) to have COVID-19 infection earlier in the pandemic (Jan 2020–Jun 2021) than in the subsequent waves (Jul 2021-Sep 2022; Supplementary Figure 2), and reported significantly ($p < 0.001$) more COVID-19 symptoms (mean 11.2 ± 4.8 vs. 7.9 ± 4.9) during the

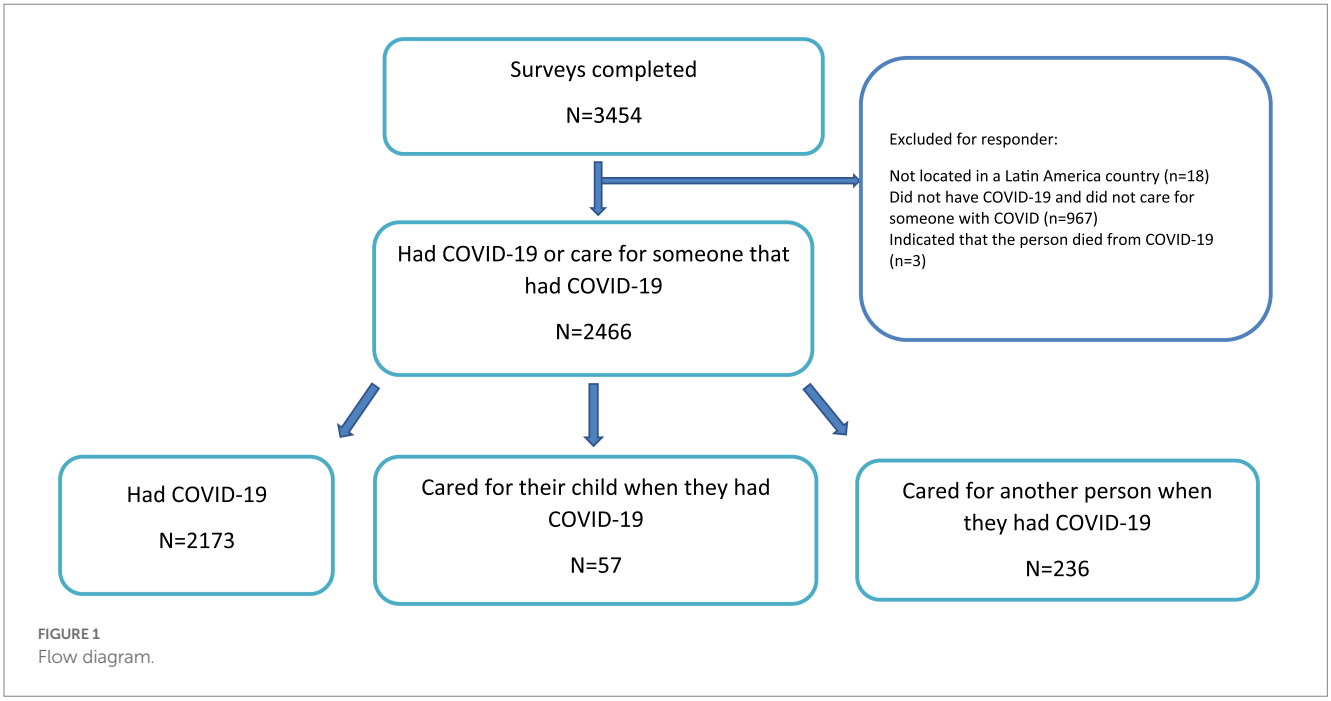

FIGURE 1
Flow diagram.

infectious period. They were significantly older, a higher proportion of them had no COVID-19 vaccines, had more comorbidities, and needed supplementary oxygen therapy at the time of infection than participants without LCC (Table 1). A logistic regression model adjusted for participants' characteristics and healthcare used during COVID-19 infection identified higher odds of having LCC in females, unvaccinated people, smokers, and people who visited the PCP, ED, or were hospitalized (Table 2). Participants with LCC that completed their surveys for themselves ($n = 1{,}036$) expressed having a good health on that day (mean 7.26 ± 1.6).

Activity limitations

A third of participants with LCC (33%) expressed that they had to decrease the time regularly spent at work, school and other usual activities (Table 3). A higher percentage of these patients were male, older, had none or one COVID-19 vaccine, had a higher prevalence of respiratory and metabolic disorders and/or diabetes, had a higher number of COVID symptoms and required supplemental oxygen during the COVID-19 infection, and used more health services than their counterparts (Supplementary Table 2). An adjusted model found that LC participants who reduced their activities had persistent difficulty sleeping (OR 1.90, 1.29–2.78), chest pain with activity (OR 1.82, 1.20–2.76), depression (OR 1.58, 1.06–3.34), and problems with concentration, thinking, and memory (OR 1.46, 1.03–2.08; Table 4).

8% of the participants needed help with ADLs, such as personal hygiene or grooming, dressing, toileting, transferring or ambulating, and eating due to LCC (Table 3). These were significantly older, with a higher number of COVID-19 symptoms during infection. A higher proportion of them had respiratory disorders and diabetes, needed supplementary oxygen during COVID-19 infection, and used various healthcare services due to LCC (Supplementary Table 2). An adjusted model found that LCC participants who needed help with ADLs were significantly more likely to have difficulty walking (OR 3.32, 1.55–7.10), and shortness of breath (SOB) at rest (OR 2.95, 1.33–6.54; Table 4).

Among the participants who self-reported LCC, those who reduced their usual activities (mean 6.5 ± 1.9 vs. 7.6 ± 1.5, $p < 0.001$), as well as those who needed help with their ADLs (mean 5.8 ± 2.5 vs. 7.3 ± 1.6, $p < 0.001$), reported poorer health on that day compared to participants without activity limitations.

Healthcare use

During the COVID-19 infection, 60% of the participants consulted their PCP, 25% visited the ED, and 8% of the participants were hospitalized (Supplementary Table 3). The main symptoms presented by the participants who used these services included extreme fatigue, headaches, issues related to pain or discomfort, and generalized muscle weakness.

Due to LCC symptoms, 33% of the participants consulted their PCP, 13% visited the ED, and 5% were hospitalized (Supplementary Table 3). The top symptoms reported by these healthcare users included extreme fatigue, headaches, SOB with activity, and difficulty sleeping. The main complaints in this group of participants (35%) who sought a specialist included fatigue, sleep difficulties, headaches, muscle or joint pain, and SOB with activity. 32% of the participants consulted one or more therapists. The most consulted therapists were respiratory therapists (15%) and psychologists (14%), followed by physical therapists (13%), occupational therapists (3%), and speech pathologists (1%).

About half of the participants who used the services of specialists (50%) or therapists (47%) stated that they reduced the time they regularly spent on their usual activities, and 14% needed help with their ADLs due to LCC.

Discussion

Almost half (48%) of the participants had LCC symptoms in our study. This finding aligns with evidence from recent studies that reported LCC prevalence in a couple of South American countries [50% in Colombia (19) and 63% in Brazil (20)]. Similar to other studies, higher odds of LCC were found in females (21, 22), smokers (23), and middle-aged subjects (24) with a higher number of COVID-19 symptoms (25) who reported using more healthcare services, suggesting severe illness during the infectious period (26–30). Participants with LCC were more likely to have had COVID-19 infection earlier in the pandemic, which aligns with existent evidence suggesting than individuals infected with Omicron are less likely to experience severe long COVID symptoms (31). In addition, our results showed that fully vaccine patients (two doses) were less likely to have LCC compared with unvaccinated or partially vaccinated subjects. These results are consistent with those observed in a recent meta-analysis that found a protective effect of vaccination in patients vaccinated with two doses (RR = 0.83, 95% CI: 0.74–0.94, $p < 0.01$), but not with a dose (RR = 0.83, 95% CI: 0.65–1.07, $p = 0.14$) (20). This meta-analysis reported that vaccination reduces the risk of cognitive dysfunction/symptoms, myalgia, and sleeping disorders, which are some of the predominant symptoms found in our study population. Furthermore, vaccination was effective against LCC in patients vaccinated before (RR = 0.82, 95% CI: 0.74–0.91, $p < 0.01$) or after SARS-CoV infection (RR = 0.83, 95% CI: 0.74–0.92, $p < 0.01$) (32, 33).

We found that a high proportion of patients with LCC had pre-existent respiratory diseases, diabetes, and other metabolic diseases. This aligns with the literature showing that comorbidities such as lung disease, diabetes, obesity, and organ transplantation are potential risk factors for LCC (21). Although the prevalence of respiratory diseases, specifically COPD, in LATAM was similar to the reported globally, considerable variability (34) was reported by country, probably explained by differences in smoking levels, industrialization, genetic factors, and other predisposing factors such as tuberculosis or asthma. Diabetes prevalence has increased over time in LATAM (22), to the point that the diabetes-associated mortality risk is higher than in any other world region (23) and it is currently a significant threat to health systems, economy, and population health (24, 25). Cardiovascular and metabolic diseases are also a big problem in LATAM (35), and the global burden of high body mass index (BMI) is well-established and quantified in low- and middle-income countries (36). Overall, it is important to consider that these comorbidities are highly prevalent in the region and, therefore, can potentially contribute to increasing the risk of LCC in these populations.

TABLE 1 Characteristics of survey respondents with and without long COVID condition (LCC).

Variable	Respondents with COVID-19 *N*=2466*	No LCC symptoms *N*=1,211	LCC symptoms *N*=1,178	*p*
Gender (*n*, % female)	1,626 (65.9%)	782 (64.7%)	803 (68.2%)	0.07
Age, mean (SD)	39.5 (53.3)	35.6 (14.4)	37.9 (14.9)	<0.001
Age group (*n*, %)				
<19	200 (8.1%)	106 (8.8%)	83 (7.1%)	<0.001
20–29	736 (29.8%)	401(33.2%)	315 (26.8%)	
30–39	556 (22.5%)	274 (22.6%)	267 (22.7%)	
40–49	478 (19.4%)	210 (17.3%)	257 (21.9%)	
50–59	295 (12.0%)	133 (11.0%)	154 (13.1%)	
60–69	130 (5.3%)	64 (5.3%)	60 (5.1%)	
70+	71 (2.9%)	21 (1.7%)	38 (3.2%)	
COVID test (*n*, % yes)	2098 (85.0%)	999 (83.0%)	984 (84.2%)	0.43
COVID vaccines at the time of infection				
0	926 (37.6%)	388 (32.1%)	470 (40.1%)	<0.001
1	239 (9.7%)	114 (9.4%)	108 (9.2%)	
2	622 (25.2%)	312 (25.8%)	255 (21.7%)	
>=3	799 (32.4%)	393 (32.6%)	340 (29.0%)	
Smoking				
No	1741 (70.6%)	901 (75.3%)	792 (68.0%)	<0.001
Former	452 (18.3%)	181 (15.1%)	256 (22.0%)	
Yes	237 (9.6%)	114 (9.5%)	116 (10.0%)	
Main health conditions at the time of COVID-19				
None	1799 (73.0%)	957 (79.1%)	791 (67.1%)	<0.001
Respiratory disorders	134 (5.4%)	39 (3.2%)	87 (7.4%)	<0.001
Cardiovascular disorders	172 (7.0%)	75 (6.2%)	90 (7.6%)	0.16
Diabetes	77 (3.1%)	29 (2.4%)	47 (4.0%)	0.03
Obesity	111 (4.5%)	47 (3.9%)	62 (5.3%)	0.11
Other metabolic disorders	93 (3.8%)	32 (2.6%)	59 (49.3%)	0.01
Rheumatic/autoimmune disorders	27 (1.1%)	14 (1.2%)	12 (1.0%)	0.74
Mental health disorders	5 (0.2%)	1 (0.1%)	3 (0.3%)	0.30
Other	42 (1.7%)	15 (1.2%)	23 (2.0%)	
Used oxygen during COVID-19, yes (%)	272 (11.0%)	72 (5.9%)	176 (14.9%)	<0.001
Education (*n*, %)				
High school or less	562 (22.8%)	272 (22.5%)	267 (22.7%)	0.24
Apprenticeship	329 (13.3%)	177 (14.6%)	142 (12.1%)	
College/some university	71 (2.9%)	41 (3.4%)	29 (2.5%)	
University degree	1,041 (42.2%)	501 (41.4%)	509 (43.2%)	
Post-graduate degree	418 (17.0%)	196 (16.2%)	212 (18.0%)	
Prefer not to answer	45 (1.8%)	24 (2.0%)	19 (1.6%)	
Annual family income (*n*, %)				
<$3,000	683 (27.7%)	329 (27.2%)	328 (27.8%)	0.62
$3,000–5,000	314 (12.7%)	147 (12.1%)	165 (14.0%)	
$5,001–10,000	252 (10.2%)	124 (10.2%)	122 (10.4%)	
≥$10,001	329 (13.3%)	169 (14.0%)	152 (12.9%)	
Prefer not to answer	888 (36.0%)	442 (36.5%)	411 (34.9%)	

*Includes people who had COVID <3 months ago and responded "prefer not to answer" to the question about COVID symptoms ≥3 months (n = 77). Survey questions were not mandatory, and some participants did not provide a response to all questions. Other metabolic disorders = kidney, liver, thyroid problems, hyperlipidemias/hypercholesterolemia. Other = neurologic conditions, vertigo, cancer, gastric problems, etc.

TABLE 2 Factors associated with reported long COVID condition.

Variables	Univariable		Multivariable	
	LCC yes		LCC yes	
	OR (CI)	*p*	OR (CI)	*p*
Sex (Ref M)				
Females	1.17 (0.9–1.4)	0.07	1.28 (1.1–1.5)	0.01
Age groups (Ref ≤ 19 years)				
20–29	1.00 (0.7–1.4)	0.98	1.05 (0.7–1.5)	0.77
30–39	1.24 (0.8–1.7)	0.19	1.26 (0.8–1.8)	0.21
40–49	1.56 (1.1–2.2)	0.01	1.47 (1.0–2.1)	0.04
50–59	1.48 (1.0–2.1)	0.04	1.44 (1.0–2.1)	0.08
60–69	1.19 (0.7–1.9)	0.43	1.03 (0.6–1.7)	0.91
≥70	2.31 (1.3–4.2)	<0.01	1.21 (0.6–2.4)	1.03
COVID-19 vaccine (Ref none)				
1	0.78 (0.6–1.1)	0.10	0.82 (0.6–1.1)	0.24
2	0.68 (0.5–0.8)	<0.001	0.75 (0.6–0.9)	0.01
≥3	0.71 (0.6–0.8)	<0.001	0.81 (0.6–1.0)	0.05
Number of COVID-19 symptoms during infection	1.14 (1.1–1.2)	<0.001	1.13 (1.1–1.2)	<0.001
Smoking (Ref No)				
Former	1.16 (0.8–1.5)	0.29	1.30 (0.9–1.7)	0.09
Yes	1.61 (1.3–1.9)	<0.001	1.52 (1.2–1.9)	0.01
Main health conditions at the time of COVID-19 (Ref No)				
None	0.41 (0.1–2.3)	0.31	0.69 (0.1–4.1)	0.67
Respiratory disorders	1.12 (0.2–6.3)	0.90	1.68 (0.3–10.6)	
Cardiovascular disorders	0.60 (0.1–3.4)	0.56	0.82 (0.1–5.1)	0.58
Diabetes	0.81 (0.1–4.7)	0.82	0.97 (0.1–6.2)	0.84
Obesity	0.66 (0.1–3.7)	0.64	0.96 (0.1–6.0)	0.97
Other metabolic disorders	0.92 (0.1–5.3)	0.93	1.18 (0.2–7.5)	0.97
Rheumatic/autoimmune disorders	0.43 (0.1–2.7)	0.37	0.58 (0.1–4.2)	0.86
Mental health disorders	1.50 (0.1–25.3)	0.78	1.11 (0.1–20.2)	0.94
Other	0.76 (0.1–4.7)	0.77	1.30 (0.2–8.9)	0.79
Used oxygen during COVID-19 (Ref No)				
Yes	2.78 (2.0–3.7)	<0.001	0.98 (0.6–1.4)	0.94
Visited the primary care provider during COVID-19 (Ref No)				
Yes	1.71 (1.5–2.0)	<0.001	1.27 (1.0–1.5)	0.02
Visited the emergency department during COVID-19 (Ref No)				
Yes	2.09 (1.7–2.5)	<0.001	1.28 (1.0–1.6)	0.04
Hospitalized during COVID-19 (Ref No)				
Yes	3.15 (2.3–4.3)	<0.001	1.76 (1.1–2.7)	0.01

COVID-19 and LCC have a wide range of symptoms, which appear to fluctuate throughout the course of infection. There are no diagnostic tests to confirm LCC, therefore, clinicians mostly rely on symptoms to identify this condition. Consistent with literature, the most common LCC symptoms reported in our study were extreme fatigue, cognitive dysfunction, sleeping difficulties, and anxiety (26–28, 37). Headache was frequently reported in the study, although this symptom is less commonly described in the literature (28). Conversely, participants experienced less shortness of breath, cough, depression, and chest pain compared to other studies (26–28, 37).

Our data shows that one-third of LCC participants have not returned to their regular activities and 8% required help to complete their ADLs ≥3 months after infection. It has been observed that LCC affects patients' physical function, ability to return to work, school

TABLE 3 Characteristics of participants with long COVID condition and impact on their activities (n=1,178).

Variable	Decreased time spent at work, school, and other activities			Needed help with ADL		
	Yes	No	p	Yes	No	p
	N=338	N=815		N=91	N=1,075	
Gender (n, % female)	216 (63.9%)	571 (70.1%)	0.04	55 (60.4%)	742 (69.1%)	0.09
Age, mean (SD)	41.0 (16.8)	36.8 (13.7)	<0.001	44.1 (19.8)	37.4 (14.2)	<0.001
Age group (n, %)						
<19	25 (7.4%)	56 (6.9%)	<0.001	6 (6.7%)	76 (7.1%)	<0.001
20–29	78 (23.1%)	227 (28.0%)		19 (21.1%)	292 (27.2%)	
30–39	55 (16.3%)	207 (25.5%)		17 (18.9%)	248 (23.1%)	
40–49	81 (24.0%)	173 (21.3%)		17 (18.9%)	237 (22.1%)	
50–59	53 (15.7%)	98 (12.1%)		9 (10.0%)	144 (13.4%)	
60–69	27 (8.0%)	32 (3.9%)		11 (12.2%)	49 (4.6%)	
70+	18 (5.3%)	19 (2.3%)		11 (12.2%)	26 (2.4%)	
COVID vaccines at the time of infection						
0	160 (47.6%)	303 (37.3%)	<0.01	34 (37.8%)	433 (40.4%)	0.87
1	33 (9.8%)	71 (8.7%)		10 (11.1%)	93 (8.7%)	
2	66 (19.6%)	183 (22.5%)		20 (22.2%)	232 (21.7%)	
>=3	77 (22.9%)	256 (31.5%)		26 (28.9%)	313 (29.2%)	
Number of COVID-19 symptoms during infection	13.4 (4.1)	10.3 (4.7)	<0.001	12.8 (5.1)	11.0(4.7)	<0.001
Smoking						
No	220 (65.9%)	557 (69.1%)	0.56	58 (64.4%)	726 (68.3%)	0.69
Former	78 (23.4%)	171 (21.2%)		21 (23.3%)	233 (21.9%)	
Yes	36 (10.8%)	78 (9.7%)		11 (12.2%)	104 (9.8%)	
Main health conditions at the time of COVID-19						
None	189 (55.9%)	586 (71.9%)	<0.001	40 (44.0%)	742 (69.0%)	<0.001
Respiratory disorders	36 (10.7%)	49 (6.0%)	0.01	18 (19.8%)	69 (6.4%)	<0.001
Cardiovascular disorders	33 (9.8%)	55 (6.7%)	0.08	10 (11.0%)	78 (7.3%)	0.19
Diabetes	22 (6.5%)	23 (2.8%)	<0.01	8 (8.8%)	38 (3.5%)	0.02
Obesity	22 (6.5%)	39 (4.8%)	0.23	5 (5.5%)	57 (5.3%)	0.93
Other metabolic disorders	20 (5.9%)	38 (4.7%)	0.38	6 (6.6%)	53 (4.9)	0.48
Rheumatic/autoimmune disorders	7 (2.1%)	5 (0.6%)	0.03	1 (1.1%)	11 (1.0%)	0.94
Mental health disorders	2 (0.6%)	1 (0.1%)	0.16	0	3 (0.3%)	0.61
Other	7 (2.1%)	15 (1.8%)	0.79	2 (2.2%)	21 (2.0%)	0.87
Used oxygen during COVID-19, yes (%)	101 (29.9%)	72 (8.8%)	<0.001	41 (45.1%)	133 (12.4%)	<0.001
Healthcare use during COVID-19						
Primary Care	165 (48.8%)	163 (20.0%)	<0.001	42 (46.2%)	288 (26.8%)	<0.001
Emergency department	85 (25.1%)	39 (4.8%)	<0.001	31 (34.1%)	95 (8.8%)	<0.001
Hospital	36 (10.7%)	12 (1.5%)	<0.001	18 (19.8%)	31 (2.9%)	<0.001
Specialist	200 (59.2%)	198 (24.3%)	<0.001	56 (61.5%)	344 (32.0%)	<0.001
Physical therapist	86 (26.1%)	66 (8.2%)	<0.001	31 (36.9%)	121 (11.4%)	<0.001
Occupational therapist	24 (7.3%)	12 (1.5%)	<0.001	8 (9.5%)	28 (2.6%)	<0.001
Respiratory therapist	86 (26.1%)	84 (10.4%)	<0.001	29 (34.5%)	142 (13.4%)	<0.001
Speech pathologist	8 (2.4%)	5 (0.6%)	0.01	5 (6.0%)	8 (0.8%)	<0.001
Physiologist	84 (25.5%)	78 (9.7%)	<0.001	15 (17.9%)	146 (13.7%)	0.29

Survey questions were not mandatory, and some participants did not provide a response to all questions. Other metabolic disorders = kidney, liver, thyroid problems, hyperlipidemias/hypercholesterolemia. Other = neurologic conditions, vertigo, cancer, gastric problems, etc.

TABLE 4 Factors associated with greater activity limitations in long COVID condition (LCC).

Variables	Decreased time spent at work, school, and other activities (yes/no)	Needed help with ADLs (yes/no)
	Adjusted	Adjusted
	OR (CI)	OR (CI)
Sex (Ref M)		
Females	**0.63 (0.45–0.86)**	0.93 (0.56–1.54)
Age	**1.02 (1.01–1.03)**	**1.03 (1.01–1.04)**
LCC symptoms		
Extreme fatigue	1.32 (0.85–2.04)	0.79 (0.34–1.82)
Headaches	0.99 (0.69–1.43)	0.83 (0.40–1.73)
Issues with pain or discomfort	0.87 (0.55–1.35)	1.14 (0.44–2.92)
Muscle or joint pain	1.31 (0.74–1.74)	1.29 (0.52–3.20)
General muscle weakness	1.29 (0.84–1.97)	0.44 (0.17–1.14)
Cough/noisy breathing	0.88 (0.62–1.79)	1.49 (0.78–2.86)
SOB with activity	1.22 (0.83–1.78)	1.17 (0.51–2.69)
Difficulty sleeping	**1.90 (1.29–2.78)**	0.72 (0.33–1.52)
Anxiety	1.12 (0.76–1.67)	1.18 (0.54–2.58)
Issues with concentration, thinking, and memory	**1.46 (1.03–2.08)**	0.73 (0.35–1.52)
SOB at rest	1.35 (0.87–2.09)	**2.95 (1.33–6.54)**
Chest pain at activity	**1.82 (1.20–2.76)**	0.86 (0.38–1.94)
Difficulty eating, drinking, and swallowing	0.76 (0.48–1.20)	1.93 (0.94–3.97)
Chest pain at rest	0.73 (0.45–1.19)	1.28 (0.55–2.97)
Depression	**1.58 (1.06–2.34)**	0.92 (0.43–1.92)
Difficulty walking	1.45 (1.26–3.38)	**3.32 (1.55–7.10)**
Difficulty controlling movement of the body	0.94 (0.591.49)	1.82 (0.86–3.86)
Dizziness, faint, and loss of consciousness	1.03 (0.69–1.54)	1.17 (0.60–2.28)
Other symptoms	**2.07 (1.26–3.38)**	0.98 (0.38–2.49)

Survey questions were not mandatory, and some participants did not provide a response to all questions. Other symptoms: change in taste and smell, congestion, gastro-intestinal symptoms, runny nose, rapid or irregular heart rate.

or other regular activities, and impacts their health-related quality of life (8, 38). However, to the best of our knowledge, this is the first study to identify that activity limitations were more likely to be reported by men and older participants. In older adults, particularly those who are frail, their ADL may be affected to the point that help from a caregiver may be necessary (8). Activity limitations can have a detrimental economic effect on affected families due to loss of income and/or additional care costs. This burden could deeply impact LATAM countries, since family income is lower than in developed nations, government support is minimal or non-existent, and care is often provided by an immediate family member.

Another critical aspect to consider is the demand for health services by patients with LCC. Worldwide, primary care was essential in diagnosing and treating COVID-19, promoting compliance with protective measures, and reducing the demand for hospital services (39). These care units have also been shown to be relevant in the care of patients with LCC (40). In countries such as Austria and Germany, all patients with LCC are referred to the general practitioner for clinical evaluation regardless of whether or not they were hospitalized during their episode of active infection (41). In our study, approximately one-third of the participants sought a PCP, specialist, and/or therapists due to LCC symptoms, especially those who experienced activity limitations. It is important to recognize that differences in referral systems, insurance coverages, and healthcare policies across countries may have restricted access to some healthcare services and therefore affected the proportion of patients who were able to consult these healthcare professionals. Preliminary evidence suggests that most COVID-related care should be provided in primary care (36); however, it must be acknowledged that PCPs are challenged to provide care to these patients who often have a wide range of symptoms and are unlikely to respond to a single intervention. Therefore, it is essential to promote the need for interdisciplinary healthcare teams to manage this condition (42). Although in the current scenario, the increased requirements for specialized health services may raise costs for already strained health systems, and rehabilitation services in the region have been impacted by operational and infrastructure adjustments needed for compliance with the biosafety regulations brought on by the pandemic (43). Alternatives to these challenges should be explored

since, according to our results, a significant proportion of patients with LCC symptoms will require an integrated approach to regain their health.

Strengths and limitations

To our knowledge, our study is the first of its kind to provide comprehensive information about characteristics, symptoms, impact on patients' activities, and healthcare access of patients who experience LCC in LATAM. Our results are also based on a large sample of people from LATAM unlike previous studies of specific cities. Also, online data collection enabled the research team to reach a large number of participants from all regions of LATAM as well as to minimize data entry errors. Nonetheless, some study limitations are worth noting. The questionnaire was completely anonymous and no personal identifiers such as names, emails, or IP addresses were collected. Furthermore, after the form was submitted, the participant was unable to make any changes to their responses. However, the survey was immediately made available again so that the respondent could fill it out for another family member. Therefore, the IP address of the participant's computer could not be used to identify potential duplicate entries from the same user, which may have contributed to potential bias. Due to the non-probability convenience sampling method, the sample was not drawn randomly from the population of interest to ensure representativeness. Therefore, these findings cannot be generalized to unrepresented countries, nor can they be used in any way to calculate the prevalence of LCC. People who use social media (and therefore were able to access the survey) could have different characteristics to those who do not use such platforms. Although we tried to reach people from other sources such as a list of patients, the online recruitment strategy and questionnaire administration could explain the oversampling of women in our study, since women tend to use Facebook and work in online environments more often than men. Some people may have been unintentionally excluded from the survey, as they may have limited or no access to a technological device and/or the Internet to complete the virtual questionnaire. Additionally, people with more symptoms or more severe symptoms may be more likely to respond to the survey. There is also the possibility of recall bias in this survey, as the data during COVID-19 (acute stage) was collected retrospectively.

Conclusion

Our results supported previous findings in terms of the main characteristics and symptoms of patients experiencing LCC, identified characteristics of these patients who reported activity limitations, and described symptoms commonly reported among healthcare users in LATAM. This information is valuable to inform future service planning and resource allocation in alignment with the needs of this population.

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

This study was approved by the University of Manitoba ethics committee (HS25587/H2022:230). Before completing the survey, the participants were informed that by clicking next and advancing to the next page, they gave their consent to participate in the study.

Author contributions

DS-R conceived the study, organized the database, and performed the statistical analysis. AA-F, RT-C, VB-C, SC, MM-S, BL-H, RS-P, SL, and DS-R helped with survey design, refinement, and distribution, and supported the data collection process. AA-F, RT-C, VB-C, and DS-R wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1168628/full#supplementary-material

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Fighting Post-COVID and ME/CFS – development of curative therapies

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The sequela of COVID-19 include a broad spectrum of symptoms that fall under the umbrella term post-COVID-19 condition or syndrome (PCS). Immune dysregulation, autoimmunity, endothelial dysfunction, viral persistence, and viral

reactivation have been identified as potential mechanisms. However, there is heterogeneity in expression of biomarkers, and it is unknown yet whether these distinguish different clinical subgroups of PCS. There is an overlap of symptoms and pathomechanisms of PCS with postinfectious myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). No curative therapies are available for ME/CFS or PCS. The mechanisms identified so far provide targets for therapeutic interventions. To accelerate the development of therapies, we propose evaluating drugs targeting different mechanisms in clinical trial networks using harmonized diagnostic and outcome criteria and subgrouping patients based on a thorough clinical profiling including a comprehensive diagnostic and biomarker phenotyping.

KEYWORDS

COVID-19, post-COVID, ME/CFS, inflammation, endothelial dysfunction, autoantibodies, clinical trials

Introduction

COVID-19 frequently results in persistent debilitating symptoms lasting longer than 3 months, referred to as post-COVID-19 syndrome (PCS). Based on large epidemiological studies, approximately 10% of adults who had a positive SARS-CoV-2 PCR suffer from persisting symptoms beyond 3 months (1). Vaccination confers partial protection against PCS (2). In the majority of adult PCS patients, severity of symptoms persists or even increases after 12 months (3). Predominantly, healthy young and middle-aged adults with female preponderance are affected. Less data is available for children and adolescents, indicating a lower prevalence and severity (4, 5).

The clinical presentation is complex with various clinical phenotypes and most likely different mechanisms (6, 7). In most younger patients, there is no evidence for organ damage, and the majority has a symptom cluster with predominance of fatigue, exertion intolerance, cognitive impairment, orthostatic intolerance, and autonomous dysfunction (8).

Postinfectious syndromes have been described for more than a century and can be triggered by various infections (9). There is now clear evidence that a subset of PCS complies with standard case definitions of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (10, 11). We will refer to such cases as post-COVID (PC) ME/CFS. Post-infectious ME/CFS (ICD-10 code G93.3) is a complex and severely disabling disease with no approved treatment and therefore, a very high and so far unmet medical need (12). Key symptoms are central and muscle fatigue, exertion intolerance with post-exertional malaise (PEM), cognitive impairment, orthostatic intolerance, headache, and muscle pain - hence a large overlap of symptoms with PCS. ME/CFS had an estimated prevalence of 0.3–0.8% before COVID-19, including children and adolescents (12). The prevalence of PCS that fits ME/CFS diagnostic criteria will likely be substantial, and poses a major problem for health care and society. A recent study from Germany that analyzed health insurance data from nearly 30 million individuals showed an annual incidence rate in 2020 of 6 versus 2/1000 in adults with and without prior COVID-19, respectively (13). So far, there is no proven effective therapy for PCS or ME/CFS (14).

Pathomechanisms of PCS and ME/CFS

There is accumulating evidence from large well-performed studies that immune activation and dysregulation with inflammation and alteration of immune cells are frequently found in PCS. Various autoantibodies have been described to be triggered by COVID-19 and to be associated with the development of PCS. Correlations of both, soluble markers of inflammation and autoantibodies, including antinuclear antibodies (ANA), neurological and G protein-coupled receptor (GPCR) antibodies with symptom severity were found (15–17). Endothelitis is common in acute COVID-19, and can persist in PCS with endothelial dysfunction and various biomarkers of endothelial inflammation, microclots and hypoperfusion shown (7, 18). There is evidence for viral persistence with detection of spike and nucleoprotein in serum in a subset of PCS (7, 19). However, there is a broad heterogeneity in expression of biomarkers, and it is unknown yet whether we face distinct subgroups of PCS or overlapping mechanisms. Although there are correlations of some biomarkers with symptom severity, it is not possible to delineate clinical phenotypes from biomarker profiles yet. Similarly, there is evidence that immune dysregulation and autoantibodies play a key role in ME/CFS, including the high frequency of autoimmune diseases among first-degree family members, associations with autoimmunity-related gene variants and MHC alleles, skewed B cell receptor genes, and association of symptom severity with GPCR antibodies (15, 20–22). Further, there is ample evidence for endothelial dysfunction affecting both medium arteries, assessed by flow-mediated dilation, and capillaries assessed by post occlusive reactive hyperemia (20, 23). Many reports have found altered cytokine levels and their correlation with severity in ME/CFS, though many are inconsistent with each other (24–26). Of interest, reactivation of Epstein–Barr virus (EBV) during COVID-19 frequently occurs and is a risk factor to develop PCS (6, 7). In a subset of individuals, infectious mononucleosis precedes ME/CFS (27).

Drugs of interest to study in PCS and ME/CFS

Conceptually, selection criteria for therapeutic strategies should be based on potential mechanisms, defined by specific biomarkers.

There are numerous drugs already licensed for other indications that target mechanisms identified in PCS and/or ME/CFS. Repurposing of such drugs may offer faster clinical approval.

In PCS, several interventional randomized controlled trials (RCT) have been initiated for targeted drug therapy worldwide (Table 1). This includes anti-inflammatory drugs, including corticosteroids, loratadine, montelukast, atorvastatin, baricitinib and phosphodiesterase inhibitors. Treatment studies depleting autoantibodies have been started with plasma exchange and immunoadsorption. The first specific drug in a clinical trial is the neonatal Fc receptor inhibitor efgartigimod, which enhances IgG degradation and was recently licensed for therapy in myasthenia gravis (28). Another study was initiated with the aptamer BC007, which has shown safety and GPCR antibody neutralizing capacity in a phase I trial (29). Antivirals include targeting of potential residual SARS-CoV-2 as well as a monoclonal antibody against a reactivated endogenous retrovirus. Further several neuromodulators are studied in RCT, including vortioxetine, an antidepressant with established pro-cognitive properties, lithium with anti-depressive and anti-inflammatory properties, fampridine, a potassium channel-blocking agent linked to working memory and approved for multiple sclerosis, and dexamphetamine with first evidence for efficacy in ME/CFS (30). Targeting endothelial dysfunction and hypoperfusion holds promise in both, PCS and ME/CFS, and a phase II RCT with the guanylate cyclase inhibitor vericiguat already licensed in heart failure has started in PCS and PC ME/CFS (31). Hyperbaric oxygen therapy (HBOT) was already shown to improve neurocognitive function in a phase II RCT in PCS, and is currently studied in another RCT (32).

In ME/CFS, there has been little interest of pharmaceutical companies in clinical trials for decades, presumably due to the complexity of the disease, conflicting concepts of etiology and paucity of research on pathomechanisms. There are now 2 trials conducted in PC ME/CFS including rintatolimod, a TLR-3 agonist. This is one of the few drugs, which has been studied in a phase III trial in ME/CFS showing evidence for efficacy in patients with shorter disease duration (33). Inclusion criteria are, however, the Fukuda criteria not requiring PEM. Further low dose naltrexone with evidence for efficacy from case reports in ME/CFS and recently also in an open trial in PCS will be studied in a RCT phase 2 trial (34, 35). For non-PC ME/CFS only one interventional RCT pharmacological trial with N-acetylcysteine could be found (NCT04542161). However, there is reasonable hope that some of the drugs that are effective in LC can also be used in ME/CFS.

Further drugs of interest to study in PCS and ME/CFS are listed in Table 2. A novel approach to alleviate inflammation is to target kinases that regulate inflammatory mediators like Janus kinase (JAK) inhibitors and several others (36, 37). Further certain drugs exert, besides their licensed indication, anti-inflammatory effects like metformin or certain antibiotics with evidence for efficacy in acute COVID or from non-controlled trials in ME/CFS like minocycline (36, 39, 40). Further, there is first data that H1 and H2 antihistamines can have beneficial effects (38). There are numerous drugs to target autoantibody-producing B cells including monoclonal antibodies and more recently Bruton tyrosinkinase (BTK) inhibitors. Rituximab has been studied in ME/CFS in several phase II and one phase III study with inconclusive results (49, 50). Newer and more effective antibodies targeting CD20, CD19 or CD38 depleting both, B cells and/or plasma cells, are thus promising candidates (41). There are further groups of drugs targeting endothelial dysfunction *via* PDE5, β2/3 adrenergic or acetylcholine receptors (43–45). A small study was already performed with the PDE5 inhibitor sildenafil in ME/CFS showing a significant improvement of fatigue in 5 treated patients compared to 6 receiving placebo (NCT00598585). There is also evidence from various small trials in ME/CFS that the neuromodulators low dose aripiprazole and methylphenidate can have efficacy (46, 47). Also guanfacine was described in a case series to ameliorate symptoms in PCS (48). PCS and ME/CFS patients frequently suffer from dysautonomia and postural tachycardia syndrome (POTS). There are several pharmacological treatment options from small clinical trials, but no licensed drugs are available. Similarly, for other key symptoms of ME/CFS and PCS, sleep disturbances and post exertional malaise there is no evidence for medications from clinical trials.

Concept for clinical trial networks

Due to the complexity of PCS and ME/CFS harmonization of diagnostic and inclusion and outcome criteria for clinical trials would be desirable. So far, many clinical trials do not specify PCS subgroups or clinical phenotypes. In several ongoing trials Long COVID (LC) is mentioned as inclusion criterium, which is poorly defined as persistent symptoms for more than 4 weeks. For ME/CFS, various diagnostic criteria exist and only stricter criteria requiring the cardinal symptom PEM should be used for clinical trials (12). Clinical trial platforms or networks would allow proof-of-concept clinical trials with various drugs in a harmonized manner using similar diagnostic criteria, evaluation tools, clinical outcome criteria and pre-enrolment phenotyping of patients to categorize them according to potential underlying mechanisms. Further clinical trial networks allow to rapidly recruit larger sample size when moving from phase II to phase III trials or to recruit ME/CFS patients triggered by another infection, e.g., EBV. Due to the diversity of pathological mechanisms, clinical trials should be accompanied by comprehensive biomarker analyses, focusing on both, classical biomarkers as well as compound biomarkers, and biomarker signatures that become increasingly accessible. Besides achieving further insights into the mechanisms and into drug efficacy, such approaches can lead to the development of companion diagnostics for consecutive trials. Specific diagnostic assessments including advanced structural and functional magnetic resonance imaging (MRI), neurocognitive testing, autonomic testing, and vascular imaging should be implemented to visualize key clinical and functional abnormalities of PCS (18, 51–53).

Based on the concept outlined above, a German consortium was recently established, the National Clinical Study Group (NKSG) for PCS and ME/CFS. The interdisciplinary team includes clinical experts from neurology, neuroimmunology, clinical immunology, rheumatology, cardiology, pediatrics, psychiatry, neuropsychology, neuroradiology, and infection medicine, with specific expertise in diagnosing and treating patients with PCS and ME/CFS, as well as experts in human immunology, molecular medicine, biochemistry, data sciences, bioinformatics, and artificial intelligence (AI), with long-standing expertise in biomedical research. Patient inclusion criteria refer to defined clinical phenotypes, objective clinical measures, and potential biomarkers. Patients with PCS and/or ME/CFS are being diagnosed according to standard diagnostic criteria as published for PCS by the WHO and for ME/CFS by the Canadian

TABLE 1 Randomized controlled trials in PCS registered in clinical trial platforms*.

Trial	Interventions under comparison	PC/subtype	Country	Current state	No. of subjects	NCT
Immunomodulatory						
Phase 2 RCT	IgG vs. methylprednisolone vs. saline	PC neurological	USA	Recruiting	45	NCT05350774
Phase 3 RCT (open)	Atorvastatin vs. standard care	LC neurocognitive	Australia	Recruiting	400	NCT04904536
Phase 2 RCT	Plasma Exchange Therapy vs. sham	PC	Spain	not yet recruiting	50	NCT05445674
Phase 2 RCT	Immunoadsorption vs. sham	PC ME/CFS (CCC) and autoantibodies	Germany	Not yet recruiting	66	NCT05710770
Phase 3 RCT	Montelukast vs. placebo	LC respiratory	Spain	Recruiting	284	NCT04695704
Phase 2 RCT	Ampligen vs. saline	PC ME/CFS (CDC)		Not yet recruiting	80	NCT05592418
Phase 3 RCT	Prednisolone (low dose) vs. placebo Vitamin B1/6/12 vs. placebo	PC	Germany	Recruiting	340	NCT05638633
Phase 2 RCT	Efgartigimod vs. placebo	PC POTS	USA	Recruiting	42	NCT05633407
Phase 2/3 RCT adaptive	Ibudilast vs. Pentoxifylline vs. placebo	PC	Canada	Not yet recruiting	1,000	NCT05513560
Phase 2 RCT	Baricitinib vs. placebo	PC cognitive	USA	Not yet recruiting	30	NCT05858515
Phase 2 RCT	BC007 aptamer vs. placebo	LC fatigue	Germany/ Europe	Not yet recruiting	114	EudraCT2022-003452-14
Phase 4 RCT	Loratidine vs. placebo	LC	India	Not yet recruiting	64	CTRI/2022/07/043679
Vascular						
Phase 2 RCT	Hyperbaric oxygen therapy vs. sham	PC or LC	Sweden	Recruiting	80	NCT04842448
Phase 2 RCT	Vericiguat vs. placebo	PC ME/CFS (CCC or IOM) and endothelial dysfunction	Germany	Not yet recruiting	104	NCT05697640
Antiviral						
Phase 2 RCT	Paxlovid vs. Ritonavir vs. placebo	PC	USA	Recruiting	200	NCT05576662
Phase 2 RCT	Temelimab vs. placebo	PC neuropsychiatric	Switzerland	Recruiting	200	NCT05497089
Phase 3 RCT	Meplazumab (anti-CD147) vs. placebo	PC (at least one symptom)	China	Not yet recruiting	144	NCT05813587
Neuro-modulators						
Phase 4 RCT (open)	Dextroamphetamine vs. app	PC cognitive	USA	Recruiting	120	NCT05597722
Phase 2 RCT	Low-dose Naltrexone (LDN) vs. placebo	PC ME/CFS	Canada	Not yet recruiting	160	NCT05430152
Phase 2 RCT	Lithium vs. placebo	LC fatigue and/or brain fog	USA	Recruiting	50	NCT05618587
Phase 2 RCT	Vortioxetine vs. placebo	PC cognitive	Canada	Complete	200	NCT05047952
Phase 2 RCT	Fampridine vs. placebo	PC cognitive	Switzerland	Recruiting	44	NCT05274477
Phase 2 RCT	Ketamine vs. placebo	PC depressive	USA	Recruiting	12	NCT05690503

*ClinicalTrials.gov, https://clinicaltrials.gov/; EU Clinical Trials Register https://www.clinicaltrialsregister.eu/; International Clinical Trials Registry Platform (ICTRP), https://www.who.int/clinical-trials-registry-platform (date 22.5.2023); RCT, randomized controlled trial; PC: Post-COVID-19 Condition or Syndrome, LC: Long Covid; NCT: National Clinical Trials Number = ClinicalTrials.gov Identifier.

Consensus Criteria (54). In addition to quantification of symptoms and functional impairment by specific questionnaires and patient reported outcome measures (PROMs), neurocognitive and autonomic testing, multimodal MRI of the brain, as well as assessment of physical fatigue and endothelial dysfunction will be performed before and after treatment (18, 51–53). Further we offer regular education and support in diagnostic assessment of ME/CFS.

Regulatory requirements make investigator-initiated clinical trials challenging. For clinical trial management, a clinical trial office (CTO) platform aids in protocol preparation and is in charge of all regulatory

TABLE 2 Further drugs of interest in PCS and ME/CFS.

Target	Drugs	References
Inflammation	Kinase inhibitors	Ref. (36, 37)
	Antihistamines (H1 + H2)	Ref. (38)
	Minocycline	Ref. (39)
	Metformin	Ref. (40)
Autoantibodies	CD20 monoclonal antibodies targeting B-cells	Ref. (20)
	CD19 monoclonal antibodies targeting B-cells	Ref. (41)
	BTK inhibitor	Ref. (42)
Vascular	Pyridostigmine	Ref. (43)
	β2/3 receptor agonists	Ref. (44)
	PDE5 inhibitor	NCT00598585
	Nicotine	Ref. (45)
Neuromodulation	Low dose aripiprazole	Ref. (46)
	Methylphenidate	Ref. (47)
	Guanfacine	Ref. (48)

and data safety affairs, trial submission, monitoring, data management, and biostatistical support. Harmonized clinical study documents including protocols, diagnostic criteria, and clinical outcome parameters are provided for all studies to allow rapid preparation of clinical trials and comparison of outcomes among the various trials. Measures for quality assurance include recruitment of patients from specialized university institutions and from observational studies, the use of standardized diagnostic criteria, and the collection of a harmonized set of data in a secure common database. This approach will allow to perform excellent systematic and comprehensive analyses, and to compare the results across all trials.

Clinical trials will be accompanied by a comprehensive biomarker program to understand pathomechanisms of relevance for drug efficacy and to identify companion diagnostics. The biomarker platform will provide comprehensive phenotyping for all trials including the analyses of soluble markers for inflammation and endothelial dysfunction, autoantibodies, immune cell phenotyping, viral persistence, and reactivation, as well as high-resolution approaches such as single-cell RNA sequencing (scRNA-seq) and proteomics (15, 55–57). Special attention needs to be given to the observation that single biomarkers often fail to capture the properties of complex diseases. New proteomic techniques allow to measure signatures in human serum und plasma at low costs, and can rapidly be translated into panel assays that suit routine testing (56, 57). High-resolution scRNA-seq can assess all immune cells and deviations of their molecular programs in parallel, allowing unravelling alterations in subpopulations unamenable by routine diagnostics as well as the development of novel signatures for disease and treatment outcome (55, 58). To assure quality of biomaterial and comparability of laboratory results, all blood samples will be collected in a harmonized manner, and then processed and stored according to standard operating procedures (SOPs) at local biobanks.

A diagnostic platform will perform structural and functional MRI studies and vascular diagnostics before and after interventions, including assessments of endothelial function and perfusion using non-invasive detection and measurement of endothelial dysfunction *via* Endo-PAT™, optical coherence tomography angiography (OCT-A), and arterial spin labeling (ASL) MRI (18, 59). Diagnostic assessments will be performed using harmonized protocols that have been previously established within the German National Pandemic Cohort Network (NAPKON) (60).

Links between clinical, diagnostic, and biomarker data will be established *via* bioinformatics, statistics, machine learning, and AI with the overarching goal to identify subgroups responding to the different therapeutic strategies, to further elucidate the pathogenesis of PCS and ME/CFS, and to identify diagnostic and prognostic biomarkers.

The first proof-of-concept trials (in phase II settings) performed are hypothesis-driven with a rationale based on clinical phenotypes and existing biomarkers. Repurposing of drugs will guarantee rapid trial initiation and drug availability. To assess the role of autoantibodies, a proof-of-concept trial with repetitive immunoadsorption in PC ME/CFS (NCT05629988) as well as a randomized controlled trial (RCT) with a sham-apheresis in postinfectious and PC ME/CFS with autoantibodies will be performed (NCT05710770) (61). Patients responding to immunoadsorption but relapsing will be treated in a consecutive trial with a B cell depleting monoclonal antibody. To treat endothelial dysfunction and hypoperfusion in PCS and PC ME/CFS, a phase II trial with the sGC stimulator vericiguat has been initiated (NCT05697640). Positive effects of prednisolone treatment in PCS with neurological symptoms have been suggested in case series (62). A RCT with high dose prednisolone will therefore be performed in PCS with predominant neurocognitive impairment, in which inflammation and autoantibodies targeting brain epitopes are common (17). Hyperbaric oxygen therapy was already shown to improve fatigue and cognitive impairment in a sham-controlled trial in long COVID patients (32). The efficacy of HBOT in patients with ME/CFS with moderate to severe cognitive impairment will be studied, too.

Based on results of these phase II trials, drugs and medical devices will be identified to be further evaluated in phase III trials together with the NAPKON-TIP (National Pandemic Cohort Network – Therapeutic Intervention Platform) supported by the German Network University Medicine (NUM) and international partners. The patient organizations Long Covid Deutschland and Deutsche Gesellschaft für ME/CFS are included and participate in the conception and conduction of all clinical trials as well as in the translation of the biomedical research results. Collaboration with the pharmaceutical industry is desired for fast access to drugs, financial support, achieving rapid licensing, and integrating further drugs to be developed.

Conclusion

Our concept of a multipronged clinical trial platform approach addresses the complexity and heterogeneity of PCS and ME/CFS, enabling to test numerous drugs in clinical trials in a harmonized manner accompanied by comprehensive mechanistic studies. Such an

approach will pave the way for more rapid development of drugs for PCS and ME/CFS to find therapeutic solutions for specific subgroups and finally all patients. Further, it will allow the development and identification of precise diagnostic, prognostic and companion biomarkers ultimately leading to targeted and individualized therapies combatting the different disease mechanisms. Finally, the identification of biomarkers predicting response to treatment provides strong evidence for causative pathomechanisms.

Author's note

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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

CS, SB, and UB developed the concept of the studies. BS, CaF, HPru, ChF, and JB-S gave important input to the study concepts. CS was the guarantor, wrote the original draft of the paper. CS, UB, BS, CaF, HA, JBS, CM, ACA, JLS, FP, MR, SS, DH, and CH reviewed and edited the paper. CH attested that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The Charité Universitaetsmedizin Berlin holds a patent for the use of vericiguat in Post-COVID Syndrome. CS, JB-S, CH, KW, ES, CaF, HPru, HPre, M-LM, HA, ChF, HZ, BS, CM, MT, AK, MR, MM, LS, FKo, FP, LB, and SB are employed at Charité Universitaetsmedizin Berlin.

CM was employed by Labor Berlin - Charité Vivantes GmbH.

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

The Handling Editor NS declared a past collaboration with the Author CS.

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Glossary

AI	artificial intelligence
ANA	antinuclear antibodies
ASL	arterial spin labeling
BTK	Bruton tyrosinkinase
CTO	Clinical trial office
EBV	Epstein–Barr virus
Endo-PAT™	Brand name
GPCR	G protein-coupled receptor
HBOT	Hyperbaric oxygen therapy
JAK	Janus kinase
LC	Long COVID
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NAPKON	National Pandemic Cohort Network
NAPKON-TIP	National Pandemic Cohort Network – Therapeutic Intervention Platform
NCT	National Clinical Trials Number = ClinicalTrials.gov Identifier
NKSG	Nationale Klinische Studien Gruppe = National Clinical Study Group
NUM	Network University Medicine
OCT-A	optical coherence tomography angiography
PC	Post COVID
PCS	post-COVID-19 syndrome
PDE5	phosphodiesterase type 5
PEM	post-exertional malaise
POTS	postural tachycardia syndrome
RCT	randomized controlled trials
RNA	Ribonucleic acid
scRNA-seq	single-cell RNA sequencing
sGC	Soluble guanylate cyclase
SOP	standard operating procedures
TLR-3	toll-like receptors 3
WHO	World Health Organisation

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Post-COVID sequelae effect in chronic fatigue syndrome: SARS-CoV-2 triggers latent adenovirus in the oral mucosa

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The post-viral fatigue syndromes long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have multiple, potentially overlapping, pathological processes. These include persisting reservoirs of virus, e.g., SARS-CoV-2 in long COVID patient's tissues, immune dysregulation with or without reactivation of underlying pathogens, such as Epstein–Barr virus (EBV) and human herpesvirus 6 (HHV6), as we recently described in ME/CFS, and possibly yet unidentified viruses. In the present study we tested saliva samples from two cohorts for IgG against human adenovirus (HAdV): patients with ME/CFS (n =84) and healthy controls (n =94), with either mild/asymptomatic SARS-CoV-2 infection or no infection. A significantly elevated anti-HAdV IgG response after SARS-CoV-2 infection was detected exclusively in the patient cohort. Longitudinal/time analysis, before and after COVID-19, in the very same individuals confirmed HAdV IgG elevation after. In plasma there was no HAdV IgG elevation. We conclude that COVID-19 triggered reactivation of dormant HAdV in the oral mucosa of chronic fatigue patients indicating an exhausted dysfunctional antiviral immune response in ME/CFS, allowing reactivation of adenovirus upon stress encounter such as COVID-19. These novel findings should be considered in clinical practice for identification of patients that may benefit from therapy that targets HAdV as well.

KEYWORDS

post-COVID condition, SARS-CoV-2, myalgic encephalomyelitis/chronic fatigue syndrome, ME/CFS, human adenovirus (HAdV), saliva antibodies, oral mucosa immune response

Introduction

There is abundant evidence for infection as a trigger of chronic fatigue, e.g., EBV-driven infectious mononucleosis (IM) causing post-viral fatigue, *Coxiella burnetii* initiating post-Q fever fatigue, Ebola virus activating post-Ebola fatigue, SARS-corona virus from 2003 inducing post-SARS syndrome, and now recently SARS-CoV-2 triggering long COVID (1, 2). These post-viral fatigue syndromes are debilitating illnesses affecting millions of individuals worldwide. The pathophysiological mechanisms are complex (1) and involve autoimmune and dysfunctional antiviral and metabolic mechanisms including failure of aerobic energy production (3, 4). The symptoms have been studied extensively in ME/CFS and include post-exertional malaise (PEM)—the cardinal diagnostic symptom, postural tachycardia syndrome (POTS), myalgia,

dysautonomia with unrestored sleep, and neurocognitive disturbance (brain fog) (5). Risk factors for developing long COVID include type 2 diabetes, SARS-CoV-2 RNAemia, EBV-viremia, and certain autoantibodies (6). ME/CFS is often (up to 70% of cases as reported in some studies) triggered by EBV-induced IM (2), and associates also with reactivation of herpesviruses, i.e., EBV and human HHV6 (1, 2). However, no convincing data are available to assign a defined causative pathogen for ME/CFS, albeit human herpesviruses and enteroviruses have been indicated (7). Previous studies have also investigated whether ME/CFS is associated with human adenovirus (HAdV) by employing antibody serology-analysis of plasma samples. No association was found, however (8, 9).

Here, we have explored HAdV reactivation in the oral mucosa and have extended our recent study by Apostolou et al. (10), in which we found strong reactivation of *Herpesviridae* family members, e.g., EBV, HHV6, as well as human endogenous retrovirus K (HERV-K) in saliva after mild/asymptomatic SARS-CoV-2 infection. HAdV are pathogenic DNA viruses both in humans and animals. There are over 110 HAdV types based on their unique genomic characteristics, which are classified into seven, serologically different, species (A–G) (11). After initial infection HAdV can establish a persistent, latent infection in various cell types. Typical sites are adenoids, tonsils, and gut-associated lymphoid tissue (12). Occasionally HAdV infections can cause keratoconjunctivitis, haemorrhagic cystitis, hepatitis, haemorrhagic colitis, pancreatitis, nephritis, or meningoencephalitis either after primary infection or after reactivation (13). In this study we have investigated the presence of HAdV by analyzing anti-HAdV antibody "fingerprints," based on the fact that antiviral IgG is detectable in a wider time-window (months) compared to virus detection by polymerase chain reaction (PCR), where viral DNA can be detected in a narrow time interval (days) after acute infection.

Methods

Human saliva panel

Saliva samples were collected from 84 ME/CFS patients that were recruited to this study from the Bragée Clinic, Stockholm, Sweden. All patients were diagnosed with ME/CFS according to the 2003 Canadian Consensus Criteria before the COVID-19 pandemic (3). Saliva samples were also collected from 94 healthy control donors (HD) recruited from Linköping University and Hospital. None of the participants were vaccinated against SARS-CoV-2 at the start of the study (inclusions from June till December 2020). Description of saliva collection, handling of samples, study participant enrolment is detailed in Apostolou et al. (10). The study was reviewed and approved by the Swedish Ethical Review Authority, Regional Ethics Committee (D.nr. 2019-0618).

Analysis of virus IgG in oral mucosa

Anti-HAdV IgG antibodies in saliva were used as markers for HAdV reactivation. The specific adenovirus IgG was analyzed in saliva samples (diluted 1:4), and in plasma samples (diluted 1:100), using an anti-HAdV IgG ELISA kit from EUROIMMUN AG (Lübeck, Germany) according to manufacturer's instructions. Antibodies against SARS-CoV-2 receptor-binding domain of the spike protein (RBD), and anti-nucleoprotein (NP) antibodies were tested in multiplex assay as previously described (10).

Statistics

Data were analyzed for the determination of statistical significance of the observed differences between groups, with a p-value < 0.05 considered as significant. All statistical analyses were performed using the SAS Institute JMP program (v 13.2.1) or GraphPad Prism software (v.9.1.2).

For the comparisons between ME/CFS and HDs groups, we used the non-parametric Kruskal-Wallis test for multiple comparisons, since data was not normally distributed, and controlled for false discovery rate (5%) by using two-stage Benjamini, Krieger and Yekutieli (BKY) procedure (14). The data from plasma samples were normally distributed and hence one-way ANOVA was used for multiple comparisons. Multiple linear regression was performed for the determination of confounding factors (age, sex, mononucleosis) and controlled for false discovery rate of 5% according to BKY. Statistically significant differences are indicated in the figures as $^{*}p < 0.05$, $^{**}p < 0.01$. Non-parametric bi-variate analysis was performed according to Pearson, e.g., linear regression, in order to analyze possible correlation between anti-HAdV IgG in plasma and anti-HAdV IgG in saliva.

Results

Saliva samples were collected from patients with ME/CFS (n = 84) and healthy control donors (HD; $n = 94$) and analyzed for anti-HAdV IgG and anti-SARS-CoV-2 IgG as described in Methods. Both patients and controls were divided in three groups based on their immune response to SARS-CoV-2: 1. Participants with a systemic response (IgG in plasma, with or without saliva IgG), termed systemic-ME or systemic-HD; 2. Participants with local (saliva) response only, named local-ME or local-HD; 3. participants with no anti-SARS-CoV-2 response (negative-ME or negative-HD).

Our data reveals a significantly elevated IgG response in saliva against HAdV following SARS-CoV-2 infection in patients with ME/CFS, whereas no difference was found in HDs (Figure 1): negative-ME vs. systemic-ME ($^{*}p = 0.0102$), and negative-ME vs. local-ME ($^{*}p = 0.0135$); negative-HD vs. systemic-HD (*ns*, $p = 0.3479$), and negative-HD vs. local-HD (*ns*, $p = 0.1796$). More importantly, comparing the HD cohort to the ME/CFS cohort, significantly elevated HAdV IgG levels were found in patients with ME/CFS with a systemic SARS-CoV-2-response compared to HD with a systemic SARS-CoV-2 response ($^{**}p = 0.0074$; Figure 1).

Baseline antibody responses against HAdV in the local oral mucosa, independently of SARS-CoV-2 infection, e.g., negative-ME vs. negative-HD cohorts, were not significantly different (Figure 1).

We also tested whether gender, age, or a history of mononucleosis were confounding factors for anti-HAdV antibody levels. Multiple regression analysis was performed using Benjamini, Hochberg, Yekutieli FDR of 5% (14). Gender, age, or mononucleosis were found not to be confounding factors for saliva HAdV IgG levels.

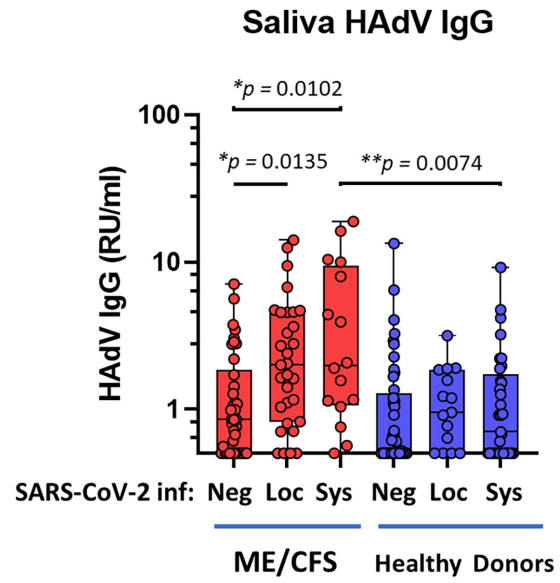

FIGURE 1
Saliva antibody reactivity to human adenoviruses in patients with ME/CFS (n =84, red dots/boxes) and healthy donors (n =94, blue dots/boxes). Sys: participants anti-SARS-CoV-2 RBD (spike protein receptor binding domain)-positive for systemic response in plasma (with or without saliva IgG; ME, n =18; HD, n =33). Loc, participants RBD-positive for local response in saliva (ME, n =31; HD, n =15). Neg, participants RBD IgG-negative both in plasma and saliva (ME, n =38; HD, n =46). Data are presented as boxplots with median values with minimum to maximum whiskers. Statistically significant differences according to non-parametric Kruskal-Wallis procedure and false discovery rate adjustment (5%) according to Benjamini, Krieger and Yekutieli procedure (14) are indicated as *p <0.05, **p <0.01. RU/ml, relative units per milliliter.

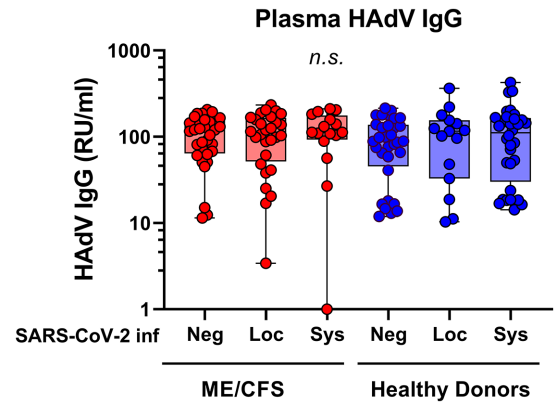

FIGURE 2
Plasma antibody reactivity to human adenoviruses in patients with ME/CFS (n =75, red dots/boxes) and healthy donors (n =79, blue dots/boxes). Sys: participants SARS-CoV-2 RBD (RBD)-positive for systemic response in plasma (with or without saliva IgG; ME, n =15; HD, n =32). Loc, participants RBD-positive for local response in saliva (ME, n =28; HD, n =15). Neg, participants RBD IgG-negative both in plasma and saliva (ME, n =32; HD, n =32). Data are presented as boxplots with median values with minimum to maximum whiskers. Statistically significant differences were not found (*n.s.*, non-significant) according to non-parametric Kruskal-Wallis procedure and false discovery rate adjustment (5%) according to Benjamini, Krieger and Yekutieli procedure (14). RU/ml, relative units per milliliter.

SARS-CoV-2 infection generates a distinct antibody fingerprint of latent HAdV reactivation in saliva, but not in plasma. The plasma anti-HAdV IgG showed no significant differences between the subgroups (Figure 2). Furthermore, there was no correlation between anti-HAdV IgG in plasma and anti-HAdV IgG in saliva (Pearson's linear regression analysis, data not shown), indicating that the immune response in the local mucosal compartment is discrete from systemic immune response.

In order to validate the saliva HAdV IgG data, we performed a longitudinal analysis. Local reactivation of latent HAdV was confirmed in pairwise analysis by following individuals before and after SARS-CoV-2 infection. Matched pairs of saliva samples were analyzed in a subgroup of participants (n = 13 HDs, and 5 ME/CFS), who were infected with SARS-CoV-2 after the first round of sampling and during the course of this study (in the second pandemic wave between December 2020 to January 2021). Infection was documented by either PCR and/or established specific symptoms and was confirmed by the significant upregulation in RBD IgG (data not shown, $p = 0.03$) and IgM response (data not shown, p = 0.04). We found significant upregulation of HAdV IgG, within the same individuals when comparing antibody levels before and after SARS-CoV-2 infection using matched pair statistical analysis (Figure 3).

Discussion

To the best of our knowledge this is the first report on adenovirus (re)activation after an infectious stress event—in this case SARS-CoV-2 infection, which is evident in saliva of patients with ME/CFS. Remarkably, the response was not observed in saliva from HD. The antibody levels were more pronounced in the subgroup of ME/CFS patients showing a systemic immune response to SARS-CoV-2 but was also significant in ME/CFS patients with a local SARS-CoV-2 response.

The results were validated in a longitudinal analysis of HAdV IgG level before and after SARS-CoV-2 infection during the first year of the pandemic. Data clearly indicate that SARS-CoV-2 reactivates latent HAdV in oral mucosa/tonsil tissue as determined by specific mucosal antibody "fingerprints." The higher levels of antibody responses against HAdV in saliva that are indicative of HAdV reactivation were not detected in plasma. The lack of significant difference in the plasma in group comparisons, contrary to the strong statistical differences in saliva, was reported in our previous study for other latent viruses like EBV and HHV6 in the same cohorts (10). Adenoviruses rely in a latent state in the adenoids and tonsils of the oral cavity (11); therefore, their reactivation and subsequent immune responses are probably confined locally in saliva and hence easier to detect.

The antibody fingerprint of HAdV after mild/asymptomatic COVID-19 observed in the current study extends our previous data in which elevated saliva IgG against EBV, HHV6, and HERV-K was noted in ME/CFS, and in particular anti-EBV nuclear antigen 1 (EBNA1) IgG elevation was found to be exclusive for ME/CFS (10). The scenario is reminiscent of a chain-reaction, where one virus triggers a second virus, as exemplified by SARS-CoV-2 triggering EBV (10), and human endogenous retroviruses (HERVs). Activation of HERV by EBV might be the missing link between an initial EBV infection and the later onset of multiple sclerosis (MS) (15). There are

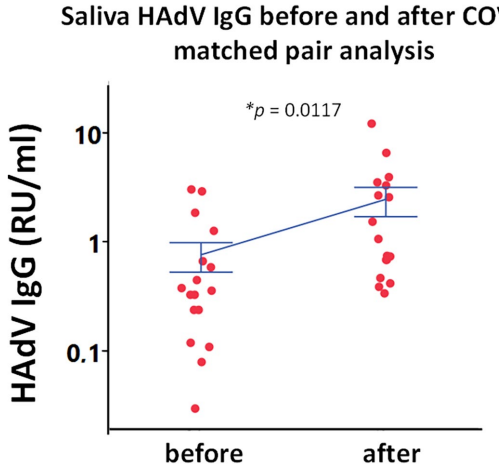

FIGURE 3
Paired analysis of saliva HAdV IgG from the same subjects before and after SARS-CoV-2 infection (n =18). Individual points represent saliva HAdV IgG concentration as relative units per ml (RU/ml) in a longitudinal analysis of 18 individuals. Blue lines represent mean±SEM. Statistically significant difference was tested in using matched pairs analysis platform (JMP statistical program). *p <0.05 indicates statistically significant differences.

considerable phenotypic and neuroimmune elements overlapping in ME/CFS and MS, including anti-EBNA1 IgG elevation (10, 16–18).

So, what is the cellular mechanism behind this HAdV elevated response effect? And why is it so unique for patients with ME/CFS and most likely patients with long COVID, as recently discussed by Davis et al. (1). Several studies report immunosuppressive effects exerted by a SARS-CoV-2 infection such as degradation of mitochondrial antiviral signaling protein (MAVS) and inhibition of type I interferon (IFN-I); reactivation of HHV6; HLA-G induced immunosuppression; reduced innate immunity, reduced antigen processing, reduced T-cell response (19–22). However, those patients had severe/moderate COVID-19 and were mainly hospitalized. In contrast, our study is focused on participants with mild/asymptomatic COVID-19. The fact that adenovirus was not activated in the oral mucosa of healthy donors, but only in patients with ME/CFS points toward a dysfunctional immune surveillance including exhausted antiviral interferon response after or even before infection by SARS-CoV-2, possibly due to previous encounter with HAdV and EBV that antagonize a proper DNA-sensing antiviral response (23, 24).

HAdV is ubiquitous in humans with nearly all individuals infected with at least one type by 6 years of age. Globally, a majority of adults have positive anti-HAdV IgG in plasma. HAdV can establish persistent infections with a chronic low-grade replication in different tissues, foremost tonsils and adenoids, and in the gastrointestinal tract gut-associated lymphoid tissue (11). Of particular importance is the fact that a majority of ME/CFS patients report irritable bowel syndrome with gut-symptoms like stomach cramps, bloating, diarrhea, and constipation, years prior to the onset of ME/CFS. This pre-ME/CFS stage could possible undermine a functional response to EBV-induced IM, which is a common trigger for ME/CFS disease onset (2). Furthermore, HAdV can be activated by a variety of stressors such as infections and toxins that exert a suppressive effect on the immune system (11).

Our findings also raise the question whether HAdV acts as a driver of the ME/CFS pathology, possibly in synergy with herpesviruses EBV and HHV6. Hanson and co-workers (9) recently published an extensive study including 122 different pathogens, i.e., HAdV, and plasma antibody response against these in ME/CFS, albeit their study did not implicate any one of the analyzed pathogens in ME/CFS, they write: "The possibility remains that ME/CFS cases arise from an uncommon variant of one or more enteroviruses or another type of virus and/or an uncommon reaction to a common endemic virus." Here in our present study, we have detected a strong candidate for this common endemic virus: human adenovirus. We propose that HAdV acts as a chronic mucosal "irritant" that facilitates frequent reactivation of another common virus, the EBV—a proposal based on data presented here that HAdV is reactivated in ME/CFS, but not in HD, taken together with our recent data on mucosal elevation of EBV, HHV6 and HERV-K in ME/CFS (10). Clinically, our findings on HAdV potential involvement along with reactivated herpesviruses in the pathogenesis of ME/CFS and/or long COVID also open doors for novel antiviral therapy strategies. In clinical practice, particularly in immunosuppressed transplant patients, the antiviral brincidofovir (BCV) is being used to curb HAdV infections. BCV is a lipid conjugate of cidofovir that exerts high activity against double-stranded DNA viruses, especially adenovirus (25). In addition to antivirals, immune therapy is being explored for HAdV infection (11).

Summary

We found a significantly elevated anti-adenovirus IgG titer in saliva of patients with ME/CFS after SARS-CoV-2 infection. This was not observed in healthy donors. We propose that this indicates an exhausted dysfunctional antiviral immune response in ME/CFS, allowing reactivation of adenovirus upon stress encounter such as COVID-19. Our findings demand further large-scale studies to better understand the role of HAdV both in ME/CFS and long COVID.

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 study was reviewed and approved by the Swedish Ethical Review Authority, Regional Ethics Committee (D.nr. 2019-0618). The patients/participants provided their written informed consent to participate in this study.

Author contributions

UH and AR conceptualized and conducted experiments, analyzed data, and wrote the manuscript. EA collected samples, organized the biobank, analyzed data, and wrote the manuscript. PS, BBe, OP, and BBr were responsible for patient contacts and provided samples and

clinical data. AR supervised and funded the project. All authors contributed to the article and approved the submitted version.

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Conflict of interest

PS, BBe, BBr, and OP declare disclosure of interest as having income from Bragée Clinics and BBr being a partial owner.

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

Publisher's note

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Fatigue presentation, severity, and related outcomes in a prospective cohort following post-COVID-19 hospitalization in British Columbia, Canada

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Introduction: Increasing evidence on long-term health outcomes following SARS CoV-2 infection shows post-viral symptoms can persist for months. These symptoms are often consistent with those of Myalgic Encephalomyelitis or Chronic Fatigue Syndrome (ME/CFS). The aim of the present study was to examine the prevalence and outcome predictors of post-viral fatigue and related symptoms 3- and 6-months following symptom onset.

Methods: A prospective cohort of patients hospitalized with Coronavirus disease (COVID-19) (n=88) were recruited from a Post-COVID-19 Respiratory Clinic (PCRC) in Vancouver, Canada to examine predictors of long-term fatigue and substantial fatigue. Multivariable mixed effects analyses examined the relationship between patient predictors, including pre-existing comorbidities, patient reported outcome measures, and fatigue and substantial fatigue at follow-up.

Results: The number of patients experiencing fatigue or substantial fatigue at 3 months post-infection were 58 (67%) and 14 (16%) respectively. At 6 months these numbers declined to 47 (60%) patients experiencing fatigue and 6 (6%) experiencing substantial fatigue. Adjusted analysis, for sex, age, and time, revealed the number of pre-existing comorbidities to be associated with fatigue (OR 2.21; 95% CI 1.09–4.49; 0.028) and substantial fatigue (OR 1.73; 95% CI 1.06–2.95; 0.033) at 3months follow-up. Except for shortness of breath, self-care, and follow-up time, all follow-up variables were found to be associated with fatigue and substantial fatigue at 3 months.

Conclusion: Fatigue and substantial fatigue are common after COVID-19 infection but often diminish over time. A significant number of patients continue to exhibit long-term fatigue at 6months follow-up. Further research is needed to clarify the causality of viral infections in the development and severity of fatigue as a symptom and in meeting post-viral fatigue syndrome or ME/CFS diagnostic criteria.

KEYWORDS

Long-COVID, post-COVID fatigue syndrome, post-COVID fatigue, chronic fatigue syndrome, myalgic encephalomyelitis

1. Introduction

Rapid global spread of Coronavirus disease (COVID-19) has resulted in an estimated 757 million confirmed cases and approximately 6.8 million deaths worldwide as of February 2023 (1). There have been extensive investigations into acute stages of viral infection however, less is known about the long-term impacts experienced after infection. As the number of patients who have recovered from COVID-19 grows, it is evident that "recovery" is not synonymous with a return to previous health status for many individuals.

Emerging evidence demonstrates that, for a significant number of individuals, post-COVID-19 sequalae persists well beyond the acute stages of viral infection (2–5). Estimates for the proportion of people who experience post-COVID conditions vary. However, symptoms that persist for more than 12 weeks are termed "Long-COVID' or Post-Acute Sequalae of coronavirus 2 (SARS-CoV-2) (6, 7). The Center for Disease Control estimates that over 30% of hospitalized individuals experience post-COVID related symptoms for 6 months or longer after infection (8).

COVID-19 is now recognized as a systemic disease with multiorgan involvement (9). Fatigue and cognitive impairment, along with abnormal respiratory function and other enduring neuropsychiatric and physical manifestations have been reported as the most prevalent and debilitating symptoms of post-COVID conditions (3, 10, 11). Literature examining long-term outcomes shows, for those hospitalized, post-COVID-19 symptoms can persist for upwards of 12 months (4). Indeed, many may experience long-term symptoms congruent with that of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), such as persistent or debilitating fatigue, also referred to as post-COVID-19 fatigue syndrome (3, 7).

Fatigue and other long-COVID related outcomes are varied across studies due to poor standardization of data collection methods and measurement tools (12). Standardized investigations into the presentation of fatigue and related symptoms after viral infection is critical to providing evidence-based post-viral care for those experiencing severe long-term forms of COVID-19 infection. In this study, we examine the clinical presentation of post-viral fatigue within a prospective cohort of individuals hospitalized with severe COVID-19 in Vancouver, Canada. Hospitalization and follow-up predictors of fatigue and patient-reported clinical outcomes are described at 3- and 6-months post-symptom onset of SARS-CoV-2 infection.

2. Materials and methods

2.1. Measurements

This study involved a prospective cohort of 88 adult individuals (≥18 years) recruited from the Post-COVID-19 Recovery Clinic (PCRC) in Vancouver, Canada. Participants included those with a confirmed SARS-CoV-2 infection who were hospitalized from March to June 2020. Detailed methods involving this cohort as well as 3- and 6-month respiratory outcomes, and some patient-reported outcome measures (PROMs) have been previously reported elsewhere (13, 14). Briefly, at hospitalization (admission) and 3- and 6-months post-symptom onset, patient medical history, clinical variables, and patient-completed standardized questionnaires were collected. Clinical predictors of fatigue included age, sex, number of pre-existing comorbidities, Intensive Care Unit (ICU) admission, and mechanical ventilation. Pre-existing comorbidities were characterized as any pre-existing lung, cardiac, liver, cerebrovascular, renal, or autoimmune disease, diabetes, Gastroesophageal reflux disease (GERD), blood clots, and/or malignancy. Patient-reported predictors included scoring on the EuroQoL 5-Dimensions (EQ-5D), the Frailty Index (FI), the University of California San Diego Shortness of Breath Questionnaire (UCSD), Patient Health Questionnaire-9 (PHQ-9), and the Pittsburgh Sleep Quality Index (PSQI).

The EQ-5D is a five dimension preference-based and quality-of-life assessment. Scores from the EQ-5D were converted to a health utility index whereby scores of 1 represent perfect health and scoring of 0 is death (15). The UCSD was used to assess the severity and impact of dyspnea (shortness of breath) on daily activities, with scores greater than 10 reflecting dyspnea (16, 17). PHQ-9 scores assessed the severity of depression symptoms through 9 questions, with higher scores indicating higher severity (18). Assessments of sleep quality and sleep patterns were ascertained using the PSQI which consists of seven domains (19). This analysis only considered the PSQI global score which is a summation of all sleep-related domains. Finally, aging and vulnerability to adverse outcomes were determined using the FI, which is scored from 0 to 1, with higher scores indicating greater frailty (20). FI is calculated as the proportion of deficits present out of a list of 40 potential health deficits across multiple organ systems.

2.2. Outcomes

Primary outcomes included the presentation and severity of persistent fatigue at 3- and 6-months post-symptom onset. Fatigue was classified as an individual reporting feeling tired or having little energy for several days or more over the last 2 weeks (PHQ-9) as well as, indicating "always feeling tired" (FI). Substantial fatigue was classified as an individual reporting fatigue, as defined above, and "slight" differences in their ability to conduct usual activities (EQ-5D).

2.3. Statistical analyses

Descriptive statistics were used to describe participant characteristics at the time of hospitalization. Associations between

all predictors (i.e., clinical and PROMs) and presentation of fatigue and substantial fatigue at 3- and 6-months were examined using multivariable mixed effect logistic regression modeling to account for correlations between timepoints and bivariate analyses were used to determine potential discrepancies between those with and without fatigue at each timepoint. Adjusted analysis of all predictor variables at 3- and 6-month timepoints did not include the EQ-5Ds "self-care" dimension due to a lack of variance in responses. Given the low number of patients with substantial fatigue at 6 months follow-up ($n = 6$), modeling for substantial fatigue included only the 3-month follow-up period. McNemar's test was then used to examine changes in the presence of substantial fatigue across time. Relationships between clinical predictors and PROMs were examined using multivariable mixed effects linear regression modeling. Statistical significance was determined by a two-sided p-value of <0.05. All analyses were conducted using the statistical software package R (Version 4.2.1).

3. Results

Table 1 shows the main characteristics of the cohort at hospitalization and 3- and 6-months as well as the prevalence of fatigue. Among those included in this analysis ($n = 88$), mean age was 61.1 (±16.2) years, 63.6% were male, 45.5% identified as white, 80.7 and 89.8% had no pre-existing lung or autoimmune disease, respectively. Approximately 48.2% were admitted to ICU, of whom 20.5% were on mechanical ventilation during hospitalization. Prevalence of fatigue and substantial fatigue were reported to be 66.7% and 16.1%, respectively, at 3 months. By 6-month follow-up, fatigue was exhibited in 59.5% and substantial fatigue in 6.9% of patients. Among participants with and without fatigue at 3- and 6- months, bivariate analysis indicated statistically significant differences in participant reported scoring on PHQ-9, EQ-5D, shortness of breath, and overall health scoring (Table 2).

TABLE 1 Characteristics of PCRC* cohort and presence of Fatigue at 3- and 6-months.

Variables	All PCRC participants (N=88)
Age	61.1 (±16.2)
Sex	
Male	56 (63.6)
Female	32 (36.4)
Ethnicity	
Asian	35 (39.8)
Other	13 (14.8)
White	40 (45.5)
Pre-existing comorbidities	1.5 (±1.3)
Lung disease	17 (19.3)
Cardiac disease	46 (52.3)
Diabetes	20 (22.7)
Cerebrovascular disease	4 (4.5)
Gastroesophageal reflux disease	12 (13.6)
Liver disease	4 (4.5)
Renal disease	10 (11.4)
Autoimmune disease	9 (10.2)
Blood clots	1 (1.1)
Malignancy	8 (9.1)
ICU*	41 (48.2)
Mechanical ventilation*	17 (20.5)
Fatigue	
3 Months	58 (66.7)
6 Months	47 (59.5)
Substantial fatigue	
3 Months	14 (16.1)
6 Months	6 (6.9)

*Post-COVID-19 Respiratory Clinic (PCRC); Data shown are mean ± standard deviation or number (%).
*Missing information for 3 individuals for ICU and 5 individuals for mechanical ventilation.

3.1. Hospitalization predictors of fatigue at 3 and 6 months

The number of pre-existing comorbidities had a trend toward association with fatigue at 3 months ($p = 0.06$). Adjusted multivariable analysis, controlling for age, sex, and time at the point of hospitalization, revealed number of comorbidities (OR 2.21; 95% CI 1.09–4.49; $p = 0.028$) to be a predictor of fatigue at 3 months post-viral infection (Table 3 and Figure 1). Interestingly, age demonstrated a subtle protective effect in the likelihood of developing fatigue by 3 months follow-up (OR 0.93; 95% CI 0.88–0.98; $p = 0.012$). Patients who did not exhibit fatigue at 3 months did not go on to exhibit fatigue at 6 months follow-up.

3.2. Predictors of fatigue at follow-up

Adjusted analysis, controlling for age and number of comorbidities, revealed correlations between fatigue and all variables measured at 3- and 6-months, with the exception of self-care and follow-up time (Table 4).

3.3. Substantial fatigue: hospitalization variables

Fourteen individuals exhibited substantial fatigue at 3 months and six continued to exhibit substantial fatigue at 6 months follow-up. No patients developed new substantial fatigue between follow-up time periods. Adjusting for age, the number of pre-existing comorbidities at hospitalization was associated with substantial fatigue at 3 months follow-up (OR 1.73; 95% CI 1.06–2.95; $p = 0.033$, Table 5). No other hospitalization variables were associated with substantial fatigue.

3.4. Substantial fatigue: follow-up

With the exception of shortness of breath, all follow-up variables were associated with substantial fatigue at 3 months. Due to the small number of cases at 6 months, we did not examine this relationship further.

TABLE 2 Characteristics of fatigue and no fatigue among participants at 3- and 6-months follow-up.

	Fatigue 3 months				Fatigue 6 months			
	Total	No	Yes	*p*-value	Total	No	Yes	*p*-value
	N = 87	*N* = 29	*N* = 58		*N* = 79	*N* = 32	*N* = 47	
Age; Mean (SD)	61.4 (16.1)	65.1 (11.7)	59.5 (17.7)	0.12	60.9 (16.6)	62.5 (14.8)	59.8 (17.9)	0.47
Sex								
Male; n (%)	55 (63.2%)	20 (69%)	35 (60.3%)	0.49	49 (62%)	20 (62.5%)	29 (61.7%)	1.0
Female; n (%)	32 (36.8%)	9 (31%)	23 (39.7%)		30 (38%)	12 (37.5%)	18 (38.3%)	
Ethnicity								
Asian; n (%)	34 (39.1%)	10 (34.5%)	24 (41.4%)	0.25	33 (41.8%)	15 (46.9%)	18 (38.3%)	0.33
White; n (%)	40 (46%)	12 (41.4%)	28 (48.3%)		37 (46.8%)	12 (37.5%)	25 (53.2%)	
Other; n (%)	13 (14.9%)	7 (24.1%)	6 (10.3%)		9 (11.4%)	5 (15.6%)	18 (38.3%)	
Number Pre-existing comorbidities; Mean (SD)	1.5 (1.3)	1.1 (1.1)	1.7 (1.4)	0.060	1.5 (1.3)	1.3 (1.3)	1.6 (1.3)	0.36
ICU								
No; n (%)	44 (50.6%)	15 (51.7%)	29 (50%)	1.0	39 (49.4%)	14 (43.8%)	25 (53.2%)	0.81
Yes; n (%)	41 (47.1%)	14 (48.3%)	27 (46.6%)		37 (46.8%)	15 (46.9%)	22 (46.8%)	
Missing	2 (2.3%)	0 (0.0%)	0 (0.0%)		3 (3.8%)	3 (9.4%)	0 (0.0%)	
Mechanical ventilation								
No; n (%)	66 (75.9%)	21 (72.4%)	45 (77.6%)	0.57	61 (77.2%)	22 (68.8%)	39 (83%)	0.54
Yes; n (%)	17 (19.5%)	7 (24.1%)	10 (17.2%)		13 (16.5%)	6 (18.8%)	7 (14.9%)	
Missing; n (%)	4 (4.6%)	1 (3.4%)	3 (5.2%)		5 (6.3%)	4 (12.5%)	1 (2.1%)	
PHQ-9 score[a]; Mean (SD)	3.6 (4.8)	0.3 (0.8)	5.8 (5.2)	<0.0001	3.6 (4.8)	0.3 (0.8)	5.8 (5.2)	<0.0001
Shortness of breath score[b]; Mean (SD)	17.2 (19.8)	7.4 (13.6)	22.1 (20.7)	0.0009	15.8 (18.0)	6.1 (8.6)	22.4 (19.8)	<0.0001
EQ-5D score[c]; Mean (SD)	7.9 (3.6)	5.5 (0.9)	9.1 (3.8)	<0.0001	7.5 (2.9)	5.8 (3.2)	8.8 (3.5)	<0.0001
Missing	3 (3.4%)	2 (6.9%)	1 (1.7%)		–	–	–	
Health today (0–100); Mean (SD)	75.8 (15.5)	87.4 (9.4)	70.1 (14.7)	<0.0001	80.7 (12.5)	87.5 (9.2)	76.0 (12.4)	<0.0001

[a]Patient Health Questionnaire-9 (PHQ-9 Score), scores range from 0 to 27; 0 = None-minimal and 27 = Severe.
[b]Shortness of Breath (UCSD), scores range 0 to 120; high scores indicate greater dyspnea.
[c]EuroQoL 5-Dimensions (EQ-5 Score), scores range from 0 to 1; 0 = Death and 1 = Perfect Health; "Self-care" not modeled due to lack of variance.

TABLE 3 Adjusted multivariate model of fatigue at hospitalization.

Predictors	Fatigue		
	OR	CI	*p*-value
Time (follow-up)	0.73	0.29–1.83	0.505
Sex			
Male	Ref	–	–
Female	1.32	0.31–5.59	0.707
Age	0.93	0.88–0.98	**0.012**
Number of comorbidities	2.21	1.09–4.49	**0.028**
ICU	1.47	0.29–7.46	0.645
Mechanical ventilation			
No	Ref	–	–
Yes	0.29	0.03–2.44	0.256

Bolded values indicate $p \leq 0.05$.

4. Discussion

The present study shows that long-term fatigue can persist for at least 6 months in 59.5% of patients previously hospitalized with SARS-CoV-2 infection. Within the PCRC cohort, reductions in the prevalence of fatigue and substantial fatigue were observed between 3- and 6-months follow-up. Greater improvements were observed among those experiencing substantial fatigue, which decreased to less than half of the original prevalence by the 6-month follow-up timepoint. These findings align with existing literature reporting a decreasing trend in the proportion of individuals experiencing fatigue across weeks since acute presentation (12, 21). Patients with more pre-existing comorbidities at the time of hospitalization were also found to be more likely to exhibit fatigue at 3- and 6- months post-viral infection. Patients who did not exhibit fatigue or substantial fatigue at 3 months did not go on to exhibit these symptoms at 6 months follow-up.

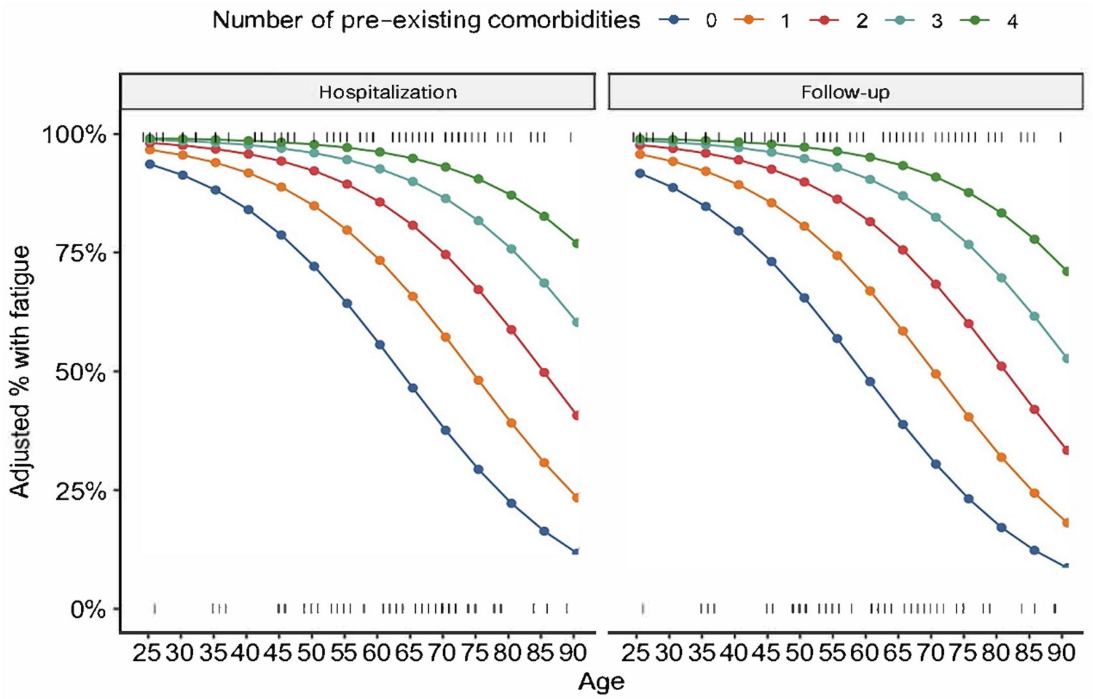

FIGURE 1
Fatigue and number of comorbidities at hospitalization and follow-up. The present figure shows the relationship between age, comorbidities and proportion with fatigue controlling for other variables in the multivariable model (no difference in proportions at 3 and 6 months).

TABLE 4 Mixed effect modeling of PROMs* follow-up variables and fatigue, adjusted for age, time, and number of pre-existing comorbidities.

	Fatigue		
	OR	95% CI	*p*
PHQ-9 score[a]	5.05	1.92–13.31	0.001
EQ-5D score[b]	2.35	1.65–3.36	<0.001
Usual activities	11.19	2.83–44.22	0.001
Mobility	5.39	1.96–14.82	0.001
Anxiety/depression	6.08	2.43–15.26	<0.001
Pain/discomfort	4.00	1.86–8.61	<0.001
Shortness of breath score[c]	1.09	1.04–1.14	<0.001
PSQI score[d]	1.71	1.24–2.36	0.001

*Patient-Reported Outcome Measures (PROMs).
[a]Patient Health Questionnaire-9 (PHQ-9 Score), scores range from 0–27; 0 = None-minimal and 27 = Severe.
[b]EuroQoL 5-Dimensions (EQ-5 Score), scores range from 0 to 1; 0 = Death and 1 = Perfect Health; "Self-care" not modeled due to lack of variance.
[c]Shortness of Breath (UCSD), scores range 0–120; high scores indicate greater dyspnea.
[d]Pittsburgh Sleep Quality Index (PSQI Score); scores range 0–21, higher scores indicate worse sleep quality.

TABLE 5 Predictors of substantial fatigue at 3 months.

Hospitalization variables	Substantial fatigue		
	OR	95% CI	*p*
Sex (Female)	1.36	0.41–4.33	0.608
Age	0.74	0.39–1.44	0.358
Number of pre-existing comorbidities[a]	1.73	1.06–2.95	0.033
ICU admission	0.77	0.23–2.44	0.660
Ventilation	0.28	0.01–1.60	0.240
3 Month follow-up variables	OR	95% CI	*p*
PHQ-9[b]	1.43	1.23–1.78	<0.001
EQ-5D[c]	1.64	1.32–2.20	<0.001
Mobility	2.43	1.47–4.33	0.001
Usual activities	5.46	2.69–13.45	<0.001
Pain/discomfort	3.98	2.06–8.81	<0.001
Anxiety/depression	3.70	1.96–8.04	<0.001
Health today	0.92	0.87–0.96	<0.001
Shortness of breath	1.02	1.00–1.05	0.062
PSQI[d]	1.43	1.21–1.77	<0.001

[a]Pre-existing comorbidity includes any pre-existing lung, cardiac, liver, cerebrovascular, renal, or autoimmune disease, diabetes, GERD, blood clots, and/or malignancy;
[b]Patient Health Questionnaire-9 (PHQ-9 Score);
[c]EuroQoL 5-Dimensions (EQ-5 Score);
[d]Pittsburgh Sleep Quality Index (PSQI Score).

While contrary to some findings, an unexpected and subtle protective effect of age on the presence of fatigue was observed at follow-up timepoints. This finding is consistent with Subramanian et al. (22) who found that after adjusting for baseline covariates, age above 30 years was associated with a lower risk of reporting post-COVID symptoms. While protective effects against fatigue among those greater than 65 years of age has also been observed, (23) other literature indicates that rates of long-COVID increase with age from about 1–2% for those in their twenties, to about 5% among those in their sixties (24). Indeed, post-viral fatigue syndrome or ME/CFS may affect young people (<30 years) more often (25). These discrepancies may be attributed to differential reporting of symptoms according to age and other factors

(e.g., those who are younger may be less accepting of feelings of disabling fatigue not previously experienced), and should be considered in future interpretations of fatigue and patient age. Additionally, those with very severe disease presentation on admission may have had lower expectations, in relation to being back to full health in the short-term, as compared to those with less severe SARS-CoV-2 infection. Research elucidating the role age and expectation of recovery play in long-term post-viral fatigue presentation necessitates further exploration.

Multimorbidity has also previously shown associations with post-viral fatigue syndrome symptoms (3, 22). Our research revealed, controlling for age, sex, and time, that the number of pre-existing comorbidities a patient had was significantly associated with fatigue and its respective severity at 3 months follow-up. Interestingly, adjusted analysis of our cohort revealed dyspnea to be associated with fatigue at 3- and 6-months but was found to only be marginally associated with substantial fatigue. These findings are likely the result of the small sample size of individuals found to be experiencing substantial fatigue at follow-up timepoints. Using the same cohort of patients, Shah et al. (13) found dyspnea to be the most common and persistent COVID-19 recovery symptom, with 42% experiencing dyspnea at 6 months follow-up. Unexplained dyspnea, (i.e., not related to abnormalities in lung function tests or imaging), was reported in 14 and 19% of cases at 3- and 6-months, respectively (13). Dyspnea in post-COVID cases has been suggested to result from multiple pathophysiological mechanisms, (26) and has also been reported in ME/CFS cases related to other causes (27). This symptom is also reported in dysautonomia, a common occurrence in ME/CFS (28).

4.1. Future directions

Our findings highlight the importance of further examinations into the role viral infections have in the presentation of long-term fatigue and related multimorbidities. While the number of individuals experiencing fatigue after viral infection is expected to decrease at follow-up timepoints, there are a subset of individuals for whom fatigue presentation and severity will persist. It is important that clinical teams remain attentive to monitoring patients for long-term fatigue after infection with SARS-CoV-2, encouraging patients to engage in practices that can aid in mitigating fatigue severity and lasting post-COVID symptoms. The considerable proportion of patients within our study continuing to exhibit symptoms of fatigue at 6 months highlights the need for further investigations into evidence-based practices that can meet the needs of those experiencing long-term fatigue after acute viral infection. Despite the change in severity with newer variants of SARS-CoV-2, it is key for provincial initiatives such as the Post-COVID-19 Interdisciplinary Clinical Care Network and national networks to support continuous data collection to assist longitudinal studies in Long COVID. Our findings add to the growing body of literature illuminating the role viral infections, such as COVID-19, may have in the development of long-term symptoms and persisting fatigue.

4.2. Limitations

This study has several limitations. Namely, our findings may be limited by the small participant sample size. As such, we were unable to examine correlates of substantial fatigue at 6 months due to limited size and subsequent lack of power. This prohibited examination of differences in the predictors of substantial fatigue at 3- and 6-months follow-up and prevented further investigation into those no longer exhibiting substantial fatigue at 6 months. Likewise, given our inability to ascertain whether criteria for ME/CFS or post-viral fatigue were met, substantial fatigue was used as a proxy. It is therefore likely that the prevalence of post-viral fatigue syndrome found in this study is substantially higher than rates adhering to strict clinical guidelines. Gaps remain in knowledge surrounding which comorbidities may predispose individuals to greater levels of long-term fatigue and its severity after hospitalization. Several studies have identified associations between self-reported measures and fatigue related outcomes, including reductions in quality of life and cognitive impairment (3, 29). However, there are limitations in such measures, highlighting the importance of objective outcome measures. We also note that the generalizability of study findings is limited to the sample of patients hospitalized with COVID-19 and cannot be extrapolated to those not exhibiting symptoms of COVID-19 or those who were not hospitalized.

5. Conclusion

After hospitalization, a significant proportion of individuals recovering from COVID-19 will continue to experience lingering symptoms for up to 6 months. For many patients, the presentation of post-viral symptoms will manifest in increased levels of fatigue. Further investigation into the presentation of fatigue, post-COVID infection, is needed to support evidence-based care and management for individuals experiencing long-term post-viral symptoms.

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 University of British Columbia Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AA performed the statistical analysis. TM and LN wrote the first draft of the manuscript. EM wrote a section of the manuscript. TB organized the database. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

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

Publisher's note

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The incidence and risk factors of selected drug prescriptions and outpatient care after SARS-CoV-2 infection in low-risk subjects: a multicenter population-based cohort study

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Background: Knowledge about the dynamics of transmission of SARS-CoV-2 and the clinical aspects of COVID-19 has steadily increased over time, although evidence of the determinants of disease severity and duration is still limited and mainly focused on older adult and fragile populations.

Methods: The present study was conceived and carried out in the Emilia-Romagna (E-R) and Veneto Regions, Italy, within the context of the EU's Horizon 2020 research project called ORCHESTRA (Connecting European Cohorts to increase common and effective response to SARS-CoV-2 pandemic) (www.orchestra-cohort.eu). The study has a multicenter retrospective population-based cohort design and aimed to investigate the incidence and risk factors of access to specific healthcare services (outpatient visits and diagnostics, drug prescriptions) during the post-acute phase from day-31 to day-365 after SARS-CoV-2 infection, in a healthy population at low risk of severe acute COVID-19. The study made use of previously recorded large-scale healthcare data available in the administrative databases of the two Italian Regions. The statistical analysis made use of methods for competing risks. Risk factors were assessed separately in the two Regions and results were pooled using random effects meta-analysis.

Results: There were 35,128 subjects in E-R and 88,881 in Veneto who were included in the data analysis. The outcome (access to selected health services) occurred in a high percentage of subjects in the post-acute phase (25% in E-R and 21% in Veneto). Outpatient care was observed more frequently than drug prescriptions (18% vs. 12% in E-R and 15% vs. 10% in Veneto). Risk factors associated with the outcome were female sex, age greater than 40 years, baseline risk of hospitalization and death, moderate to severe acute COVID-19, and acute extrapulmonary complications.

Conclusion: The outcome of interest may be considered as a proxy for long-term effects of COVID-19 needing clinical attention. Our data suggest that this

outcome occurs in a substantial percentage of cases, even among a previously healthy population with low or mild severity of acute COVID-19. The study results provide useful insights into planning COVID-19-related services.

KEYWORDS

SARS-CoV-2, post-COVID, COVID-19 sequelae, outpatient care, drug prescriptions, low-risk subjects, population-based cohort, ORCHESTRA project

1. Introduction

The COVID-19 pandemic has caused a global health, social and economic emergency (1). Over time, knowledge about the dynamics of transmission of SARS-CoV-2 and the clinical aspects of COVID-19 has steadily increased, although evidence of the determinants of disease severity and duration is still limited and mainly focused on older adult and fragile populations. In vulnerable populations there is also an increasing number of reports showing that individuals with comorbidities or admitted to the ICU for severe SARS-CoV-2 infection have a higher incidence of long-term effects of COVID-19 (2–6). Symptoms of sequelae vary widely in type and timing, as they can follow initial recovery or persist from the acute episode. They may also fluctuate, relapse, or change over time (6–9). The National Institute for Health and Care Excellence (NICE) provided clinical case definitions to identify and diagnose the long-term effects of COVID-19. Ongoing symptomatic COVID-19 is defined as the presence of persistent COVID-19 signs and symptoms after 4 weeks from diagnosis and up to 12 weeks. Post-COVID-19 syndrome is the presence of signs and symptoms that developed during or after a SARS-CoV-2 infection and persist for more than 12 weeks, not explained by an alternative diagnosis (8). Another definition was provided by the World Health Organization (WHO). According to WHO, the post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis (9). Effects of ongoing symptomatic and post-COVID-19 include fatigue/weakness, dyspnea, decreased exercise tolerance, cognitive impairment, prolonged smell and taste disorders, headache, anxiety, depression, insomnia, arthromyalgia, diabetes, and renal sequelae (2, 4–8, 10–16). These symptoms tend to cluster and can lead to a lower perceived quality of life and to an increased demand for and access to specific healthcare services (8, 14). The etiology of long-term effects of COVID-19 is likely multifactorial, with endothelial damage and immunological phenomena playing a significant role (7). Female sex, older age, presence of comorbidities, and severity in the acute phase of COVID-19 are associated with an increased risk of ongoing symptomatic and post-COVID-19 syndrome (3–5). Major limitations of previous studies include the study population, sample size, length of follow-up, case definition, and study design (3, 17). A few reports have recently highlighted diagnoses of long COVID in outpatients and/or previously healthy populations (18, 19). The present study was conceived and carried out in the Emilia-Romagna (E-R) and Veneto Regions, Italy, within the context of the EU's Horizon 2020 research project called ORCHESTRA (Connecting European Cohorts to increase common and effective response to SARS-CoV-2 pandemic).[1] The major aim of the study is to assess the incidence and risk factors of access to specific healthcare services (outpatient visits and diagnostics, drug prescriptions) within 12 months from confirmed SARS-CoV-2 diagnosis in a healthy population at low risk of severe acute COVID-19.

2. Materials and methods

2.1. Data source

The study was carried out in E-R and Veneto, two neighboring regions of northern Italy with a population of approximately 4.4 and 4.9 million residents, respectively. Both these two regions oversee a regional healthcare system and have exclusive competence in regulating, financing, and organizing healthcare services and activities carried out within their territory. Data were extracted from the E-R and Veneto Regions healthcare administrative databases. They include comprehensive information about healthcare provision by the regional healthcare systems. Secure record-linkage procedures were carried out at the individual level to merge pseudonymized data related to: official notifications of SARS-CoV-2 infections; drug prescriptions; outpatient care; residence and vital status; acute hospital admissions; community hospital admissions; emergency room access; long-term care facilities; and integrated home care. In the E-R cohort, an individual risk of hospitalization and death score was also assigned using a previously developed standardized algorithm. This algorithm relies on a multivariable prediction model which estimates a punctual measure for the individual risk of hospitalization or death within the reference year. The risk of hospitalization and death is then scored according to a four-level scale: low (probability <6%), moderate (≥ 6% and < 15%), high (≥ 15% and < 25%), very high (≥ 25%). This score is assigned yearly based on demographic and residence characteristics, comorbidities, and access to a wide spectrum of healthcare resources in a multiyear period before the reference year, and is routinely available in E-R administrative databases (20). The extracted data include updates of databases up to November 2021 for E-R and up to December 2021 for Veneto.

1 www.orchestra-cohort.eu

2.2. Study Aim and design

The study is a multicenter retrospective population-based cohort study aiming to investigate the incidence and risk factors of access to healthcare services. It focused on a largely healthy population, at low risk of acute severe COVID-19, to ensure that a high fraction of outcomes is attributable to COVID-19. Eligible participants included all adult subjects aged ≥18 years at diagnosis and with continuous residence status in the two regions in the 365 days before diagnosis. Low risk of severe acute COVID-19 was characterized by the absence of all the following types of care, in the 365 days prior to the SARS-CoV-2 diagnosis: hospitalization; visits to the emergency room; integrated home care; residence in a long-term care facility; selected drug prescriptions (at least one drug within the selected list; see Supplementary Table 1); selected outpatient care (at least one visit/diagnostics within the selected list; see Supplementary Table 1). Additionally, in the E-R cohort, low risk of severe acute COVID-19 was assigned only to subjects with a low-to-moderate risk of hospitalization and death score (19). The population of interest included all consecutive adult individuals with confirmed SARS-CoV-2 infection (PCR or antigen tests) in the E-R and Veneto Regions between February 2020 and November 2020 (E-R) or December 2020 (Veneto) who, at the time of diagnosis, were at low risk of severe acute COVID-19 disease. None of these subjects was vaccinated at the time of SARS-CoV-2 diagnosis, as the vaccination campaign in Italy only started in late December 2020. Individuals entered the cohort on the day of SARS-CoV-2 diagnosis. Outcomes were assessed within 365 days before and after the diagnosis. In the follow-up period we distinguished an acute phase (AP) from diagnosis till day 30 and a post-acute phase (PAP) from day 31 till day 365. For patients who were hospitalized at day 30, PAP started on the first day after hospital discharge. Outcomes were assessed during the PAP. Individuals who were continuously hospitalized from the AP to more than 365 days after SARS-CoV-2 diagnosis, or who had moved their residence outside the region during the AP, were excluded. Duplicate or incomplete records were discarded. The study was carried out and reported according to the GATHER statement (21).

2.3. Study outcomes

The outcome of interest was the access to specific healthcare services during the PAP, defined through a selected list of drug prescriptions and outpatient visits and diagnostics. This combined outcome was considered a proxy for the long-term effects of COVID-19 requiring medical attention (22). A broad range of drug prescriptions and outpatient care services was considered, to reflect the multifactorial nature of COVID-19, which can affect several organs and systems. Selected drug prescriptions included cardiovascular system (e.g., antithrombotics, antiarrhythmics, antihypertensives, beta blockers), antidiabetic, nervous system (e.g., antidepressants), and respiratory system (e.g., adrenergics and other drugs for obstructive airway diseases) drugs, oxygen and corticosteroids (22–24). Selected outpatient visits and diagnostics included ambulatory visits in cardiology, pneumology, angiology, neurology, psychiatry, rehabilitation-motor, nephrology, and diabetes, as well as other diagnostic and therapeutic procedures such as chest imaging, cardiac ultrasound imaging, pneumological diagnostics, electrocardiography, oxygen therapy, respiratory, and cardiological rehabilitation, peripheral vascular ultrasound imaging, training for cognitive disorders, hemodialysis, renal imaging, and glycated hemoglobin analysis (22–24). Only drugs and outpatient care provided by the regional healthcare system were included in the analysis. Drugs that are not reimbursed as well as private outpatient care not provided by the regional healthcare systems are not recorded. Details of drugs and outpatient care are reported in Supplementary Table 1, together with extraction criteria based on ATC classification and on E-R regional outpatient codes. Two analyses were performed, each with a different definition of the outcome variable. In the first analysis we considered a combined outcome including selected drug prescriptions and selected outpatient care, whichever came first. In the second analysis, each of the two outcomes of interest (drug prescriptions and outpatient care) was analyzed separately and the other was considered neither as a competing event nor as censoring. Hospitalization and death were always considered as competing events following a competing risk analysis framework. Hospitalization was considered a competing event due to drug prescriptions and clinical consulting not being tracked at the individual level during acute care stay: This prevented us from observing these events in administrative databases during the period a patient was hospitalized.

2.4. Other extraction criteria

Some clinically relevant variables were determined based on data recorded in administrative databases. COVID-19 severity (expressed on a four-level ordinal scale as low, mild, moderate or severe) was algorithmically assigned. The algorithm was based on respiratory system diagnoses (i.e., acute respiratory insufficiency, pneumonia, acute lower respiratory tract infections, other respiratory diagnoses), on ventilation procedures administered (i.e., oxygen therapy, non-invasive ventilation, invasive ventilation), and on intensive or sub-intensive care unit stay during hospitalizations in the AP. For subjects not hospitalized in the AP, the "low" level of severity was assigned. The algorithm is reported in Figure 1. Acute extrapulmonary complications (i.e., vascular, hemorrhagic, thrombotic, cardiac, neurological, septicemia and acute organ failure) were also identified, based on diagnoses during hospitalizations in the AP. These variables can occur only for hospitalized subjects. Criteria for the identification of respiratory diagnoses, ventilation procedures and acute extrapulmonary Complications, based on ICD-9-CM codes, are reported in Supplementary Table 2.

2.5. Statistical analysis

The statistical analysis was carried out separately in the two Regions, and results were pooled using meta-analysis. The frequency distributions of the categorical characteristics were described as absolute and percentage numbers. The numerical variables were described as the mean ± standard deviation and range. To evaluate potential risk factors, multivariable regression models were carried out. The incidence of outcomes in the PAP was analyzed with a competing risk approach: selected drug prescriptions and/or selected outpatient care were the outcomes of interest, whereas hospitalization

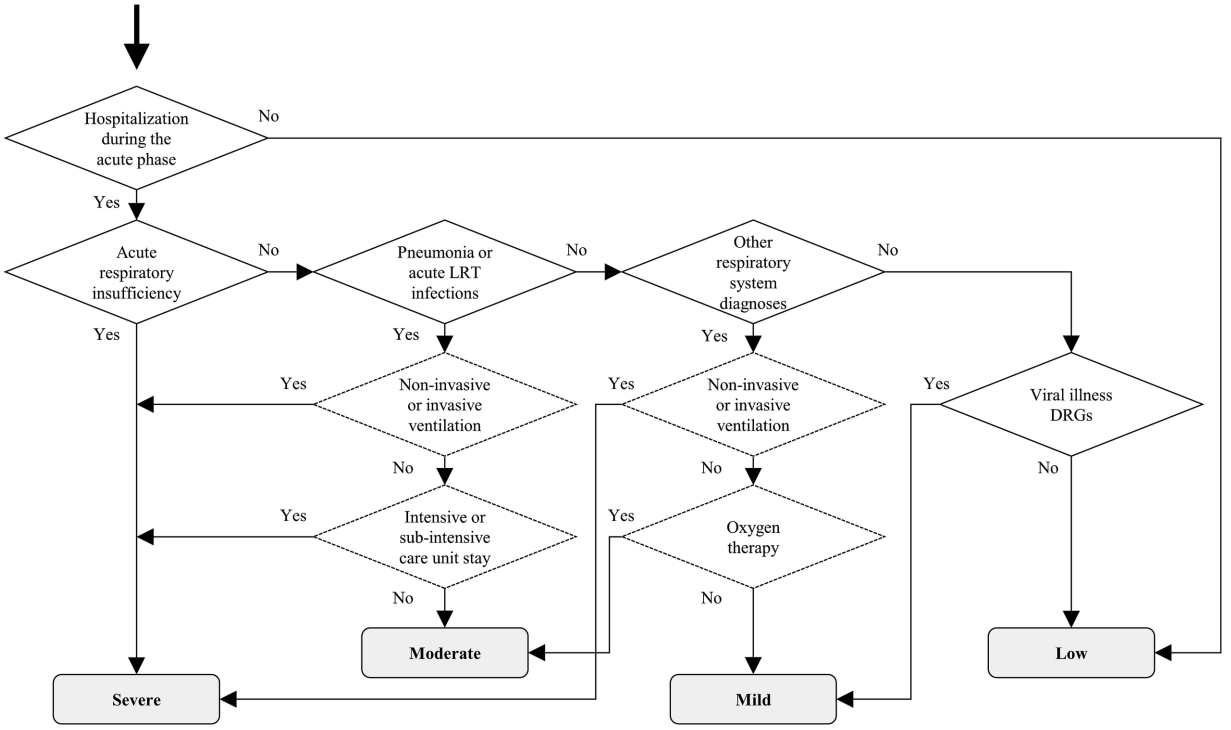

FIGURE 1
Algorithm for the assignment of COVID-19 severity. Notes: The decision tree shows the algorithm for the assignment of COVID-19 severity during the acute phase. The rhombuses indicate binary decision rules based on hospitalizations, respiratory diagnoses, Diagnosis-related groups (continuous border line) and ventilation procedures (dotted border line). The gray boxes indicate the assigned COVID-19 severity level (low, mild, moderate, severe). The data extraction criteria for each element in the decision tree are reported in Supplementary Table 2. LRT = lower respiratory tract; DRG = Diagnosis-related group.

and death were the competing events. Individuals who moved their residence outside of the E-R region during the PAP, as well as those who did not experience any outcome or competing event by the end of the PAP, were treated as having censored follow-up times. The incidence of outcomes over time was described using cumulative incidence functions curves (25). Uncertainty in curves was expressed with 95% confidence interval (CI) calculated with the asymptotic Aalen method (26). A multivariable Fine-Gray (FG) proportional subdistribution hazard regression model was used to assess the relationship between subjects' characteristics and the hazard of outcomes over time, also accounting for the occurrence of competing events (27). The explanatory variables were: time period (1st wave: February–May 2020, intermediate period: June–September 2020, 2nd wave: October–December 2020); age class at diagnosis (18–39, 40–49, 50–59, 60–69, 70–79, ≥80 years); sex (male, female); Italian citizenship (yes, no); only in the E-R cohort, the risk of hospitalization and death score (low, moderate); COVID-19 severity during the AP (low, mild, moderate, severe); acute extrapulmonary complications occurring in hospital during the AP (yes, no). Moreover, the area of residence (8 Local Health Units in E-R and 9 in Veneto) was also used as an independent variable to account for potentially different health policies. Associations were measured using the subdistribution hazard ratio (HR) and the uncertainty in results was expressed with 95% CI. Cis for HRs were calculated with the Wald method based on normal approximation. Pooling of hazard ratios obtained in the E-R and Veneto Regions' cohorts was carried out using random effects meta-analysis (MA). MA was performed with the inverse variance weights method and maximum likelihood estimator for between-study variance. Between-cohort heterogeneity was measured with the tau statistic (28) and its significance was assessed with the Cochran's Q test. All statistical tests were two-sided. Analyses were carried out by E-R with SAS/STAT 15.1 (SAS Institute Inc., Cary, NC) and R 4.0.4 (The R Foundation for Statistical Computing, Wien) and by Veneto with SAS/STAT 13.1 statistics software.

3. Results

There were 125,782 individuals positive for SARS-CoV-2 in the E-R region in the period from February 2020 to November 2020, and 261,178 in the Veneto Region from February 2020 to December 2020. Of these, 81.8 and 87.1% were adult individuals with complete data. Those who fulfilled the inclusion and exclusion criteria for the low-risk cohort and who were included in the data analysis numbered 35,128 in Emilia-Romagna and 88,881 in Veneto (Figure 2).

3.1. Characteristics of individuals

Descriptive characteristics of the cohort are reported in Table 1. Most subjects were diagnosed for SARS-CoV-2 in Emilia-Romagna in October–November 2020 (80.3%) and in Veneto in October–December 2020 (91.8%), during the second epidemic wave in Italy. The average age at diagnosis was 41.1 ± 14.1 years (range: 18–91) in

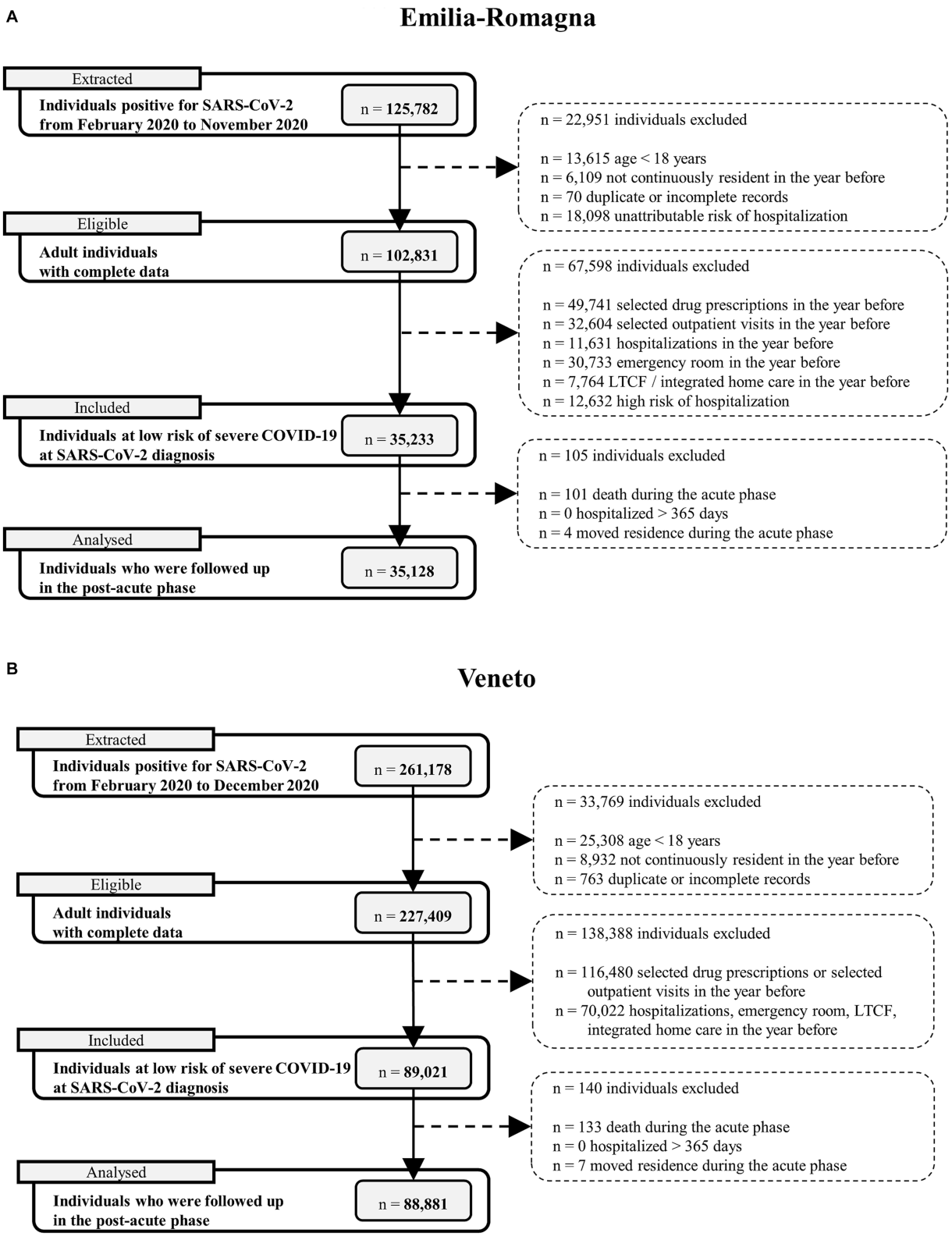

FIGURE 2
Flow charts describing selection of subjects in the two cohorts. Notes: **(A)** = Emilia-Romagna Region; **(B)** = Veneto Region. The total number of excluded individuals is the number of subjects who had at least one of the specific exclusion criteria listed in the flow-chart.

Emilia-Romagna and 41.8 ± 14.1 years (range: 18–97). Those aged more than 60 years were a small part (9.1 and 10.0%, respectively). About half of the included individuals were female (50.3 and 49.9%) and the most part had Italian citizenship (88.7 and 89.6%). At baseline, the risk of hospitalization and death score estimated in E-R was low for 98.7% and moderate for 1.3% of subjects. During the AP, 96.1% of

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TABLE 1 Characteristics of subjects at low risk of severe COVID-19 disease.

		Emilia-Romagna (*N* = 35,128)		Veneto (*N* = 88,881)	
		n	%	n	%
Baseline characteristics					
SARS-CoV-2 diagnosis period	1st wave	4,527	12.9%	4,010	4.0%
	Intermediate	2,384	6.8%	3,305	3.7%
	2nd wave	28,217	80.3%	81,566	91.8%
Sex	Female	17,662	50.3%	44,356	49.9%
Age at diagnosis	18–39	15,943	45.4%	38,795	43.7%
	40–49	8,797	25.0%	21,808	24.5%
	50–59	7,197	20.5%	19,396	21.8%
	60–69	2,370	6.7%	6,678	7.5%
	70–79	674	1.9%	1,742	2.0%
	80–91	147	0.4%	462	0.5%
Italian citizenship	Yes	31,154	88.7%	79,601	89.6%
Risk of hospitalization and death score	Low	34,670	98.7%	-	-
	Moderate	458	1.3%	-	-
Acute phase characteristics[a]					
COVID-19 severity	Low	33,765	96.1%	87,703	98.7%
	Mild	84	0.2%	38	0.0%
	Moderate	498	1.4%	526	0.6%
	Severe	781	2.2%	614	0.7%
Oxygen therapy	Yes	711	2.0%	701	0.8%
Non-invasive ventilation	Yes	139	0.4%	180	0.2%
Invasive ventilation	Yes	103	0.3%	88	0.1%
Intensive care unit stay	Yes	161	0.5%	137	0.2%
Sub-intensive care unit stay	Yes	52	0.1%	0	0.0%
Pneumonia or acute LRT infections	Yes	1,267	3.6%	1,134	1.3%
Acute respiratory insufficiency	Yes	756	2.2%	603	0.7%
Other respiratory infections	Yes	40	0.1%	12	0.0%
Hospitalization	Yes	1,507	4.3%	1,412	1.6%
Acute extrapulmonary complications[b]	Yes	112	0.3%	149	0.2%
Vascular complication	Yes	11	0.0%	92	0.1%
Cardiac complication	Yes	18	0.1%	9	0.0%
Neurological complication	Yes	1	0.0%	4	0.0%
Septicemia	Yes	37	0.1%	36	0.0%
Acute organ failure complication	Yes	55	0.2%	19	0.0%

Notes: LRT = lower respiratory tract; [a] = the following variables can only occur for hospitalized patients; [b] = acute extrapulmonary complications include the five types of complications which are listed.

low-risk individuals in Emilia-Romagna and 98.7% in Veneto experienced low severity COVID-19. Conversely, 0.2% and less than 0.1% of subjects had mild severity, 1.4 and 0.6% had moderate severity, and 2.2 and 0.7% experienced severe COVID-19 disease. Those who were hospitalized during the AP (in acute care hospitals or community hospitals) were 4.3 and 1.6%. Acute extrapulmonary complications have occurred in 0.3 and 0.2% of individuals (Table 1). The higher frequency of individuals who were not hospitalized and who were assigned the lowest severity level in the Veneto cohort likely reflects the wider use that was made of diagnostic testing in 2020 in that Region to detect positive cases even among asymptomatic people (29).

3.2. Incidence of drug prescriptions and outpatient care

The total follow-up time in the PAP was equal to 26,826.7 person-years in E-R and 68,333.1 in Veneto. During this time, 9,208 (26.2%)

of low-risk individuals in E-R and 19,769 (22.2%) in Veneto experienced at least one outcome of interest during the PAP. 4,633 (13.2%) and 9,409 (10.6%) subjects, respectively, had at least one selected drug prescription. On the other hand, 6,523 (18.6%) and 14,108 (15.9%) individuals had at least one selected outpatient care visit or diagnostic procedure, respectively. In the competing risks analysis, as reported in Figure 3, the cumulative incidence of the combined outcome at 11 months in the PAP was equal to 24.9% (95% CI = 24.5–25.4%) in E-R and to 21.2% (95% CI = 20.9–21.5%) in Veneto. Drug prescriptions were less frequent than outpatient care: at 11 months in the PAP, the incidence of the former was 11.9% (95% CI = 11.5–12.2%) in E-R and 9.5% (95% CI = 9.3–9.7%) in Veneto, whereas the incidence of the latter was 17.9% (95% CI = 17.5–18.3%) and 15.4% (95% CI = 15.1–15.6%), respectively. Monthly outcomes incidence data are reported in Supplementary Table 3. Competing events such as hospitalization and mortality occurred during the PAP in 1,292 (3.7%) and 26 (0.1%) individuals in E-R, and in 2,837 (3.2%) and 80 (0.1%) individuals in Veneto. The frequency of individuals who accessed healthcare services during the PAP is reported in detail in Table 2. Among selected drug prescriptions, cardiovascular system drugs (6.0% in E-R and 4.7% in Veneto), followed by corticosteroids for systemic use (4.8 and 3.9%) and respiratory system drugs (2.3 and 1.8%) were administered more frequently during the PAP. Among selected outpatient ambulatory services, the most frequent during the PAP were cardio-respiratory visits and procedures (11.6% in E-R and 9.1% in Veneto), followed by diabetic ambulatory visits or procedures (3.9 and 4.3%), and rehabilitation-motor visits (2.0 and 2.3%).

3.3. Assessment of risk factors for drug prescriptions and outpatient care

According to the confounder-adjusted pooled analysis reported in Figure 4, the major risk factor was the level of COVID-19 severity during the AP. Those with mild severity had +174% hazard of combined outcome compared to those with low severity (HR = 2.74, 95% CI = 1.49–5.02), whereas those with intermediate severity had +260% hazard (HR = 3.60, 95%CI = 2.41–5.36). Finally, those with severe COVID-19 had +321% hazard (HR = 4.21, 95%CI = 3.22–5.48). Such differences among severity groups were not homogeneous in the two regional cohorts, being HRs for Veneto higher than those for E-R. The reason for such a heterogeneity is shown in Figure 3, which describes cumulative incidence curves by severity groups in the two regional cohorts. In the E-R cohort, the risk of the combined outcome at the end of the PAP was 23.5% (95% CI = 23.0–23.9%) for low severity patients, 37.2% (95% CI = 26.6–47.4%) for mild-severity ones, 56.9% (95% CI = 52.2–61.1%) for moderate-severity ones and 66.5% (95% CI = 63.0–69.7%) for severe patients. In the Veneto cohort, the same figures were equal to 20.5% (95% CI = 20.2–20.7%), 59.5% (95% CI = 41.6–73.5%), 67.8% (95% CI = 63.6–71.7%) and 74.3% (95% CI = 70.6–77.6%), respectively. The occurrence of an acute extrapulmonary complication during the AP was associated with a higher risk (HR = 1.84, 95% CI = 1.44–2.35). Age at diagnosis was also a risk factor for the combined outcome, as the risk in higher age groups was always greater than or equal to the risk in the group of individuals aged 18–39. In particular, those aged 60–69 or 70–79 had more than a two-fold hazard (HR = 2.10, 95%CI = 2.01–2.19 and HR = 2.31, 95%CI = 1.96–2.73, respectively) and those aged ≥80 had less than a two-fold hazard (HR = 1.73, 95%CI = 1.15–2.60). Male individuals had −18% hazard of outcome compared to females (HR = 0.82, 95%CI = 0.80–0.84). Italians had a slightly higher level of risk compared to non-Italian citizens (HR = 1.09, 95%CI = 1.05–1.14). Finally, there were only minor differences between individuals diagnosed in the second epidemic wave (HR = 0.92, 95%CI = 0.88–0.97) or between individuals diagnosed in the intermediate period (HR = 0.81, 95%CI = 0.73–0.90) and those diagnosed in the first epidemic wave. The analysis of risk factors for each separate outcome (drug prescriptions or outpatient care), is reported in Figures 5, 6. Overall, the risk factors were similar to those already described for the combined outcome, with the following three exceptions. Firstly, COVID-19 severity in the AP was associated with a higher increase in the risk of outpatient care, compared to the increase in the risk of drug prescriptions. Secondly, individuals with Italian citizenship had a lower hazard of drug prescriptions (HR = 0.90, 95%CI = 0.85–0.96), whereas the opposite was observed in relation to outpatient care (HR = 1.14, 95%CI = 1.09–1.20). Thirdly, the presence of acute extrapulmonary complications during the AP was strongly associated with drug prescriptions (HR = 3.83, 95%CI = 2.96–4.95), whereas its relationship with outpatient care was of minor relevance (HR = 1.36, 95%CI = 1.10–1.66). Other minor differences in risk factor intensity were present, although they did not alter the overall interpretation of the results (Figures 5, 6).

4. Discussion

4.1. Major findings

The present study focused on the incidence and determinants of access to selected healthcare services in a largely healthy population of subjects who had a diagnosis of SARS-CoV-2 in the Emilia-Romagna and Veneto regions, Italy. The analysis covers people diagnosed in the period from February to December 2020, when vaccination against COVID-19 was not yet available. The outcome (combination of outpatient care and drug prescriptions) occurred in a high percentage of subjects (25% cumulative incidence in E-R and 21% in Veneto) during the PAP, i.e., from day 31 to day 365 after diagnosis of SARS-CoV-2. It should be however noted that the incidence in a health population in the absence of COVID-19 was not measured, leaving uncertainty about the proportion of outcomes directly attributable to the disease. Considering the two outcomes separately, outpatient care was observed more frequently than drug prescriptions (18% vs. 12% in E-R and 15% vs. 10% in Veneto). The most frequently administered drugs were cardiovascular system drugs and corticosteroids, whereas the most common category of outpatient care was the cardio-respiratory one. Hospitalization occurred more rarely (about 3%). The cumulative incidence curve grows steadily for the combined outcome and for the outpatient care outcome. For drug prescriptions, growth appears steeper in the first month of follow-up in the PAP. The curves show significant differences if the analysis is stratified by severity of acute COVID-19. In particular, subjects with severe forms showed a much steeper increase in cumulative incidence in the first part of the follow-up, especially for drug prescriptions. Risk factors associated with the combined outcome were female sex, age over 40 years, moderate to severe acute COVID-19, and acute extrapulmonary complications occurring during the AP. Although there are differences, the risk factors

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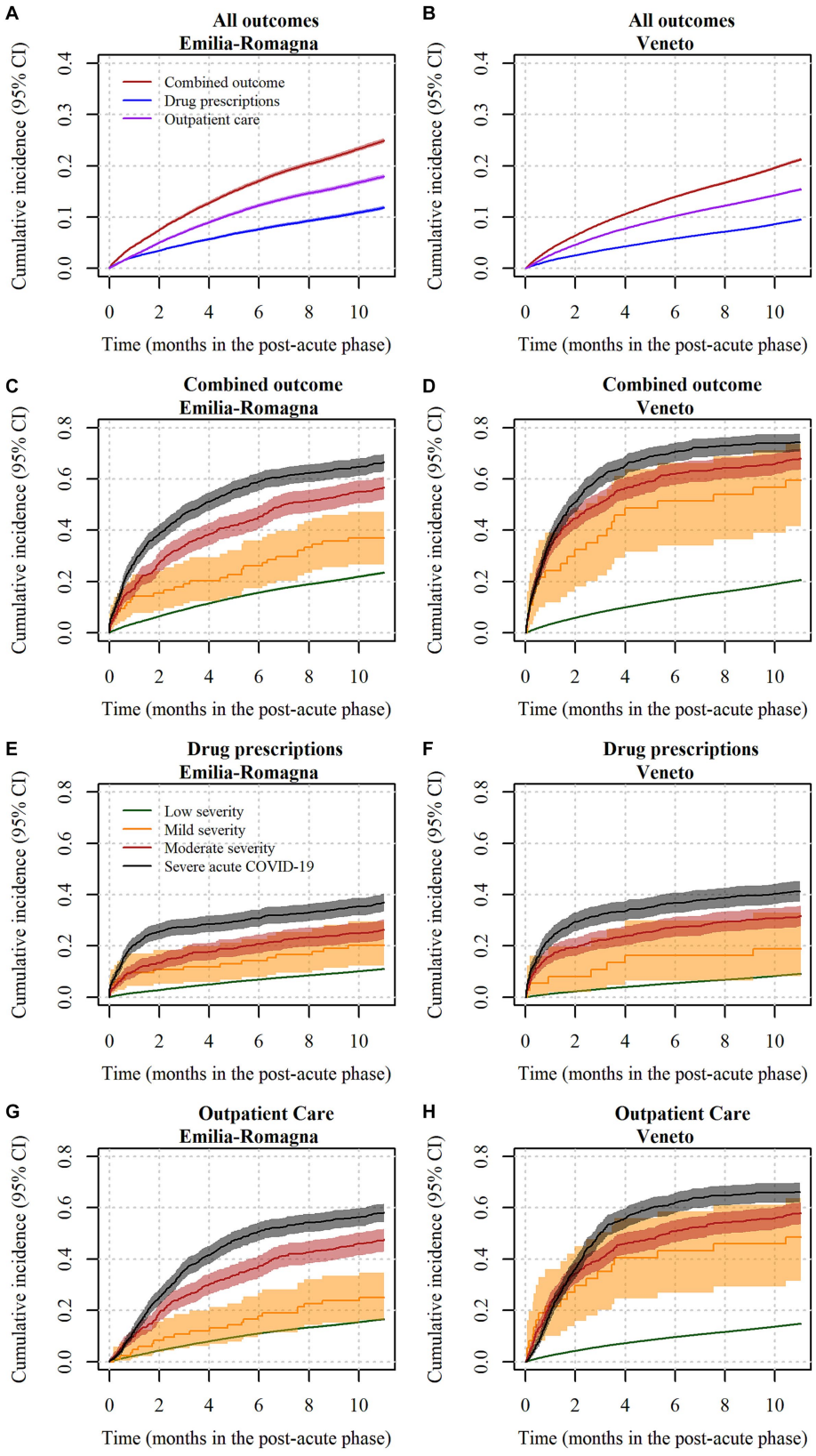

FIGURE 3
Cumulative incidence curves of drug prescriptions and outpatient care in subjects at low risk of severe COVID-19 disease, by COVID-19 severity. Notes: **(A)** = incidence of outcomes in Emilia-Romagna; **(B)** = incidence of outcomes in Veneto; **(C)** = incidence of the combined outcome in Emilia-Romagna, by COVID-19 severity; **(D)** = incidence of the combined outcome in Veneto, by COVID-19 severity; **(E)** = incidence of selected drug prescriptions in Emilia-Romagna, by COVID-19 severity; **(F)** = incidence of selected drug prescriptions in Veneto, by COVID-19 severity; **(G)** = incidence of selected outpatient care in Emilia-Romagna, by COVID-19 severity; **(H)** = incidence of selected outpatient care in Veneto, by COVID-19 severity. In

(Continued)

FIGURE 3 (Continued)
sub-figures **(A)** and **(B)**, red lines indicate the composite outcome, blue lines indicate the drug prescription outcome, and purple lines indicate the outpatient care outcome. In sub-figures from **(C–H)**, green lines indicate low severity subjects, yellow lines indicate mild severity subjects, red lines indicate moderate severity subjects and black lines indicate severe subjects. In all sub-figures, lines indicate punctual estimates of the cumulative incidence function and areas represent 95% confidence intervals. Confidence intervals were calculated with the asymptotic Aalen method.
CI = confidence interval.

TABLE 2 Access to healthcare services of subjects at low risk of severe COVID-19 disease during the post-acute phase.

Type of care	Emilia-Romagna (*N* = 35,128)		Veneto (*N* = 88,881)	
	n	%	n	%
Combined outcome	9,208	26.2%	19,769	22.2%
Selected drug prescriptions	4,633	13.2%	9,409	10.6%
Selected outpatient care	6,523	18.6%	14.108	15.9%
Drug prescriptions	15,513	44.2%	33,622	37.8%
Cardiovascular system / antithrombotic[a]	2,114	6.0%	4,202	4.7%
Antidiabetic[a]	165	0.5%	256	0.3%
Nervous system[a]	563	1.6%	1,036	1.2%
Respiratory system[a]	798	2.3%	1,580	1.8%
Oxygen[a]	6	0.0%	32	0.0%
Corticosteroids[a]	1,671	4.8%	3,433	3.9%
Antibacterial	5,936	16.9%	13,219	14.9%
Hydroxychloroquine	48	0.1%	131	0.2%
Other drugs	11,208	31.9%	22,699	25.5%
Outpatient care	23,248	66.2%	36,965	41.6%
Cardio-respiratory[b]	4,059	11.6%	8,103	9.1%
Vascular[b]	949	2.7%	1,515	1.7%
Neuro-psychiatric[b]	668	1.9%	1,271	1.4%
Rehabilitation-motor[b]	685	2.0%	2,005	2.3%
Nephrology[b]	33	0.1%	58	0.1%
Diabetes[b]	1,362	3.9%	3,805	4.3%
Other visits / procedures	22,590	64.3%	32,214	36.2%
Acute care hospitalization	1,292	3.7%	2,837	3.2%
Community hospital	3	0.0%	4	0.0%
Long-term care facility	10	0.0%	49	0.1%
Emergency room	5,099	14.5%	12,738	14.3%
Integrated home care	54	0.2%	350	0.4%

Notes: [a] = included in selected drug prescriptions outcome; [b] = included in selected outpatient care outcome. The sum of individual items may differ from the totals, as subjects may have more than one outpatient care episode or drug prescription during the post-acute phase.

associated with outpatient care and drug prescriptions (considered separately) are the same as those associated with the combined outcome. Having Italian citizenship is an exception, as it was a risk factor for the prescription of drugs and a protection factor for outpatient visits in the follow-up. This finding may be related to a different use of private outpatient care. Acute COVID-19 extrapulmonary complications is another exception, as it was strongly associated with drug prescriptions, but not with outpatient care.

4.2. Consistency between cohorts

The results of the two cohorts, although providing quite consistent results, show a greater frequency of outcomes in E-R than in Veneto Region. The meta-analysis of the factors associated with the outcome shows heterogeneity which is high for some variables such as the severity of the acute COVID-19. In particular, the negative effect of increasing COVID-19 severity on the need for outpatient care was more intense in Veneto than in E-R. These findings can be explained

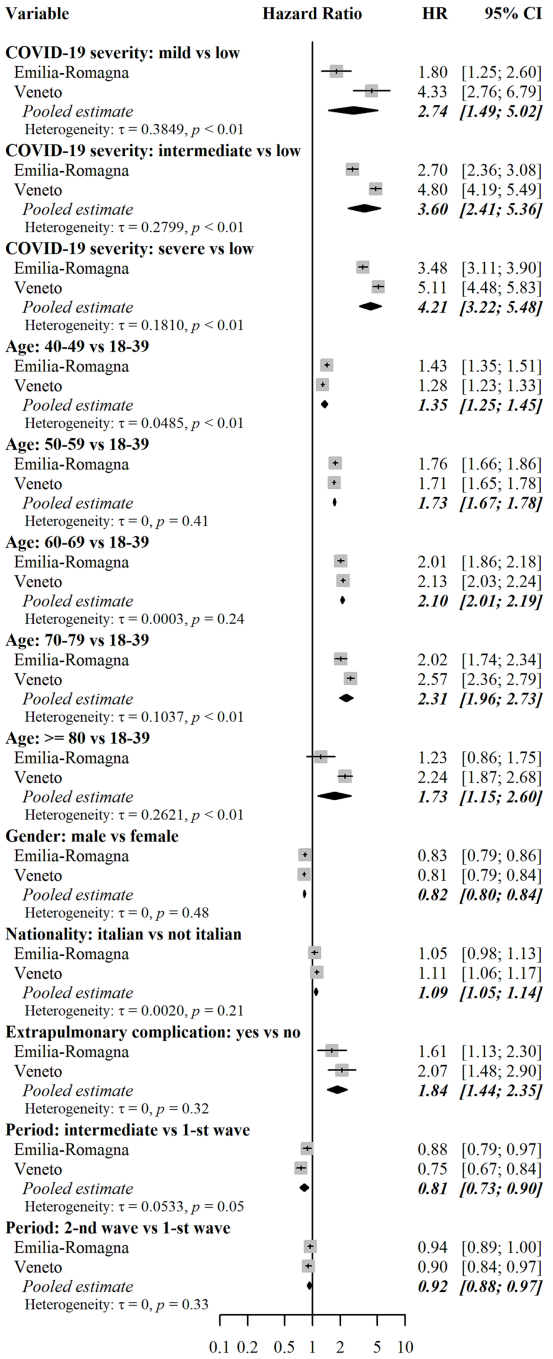

FIGURE 4
Assessment of risk factors for the combined outcome. Notes: Results for each cohort were estimated using multivariable Fine-Gray subdistribution hazard models. Confidence intervals for hazard ratios in the two cohorts were calculated with the Wald method based on normal approximation and were two-sided. Pooled results were estimated using random effects meta-analysis with inverse variance weights and maximum likelihood estimator for between-study variance. The models also included the following independent variables: risk of hospitalization and death score (only in the E-R cohort), and Local Health Units (8 in E-R and 9 in Veneto). Additional results for these variables are reported in Supplementary Table 4. The combined outcome includes selected drug prescriptions and selected outpatient care, whichever came first. Heterogeneity was measured with the tau (τ) statistic and its significance was assessed with the Cochran's *Q* test. HR = subdistribution hazard ratio. CI = confidence interval. *p* = *p*-value.

by the differences in diagnostic testing policies in place in the two Regions in early 2020, when Veneto Region was the first to implement intensive diagnostic testing and contact tracing procedures, leading to a higher share of asymptomatic individuals as opposed to paucisymptomatic or weakly symptomatic ones (29). The lower incidence of outcomes observed in the Veneto cohort for subjects classified at low severity is consistent with this hypothesis. Furthermore, the cumulative incidence for mild, moderate, and severe patients was higher in Veneto than in E-R. This may depend on different long-term case management policies for hospitalized subjects in the two Regions.

4.3. Implications for clinical practice

The study results showed a remarkable frequency of outpatient care and drug prescriptions in the post-acute follow-up period. These data suggest that long-term effects of COVID-19 needing clinical attention occur in a substantial percentage of cases, even among a previously healthy population with low or mild severity of acute COVID-19. The latter finding may be very important for clinicians and for healthcare policy makers as, thus far, an active follow-up has often been restricted to COVID-19 patients with moderate or severe infection (3). Our data may indeed suggest the need for a greater clinical attention in the follow-up after SARS-CoV-2 infection, also in a non-hospitalized low-risk population, as other recent reports have suggested (4, 18, 23). Furthermore, in subjects with severe acute COVID-19, a high frequency of outpatient visits and prescriptions is observed in the first part of the follow-up, suggesting that there may be a continuation of the AP (defined by NICE as ongoing COVID). Our results also contribute to the evidence on risk factors for the post-COVID syndrome and are in line with previous studies carried out in other populations of COVID-19 patients (3–6, 18, 23).

4.4. Implications for research

Based on the results of our study, the access to outpatient care and drug prescriptions was very frequent even in a low-risk population. The significant healthcare resource consumption related to such outpatient care and administration of drugs should therefore be considered by researchers when evaluating the healthcare burden after a SARS-CoV-2 diagnosis. Moreover, our data can be useful for setting benchmarks in the levels of access to selected healthcare services, as they are referred to a large unvaccinated population at low risk of severe acute COVID-19.

4.5. Limitations

This study used healthcare administrative databases as data sources; therefore, only drug prescriptions and outpatient care provided by the regional healthcare systems were included in the analysis. In addition, there are no data on diagnoses of outpatient care and indications for drug prescriptions. The occurrence of selected drug prescriptions and selected outpatient care was indeed used as the outcome variable and considered as a proxy for long COVID. Therefore, the present analysis was only able to assess a variation in prescriptions and outpatient services in general terms, whereas no information on the incidence and risk factors of single

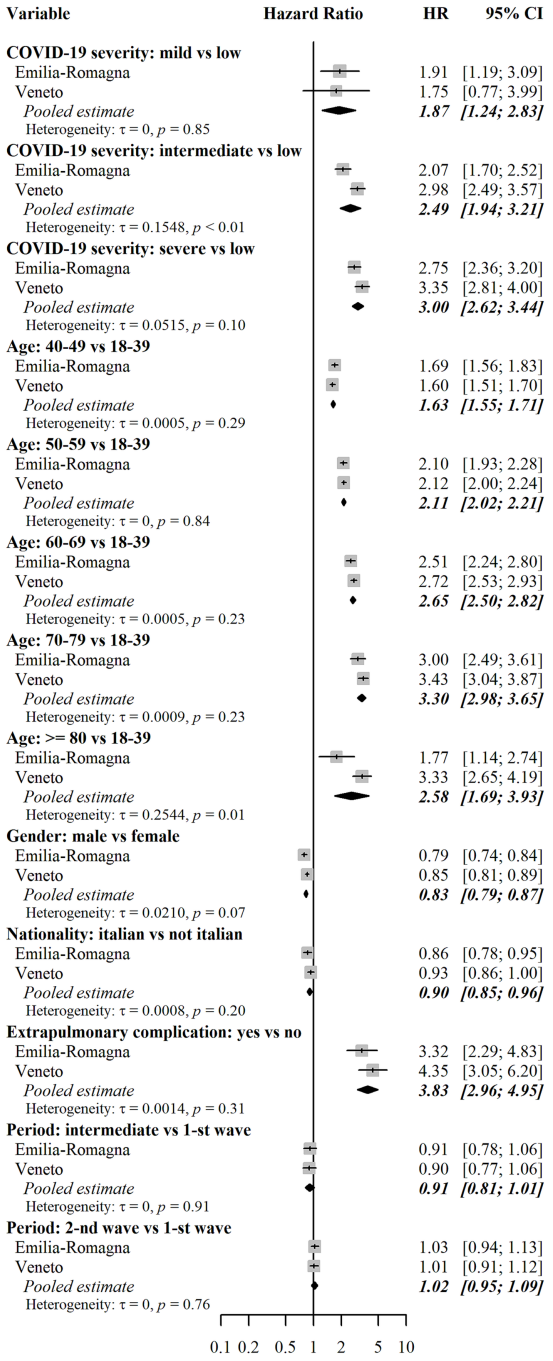

FIGURE 5
Assessment of risk factors for drug prescriptions. Notes: Results for each cohort were estimated using multivariable Fine-Gray subdistribution hazard models. Confidence intervals for hazard ratios in the two cohorts were calculated with the Wald method based on normal approximation and were two-sided. Pooled results were estimated using random effects meta-analysis with inverse variance weights and maximum likelihood estimator for between-study variance. The models also included the following independent variables: risk of hospitalization and death score (only in the E-R cohort), and Local Health Units (8 in E-R and 9 in Veneto). Additional results for these variables are reported in Supplementary Table 4. Heterogeneity was measured with the tau (τ) statistic and its significance was assessed with the Cochran's Q test. HR = subdistribution hazard ratio. CI = confidence interval. *p* = *p*-value.

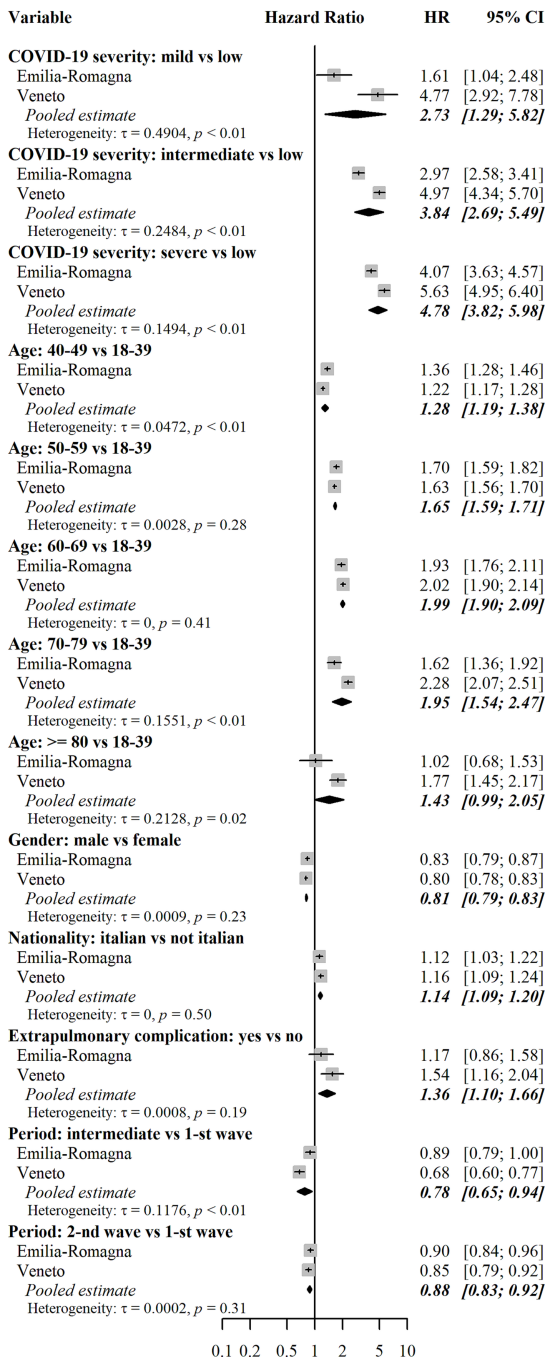

FIGURE 6
Assessment of risk factors for outpatient care. Results for each cohort were estimated using multivariable Fine-Gray subdistribution hazard models. Confidence intervals for hazard ratios in the two cohorts were calculated with the Wald method based on normal approximation and were two-sided. Pooled results were estimated using random effects meta-analysis with inverse variance weights and maximum likelihood estimator for between-study variance. The models also included the following independent variables: risk of hospitalization and death score (only in the E-R cohort), and Local Health Units (8 in E-R and 9 in Veneto). Additional results for these variables are reported in Supplementary Table 4. Heterogeneity was measured with the tau (τ) statistic and its significance was assessed with the Cochran's *Q* test. HR = subdistribution hazard ratio. CI = confidence interval. *p* = *p*-value.

drugs and outpatient services can be derived. Secondly, our results refer to unvaccinated subjects, but the epidemiological features of long COVID have changed significantly since the introduction of vaccines. Thirdly, unmeasured characteristics (e.g., environmental, lifestyle and genetic characteristics, SARS-CoV-2 variants) may have affected our results. Furthermore, outpatient care could result to some extent from the implementation of algorithms for the patient's follow-up, regardless of persistence or recurrence of symptoms or the emergence of new ones. This limitation could have caused an overestimation of the incidence of study outcomes, particularly those related to outpatient diagnostics. Another potential limitation is in the criteria for the selection of a healthy population at low risk of severe acute COVID-19 from administrative databases. It is indeed possible that some non-healthy subjects, especially those with chronic diseases of minor clinical relevance (e.g., asthma), were included in the cohort due to the absence of relevant access to healthcare services in the one-year period before SARS-CoV-2 diagnosis. Similarly, the criteria for acute COVID-19 severity, being based on information available only for hospitalized subjects, may have been influenced by different health policies and hospital capacity during different pandemic periods. Finally, no control group of subjects who were not diagnosed with SARS-CoV-2 infection was considered, leaving uncertainty on the incidence and risk factors of outcomes directly attributable to COVID-19.

4.6. Strengths

The study data sources allowed for a multicenter population-based design (all cases of COVID-19 that met the inclusion criteria in two Italian Regions) and for a long follow-up period (one year from the diagnosis of SARS-CoV-2 infection). These are strengths compared to most published studies which present one or more limitations reducing the validity and generalizability of the results (3.17). The most frequent flaws of published studies refer to small or selected samples (e.g., focus on hospitalized or more symptomatic patients) and short follow-up periods (e.g., less than 12–24 weeks). Other limitations of the available studies relate to design (e.g., in surveys, people who are still unwell or who have had a long-lasting illness are more likely to participate and recall symptoms) and case definition (e.g., the use of serology as an inclusion test makes the dating of the infection inaccurate) (3.17). Moreover, the selection of low-risk subjects (i.e., no hospitalization, visit to the emergency room, prescription of specific drugs or specific outpatient visits in the year preceding the diagnosis of SARS-CoV-2 infection) makes the observed outcomes in the follow-up period largely attributable to the post-COVID syndrome.

5. Conclusion

Management of patients with a previous SARS-CoV-2 infection should be targeted to ongoing symptoms and new ones that have occurred. It must therefore take into account the severity of acute COVID-19 but also adapt to the clinical needs that may have emerged later on.

Data availability statement

The datasets presented in this article are not readily available because of security measures in place to protect the privacy of participants. The data supporting the findings of this study are available at aggregated level upon reasonable request and with the written permission of Emilia-Romagna and Veneto Regions. Requests to access the datasets should be directed to EB, elena.berti@regione.emilia-romagna.it for the Emilia-Romagna cohort and to FR, francesca.russo@regione.veneto.it for the Veneto cohort.

Ethics statement

The studies involving humans were approved by Comitato Etico Area Vasta Emilia Nord (on 8-th February 2022), Comitato Etico Area Vasta Emilia Centro (on 19-th January 2022), and Comitato Etico della Romagna (on 18-th February 2022) for the E-R cohort, and by Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo (on 21-st July 2021) for the Veneto Cohort. The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/Institutional Review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this study was considered an exemption to Art. 14 of the General Data Protection Regulation (GDPR), due to the disproportionate effort to provide the information to data subjects about the existence of the study processing operation and that personal (health) data were processed for scientific purposes.

Author contributions

CG, RB, ER, ET, MM, FR, GP, SB, ES, AP, and EN: conceptualization. FB, RB, and EN: data curation. FB and EN: formal analysis. ET, MM, and FR: funding acquisition. CG, FB, RB, ER, MM, GP, SB, ES, AP, and EN: methodology. FB, ET, EB, MM, EN, MT, FR, and LC: project administration. FB and RB: software. CG, MR, ET, EB, MM, FR, and MT: supervision. FB, CG, ER, ET, EB, MM, FR, and LC: validation. FB: visualization. CG and FB: writing – original draft. CG, FB, RB, ER, MR, ET, EB, and MM: writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1241401/full#supplementary-material

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One-year quality of life among post-hospitalization COVID-19 patients

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Introduction: The long-term effects of SARS-CoV-2 are unclear, as are the factors influencing the evolution. Objective: to assess health-related quality of life 1 year after a hospital admission due to COVID-19 and to identify factors that may influence it.

Materials and methods: Retrospective observational study in a tertiary hospital from March 2021 to February 2022. Inclusion criteria: ≥18 years old and admitted for SARS-CoV-2 infection. Exclusion criteria: death, not located, refusal to participate, cognitive impairment, and language barrier. Variables: demographic data, medical history, clinical and analytical outcomes during hospital admission, treatment received, and vaccination against SARS-CoV-2 following admission. Participants were interviewed by phone 1 year after admission, using the SF-36 quality of life questionnaire.

Results: There were 486 included patients. The domains yielding the lowest scores were general health (median 65%, interquartile range [IQR] 45–80), vitality (median 65%, IQR 45–80), and mental health (median 73.5%, IQR 60–100). Multivariable analysis showed that female sex and fibromyalgia/fatigue had a negative influence on all domains. Obesity was associated with worse outcomes in physical functioning, physical role, bodily pain, and vitality. Other factors associated with worse scores were an older age in physical functioning and high age-adjusted Charslon comorbidity in physical functioning and general health. Age was associated with better results in emotional role and High C-reactive protein at admission on vitality.

Conclusion: One year after admission for COVID-19, quality of life remains affected, especially the domains of general health, vitality, and mental health. Factors associated with worse outcomes are female sex, fibromyalgia/chronic fatigue, and obesity.

KEYWORDS

COVID-19, long COVID, post-acute COVID-19 syndrome, quality of life, SARS-COV-2

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1. Introduction

To date, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused 676,609,955 confirmed cases and at least 6,881,955 deaths worldwide (1). The pathophysiology and clinical forms of the disease during its acute phase are already well known (2), but its long-term evolution is more uncertain, and the factors determining it, even more so. Long COVID, defined by the World Health Organization (WHO) in October 2021 as the presence of symptoms 3 months after SARS-CoV-2 infection, with a minimum duration of 2 months, which cannot be explained by an alternative diagnosis (3), now represents a significant challenge for health systems given its high prevalence, its great impact on quality of life, and the dearth of knowledge regarding its etiopathogenesis, predisposing factors, and even treatment. In addition, long COVID, also known as post-COVID condition or post-acute sequelae of COVID-19, can affect any organ system, including the central and peripheral nervous system and the cardiovascular, respiratory, or digestive systems, among others (4–7).

A recent meta-analysis in 1.2 million patients who had had a symptomatic SARS-CoV-2 infection showed that around 6.2% of them had symptoms associated with long COVID 3 months after infection (8). The mean duration of these symptoms was 9 months in those who required hospital admission and 4 months in those who did not (8). Although fatigue syndromes after infection have been previously described with other microorganisms, such as Epstein–Barr virus and cytomegalovirus, their pathogenesis is still unknown, and treatment is only symptomatic (9). However, as is the case after these infections, the long COVID syndrome may be very similar and even difficult to differentiate from myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Thus, this study aims to assess health-related quality of life 1 year after a hospital admission due to SARS-CoV-2 infection and to identify factors that may influence it.

2. Materials and methods

2.1. Study design, setting, and participants

This retrospective observational study was performed in the city of Castellón (Spain), in a tertiary hospital with a catchment population of 283,000 inhabitants, from March 2021 to February 2022. Eligible patients were adults (≥ 18 years) admitted to the infectious diseases unit due to SARS-CoV-2 infection from March 2020 to February 2022, confirmed by real-time polymerase chain reaction (RT-PCR) or antigen test. Exclusion criteria were: died during the first admission or during follow-up ($n = 137$), could not be located at the time of the interview ($n = 139$), refused to participate ($n = 9$), presented prior to infection notable cognitive impairment at the time of the interview ($n = 46$), or had a language barrier ($n = 3$; Figure 1).

Abbreviations: IQR, Interquartile range; WHO, World Health Organization; ME/CFS, Encephalomyelitis/chronic fatigue syndrome; RT-PCR, Real-time polymerase chain reaction; EMRs, Electronic medical records; ARDS, Acute respiratory distress syndrome; ICU, Intensive unit care; RCP, C-Reactive protein; SF-36, 36-Item Short Form Survey; SD, Standard deviation; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; CI, Confidence interval; COVID-19, Coronavirus disease 2019.

2.2. Variables

Participants' electronic medical records (EMRs) were reviewed using Orion Clinic software (Council for Universal Health Care and Public Health, Valencian Community, Spain). Data collected included *demographic variables* (age, sex), *medical history* [comorbidities including obesity, defined as body mass index ≥30 kg/m^2, and age-adjusted Charlson comorbidity index (with higher scores indicating more comorbidity)], *clinical outcomes* [length of hospital stay, evolution to acute respiratory distress syndrome (ARDS), need for admission to the intensive care unit (ICU), type of respiratory support required, need for FiO_2 (fraction of inspired oxygen), and Pa/FiO_2 ratio on admission and extreme values during the hospital stay], *laboratory test results* [lymphocyte values, C-reactive protein (CRP), ferritin, and IL-6 and D-dimer at admission and extremes during the hospital stay], *treatment* (systemic corticosteroid therapy during admission and total days of corticosteroid therapy), *vaccination against SARS-CoV-2 following the hospital admission* (yes/no).

Following recruitment and provision of informed consent, the 36-item Short Form Survey (SF-36) on health-related quality of life questionnaire was administered by telephone by the investigators (all internal medicine specialists) 1 year after hospital discharge. The SF-36 evaluates eight domains, including physical functioning, physical role limitations, bodily pain, general health perceptions, energy/vitality, social functioning, emotional role limitations, and mental health (10). For each domain, a percentage value is generated, with higher scores indicating better quality of life in that domain.

Outcome variables were the score in the eight domains of the SF-36.

2.3. Statistical analysis

Statistical analysis was performed using SPSS software (version 23, IBM). First, a descriptive study was performed: quantitative variables were described as means (standard deviation, SD) or medians (interquartile range, IQR), depending on the normality of their distribution, and qualitative variables were described as absolute or relative frequencies. To test the association between the outcomes and the quantitative explanatory variables, the Pearson or Spearman correlation tests were performed, as appropriate. To compare the scores in each domain of the SF-36 test between the two groups of qualitative variables, the Mann–Whitney U test was used. The Bonferroni test was used to correct for multiple comparisons, so that taking into account a $p = 0.05$ and the fact that 42 variables were studied in the univariate study, only $p < 0.0012$ were considered statistically significant. Subsequently, a multivariable analysis was performed using multiple linear regression. The model included the variables that had shown a significant association with the outcome in the univariable analysis, plus sex and age.

3. Results

3.1. Study sample

A total of 486 patients were included (Figure 1). Their mean age was 61 years (SD 14), and 194 were women (39.9%). The review of the

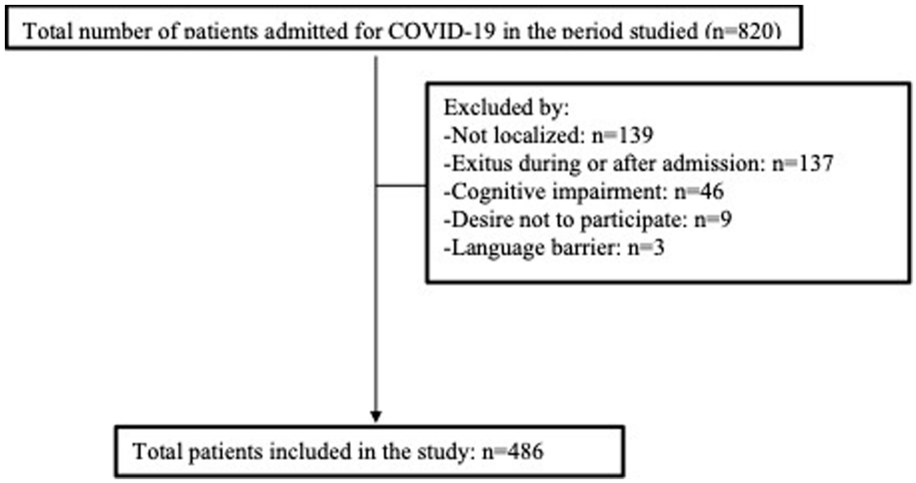

FIGURE 1
Flowchart.

medical history showed that 111 (22.8%) were smokers or ex-smokers, 205 (44.2%) hypertensive, and 153 (31.5%) obese. The median age-adjusted Charlson comorbidity index was 2 (IQR 1–3). Median length of hospital stay was 10 days (IQR 6–15), and 100 patients (20.6%) required ICU admission, with a median stay in the unit of 6 days (IQR 4–10). ARDS was diagnosed in 193 patients (39.7%), and 93 (19.1%) required non-invasive—and 17 (3.5%) invasive—mechanical ventilation. Systemic corticosteroid therapy was administered to 432 (88.9%) patients during admission, with a median duration of 36 days (IQR 19–49). Of the total sample, 398 participants (81.9%) subsequently completed the vaccination regimen recommended at that time against SARS-CoV-2. Table 1 presents the results for FiO_2, the Pa/FiO_2 ratio, laboratory variables, and other descriptive indicators.

3.2. SF-36 quality of life scores

According to each domain of the SF-36, median scores were as follows: physical functioning, 95% (IQR 70–100); physical role limitations, 100% (IQR 75–100); bodily pain, 90% (IQR 66.9–100); general health, 65% (IQR 45–80); vitality, 65% (IQR 45–80); social functioning, 100% (IQR 87.5–100); emotional role limitations, 100% (IQR 100–100); and mental health, 73.5% (IQR 60–100).

3.3. Association between explanatory variables and SF-36 quality of life scores

The influence of each of the variables studied on the results of each of the eight domains of the SF-36 test was analyzed. In the univariable study, female sex, obesity, and a history of fibromyalgia/chronic fatigue were significantly associated with poorer quality of life in all domains of the SF-36. A history of anxiety and depression also showed a negative influence in most domains. In contrast, the greater inflammatory response, represented especially by high levels of ferritin at and during admission, was significantly associated with better scores in some domains. Systemic treatment with corticosteroids during admission showed some protective effect in terms of body pain, regardless of the duration of treatment, although after correction by the Bonferroni test it did not show statistical significance and also showed no relationship with the rest of the domains. The rest of the results are presented in Tables 2, 3.

The multivariable model included all variables showing a statistically significant association in the univariable study and was adjusted for sex and age (Table 4). Both female sex and history of fibromyalgia/chronic fatigue continued to show a significant and negative association with all domains of the SF-36 test. Obesity had a smaller influence and was related to worse outcomes in physical functioning ($p = 0.002$), physical role ($p < 0.001$), bodily pain ($p = 0.040$) and vitality ($p = 0.009$). Other factors associated with worse scores on a particular domain of the SF-36 were: an older age in physical functioning ($p = 0.047$) and high age-adjusted Charslon comorbidity index in physical functioning ($p = 0.013$) and general health ($p = 0.027$). In contrast, older age was associated with better results in emotional role ($p = 0.041$) and a higher RCP value at admission showed better results in vitality ($p = 0.031$). No other statistically significant associations were observed.

4. Discussion

Our cohort of patients is made up of adults in their 60s, mainly men, without particularly high comorbidity. None of them were vaccinated against SARS-CoV-2 at the time of their admission; slightly less than half presented ARDS, and practically all of them were treated with corticosteroids. The worst quality of life outcomes were obtained in the domains of general health, vitality, and mental state, with similar results to those observed by Koullias et al. (11), who administered a simpler version of the SF-36 at 6 months after admission for coronavirus disease 2019 (COVID-19). Our results are also consistent with theirs in terms of the acceptable scores obtained in the domains referring to physical issues. Those authors also observed significantly worse results in patients who had required

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TABLE 1 Descriptive analysis.

	n = 486
Antecedents, *n* (%)	
Age, average (SD) (*n* = 486)	61 (14)
Female	194 (39.9)
Smoker (and ex-smoker)	111 (22.8)
Hypertension	205 (44.2)
Dyslipemia	140 (28.8)
Anxiety	56 (11.5)
Depression	27 (5.6)
Fibromyalgia/chronic fatigue	13 (2.7)
Obesity (BMI > 30)	153 (31.5)
Ischemic cardiopathy	14 (2.9)
Cardiac insufficiency	17 (3.5)
COPD	5 (1)
Chronic bronchitis	8 (1.6)
Asthma	4 (0.8)
Chronic renal disease	14 (2.9)
Diabetes	71 (14.6)
Diabetes with target organ damage	11 (2.3)
Age-adjusted Charlson Comorbidity Index, median (IQR)	2 (1–3)
Clinical evolution	
PaO2/FiO2 at admission, median (IQR) (n = 385)	333 (300–373)
FiO2 at admission (%), median (IQR) (n = 486)	21 (21–21)
Minimum PaO2/FiO2, median (IQR) (n = 381)	300 (145–357)
Maximum FiO2 (%), median (IQR) (n = 486)	*32 (21–60)*
ARDS, n (%)	193 (39.7)
Intensive care unit, n (%)	100 (20.6)
CPAP-Helmet, n (%)	93 (19.1)
High flow oxygen, n (%)	26 (5.3)
Mechanical ventilation, n (%)	17 (3.5)
Hospital stay (days), median (IQR)	10 (6–15)
Stay in the Intensive Care Unit (days), median (IQR)	6 (4–10)
Analytical parameters, median (IQR)	
Lymphopenia at admission (/μL) (n = 484)	990 (712–1320)
RCP at admission (mg/L) (n = 486)	64 (30–116)
Ferritin at admission (mcg/L) (n = 443)	482 (258–886)
IL-6 at admission (ng/L) (n = 285)	34 (16–60)
d-dimer at admission (ng/mL) (n = 431)	610 (380–1080)
Minimum lymphocytes during admission (/μL) (n = 484)	720 (520–1097)
Maximum RCP during admission (mg/L) (n = 485)	83 (40–136)
Maximum ferritin during admission (mcg/L) (n = 447)	655 (354–1189)
Maximum IL-6 during admission (ng/L) (n = 357)	38 (16–67)
Maximum d-dimer during admission (ng/mL) (n = 480)	940 (570–2120)
Treatment	
Systemic corticosteroids during admission, *n (%)*	432 (88.9)
Total days of corticotherapy, median (IQR; *n* = 486)	36 (19–49)
SARS-CoV-2 vaccination after admission, *n* (%)	398 (81.9)

hospital admission compared to those who had not and to the control group. The analysis of an Italian cohort also found, on this occasion using the EQ-5D-5L quality of life survey by phone call, that at 2 years after the index admission for COVID-19, the score was worse in the mental health domain, but scores were good in the other domains, including those related to physical aspects (12). Another study in our country, Spain, used the SF-36 to assess telematically quality of life in patients admitted to the hospital for COVID-19 during the first wave (as we did), at 3 and 12 months after the onset of infection (13). They compared the results with the reference population values in Spain in 1998, observing a statistically significant decrease in the score in all domains at 3 months (especially for physical role and emotional role), and in all domains except mental health at 12 months (14). Muñoz-Corona et al. (15) also described a much more evident deterioration in the domain of physical role in patients who required hospital admission, although in this case results were probably influenced by the fact that the SF-36 test was carried out 90 days after discharge, much sooner than in the other studies mentioned, including ours.

There was evidence, based on our results and the data already published in this regard, that COVID-19, and in our case hospital admission for this disease, produces a long-term deterioration in quality of life. Moreover, understanding the predisposing factors of this deterioration is very important, since it could enable preventive interventions and help identify the most susceptible groups of patients for more intense medical follow-up. In this sense, we observed that quality of life in practically all domains, is especially compromised for a very specific patient profile: female and with a history of fibromyalgia/chronic fatigue and to a lesser extent obesity. In contrast, the severity of the disease (represented by the degree of respiratory failure, the FiO_2 required, the type of respiratory support, and the need for ICU admission) did not appear to have an impact on subsequent quality of life. In addition, in the univariable analysis, a greater inflammatory response showed a protective effect on quality of life 1 year after hospital admission, especially elevated ferritin levels on admission and the maximum levels during the hospital stay. However, this effect did not reach statistical significance in multivariable analysis. After an extensive literature review, we found no data on how elevation of acute phase reactants during acute infection influences long-term clinical course. However, it is likely that potential contributors to Long COVID include multiple organ injury due to excessive inflammation or clotting/coagulation issues in the acute phase (16). In addition, Qu et al. (17) observed that the C-reactive protein value after hospital discharge was not associated with changes in long-term physical or mental status. These results raise the hypothesis that the long COVID would be more influenced by a certain patient profile than by the severity of the acute infection.

Different studies have tried to identify what factors influence long-term quality of life outcomes in COVID-19. Female sex is the most frequently described determinant, in keeping with our findings (11, 12, 17–22). Likewise, obesity has been described as another relevant factor (21). Other long-term determinants mentioned in the literature are advanced age, chronic diseases like diabetes, heart failure, and chronic kidney disease, hospital stay, and the need for ICU admission (17, 20–22). In our sample, only age and age-adjusted Charlson comorbidity index were also associated with worse outcomes, although in the multivariate analysis both only maintained their negative effect on physical functioning and the age-adjusted Charslon comorbidity index also in general health.

TABLE 2 Association between qualitative variables and median scores for each SF-36 domain 1 year after hospital admission for COVID-19.

Qualitative variables	Comparison of median scores and IQR (in brackets) in each SF-36 domain, according to dichotomous explanatory variables (no/yes; Mann–Whitney U test)																							
	Physical functioning			Physical role			Bodily pain			General health			Vitality			Social functioning			Emotional role			Mental health		
	No	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*
Medical history																								
Female	95 (80–100)	80 (49–95)	**<0.001**	100 (100–100)	100 (0–100)	**<0.001**	100 (80–100)	70 (45–100)	**<0.001**	70 (60–80)	55 (35–70)	**<0.001**	70 (55–85)	55 (35–75)	**<0.001**	100 (88–100)	100 (62–100)	**<0.001**	100 (100–100)	100 (67–100)	**<0.001**	80 (64–88)	64 (48–80)	**<0.001**
Smoker/ ex-smoker	90 (70–100)	95 (70–100)	0.600	100 (75–100)	100 (75–100)	0.700	90 (60–100)	90 (67–100)	0.910	65 (45–80)	65 (45–75)	0.810	65 (45–80)	65 (45–80)	0.960	100 (75–100)	100 (87–100)	0.880	100 (100–100)	100 (100–100)	0.071	72 (60–88)	76 (60–84)	0.670
Hypertension	95 (75–100)	90 (57–100)	**<0.001**	100 (75–100)	100 (75–100)	0.870	100 (67–100)	90 (57–100)	0.610	70 (45–80)	65 (45–75)	0.082	70 (45–80)	65 (45–80)	0.710	100 (87–100)	100 (87–100)	0.540	100 (100–100)	100 (100–100)	0.860	72 (60–84)	76 (60–88)	0.150
Dyslipidemia	95 (70–100)	90 (55–100)	0.044	100 (78–100)	100 (75–100)	0.300	90 (67–100)	90 (57–100)	0.980	65 (45–80)	65 (45–75)	0.180	65 (45–80)	67 (45–80)	0.950	100 (87–100)	100 (75–100)	0.790	100 (100–100)	100 (100–100)	0.920	72 (59–84)	76 (60–88)	0.270
Anxiety	95 (70–100)	77 (55–95)	**0.001**	100 (75–100)	100 (0–100)	0.110	100 (67–100)	80 (58–100)	0.130	70 (45–80)	60 (36–70)	0.006	70 (45–84)	50 (35–65)	**<0.001**	100 (87–100)	88 (63–100)	0.015	100 (100–100)	100 (33–100)	0.003	76 (60–88)	64 (53–79)	**<0.001**
Depression	95 (70–100)	70 (55–90)	0.005	100 (75–100)	100 (75–100)	0.720	90 (67–100)	90 (60–100)	0.700	65 (45–80)	55 (30–75)	0.006	70 (45–80)	45 (30–65)	**0.001**	100 (87–100)	100 (38–100)	0.270	100 (100–100)	100 (67–100)	0.400	76 (60–88)	68 (56–84)	0.250
Fibromyalgia/ chronic fatigue	95 (70–100)	40 (22–55)	**<0.001**	100 (77–100)	0 (0–100)	**<0.001**	100 (67–100)	45 (23–62)	**<0.001**	65 (45–80)	30 (17–42)	**<0.001**	70 (45–80)	30 (17–37)	**<0.001**	100 (87–100)	63 (37–87)	**<0.001**	100 (100–100)	33 (0–100)	**0.001**	76 (60–88)	48 (42–66)	**<0.001**
Obesity (BMI > 30 kg/ m^2)	95 (80–100)	80 (50–95)	**<0.001**	100 (100–100)	100 (0–100)	**<0.001**	100 (70–100)	80 (52–100)	**<0.001**	70 (50–80)	60 (40–75)	**0.001**	70 (50–85)	60 (40–75)	**<0.001**	100 (87–100)	100 (75–100)	0.010	100 (100–100)	100 (67–100)	0.015	76 (60–88)	72 (54–84)	**0.027**
Ischemic cardiopathy	95 (70–100)	75 (54–95)	0.040	100 (75–100)	100 (62–100)	0.560	95 (61–100)	80 (68–100)	0.340	65 (45–80)	47 (40–64)	0.037	65 (45–80)	70 (54–85)	0.450	100 (87–100)	100 (84–100)	0.570	100 (100–100)	100 (100–100)	0.600	72 (60–87)	82 (67–92)	0.140
Cardiac insufficiency	95 (70–100)	75 (10–95)	0.004	100 (75–100)	100 (87–100)	0.820	100 (67–100)	70 (54–100)	0.130	65 (45–80)	55 (40–65)	0.015	65 (45–80)	70 (57–82)	0.310	100 (87–100)	100 (81–100)	0.870	100 (100–100)	100 (100–100)	0.400	72 (58–84)	80 (66–92)	0.120

(Continued)

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TABLE 2 (Continued)

Qualitative variables	Comparison of median scores and IQR (in brackets) in each SF-36 domain, according to dichotomous explanatory variables (no/yes; Mann–Whitney U test)																							
	Physical functioning			Physical role			Bodily pain			General health			Vitality			Social functioning			Emotional role			Mental health		
	No	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*
COPD	95 (70–100)	90 (57–95)	0.410	100 (75–100)	100 (87–100)	0.590	90 (67–100)	70 (21–90)	0.130	65 (45–80)	75 (37–82)	0.770	65 (45–80)	85 (47–95)	0.170	100 (87–100)	100 (81–100)	0.480	100 (100–100)	100 (100–100)	0.270	72 (60–88)	80 (56–84)	0.940
Chronic bronchitis	95 (70–100)	80 (59–99)	0.420	100 (75–100)	100 (25–100)	0.950	90 (67–100)	90 (34–100)	0.820	65 (45–80)	60 (46–74)	0.520	65 (45–80)	75 (52–84)	0.330	100 (87–100)	100 (81–100)	0.550	100 (100–100)	100 (100–100)	0.540	72 (60–88)	76 (61–83)	0.930
Asthma	95 (70–100)	47 (21–77)	0.023	100 (75–100)	0 (0–75)	0.012	90 (67–100)	34 (22–86)	0.064	65 (45–80)	25 (20–56)	0.020	65 (45–80)	20 (15–44)	0.008	100 (87–100)	63 (41–94)	0.060	100 (100–100)	50 (0–100)	0.084	75 (60–88)	54 (37–74)	0.110
Chronic kidney disease	95 (70–100)	70 (12–91)	0.006	100 (75–100)	100 (0–100)	0.280	90 (67–100)	70 (39–100)	0.270	65 (45–80)	47 (32–66)	0.040	65 (45–80)	55 (30–76)	0.240	100 (87–100)	100 (47–100)	0.400	100 (100–100)	100 (67–100)	0.420	73 (60–88)	70 (39–85)	0.320
Diabetes	95 (70–100)	90 (60–100)	0.240	100 (75–100)	100 (0–100)	0.450	90 (67–100)	100 (55–100)	0.750	65 (45–80)	65 (45–80)	0.600	65 (45–80)	65 (40–85)	0.580	100 (87–100)	100 (75–100)	0.930	100 (100–100)	100 (100–100)	0.580	75 (60–84)	72 (52–88)	0.870
Diabetes with target organ damage	95 (70–100)	75 (35–95)	0.044	100 (75–100)	100 (75–100)	0.560	100 (67–100)	68 (57–90)	0.110	65 (45–80)	45 (35–60)	0.039	65 (45–80)	65 (45–85)	0.890	100 (87–100)	100 (87–100)	0.690	100 (100–100)	100 (100–100)	0.418	72 (60–84)	84 (68–92)	0.140
Clinical outcomes																								
ARDS	95 (70–100)	90 (70–100)	0.830	100 (75–100)	100 (100–100)	0.310	90 (67–100)	100 (62–100)	0.620	65 (45–75)	65 (50–80)	0.780	65 (40–80)	70 (50–85)	0.054	100 (75–100)	100 (87–100)	0.580	100 (100–100)	100 (100–100)	0.350	72 (56–84)	76 (62–88)	0.091
ICU admission	95 (70–100)	95 (66–100)	0.950	100 (75–100)	100 (75–100)	0.710	95 (67–100)	90 (57–100)	0.500	65 (45–80)	70 (50–80)	0.230	65 (45–80)	70 (46–89)	0.041	100 (87–100)	100 (75–100)	0.370	100 (100–100)	100 (67–100)	0.054	74 (60–85)	73 (60–88)	0.540
Helmet-CPAP	95 (70–100)	95 (65–100)	0.990	100 (75–100)	100 (75–100)	0.620	100 (67–100)	90 (57–100)	0.370	65 (45–80)	70 (47–80)	0.330	65 (45–80)	70 (45–85)	0.086	100 (87–100)	100 (75–100)	0.470	100 (100–100)	100 (67–100)	0.041	76 (60–86)	72 (58–88)	0.640
High-flow oxygen	95 (66–100)	95 (81–100)	0.300	100 (75–100)	100 (100–100)	0.170	90 (61–100)	100 (77–100)	0.260	65 (45–80)	70 (60–80)	0.161	65 (45–80)	70 (60–86)	0.035	100 (87–100)	100 (87–100)	0.980	100 (100–100)	100 (100–100)	0.360	72 (57–84)	80 (63–88)	0.210

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TABLE 2 (Continued)

Qualitative variables	Comparison of median scores and IQR (in brackets) in each SF-36 domain, according to dichotomous explanatory variables (no/yes; Mann–Whitney U test)																					
	Physical functioning			Physical role			Bodily pain			General health			Vitality			Social functioning			Emotional role			Mental health		
	No	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*	*No*	*Yes*	*p*
Mechanical ventilation	95 (70–100)	90 (60–100)	0.730	100 (75–100)	100 (50–100)	0.950	90 (67–100)	80 (46–100)	0.250	65 (45–80)	70 (52–87)	0.500	65 (45–80)	75 (39–90)	0.370	100 (87–100)	87 (69–100)	0.140	100 (100–100)	100 (100–100)	0.880	72 (60–88)	80 (56–88)	0.720
Systemic corticosteroids during admission	90 (45–100)	95 (70–100)	0.170	100 (25–100)	100 (75–100)	0.210	80 (57–100)	100 (67–100)	0.023	62 (35–76)	65 (45–80)	0.330	60 (39–85)	70 (45–80)	0.340	100 (75–100)	100 (87–100)	0.061	100 (100–100)	100 (100–100)	0.820	76 (51–88)	72 (60–84)	0.980
SARS-CoV-2 vaccination after admission	95 (65–100)	95 (71–100)	0.960	100 (75–100)	100 (76–100)	0.670	90 (60–100)	90 (68–100)	0.200	70 (45–80)	65 (45–75)	0.410	70 (50–85)	70 (50–80)	0.360	100 (75–100)	100 (88–100)	0.450	100 (100–100)	100 (100–100)	0.820	80 (60–88)	75 (60–84)	0.180

ARDS, Acute respiratory distress syndrome; BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; ICU, Intensive care unit; and SF-36, 36-item Short Form health survey.
Values in bold have reached statistical significance.

Strengths of this study include its analysis of the impact of psychological and psychiatric comorbidities, not just physical ones, on long-term quality of life after admission for COVID-19. We also report laboratory results during the acute phase of infection. We also analyzed the use of corticosteroids, since there are data that suggest a protective effect on the persistence of symptoms after infection, probably due to its anti-inflammatory effect with consequent reduction of organ and tissue damage (23). In practically all of the studies cited, these variables are not analyzed, so our data are of special interest.

On the other hand, the study also presents several limitations, such as its retrospective nature or lack of estimation of size calculation/power calculation. The absence of a control group is also a limitation, as well as the lack of reference or expected values of the SF-36 test for a population similar to ours. In addition, we also do not have the score on the SF-36 test prior to infection. Finally, as included patients were infected in the early stages of the pandemic, the protective effect that vaccination against SARS-Cov-2 could have had prior to infection could not be assessed, although a recent systematic review and meta-analysis provides strong support in that line (24). The same occurs with antiviral drugs against SARS-CoV-2, as these were not contemplated in our center's therapeutic protocol during the period when participants were admitted. At that time, the therapeutic protocol for COVID-19 pneumonia in our hospital only contemplated systemic corticotherapy, thromboprophylaxis with low molecular weight heparins and the consideration of empirical antibiotherapy if there was suspicion of bacterial coinfection. Recent data indicate that the use of nirmatrelvir/ritonavir in acute infection would significantly decrease the subsequent incidence of long COVID (25).

5. Conclusion

Patients who required admission for COVID-19 in 2020 and early 2021 continued to show a diminished quality of life 1 year after hospital discharge, especially in the domains of general health, vitality, and mental health. The main factors that may influence this would be female sex, a history of fibromyalgia/chronic fatigue, and, to a lesser extent, obesity. More data are needed to evaluate the role of the inflammatory response and specifically serum ferritin in it.

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 humans were approved by Ethics and Drug Research Committee of the Castellón General University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because informed consent was given verbally.

TABLE 3 Association between quantitative variables and quality of life outcomes, according to the different domains of the SF-36 test 1 year after hospital admission.

Quantitative variables	Correlation * between quantitative variables and quality of life outcomes, according to SF-36 domain															
	Physical functioning		Physical role		Bodily pain		General health		Vitality		Social functioning		Emotional role		Mental health	
	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*
Medical history																
Age* ($n = 486$)	−0.302	**<0.001**	−0.036	0.440	−0.054	0.230	−0.132	0.004	−0.032	0.480	0.025	0.590	0.086	0.059	0.052	0.250
Age-adjusted Charlson Comorbidity Index ($n = 486$)	−0.294	**<0.001**	−0.059	0.200	−0.077	0.092	−0.166	**<0.001**	−0.043	0.350	0.006	0.900	0.067	0.140	0.038	0.410
Clinical outcomes																
Hospital stay (days) ($n = 486$)	−0.188	**<0.001**	−0.650	0.150	−0.091	0.045	−0.074	0.100	−0.016	0.720	−0.084	0.064	−0.050	0.27	0.038	0.410
ICU admission (days) ($n = 100$)	−0.043	0.670	0.067	0.510	−0.017	0.870	0.016	0.870	0.011	0.920	−0.047	0.640	0.043	0.670	0.029	0.780
PaO_2/FiO_2 at admission ($n = 385$)	0.124	0.015	0.005	0.920	0.047	0.360	0.069	0.180	−0.035	0.490	0.038	0.460	0.040	0.430	−0.040	0.430
FiO_2 at admission (%) ($n = 486$)	−0.098	0.031	−0.021	0.640	−0.084	0.064	−0.024	0.590	0.058	0.200	−0.019	0.670	−0.034	0.460	−0.022	0.620
Min PaO_2/FiO_2 ($n = 381$)	0.017	0.750	−0.069	0.180	−0.020	0.700	−0.033	0.520	−0.132	0.010	−0.008	0.880	0.023	0.660	−0.116	0.023
Max FiO_2 (%) ($n = 486$)	−0.145	**0.001**	−0.006	0.900	−0.029	0.520	−0.054	0.230	0.043	0.350	−0.018	0.690	−0.048	0.290	0.035	0.440
Analytical parameters																
Lymphopenia at admission (/μL) ($n = 484$)	−0.021	0.640	−0.084	0.064	−0.077	0.089	−0.060	0.190	−0.096	0.034	−0.031	0.500	−0.070	0.880	−0.062	0.180
CRP at admission (mg/L) ($n = 486$)	0.017	0.720	0.089	0.049	0.075	0.100	0.086	0.058	0.150	**0.001**	0.033	0.470	0.057	0.210	0.114	0.010
Ferritin at admission (μg/L) ($n = 443$)	0.233	**<0.001**	0.127	0.007	0.185	**<0.001**	0.170	**<0.001**	0.222	**<0.001**	0.164	**0.001**	0.135	0.005	0.211	**<0.001**
IL-6 at admission (ng/L) ($n = 285$)	0.043	0.470	0.114	0.055	0.088	0.140	0.054	0.360	0.138	0.020	−0.017	0.780	0.066	0.270	0.106	0.073

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TABLE 3 (Continued)

Quantitative variables	Correlation * between quantitative variables and quality of life outcomes, according to SF-36 domain															
	Physical functioning		Physical role		Bodily pain		General health		Vitality		Social functioning		Emotional role		Mental health	
	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*
D-dimer at admission (ng/mL) (*n* = 431)	−0.068	0.160	−0.031	0.520	−0.034	0.480	0.003	0.950	0.030	0.540	−0.014	0.770	0.009	0.850	0.008	0.880
Min lymphocytes during admission (/μL) (*n* = 484)	0.045	0.320	−0.036	0.430	−0.039	0.390	−0.051	0.270	−0.069	0.130	−0.006	0.890	0.003	0.940	−0.094	0.039
Max RCP during admission (mg/L) (*n* = 485)	−0.001	0.980	0.072	0.110	0.088	0.054	0.070	0.120	0.135	0.003	0.023	0.610	0.045	0.330	0.112	0.014
Max ferritin during admission (mcg/L) (*n* = 447)	0.169	**<0.001**	0.100	0.028	0.167	**<0.001**	0.153	**0.001**	0.177	**<0.001**	0.171	**<0.001**	0.103	0.025	0.188	**<0.001**
Max IL-6 during admission (ng/L) (*n* = 357)	−0.035	0.510	0.001	0.980	0.041	0.440	−0.028	0.600	0.088	0.098	−0.063	0.240	0.004	0.950	0.031	0.570
Max d-dimer during admission (ng/mL) (*n* = 480)	−0.124	0.006	−0.058	0.200	−0.034	0.460	<0.001	1.000	0.026	0.580	−0.046	0.320	−0.032	0.490	0.028	0.540
Total days of corticosteroid treatment (*n* = 486)	−0.049	0.280	−0.043	0.350	0.060	0.190	−0.031	0.490	0.001	0.980	−0.014	0.750	−0.028	0.530	0.009	0.840

CRP, C reactive protein; IQR, Interquartile range. *Correlation presented as Spearman's rho (rs), except in the case of age, where it is Pearson's correlation coefficient.
Values in bold have reached statistical significance.

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TABLE 4 Results of the multivariable linear regression analysis of the association between explanatory variables and quality of life domains on the SF-36.

	Physical functioning		Physical role		Bodily pain		General health		Vitality		Social functioning	Emotional role			Mental health	
Variables	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Female	**−15.074 (−20.097, −10.050)**	**<0.001**	**−16.466 (−23.286, −9.645)**	**<0.001**	**−15.322 (−20.672, −9.971)**	**<0.001**	**−12.546 (−16.795, −8.298)**	**<0.001**	**−10.264 (−15.106, −5.422)**	**<0.001**	**−12.334 (−16.938, −7.731)**	**<0.001**	**−12.447 (−18.591, −6.303)**	**<0.001**	**−9.522 (−13.515, −5.529)**	**<0.001**
Hypertension	1.865 (−3.399, 7.129)	0.487	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Anxiety	−2.478 (−9.327, 4.371)	0.477	—	—	—	—	—	—	−7.269 (−14.616, 0.077)	0.052	—	—	—	—	−3.250 (−8.716, 2.215)	0.243
Depression	—	—	—	—	—	—	—	—	−3.589 (−13.639, 6.461)	0.483	—	—	—	—	—	—
Fibromyalgia/ chronic fatigue	**−25.666 (−39.481, −11.851)**	**<0.001**	**−28.310 (−49.099, −7.520)**	**0.008**	**−26.975 (−41.962, −11.988)**	**<0.001**	**−23.478 (−35.369, −15.586)**	**<0.001**	**−23.370 (−36.646, −10.094)**	**0.001**	**−16.190 (−29.037, −3.343)**	**0.014**	**−26.531 (−45.175, −7.887)**	**0.005**	**−12.143 (−23.173, −1.113)**	**0.031**
Obesity (BMI > 30 kg/ m^2)	**−8.192 (−13.232, −3.152)**	**0.002**	**−15.430 (−22.521, −8.338)**	**<0.001**	**−5.467 (−10.672, −0.263)**	**0.040**	−2.902 (−7.109, 1.306)	0.176	**−6.075 (−10.650, −1.500)**	**0.009**	—	—	—	—	−2.278 (−6.087, 1.532)	0.241
Age	**−0.281 (−0.557, −0.004)**	**0.047**	−0.056 (−0.289, 0.177)	0.638	−0.069 (−0.238, 0.100)	0.424	0.039 (−0.196, 0.274)	0.744	−0.088 (−0.239, 0.063)	0.254	0.064 (−0.082, 0.209)	0.390	**0.219 (0.009, 0.429)**	**0.041**	0.084 (−0.040, 0.208)	0.185
Age-adjusted Charlson Comorbidity Index	**−2.611 (−4.675, −0.547)**	**0.013**	—	—	—	—	**−1.996 (−3.768, −0.223)**	**0.027**	—	—	—	—	—	—	—	—
Length of hospital stay	−0.239 (−0.623, 0.146)	0.223	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Max FiO_2	−0.065 (−0.209, 0.079)	0.376	—	—	—	—	—	—	—	—	—	—	—	—	—	—

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TABLE 4 (Continued)

	Physical functioning		Physical role		Bodily pain		General health		Vitality		Social functioning	Emotional role			Mental health	
Variables	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
CRP on admission	—	—	—	—	—	—	—	—	**0.033 (0.003, 0.063)**	**0.031**	—	—	—	—	—	—
Ferritin at admission	0.001 (−0.005, 0.006)	0.779	—	—	0.001 (−0.006, 0.006)	0.998	0.002 (−0.003, 0.007)	0.365	0.003 (−0.002, 0.008)	0.276	0.002 (−0.003, 0.007)	0.393	—	—	0.001 (−0.003, 0.005)	0.654
Max ferritin during admission	0.000 (−0.005, 0.005)	0.961	—	—	−0.001 (−0.006, 0.004)	0.756	−0.003 (−0.007, 0.001)	0.173	−0.003 (−0.007, 0.002)	0.200	−0.003 (−0.007, 0.002)	0.204	—	—	0.000 (−0.004, 0.003)	0.825
Model parameters																
R^2	0.271		0.111		0.133		0.157		0.155		0.089		0.059		0.101	
F (*p*)	14.457 (<0.001)		15.090 (<0.001)		11.046 (<0.001)		11.468 (<0.001)		8.740 (<0.001)		8.492 (<0.001)		11.065 (<0.001)		6.967 (<0.001)	
Df	11, 428		4, 481		6, 433		6, 433		9, 430		5,434		3, 482		7, 432	
1-β	1		1		1		1		1		1		1		1	

BMI, Body mass index; CI, Confidence interval; CRP, C-reactive protein; ICU, Intensive care unit; SF-36, 36-item Short Form health survey; Df, Degree of freedom. "—": not included in the multivariate study.
Values in bold have reached statistical significance.

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Author contributions

IP and CR: conception and design of the study, writing of the manuscript, bibliographic search, data collection, and analysis and interpretation of data. SeF, ED, GH, AS, MV, SoF, ME, DP, and AC: data collection and bibliographic search. MM, JU, and JR: conception and design of the study and writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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The importance of estimating prevalence of ME/CFS in future epidemiological studies of long COVID

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ME/CFS, long COVID, prevalence, diagnostic criteria, fatigue, post-exertional malaise, disease duration, unrefreshing sleep

1. Introduction

The end of the COVID-19 pandemic is generating a wide interest on long COVID (LC) (1), a heterogeneous medical condition known by many alternative names, such as post-COVID-19 syndrome (2), post-acute COVID-19 syndrome (3), and post-acute sequelae of SARS-CoV-2 infection (4), and persistent post-COVID-19 syndrome (5). This condition is a top priority in the current biomedical research agenda due to its great impact on public health (6). The clinical manifestation of LC varies from mild and temporary symptoms, such as anosmia and ageusia, to highly debilitating and chronic fatigue and post-exertional malaise (PEM) (7). This spectrum of symptoms might be explained by immune dysregulation, microbiota dysbiosis, autoimmunity and immune priming, abnormal blood clotting and endothelial-related problems, and neurological signaling dysfunction, among other pathological mechanisms (1, 8).

The real burden of LC remains elusive even though systematic reviews aggregate data from hundreds of studies and thousands of individuals (9–11). The underlying problems are the reliance on self-reporting of symptoms for the LC diagnosis and the challenge of conducting studies without any sources of sampling bias (10). The same problems emerge in the few epidemiological studies on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (12, 13). This disease remains without a specific biomarker (14), but might share some pathological mechanisms and symptoms with LC (4, 15–18). According to a recent meta-analysis (13), the pooled estimate of ME/CFS prevalence across multiple studies is 0.89% [95% CI = (0.60%−1.33%)]. This estimate shows some variations according to gender (1.36% in women vs. 0.86% in men), age (0.65% in adults vs. 0.55% in children and adolescents), or study setting (0.76% in community-based study vs. 0.63% in primary care studies). This disease inflicts dramatic individual and societal costs, such as health deterioration, reduced productivity, earnings and employment, mental health problems, and burnout (19).

Given the global urgency of managing and treating LC, several studies (20–23) are combining basic research on this disease and ME/CFS with the idea of accelerating knowledge of the underlying pathological mechanisms. However, similar combined approach remains to be adopted in epidemiological studies of LC. Therefore, these studies could expand their objectives to include the estimation of ME/CFS prevalence as well. These additional data offer a better quantification of the real burden of LC due to people that develop ME/CFS-related symptoms. Such a quantification provides the foundation for using consensual guidelines for ME/CFS healthcare to LC case management (15) that could be adopted and adapted for the specificities of a given national health system.

Such an expansion of objectives comes at a minimal cost by simply incorporating standard symptom questionaries used for the ME/CFS diagnosis and then running a diagnostic algorithm based on consensual case definitions. With this in mind, we reviewed the most consensual case definitions of ME/CFS. We also compared the symptoms assessed in the UK ME/CFS Biobank (UKMEB) (24, 25) with those documented in recent LC epidemiological studies. Finally, we provided some practical recommendations for future studies.

2. Brief review of ME/CFS and LC diagnostic criteria

ME/CFS has more than 20 proposed case definitions (26, 27). Among these definitions, the 1994 CDC (28), the 2003 Canadian Consensus Criteria (CCC) (29), and the 2015 Institute of Medicine (IOM) criteria have been used as diagnostic tools for research purposes (30). These criteria are also used for patients' enrollment in the UKMEB (24, 25).

The 1994 CDC criteria is mainly a research tool for ME/CFS diagnosis. In these criteria, an individual receives an ME/CFS diagnosis if she (or he) experiences unexplained, persistent, or relapsing fatigue for at least 6 months. The fatigue experienced should substantially reduce the normal levels of daily activities. Resting is also insufficient to restore normal energy levels. The individual should also experience four or more of the following eight symptoms:

I Substantial impairment in short-term memory or concentration;
II Sore throat;
III Tender cervical and axillary lymph nodes;
IV Muscle pain;
V Multi-joint pain without swelling or redness;
VI Headaches of a new type, pattern, or severity;
VII Unrefreshing sleep;
VIII PEM.

Note that a group of experts recommend PEM as a hallmark rather than an optional symptom to consider the diagnosis of ME/CFS based on these criteria (30). Exclusion criteria include all medical conditions that could explain fatigue (e.g., untreated hypothyroidism or sleep apnea), alcohol or other substance abuse, and severe obesity (body mass index greater than 45 kg/m^2). Other authors discussed the possibility of defining a severely obese individual by a body mass index equal to or greater than 40 kg/m^2 (31).

The 2003 CCC is basically a diagnostic tool for clinical settings. However, many research studies are using this tool for ME/CFS diagnosis. This criterion also recognizes 6 months as the minimal symptom duration. The hallmark symptoms are pathological fatigue, PEM, sleep abnormalities (unrefreshing sleep, reduced sleep quality or quantity, reversed or chaotic diurnal sleep rhythms), muscle or multi-joint pain, and two or more cognitive symptoms. The diagnosis also requires the presentation of one or more symptoms belonging to at least two additional domains: autonomic, neuroendocrine, and immune. Exclusion criteria also apply.

The 2015 IOM criterion is also a primary diagnostic tool for clinical settings. It also requires the presence of fatigue for more than 6 months, PEM, and unrefreshing sleep. This case definition also requires at least one of the following manifestations: cognitive impairment and orthostatic intolerance. In contrast to the 1994 CDC and 2003 CCC criteria, the 2015 IOM criterion does not contemplate any list of exclusionary medical conditions or co-morbidities. However, one should not diagnose a patient as having ME/CFS if treatment for the alternative diagnosis eliminates all symptoms in a patient. A recent discussion about the exclusionary medical conditions can be found elsewhere (32).

According to the World Health Organization, the definition of LC is the presence of at least one unresolved symptom after 3 months of a confirmed SARS-CoV-2 infection (2). Another definition is based on an international Delphi consensus of 11 outcomes for the core symptom set of LC (33). These outcomes are: fatigue; pain; post-exertion symptoms; work or occupational and study changes; survival; and functioning, symptoms, and conditions for each of cardiovascular, respiratory, nervous system, cognitive, mental health, and physical outcomes. Alternatively, the LC diagnosis might be diagnosed by a disease scoring system based on 37 symptoms (34).

3. Symptoms reported by patients in UKMEB and in current LC prevalence studies

Given the broad clinical spectrum of LC patients, prevalence studies of LC typically estimate the individual prevalence of a large number of symptoms. The basic question is whether these studies collect symptom data that would also allow them conducting a possible diagnosis of ME/CFS in the study participants.

Previously, we reported the prevalence of each of 47 symptoms evaluated in 222 ME/CFS patients upon their enrollment in the UKMEB, as reported elsewhere (35). Excluding fatigue (with 100% prevalence), the prevalence per symptom varied from 33.9% (palpitations) to 98.7% (unrefreshing sleep) with an average prevalence of 72.0%. Therefore, we can conclude that these 47 symptoms are highly prevalent in patients with ME/CFS complying with the 1994 CDC or the 2003 CCC criteria.

We then investigated whether three large systematic reviews of LC prevalence reported these symptoms. Besides the prevalence of fatigue (data not shown), there were only

TABLE 1 Forty-seven symptoms in the UKMEB symptom assessment questionnaire (based on 2003 CCC) and their reporting in three systematic reviews on the prevalence of LC and its symptoms.

Domain	Description	UKMEB prevalence (%)	Prevalence in percentage (95% CI); number of studies (*n*)		
			O'Mahoney et al. (9)	Woodrow et al. (10)	Natarajan et al. (11)
Autonomic	Air hunger, difficulty breathing, or shortness of breath on exertion/activity	58.5	22.6 (18.3–27.4); $n = 70$ (dyspnea) 19.6 (8.8–38.0); $n = 6$ (exertional breathlessness)	14.9 (1.6–64.9); $n = 78$ (breathing problems)	21.5 (14.4–32.1); $n = 17$ (dyspnea)
	Bladder problems	56.7	2.1 (0.7–5.9); $n = 5$ (affected urinary system)	NR	NR
	Dizziness	68.3	6.2 (3.5–10.8); $n = 15$	7.4 (0.8–45.4); $n = 26$	9.1 (4.3–19.6); $n = 7$
	Paleness	49.6	NR	NR	NR
	IBS symptoms	78.1	6.4 (3.8–10.6); $n = 13$ (gastrointestinal symptoms) 3.4 (2.1–5.4); $n = 21$ (diarrhea) 2. (1.2–3.8); $n =$ 16 (vomiting/nausea)	3.9 (0.4–28.8); $n = 49$ (nausea/vomiting)	7.8 (4.8–12.6); $n = 5$ (diarrhea) 1.2 (0.7–2.3); $n = 3$ (vomiting) 14.6 (1.7–124.5); $n =$ 2 (diarrhea/vomiting)
	Intolerance to standing up	51.8	NR	NR	NR
	Feeling lightheaded	73.2	NR	NR	NR
	Palpitations	33.9	6.3 (4.5–8.7); $n = 22$	5.8 (1.2–24.5); $n = 26$	14.2 (7.1–28.2); $n = 6$
Immunological	Fever/Chills	57.6	2.2 (0.5–9.2); $n = 13$	1.9 (0.1–34.7); $n = 24$ (fever) 1.0 (0.0–98.8); $n =$ 4 (chills)	3.1 (1.5–6.3); $n = 9$
	Flu symptoms	71.9	10.2 (7.4–13.8); $n = 50$ (cough) 4.54 (1.5–13.1); $n = 7$ (nasal symptoms)	7.4 (1.3–33.5); $n = 52$ (cough)	17.8 (13.3–23.9); $n = 14$ (cough)
	Frequent viral infections with long recovery periods	52.7	NR	NR	NR
	Worsen sensitivity to light	66.1	NR	NR	NR
	Sore throat	71.9	2.8 (1.8–4.3); $n = 14$	3.5 (0.6–17.1); $n = 22$	6.4 (3.0–13.6); $n = 9$
	Morning stiffness	71.0	NR	NR	NR
	Tender glands	75.4	NR	NR	NR
Neuroendocrine	Intolerance to extremes of heat/cold	74.6	NR	NR	NR
	Decreased sexual function or interest	57.1	NR	NR	NR
	Unusually sweaty	55.4	9.7 (5.7–16.0); $n = 8$ (sweating/night sweats)	NR	NR
	Worsening of symptoms post stress	89.3	NR	NR	NR
Neurocognitive	Back weakness	64.0	NR	NR	NR
	Brain fog or confusion	77.2	4.1 (1.6–10.1); $n = 9$	NR	NR
	Trouble concentrating	96.0	18.6 (13.4–25.2); $n = 11$ (poor concentration)	NR	20.2 (12.9–31.8); $n = 5$ (attention/concentration deficit)
	Difficulty retaining or recalling information	81.7	19.9 (15.8–24.7); $n = 23$ (impaired memory)	10.1 (0.8–60.2); $n = 49$ (cognitive or memory problems)	NR
	Difficulty understanding things/thinking clearly	82.6	17.1 (10.1–27.4); $n = 13$ (cognitive dysfunction)	10.1 (0.8–60.2); $n = 49$ (cognitive or memory problems)	28.8 (10.0–83.2); $n = 3$ (cognitive impairment)

(Continued)

TABLE 1 (Continued)

Domain	Description	UKMEB prevalence (%)	Prevalence in percentage (95% CI); number of studies (*n*)		
			O'Mahoney et al. (9)	Woodrow et al. (10)	Natarajan et al. (11)
	Disorientation	50.5	NR	NR	NR
	Eyesight disturbance (temporary)	60.7	6.3 (3.8–10.3); $n = 8$ (affected vision)	10.0 (0.0–96.5); $n = 4$ (eye problems)	NR
	Loss of balance or unsteadiness while standing, unable to focus the vision	73.7	3.8 (1.2–11.1); $n = 5$ (vertigo)	NR	NR
	Muscle discomfort	86.2	NR	NR	NR
	Muscle weakness	85.3	NR	10.2; 0.5–72.2; $n = 21$ (weakness)	NR
	Neck weakness	54.9	NR	NR	NR
	Poor coordination or unsteady movements (while walking)	62.1	14.8 (9.8–21.5); $n = 14$ (impaired walking/mobility)	NR	NR
	Sensitivity to light/noise	77.7	3.1 (1.7–5.6); $n = 21$ (affected hearing)	3.8; 0.2–45.0; $n = 11$	NR
	Short term memory problems	83.5	19.9 (15.8–24.7); $n = 23$ (impaired memory)	10.1 (0.8–60.2); $n = 49$ (cognitive or memory problems)	18.4 (11.7–28.9); $n = 5$ (memory deficit)
	Slow thinking	75.9	NR	NR	NR
	Tingling/numbness in arms and/or legs	69.6	6.2 (2.8–13.2); $n = 6$ (paresthesia)	11.3 (0.7–69.5); $n = 14$ (tingling or itching)	NR
Pain	Pain in chest or abdomen	77.2 (chest)	7.2 (5.2–9.8); $n = 39$ (chest) 4.0 (2.2–7.1); $n = 10$ (abdomen)	6.7 (0.9–35.8); $n = 43$ (chest) 3.7 (0.1–63.8); $n = 15$ (abdomen)	12.1 (6.1–24.0); $n = 11$ (chest) 9.2 (3.6–23.8); $n = 3$ (abdomen)
	Migraine/headaches	38.4 (migraines) 77.2 (headaches)	6.8 (4.9–9.4); $n = 27$	6.5 (0.6–45.6); $n = 51$ (headaches)	10.5 (5.3–20.5); $n = 14$ (headaches)
	Joint/muscle pain	55.4 (joint) 88.0 (muscle)	14.3 (8.0–24.1); $n = 16$ (joint) 10.3 (6.9–14.9); $n = 28$ (muscle)	10.6 (1.0–57.5); $n = 61$	28.2 (14.8–54.1); $n = 5$ (joint) 13.3 (7.5–23.7); $n = 13$ (muscle)
PEM	Intolerance to exercise	81.7	NR	NR	NR
	Fatigue/exhaustion after activity that would not cause fatigue before	96.4	NR	NR	NR
	Malaise after exertion, lasting >24 h	96.0	NR	NR	NR
	Marked physical/mental fatigue/exhaustion after minimal effort, lasting >24 h	77.7	NR	NR	NR
	Pain after exertion/effort, lasting >24 h	75.9	NR	NR	NR
	Worsening of symptoms after exertion/effort, lasting >24 h	91.1	NR	NR	NR
Sleep	Problems in sleep, quality of duration; insomnia	85.7	23.5 (18.1–29.8); $n = 34$ (affected sleep)	13.2 (1.2–64.9); $n = 42$ (sleep problems)	19.1 (12.4–29.4); $n = 10$ (sleep disturbance)
	Unrefreshing sleep	98.7	NR	NR	NR

O'Mahoney et al. (9) included 194 studies on SARS-CoV-2 infected individuals who confirmed and self-reported symptoms at least 28 days after infection onset (mean follow-up of 126 days). Woodrow et al. (10) included 120 studies in which SARS-CoV-2 infected individuals were followed up for 3–12 months. Natarajan et al. (11) reported a meta-analysis of 36 studies among LC patients.
NR, not reported.

individual prevalence estimates for 23, 18, and 14 of the 47 UKMEB-related symptoms reported by O'Mahoney et al. (9), Woodrow et al. (10), and Natarajan et al. (11), respectively (Table 1). More importantly, these reviews did not report data related to PEM, although post-exertion symptoms are in the core outcome set of LC (33). Besides that, two large survey reported the prevalence of PEM higher than 80% in LC patients (7, 34). This lack of reporting indicates that current LC epidemiological studies have not collected sufficient symptom data to allow for a preliminary symptom assessment necessary for an ME/CFS diagnosis.

These systematic reviews also did not provide any data for other highly prevalent ME/CFS-related symptoms in the patients from the UKMEB, such as unrefreshing sleep (98.7%), sensitivity to light or noise (77.7%), tender lymph nodes (75.5%), and intolerance to heat and cold (74.6%; Table 1).

4. Discussion

Since the beginning of the COVID-19 pandemic in early 2020, it became clear that many people who experienced a SARS-CoV-2 infection remained ill with a clinical manifestation consistent with ME/CFS. However, most of the epidemiological studies of LC ignored this fact and, therefore, they did not assess the presence and severity of cardinal symptoms of ME/CFS diagnosis. This is an unfortunate missed opportunity, especially, in what estimating ME/CFS prevalence is concerned. One can seize this opportunity by conducting a study prospectively. These studies should be clear in the LC case definition, criteria for an acute COVID-19 episode, and the duration of follow-up, because these aspects might influence the subsequent statistical results. Studies using a retrospective design as reported in recent meta-analyses of LC should be avoided, because they might miss crucial data (e.g., PEM) unavailable from routine healthcare records.

There is evidence for a limited assessment of symptoms in LC patients related to ME/CFS, including PEM, unrefreshing sleep, and sensitivity to light or noise in epidemiological studies of LC. Most of these unreported symptoms are auxiliary rather than strictly mandatory for an ME/CFS diagnosis, but they might be useful for defining disease subtypes (36, 37). The only exceptions are the PEM-related symptoms, which are key in the 2003 CCC, the 2015 IOM criteria, and in the modified 1994 CDC criterion (30). The assessment of PEM or other symptoms is becoming more important, given that the duration of LC can reach 3 years by now in some patients (6). In the case of ME/CFS, a 2-year disease duration might reflect the transition from an early to an established disease stage (38). Hence, it is conceivable that LC cases without typical symptoms of ME/CFS at an early disease stage might develop key symptoms of this disease when the chronicity of LC symptoms becomes established.

We recommend that future epidemiological studies of LC use the DePaul Symptoms Questionnaire (DSQ) (39) or the UKMEB Symptoms Assessment Questionnaire (35), as diagnostic tools enabling the identification of cases meeting commonly used diagnostic criteria for ME/CFS. Given the cardinal importance of PEM in ME/CFS diagnosis, one should make the effort to capture accurately its different aspects, such as recovery time, frequency, and severity (40). In this scenario, one can use the DSQ dedicated to PEM specifically, the so-called DSQ-PEM (41). The use of this questionnaire is likely to be more informative than simply asking for the presence of symptoms worse after even minor physical or mental effort, as done in large study of LC (34). The reporting of the epidemiological findings could be done via a recommended guideline for the minimal data elements on ME/CFS research (42). Besides typical information about study design and demographics, one should report the case definition used, the symptom inventory, the excluded medical and psychiatric conditions and co-morbidities, and self-reported functional impairment/levels of activity.

The major difficulty to comply with the 1994 CDC and the 2003 CCC in epidemiological studies lies in the exclusion of other medical conditions that could explain fatigue. The 2015 IOM criterion, alternatively, does not impose any exclusionary conditions (32), however, they still require a clinical assessment and consideration of differential diagnosis. This case definition is already being used to report the frequency of ME/CFS cases among LC cases (34, 43). However, the use of the 2015 IOM criteria might lead to inconsistent findings across studies due to variations in frequency of co-morbidities present in different populations. It might also overestimate the prevalence of ME/CFS due to highly-frequent conditions, such as diabetes and obesity in suspected cases. For example, 43% of participants fit the 2015 IOM criterion for ME/CFS in an LC study (43). Among these compliant individuals, some had a BMI of 45 kg/m^2.

We also recommend raising the standard of research and reporting in LC, ME/CFS, and other chronic diseases; we made a similar recommendation for genetic association studies in ME/CFS (44). Our recommendation is based on two systematic reviews of LC prevalence data. One systematic review suggested that 45% of LC cases had ME/CFS (45). However, this review incorrectly assumed that the persistence of fatigue was equivalent to ME/CFS. The other systematic review suggested that only a few epidemiological studies collected representative samples from the LC population (10). Low population representativeness, convenience sampling, and different sources of bias might be present in the remaining published studies (10). Randomness and sample representativeness are the pillars of a sound statistical inference. If a study does not minimally ensure these foundational assumptions, the subsequent statistical inference might be tricky, or even impossible (46).

Author contributions

ADG: Investigation, Validation, Writing – review & editing. FW: Investigation, Validation, Writing – review & editing. LN: Data curation, Resources, Writing – review & editing. EL: Data curation, Resources, Writing – review & editing. NS: Conceptualization, Investigation,

Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

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Focus on post-exertional malaise when approaching ME/CFS in specialist healthcare improves satisfaction and reduces deterioration

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Background: Post-exertional malaise (PEM) is considered a hallmark characteristic of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). This may also apply to subgroups of patients with long COVID-induced ME/CFS. However, it is uncertain to what extent PEM is acknowledged in routine specialist healthcare for ME/CFS patients, and how this affects patient outcomes.

Objective: This study aims to evaluate to what extent ME/CFS patients experienced focus on PEM in specialist healthcare practice and its significance for outcome and care quality.

Methods: Data from two online cross-sectional surveys covering specialist healthcare services for ME/CFS patients at rehabilitation institutes in Norway and two regional hospitals, respectively, were analyzed. Evaluations of 788 rehabilitation stays, 86 hospital consultations, and 89 hospital interventions were included. Logistic regression models and Mann–Whitney U-tests were used to quantify the impact of addressing PEM on health and functioning, care satisfaction, or benefit. Spearman's rank correlation and Cronbach's alpha of focus on PEM with the respondents' perception of healthcare providers' knowledge, symptom acknowledgment, and suitability of intervention were assessed as measures for care quality and their internal consistency, respectively.

Results: PEM was addressed in 48% of the rehabilitation stays, 43% of the consultations, and 65% of the hospital interventions. Failure to address PEM roughly doubled the risk of health deterioration, following rehabilitation (OR = 0.39, 95% CI 0.29–0.52; 40.1% vs. 63.2% $P = <0.001$) and hospital intervention (OR = 0.34, 95% CI 0.13–0.89; 22.4% vs. 45.2%, $p = 0.026$). The focus on PEM (PEM-focus) during the clinical contact was associated with significantly higher scores on patients' rated care satisfaction and benefit of both consultation and intervention. Furthermore, addressing PEM was (inter)related to positive views about healthcare providers' level of knowledge of ME/CFS, their acknowledgment of symptoms, obtained knowledge, and the perceived suitability of intervention (Cronbach's alpha ≥0.80).

Discussion: PEM is still frequently not acknowledged in specialist healthcare practice for ME/CFS patients in Norway. Not addressing PEM substantially increased the probability of a decline in health and functioning following the intervention and was strongly associated with reduced perceived care quality, satisfaction, and benefit. These findings may be related to the applied explanatory models for ME/CFS and are most likely of relevance to long COVID.

KEYWORDS

ME/CFS, myalgic encephalomyelitis, chronic fatigue syndrome, post-exertional malaise, post-exertional symptom exacerbation, patient experience, specialist healthcare, healthcare quality

1 Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a long-term, severe multisystem disease with a distinctive clinical picture, often, but not necessarily, preceded by an infection. Its pathophysiology is still uncertain; therefore, some clinical and research settings apply a biopsychosocial explanatory model for ME/CFS. In these settings, ME/CFS is perceived as a fatigue illness, explained with a psychosomatic understanding as a maladaptive response to an infection or overload, perpetuated by dysfunctional personality factors or beliefs, health anxiety, and deconditioning (1–3). This approach has been criticized for overlooking the evidence of detectable pathophysiological disturbances explaining the symptoms of ME/CFS patients (4–7). Others, however, apply a biomedical approach and consider ME/CFS as a maladaptive pathophysiological response, following an infection or other trigger that remains inadequately studied.

This biomedical explanatory model is acknowledged in the diagnostic criteria sets for ME/CFS that have been defined during the last two decades (6, 8–11). These criteria are more specific than earlier criteria. Core symptoms are fatigue, exertion-induced worsening of disease and symptoms, cognitive dysfunction, and sleep dysfunction (11). Furthermore, immune dysfunction, orthostatic intolerance, neuroendocrine, circulatory, and gastrointestinal dysfunction are common symptoms, while mental illness as the cause of the symptoms is explicitly excluded.

Exertion-induced aggravation of symptoms in ME/CFS is generally called post-exertional malaise (PEM) or post-exertional symptom exacerbation (PESE). It involves a relatively long-lasting and severe worsening of symptoms and/or the appearance of new symptoms, with a further substantial reduction in functioning (9, 12, 13). It may be an immediate or a delayed, disproportionate response to physical, orthostatic, or cognitive effort, or sensory stimuli, which previously were tolerated. It can take days, weeks, or longer to return to baseline (12, 14, 15). Sometimes, a new, more severe baseline is established. The delayed onset and the broad constellation of symptom deteriorations distinguish ME/CFS from other diseases with severe fatigue or deconditioning (6, 16–21). PEM is widely recognized as the most debilitating and persistent feature of ME/CFS (22). The PEM phenomenon has been demonstrated in multiple studies, both with patient-reported outcome measures and with objective measures. Objective findings include new or increased structural and functional abnormalities, following controlled exertion situations (23–26). These findings indicate disturbances in energy metabolism and a dysfunctional autonomic nervous system, impairing the body's ability to recover from exertion (27, 28). In current practice in Norway, PEM is at best evaluated by anecdotal described experiences; standardized questionnaires (18) or clinical objective PEM, e.g., repeated hand grip strength (29) or cardiopulmonary exercise tests (25), is not routine practice.

If a psychosomatic understanding is applied to approach ME/CFS, PEM is usually disregarded and rather considered as a dysfunctional cognition and extreme behavioral response (30). Interventions typically aim at interrupting the self-perpetuating vicious circle that is thought to maintain symptoms. Assumed mistaken illness beliefs, dysfunctional cognitions, and fear of activity are aimed to be corrected by increasing physical activity to overcome avoidance behavior and regain physical fitness (31, 32). In this view, commonly applied approaches are cognitive behavioral therapy (CBT) and graded exercise therapy (GET), respectively, or varieties that share central conceptual elements.

Current research and clinical recommendations that acknowledge a biomedical base and the PEM phenomenon, however, recognize that there is currently no scientific evidence for effective treatment of ME/CFS and explicitly discourage curative CBT and GET forms (10, 33–37). Instead, pacing strategies are considered to be the most effective approach to reduce the risk of PEM relapse and retain or improve physical functioning and quality of life (10, 36–40).

In Norway, the main responsibility of the diagnosing process of adults with ME/CFS symptoms is held by the general practitioner (GP), preferably a specialist in general medicine (41). In case of unclear differential diagnostic issues, the GP should refer to relevant clinical specialists for further evaluation. The European Network on ME/CFS (EUROMENE) expert consensus (36) recommends referral to specialist service for confirmation of diagnosis, drug treatment, and a range of service offerings, such as multidisciplinary rehabilitation, supportive counseling, education on self-management, and symptom-contingent pacing.

In several studies (42–45), various aspects of perceived care quality in specialist healthcare for ME/CFS patients have been evaluated, but they did not focus on the attention to PEM. In general, only a minority was satisfied with the obtained care and specialists' knowledge about ME/CFS. In another, recent Norwegian study, however, perceived care quality was evaluated related to the specificity of the diagnosis and PEM severity (42). Patients meeting more specific criteria and patients with higher PEM scores reported more negative experiences with specialist care.

It appears essential to acknowledge PEM in the diagnostic process and therapeutic approach of ME/CFS. To our knowledge, it is inadequately documented to what degree PEM generally is addressed in ordinary healthcare practice or more specifically in specialist healthcare practice in Norway. Likewise, it is insufficiently documented what the consequences are of not addressing PEM for the patient-related outcome and the perceived quality of these services regarding clinical effectiveness, patient safety, and patient experiences.

Awareness and knowledge about PEM seem also of specific relevance for a new growing subgroup of patients facing similar symptoms and biological abnormalities, and PEM (46–52). In the patients with persistent, debilitating symptoms following acute COVID-19 (long COVID), approximately up to half of the patients will meet the diagnostic criteria for ME/CFS (46, 51, 53). Consequently, ME/CFS prevalence is increasing dramatically.

Addressing PEM in the approach of long COVID patients is of specific importance as well (54–56).

The aim of this present study was to assess the significance of acknowledging the PEM phenomenon in the clinical approach of ME/CFS patients in specialist healthcare practice.

The first objective was to evaluate to what extent ME/CFS patients experienced focus on PEM during clinical consultations, hospital intervention, or rehabilitation.

The second objective was to estimate to what degree focus on PEM in the received care is related to patient-reported outcomes. The primary outcome is the impact of addressing PEM during an intervention on subsequent changes in health status. The secondary outcome measures are the reported care satisfaction or the perceived general benefit of the obtained care.

The third objective was to assess whether the acknowledgment of PEM in a clinical situation is associated with patient-reported experiences of perceived healthcare quality.

2 Materials and methods

This study is a non-prespecified secondary analysis, applying data from two patient surveys executed by the Norwegian ME Association (NMEF). The two patient surveys focused on different healthcare settings, but objectives, methods, and questionnaires are partly similar and described below.

Both surveys were retrospective, anonymous, Internet-based on the platform SurveyMonkey and limited to one response per IP address. There were no time restrictions on response during the study period as the questionnaire remained open until submitted.

The objective of the hospital survey (57) was to evaluate the experiences of ME/CFS patients with specialist healthcare services at two regional hospitals in Southeast Norway. These healthcare services covered two different types of clinical settings: consultations and interventions. Experiences with these settings were evaluated separately in the analyzes. Data collection was performed in the period 5–31 March 2022 and aimed at covering the period since 2017. If they in that period had received care at different departments, the respondents reported that separately, but for each department, only once per consultation and once per intervention.

The rehabilitation survey (58) aimed at retrospectively mapping the experiences of ME/CFS patients with Norwegian rehabilitation services. Data collection was carried out from 4 September 2017 until 15 October 2017 with no restrictions on region and date of stay at one of the rehabilitation facilities.

For the current study, analyzes were restricted to adult respondents included in the surveys. Respondents should have obtained hospital care at one of the two concerning hospitals or rehabilitation at an institute in Norway. Furthermore, they should have an ME/CFS diagnosis or long COVID with PEM and have answered the question concerning PEM-focus in the obtained healthcare setting. Figure 1 presents the flow chart of the study.

2.1 Subjects

For both surveys, invitations were shared on various relevant open and closed Norwegian Facebook groups for ME/CFS patients, their relatives, and other interested parties, both within and outside the ME Association's auspices. Relatives could answer on behalf of patients who were too ill to answer themselves.

In the hospital survey, members of Vestfold and Telemark Regional ME Association were also directly approached by email. The survey was open for respondents who had been referred to the relevant hospitals during the last 5 years and had an ME/CFS or long COVID diagnosis, were in a diagnosing process for this, or considered themselves as having ME/CFS, post-viral syndrome, or long COVID with PEM. Before evaluating the occurrence of PEM, as well as other typical ME/CFS symptoms, PEM was explained in the survey. Then, the respondents reported which diagnosis they regarded as the most appropriate for them. Only the respondents that answered, "ME/CFS or ME," "sequela after COVID-19 infection with PEM" or "Post-viral syndrome" and had PEM could progress further in the survey. Respondents not being adults (here below 20) were excluded from the analyzes in the analysis.

In the rehabilitation survey, respondents residing in Norway who previously had obtained an ME/CFS diagnosis G93.3 (59) from the specialist health service or A04 (60) from a GP specialist in general medicine were invited to participate.

2.2 Measures

All measures are presented in Tables 1, 2, including applied methods for dichotomization of variables, if relevant. The complete questionnaires (in Norwegian) can be found in the underlying reports (57, 58).

2.2.1 Respondent characteristics

The operationalization of respondents' characteristics is presented in Table 1. Sociodemographic characteristics covering gender, age, and participation degree in work and school were only evaluated in the hospital survey. Both surveys evaluated some disease characteristics such as diagnosis, disease duration, and severity grading.

2.2.2 Post-exertional malaise-focus as an explanatory variable

The primary variable of interest was the focus on PEM (PEM-focus) in specialist healthcare settings and its impact. PEM-focus in the three types of healthcare settings was operationalized with closed questions, but with different wording and different scales for each type of healthcare setting (see Table 2). In the analyzes, PEM-focus was dichotomized as PEM+ (PEM was addressed) or no-PEM (PEM was not addressed); this is described in Table 2 as well.

2.2.3 Patient-reported outcome

The assessments of the outcome measures are presented in Table 2. The impact of hospital intervention on health status was operationalized by computing changes in the evaluated disease severity before and after the intervention–in the first 2 weeks (post-intervention) and 3 to 6 months (short-term follow-up). Disease severity classification was based on the Norwegian National Guidelines for CFS/ME (41) and ICC (9). More severe disease severity after the intervention was classified as 'deteriorated'. 'Not deteriorated' includes both unchanged and improved health status. In addition, the benefit of the hospital interventions was more specifically evaluated

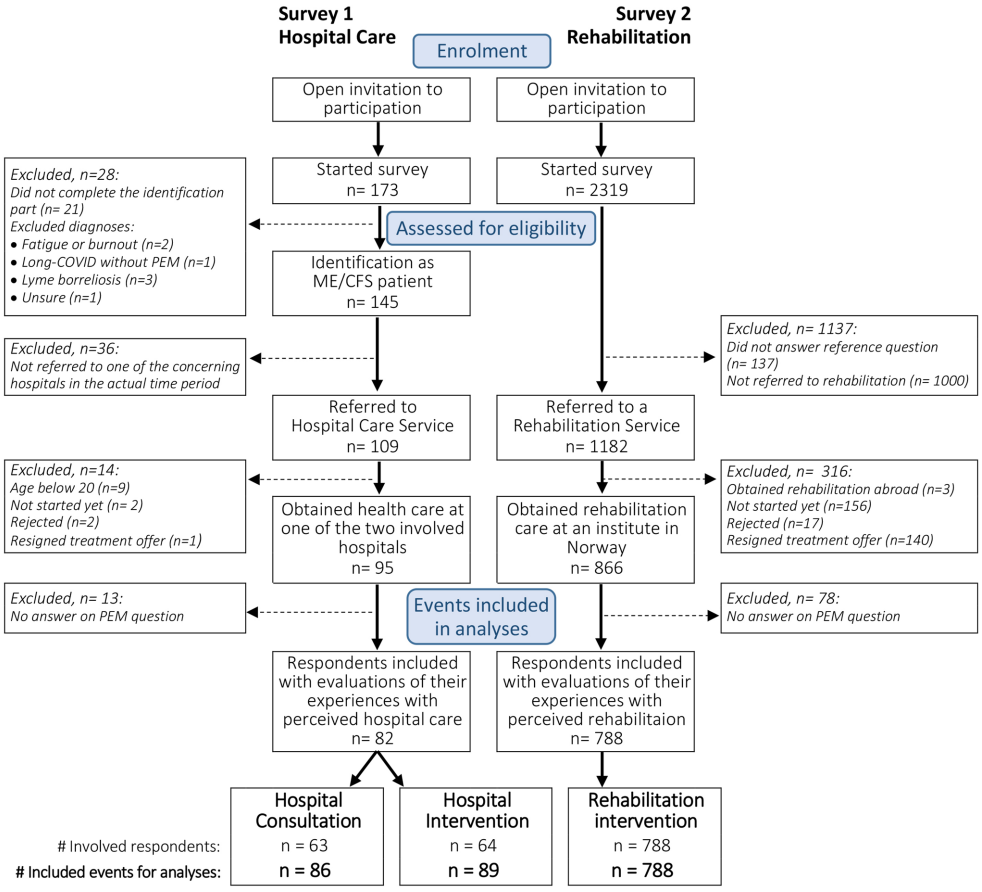

FIGURE 1
Study flow chart of survey 1 and survey 2, showing the inclusion of respondents and identification of corresponding evaluated care events for analyzes.

related to various domains: physical health, cognitive effort, mental health, ability to master daily tasks, ability to regulate activity level, and quality of life. The answer options "much worse" and "somewhat worse" were rated as "deteriorated."

Post-intervention changes in health status following rehabilitation were operationalized as 'deteriorated' if the respondents strongly disagreed with the statement "*I felt healthier just after the stay than before*." Short-term changes reported as "*I felt better one month after the stay than before*" were considered as "deteriorated" if the respondent strongly disagreed. Other replies were valued as 'not deteriorated'.

In addition, satisfaction with the consultation or the rehabilitation program and perceived general benefit of the hospital intervention were assessed with 5-point Likert scales and applied as outcome measures.

2.2.4 Patient-reported experiences of perceived healthcare quality

Relevant items are presented in Table 2. In addition to treatment completion, all care quality variables were assessed with 5-point Likert scales. Operationalization varies by care setting. Appraisal of the quality of the clinical consultations (the hospital survey) was assessed by evaluating the patients' view on the ME/CFS-specific knowledge and experienced symptom with respect to the healthcare professionals. Rated suitability of the intervention to the respondents' condition and the proportion who completed treatment were considered as additional indicators for care quality of intervention and rehabilitation. An item of the rehabilitation survey that evaluated whether the respondents felt they had obtained useful knowledge was included. For hospital intervention, respondents' opinion of the extent to which they had acquired PEM coping skills and whether they had obtained incorrect treatment was included as well.

2.2.5 Situational context

In both surveys, the intervention duration and the involved hospital, department, or rehabilitation institution were assessed with closed questions and an 'other' option (see Table 1).

In the hospital survey, the type of intervention options was assessed systematically as well: individual treatment, group course, or both. The types of treatment options were exercises to increase mobility, aerobic condition, or relaxation, cognitive behavioral therapy (CBT) aimed at reducing symptom focus and increasing activity, CBT focused on support and illness coping, or medication.

Apart from which particular rehabilitation institution was evaluated, no context variables were assessed systematically in the rehabilitation survey.

TABLE 1 Relevant questions describing the respondents' characteristics and the situational context.

Domain	Survey 1 Hospital consultation	Survey 1 Hospital intervention	Survey 2 Rehabilitation
Respondents' characteristics			
Gender	*Female/male*	*1. Female, 2. male*	-
Age	*< 10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, ≥ 70*	*< 10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, ≥ 70*	… over 18
Participation work/education	*1. 0%, 2. 25%, 3. 50%, 4. 75%, 5. 100% Sickness benefits (≥75%)/ No education lessons*	*1. 0%, 2. 25%, 3. 50%, 4. 75%, 5. 100% Sickness benefits (≥75%)/ No education lessons*	
Diagnostician	Who made the diagnosis?	Who made the diagnosis?	Who made the diagnosis?
Disease duration	For how long have you had CFS/ME fatigue symptoms? *< 6 months, 6–12 months, 1–2 years, 2–5 years, 5–10 years, > 10 years*	For how long have you had CFS/ME fatigue symptoms? *< 6 months, 6–12 months, 1–2 years, 2–5 years, 5–10 years, > 10 years*	When was the ME/CFS diagnosis set? (*year*)—*was recalculated to the categories* < 1 year, 1–2 years, 2–5 years, 5–10 years, > 10 years
Disease severity	What severity degree of ME/CFS do you have? 1. *Below mild, 2. Mild, 3, mild–moderate, 4. Moderate, 5. Moderate–severe, 6. Severe, 7. Sever-very severe, 8. Very severe*	What severity degree of ME/CFS do you have? What severity degree of ME/CFS did you have at start of the intervention? *1. Below mild, 2. Mild, 3, mild–moderate, 4. Moderate, 5. Moderate–severe, 6. Severe, 7. Sever-very severe, 8. Very severe*	What was the severity degree at start of the rehabilitation stay? *2. Mild, 4. Moderate, 6. Severe, 8. Very severe*
Situational context			
Medical specialty	Which department or clinic?	Which department or clinic? What sort of intervention?	Which rehabilitation facility?
Intervention duration		How many days? (*open answer*)	How many weeks? *1 /2/3/4/other*
Type of treatment		Counseling, group course, training to increase flexibility, training to increase activity and fitness, relaxation, CBT aimed at coping of severe illness, CBT aimed at symptom reduction and activity increase, medications or supplements, or other	
Group course-target patient group		ME/CFS, fatigue, or various health complaints	

Answer alternatives are italicized.

2.3 Analysis

Analyzes are based on available data from two surveys: a hospital survey (57) and a rehabilitation survey (58).

Perceived PEM-focus (PEM+ or no-PEM) in provided specialist healthcare is the main object of interest. For the different healthcare settings, PEM-focus, as evaluated by the respondents, is mainly analyzed as dichotomized variables.

Situational context variables, such as which hospital, department, or rehabilitation institution, as well as type of intervention, are not presented in detail. General context differences in PEM-focus were evaluated with chi-square tests.

To determine the impact of PEM-focus on the outcome, binary univariate and multivariate logistic regression were used with PEM-focus as the explanatory variable and disease duration and severity (14, 61, 62) included as covariates if available. The response variables were dichotomized outcome measures of satisfaction or rated general benefit, impact on health status following the intervention, and additionally for the hospital interventions, the impact on various ME/CFS-related domains. Because of the limited expected improvement in health status and the real possibility of deterioration following the intervention, health impact was evaluated as 'no-deterioration' versus 'deterioration'.

Satisfaction with clinical consults was only evaluated with univariate analyzes; crude odds ratios (ORs) with corresponding 95% confidence intervals (95% CI) are presented. For both intervention settings, both crude and adjusted OR were calculated. Hence, OR > 1.0 indicates that the variable is associated with a higher probability of the response variable (satisfaction, benefit, health, or function deterioration), whereas OR < 1.0 indicates an association with a lower probability. The results were also presented as bar diagrams with full-scale outcome variables. Mann–Whitney U-test was applied to assess group differences. The impact of PEM-focus on changes in health status following hospital intervention was evaluated with paired-sample Wilcoxon signed rank-sum tests for PEM+ and no-PEM.

The care quality variables are presented with Spearman's rank correlation coefficient (Spearman's rho: ρ) as a measure of association with PEM-focus. In addition, Cronbach's alpha was calculated as a measure of internal consistency of the care quality variables and the full scale of PEM-focus answers.

TABLE 2 Relevant questions that were applied in the analyzes: PEM-focus in the clinical contacts, variables assessing patient-reported outcome, and patient-reported experiences of perceived healthcare quality.

Domain	Survey 1 Hospital consultation	Survey 1 Hospital intervention	Survey 2 Rehabilitation
Post-exertional malaise (PEM)			
PEM-focus	Were you asked, directly or indirectly, if you had PEM? *1. No, 3. Unsure, 5. Yes*	Did you gain any new knowledge or understanding about PEM?	Was PEM explained during the stay? *1. No, 5. Yes*
1. PEM was not seen as typical or relevant, 2. No information, 3. Nothing new, 4. Some, 5. A lot			
Patient-reported outcome			
Care satisfaction/Benefit	Overall, were you satisfied with the consultation? **	What benefit have you had, overall, from the intervention? *1. No benefit, 2. Little benefit, 3. Some benefit, 4. Large benefit, 5. Very large benefit*	I am satisfied with my stay at the rehabilitation facility *
Impact on health		What severity degree of ME/CFS did you have the first following 2 weeks/the following 3 to 6 months? *1. below mild, 2. Mild, 3. Mild–moderate, 4. Moderate, 5. Moderate–severe, 6. Severe, 7. Sever-very severe, 8. Very severe*	I felt better just after the stay than before I felt better 1 month after the stay than before *1. Strongly disagree, 2. Disagree, 3. Neither agree nor disagree, 4. Agree, 5. Strongly agree*
Impact on various domains		How did you benefit from the intervention, when it comes to: physical health, cognitive effort, mental health, and ability to master daily tasks, ability to regulate activity level, quality of life? *1. Much worse, 2. Somewhat worse, 3. No, change, 4. Somewhat improved, 5. Strongly improved*	
Patient-reported experiences of perceived healthcare quality			
Suitability of the intervention		Did you feel that the intervention was suitable for your situation? *	The activity level was adapted to my illness*
Healthcare provider knowledge[2]	Do you think that the doctor or possibly other healthcare provider had a good knowledge of M//CFS? *1. Very little, 2. Not much, 3. Both, 4. Good, 5. Very good*	Do you think that this therapist/ supervisor/institution had good knowledge of ME/CFS? 1. Very *little, 2. Not much, 3. Both, 4. Good, 5. Very good*	The healthcare providers had good knowledge on ME/CFS*
Symptom acknowledgment[2]	Did you feel that your symptoms were taken seriously? *	Did you feel that your symptoms were taken seriously? **	The staff at the rehabilitation facility were understanding when I told them about my symptoms *
Gained beneficial knowledge or skills		Did the intervention help you to be able to prevent and manage PEM? 1. *PEM was not seen as typical or relevant, 2. No information, 3. Nothing, 4. Somewhat, 5. A lot*	I learned a lot that I have benefited from later *
Incorrect treatment		Do you think you obtained incorrect treatment in some way?**	–
Intervention completed		Did you complete the intervention? 1. *No I quit because I got worse/ no I quit because I did not think it was helpful, 2. Yes*	Were you at the rehabilitation facility for the entire period? *1. No, I got worse and chose to go home/ no, I got worse and was sent home by the staff, 2. Yes*

Answer alternatives are italicized, and in the case of dichotomized response options, the desirable responses are underlined. *1. Strongly disagree, 2. Disagree, 3. Neither agree nor disagree, 4. Agree, 5. Strongly agree; **1. Not at all, 2. To a small degree, 3. To some degree, 4. To a great degree, 5. To a very great degree.

TABLE 3 Disease duration and severity.

	Hospital survey		Rehabilitation survey	
	n	(%)	*n*	(%)
ME disease duration*	82		770	
< 1 yr.	0	0.0%	21	2.7%
1–2 yr.	5	6.1%	182	23.7%
2–5 yr.	19	23.2%	247	32.2%
5–10 yr.	33	40.2%	217	28.3%
> 10 yr.	25	30.5%	100	13.0%
Disease severity at intervention start	52		788	
Mild	2	3.7%	162	20.6%
Mild to moderate	20	37.0%		
Moderate	17	31.5%	519	65.9%
Moderate to severe	12	22.2%		
Severe	3	5.6%	106	13.5%
Severe to very severe	0	0.0%		
Very Severe	0	0.0%	1	0.1%

*Hospital survey: duration of ME/CFS symptoms at the date of survey response. Rehabilitation survey: time from year of diagnosis until intervention start.

No power calculation was performed as the primary surveys were considered explorative. Differences between respondents that were included and excluded in the analyzes of this study are compared in the available disease characteristics within both surveys with chi-square tests. In the hospital survey, screening for ME/CFS diagnosis and possible exclusion if ME/CFS was not considered as their main diagnosis was done in the first part of the survey. Sociodemographics were questioned at the end of the survey and thus were not answered by most of the excluded respondents. In the rehabilitation survey, no sociodemographic characteristics were collected. This made it impossible to compare the sociodemographics of respondents who completed vs. not completed the surveys.

Data analyzes were performed using IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, N.Y., United States). A *p*-value of less than 0.05 was considered statistically significant.

3 Results

3.1 Subjects

Figure 1 shows the study flow chart including both surveys. In the hospital survey, 82 respondents were included in the analyzes. In total, 86 consultations and 89 interventions were evaluated. The majority had evaluated only one consultation (71%) or intervention (69%), 21 and 23%, respectively, had evaluated two, and 8% had evaluated consultations and interventions with three different departments. In the rehabilitation survey, 788 respondents who had participated in a rehabilitation program at a rehabilitation facility in Norway were included.

The non-completers of the hospital survey did not differ in illness duration, age of symptom debut, diagnosis and disease severity, the degree they experienced PEM, and fulfillment of the Canadian Consensus Criteria (8) as evaluated in this survey. The non-completers had less often obtained an ME/CFS or long COVID with PEM diagnosis (80.5% vs. 97.5%, $p = 0.002$). In the rehabilitation survey, there was no difference in how long ago the diagnosis was set and by whom, between the respondents that were included or excluded for analyzes (see Figure 1).

3.1.1 Sociodemographic and disease characteristics

In the hospital survey, 84.5% was female and the age distribution at the time of the survey was 26.4% 20–29 yr., 18.1% 30–39 yr., 27.8% 40–49 yr., 26.4% 50–59 yr., and one respondent older than 60. The majority (88.7%) was not working or studying at all, 5.6% worked or studied 1–5 h weekly, 4.2% 6–20 h, and only one respondent worked or studied more than 20 h weekly. There were no sociodemographic data available from the respondents of the rehabilitation survey.

ME/CFS was self-reported as the main diagnosis by 80 of the 82 respondents of the hospital survey; for 79, a physician had set this diagnosis as well. One respondent had obtained a 'burnout or chronic fatigue' diagnosis. Two respondents had long COVID; this was confirmed for one respondent. In total, 24% of the respondents were diagnosed by a GP only, 39% by a specialist of one of the hospitals only, or by other specialists in private practice only (7%). The remaining respondents were diagnosed by both a GP and a specialist (24%) or by both a hospital and a private specialist (5%). No respondents had reported that they 'had a fatigue illness (including ME/CFS) before but not now'.

All patients in the rehabilitation survey self-reported that they had been diagnosed with ME/CFS. Twenty patients (0.9%) of the subjects that had started the survey reported they were neither a ME/CFS patient nor a relative and had been excluded. 20% of the respondents had received the diagnosis from their GP, 23% had consulted a specialist in private practice, and 49% had received the diagnosis from the local or regional hospital. 8% had received the diagnosis from the national CFS/ME center, a third-line service for advanced interdisciplinary assessment and guidance for adult patients.

Disease duration and severity are reported in Table 3.

3.2 Situational context and PEM-focus

The clinical consultations with a health provider at the two relevant hospitals ($n = 86$) were received at mainly six different types of departments. The majority had been at an ME/CFS Medicine Clinic (30.2%), a department of Physical Medicine (23.3%), or Neurology (20.9%). The others had been at a department of Infectious Diseases (8.1%), Mental Health (8.1%), or an ME/CFS Outpatient Clinic (5.8%), Gastroenterology (2.3%), or Pulmonary (1.2%). The hospital interventions ($n = 89$) were mainly received at a department of Physical Medicine (38.2%) or a department for Therapeutic Patient Education (38.2%). The remaining interventions were received at an ME/CFS Medicine Clinic (6.7%), departments of Mental Health (6.7%), Health and Work (5.6%), or Neurology (4.5%).

The type and duration of the hospital interventions varied. Intervention could include educational group courses (70.8%), individual consultation/one-to-one counseling (57.3%), or both. In addition to education in the group courses, the interventions comprised CBT aimed at reducing symptom focus and increasing activity (14.6%), CBT focused on support and illness coping (11.2%), exercises to increase mobility (4.5%), aerobic condition (3.4%), or relaxation (4.5%), as well as medication or dietary supplements (2.2%). Most hospital interventions were delivered on an outpatient basis, generally once or a few times. The educational courses were either intensive (3 days within 1 week) or spread over a longer period (6–8 times, once every 1 or 2 weeks). Only 67.2% of the respondents attended educational courses aimed specifically at ME/CFS, and the rest of the courses were aimed at patients with either general fatigue (21.8%) or other health complaints (10.9%).

Experiences of obtained rehabilitation services ($n = 788$) were evaluated for over 20 rehabilitation facilities in Norway. Two rehabilitation facilities were each evaluated by over 100 respondents (32.1% of respondents), four by over 50 respondents (35.3%), and four by at least 20 respondents. In the rehabilitation survey, applied intervention methods were not evaluated systematically. However, according to the open-ended comments in the survey, the rehabilitation institutions had different approaches to the rehabilitation of ME/CFS patients. Some encouraged CBT aimed at reducing symptom focus combined with a graded activity increase. Other rehabilitation facilities provided explanations about exertion-induced symptom exacerbation (PEM) and focused on the importance of managing and adjusting activity levels according to the patient's capacity ("energy envelope theory") to prevent PEM (58).

Overall, respondents reported that PEM was addressed in 43.0% of the consultations, 65.2% of the hospital interventions, and 47.5% of the rehabilitation stays. A more detailed distribution is presented in Figure 2. Whether PEM was addressed (PEM+) or not (no-PEM) varied significantly across the different settings from zero to 81% for clinical consultations ($p < 0.001$) and from 29 to 100% for hospital intervention ($p < 0.001$). Among the respondents who had participated in an educational group course or had received counseling, 71.4 and 45.1%, respectively, reported that PEM had been addressed. In the group courses specifically aimed at ME/CFS patients, 97.7% perceived PEM+, while PEM+ was 14.3% in the groups for fatigue and other health complaints. Among the rehabilitation facilities, reported PEM+ varied significantly as well, from 2.2 to 68.8% ($p < 0.001$).

3.3 Post-exertional malaise-focus as an explanatory variable for the outcome

Differences in several outcome measures stratified by PEM-focus (no-PEM or PEM+) are presented in Figures 3–5. In addition, Table 4 summarizes the results of logistic regression analyzes for the association between PEM-focus and binary outcome measures. Multivariate logistic regression analyzes produced nearly identical results as univariate logistic regression for the impact of PEM. The results of the univariate regression analyzes are, therefore, not presented here.

Figure 3 and Table 4 present the impact of PEM-focus on the health state after finishing the intervention. For the majority, their health state did not change. On average, for respondents in both groups, disease severity was worsened in the first 2 weeks following hospital intervention ($p = 0.005$ in no-PEM and $p = 0.008$ in PEM+). From baseline until 3 to 6 months following baseline, differences were only significant in no-PEM ($p = 0.042$ and $p = 0.13$ in PEM+).

However, there was a tendency that at both time points, around twice as many respondents from the no-PEM group experienced a deterioration of health status, following the intervention compared to the PEM+ group. Overall, if PEM had not been addressed in the intervention, logistic regression showed that the odds of experiencing health deterioration on at least one of the two time points increased significantly following both hospital intervention (proportion 22.4% in PEM+ vs. 45.2% in no-PEM, $p = 0.026$) and rehabilitation (40.1% vs. 63.2% $P = <0.001$) [adjusted OR: 0.34 (95% CI 0.13–0.89; $p = 0.027$) and 0.39 (95% CI 0.29–0.52; $P = <0.001$), respectively]. At the time of data collection (up to 5 years after hospital intervention), 35.5% of no-PEM respondents and 17.2% of PEM+ respondents had a more severe disease degree (OR 0.38, 95% CI 0.14–1.03, $p = 0.058$) compared to the start of the intervention. In the rehabilitation survey, changes in disease severity were not assessed.

The lack of focus on PEM in the hospital intervention had a significant impact on physical and mental health, cognitive effort, ability to master daily tasks, ability to regulate activity level, and quality of life (see Figure 4; Table 4). The respondents from the no-PEM group experienced over three times more often any physical, cognitive, or mental function worsening following hospital intervention [61.3% vs. 19.0%, $p < 0.001$, adjusted OR = 0.13 (95% CI 0.05–0.37), $p < 0.001$].

Figure 5 and Table 4 show the treatment outcome assessed as patient satisfaction or benefit following hospital consultations, interventions, or rehabilitation, stratified on PEM-focus. Evaluated satisfaction or benefit was generally significantly higher (all $p < 0.001$) in all three clinical settings when PEM was addressed. Satisfaction with consultation and rehabilitation was twice as high and over 4-fold as many respondents reported to have perceived at least some benefit of the hospital intervention.

In the educational group courses at the hospitals, outcome measures were strongly related to the specificity of the intervention. Deterioration of health and functioning and perceived benefit was significantly less frequently reported after the ME/CFS-specific courses, compared to the courses for general fatigue or health complaints. Worsening of health was experienced by 25.6% vs. 52.4% ($p = 0.034$), and deterioration of physical, cognitive, or mental function was reported by 18.6% vs. 71.4% ($p < 0.001$). Perceived benefit was low in both groups:

TABLE 4 Results of logistic regression analysis for the association between PEM-focus (no-PEM or PEM+) and outcome.

Setting	*n*	Response variables (Outcome)	Explanatory variables	OR	[95% CI]	*p*
Hospital consultation	79	Satisfaction	PEM-focus	11.57	[3.72–35.96]	**<0.001**
Hospital intervention	89	Benefit	PEM-focus	9.74	[1,21–78.57]	**0.033**
			Disease severity[a]	0.93	[0.83–1.05]	0.26
	89	Function deterioration[b]	PEM-focus	0.13	[0.05–0.37]	**<0.001**
			Disease severity[a]	1.12	[1.01–1.24]	**0.034**
	88	Worsening disease severity- post, 1–2 wk[c]	PEM-focus	0.37	[0.14–1.04]	0.058
			Disease severity[a]	0.93	[0.84–1.03]	0.166
	89	Worsening disease severity- 3-6 mos[c]	PEM-focus	0.38	[0.14–1.08]	0.07
			Disease severity[a]	0.97	[0.88–1.08]	0.57
Rehabilitation	742	Satisfaction	PEM-focus	5.75	[4.14–7.98]	**<0.001**
			Disease severity[a]	0.63	[0.48–0.84]	**0.002**
			Disease duration	0.99	[0.94–1,05]	0.77
	768	Worsening health–post	PEM-focus	0.46	[0.34–0.63]	**<0.001**
			Disease severity[a]	1.29	[1.00–1.67]	0.052
			Disease duration	0.98	[0.93–1.03]	0.44
	769	Worsening health–1 mo.	PEM-focus	0.35	[0.26–0.48]	**<0.001**
			Disease severity[a]	1.48	[1.13–1,94]	**0.005**
			Disease duration	0.99	[0.94–1.05]	0.83

Relevant disease variables were included as covariates, if available. 'No-PEM' is the reference category for PEM focus. [a]Disease severity at intervention start; [b]Worsening physical, cognitive, or mental functioning; [c]changes in disease severity compared to baseline.

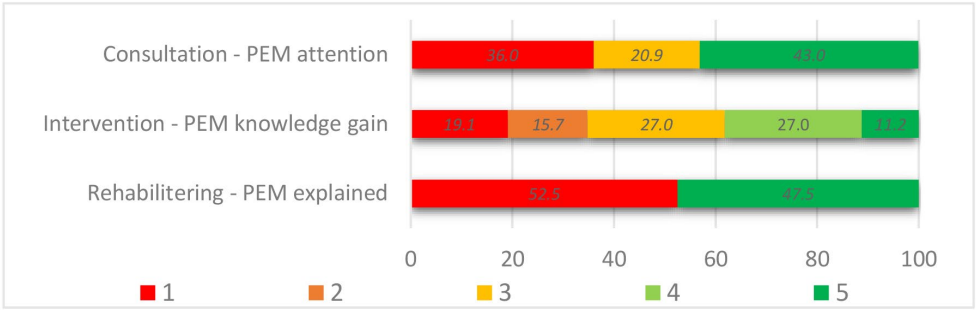

FIGURE 2
PEM-focus in the healthcare settings. Answer options of Assessment of PEM, in consultation (*n* = 86): 1. No (no-PEM), 3. Unsure (no-PEM), 5. Yes (PEM+). Knowledge gain following hospital intervention (*n* = 89): 1. PEM was not seen as typical or relevant (no-PEM), 2. No information (no-PEM) n, 3. Yes, but nothing new (PEM+), 4. Some (PEM+), 5. A lot (PEM+). PEM explained in rehabilitation setting (*n* = 788): 1. No (no-PEM), 5. Yes (PEM+).

23.3% of the respondents that had participated in ME/CFS-specific courses and 9.5% of the participants of less specific courses ($p = 0.19$) had reported large or very large benefits of the education.

3.4 Care quality related to PEM-focus

Table 5 presents the correlation between focus on PEM in different clinical situations and care quality as perceived by the respondents. In all three types of healthcare settings, respondents' perceptions of the healthcare provider's level of ME/CFS knowledge and symptom acknowledgment were strongly associated with whether or not there had been attention to PEM. PEM-focus in hospital intervention and rehabilitation was also strongly correlated with respondents' opinion on whether the intervention was suitable and sufficiently adjusted to their situation. Cronbach's alpha of respective 0.89, 0.89, and 0.80 of the care quality variables and PEM-focus indicates high internal consistency.

During rehabilitation, 28.4% of the no-PEM respondents vs. 73.5% of the PEM+ respondents ($p < 0.001$) had learned a lot which they had benefited from afterward. In hospital intervention, none of

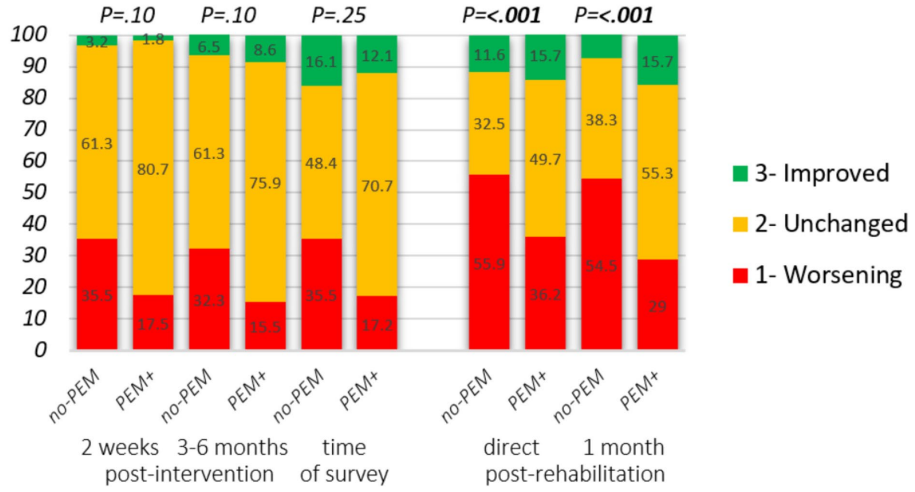

FIGURE 3
Impact of hospital intervention and rehabilitation on the state of health stratified by PEM-focus in the therapeutic approach. Changes from intervention start. Hospital intervention: self-reported severity degree at baseline, 2 weeks ($n = 88$), and 3 to 6 months ($n = 89$) following the intervention. Change in clinical severity degree: 1. Higher disease degree, 2. Unchanged, 3. Lower disease degree. Rehabilitation: reply to the statements "I felt better just after the stay than before" and "I felt better 1 month after the stay than before," answer options: 1. Strongly disagree, 2. Disagree/neither agree nor disagree, 3. Strongly agree. Mann–Whitney U-test was applied to assess group differences.

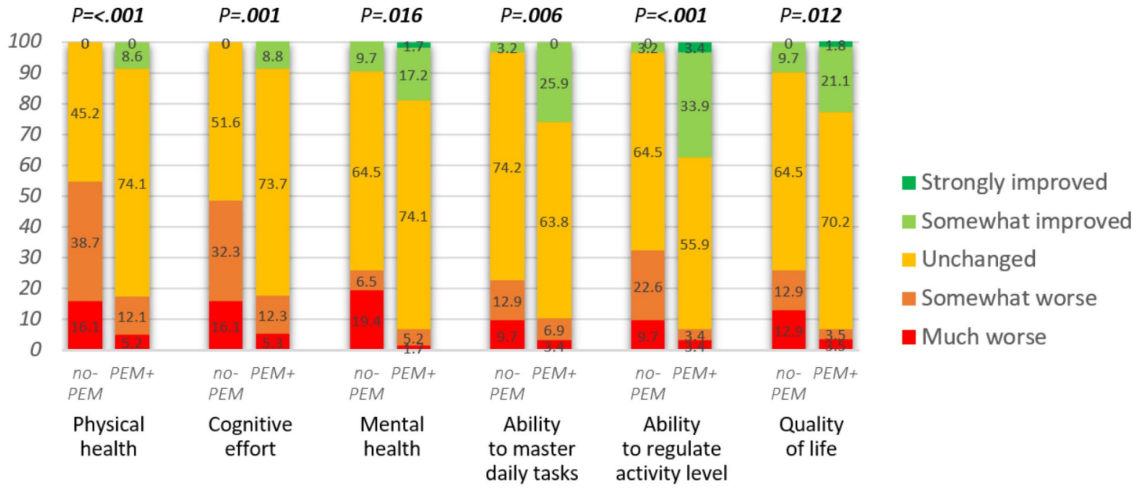

FIGURE 4
Impact of hospital intervention on various domains ($n = 88$ or 89). Mann–Whitney U-test was applied to assess the group differences.

the no-PEM respondents versus 58.6% ($p < 0.001$) of PEM+ had obtained new knowledge or understanding about PEM, and 3.3% of no-PEM vs. 46.5% of PEM+ ($p < 0.001$) had obtained new PEM coping skills. Almost half (48.4%) of the no-PEM group vs. 5.2% ($p < 0.001$) of the PEM+ group felt that they had been treated incorrectly in the intervention obtained at the hospital.

For the educational group courses, most care quality measures were also strongly correlated with whether the target group was specific for ME/CFS patients or not [healthcare providers' ME/CFS knowledge, $\rho = 0.64$ ($p < 0.001$); symptom acknowledgment, $p = 0.59$ ($p < 0.001$); and suitability of intervention, $\rho = 0.63$ ($p < 0.001$)]. There were, however, no significant differences in dropout ratios: 5.3% in the ME/CFS-specific education and 10.0% in the other courses ($p = 0.50$).

4 Discussion

The PEM phenomenon is a hallmark feature of ME/CFS and essential to acknowledge in both clinical consultation and intervention. This study was conducted in Norway, generally featuring high-quality care. Nevertheless, according to a significant proportion of the ME/CFS patients, PEM had frequently not been addressed during their contact with specialist healthcare services. This concerned both consultation services at the hospitals as well as the interventions delivered at the hospitals and rehabilitation institutions. This lack of focus on PEM increased the probability of experiencing deterioration, following hospital intervention and rehabilitation care. On the other hand, addressing PEM was related to increased rated care satisfaction, healthcare quality, and benefit.

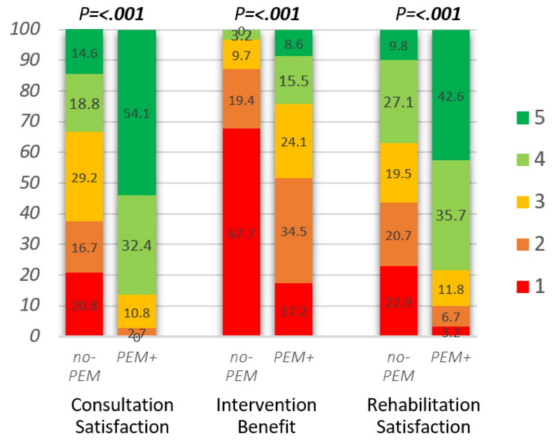

FIGURE 5
Impact of hospital consultation (n = 85), intervention (n = 89), and rehabilitation (n = 783) on rated satisfaction or benefit, stratified by PEM-focus during clinical contact. Consultation satisfaction: "All in all, were you satisfied with the consultation?," answer options: 1. not at all, 2. to a small degree, 3. to some degree, 4. to a great degree, 5. to a very great degree. Intervention benefit, hospital intervention: "What benefit have you had, all in all, from the intervention?" answer options: 1. No, 2. Little, 3. Some, 4. Large, 5. Very large. Rehabilitation satisfaction: "I am satisfied with my stay at the rehabilitation facility," answer options: 1. Strongly disagree, 2. Disagree, 3. Neither agree nor disagree, 4. Agree, 5. Strongly agree. Mann–Whitney U-test was applied to assess the differences between no-PEM and PEM+.

4.1 Addressing PEM in the intervention

Over one-third of the respondents of the hospital interventions and half of the individuals who had stayed at a rehabilitation institute reported that PEM had not been addressed. This doubled the number of respondents that acquired a more severe disease degree for a long time; for the hospital respondents, the data demonstrated that these differences were still present at the time of data collection (i.e., up to 5 years after the intervention).

From a psychosomatic point of view (3, 63, 64), PEM is ignored as a direct physiological response to physical or mental exertion. From this perspective, GET and CBT are considered as effective therapies. Although the Norwegian Guidelines regard PEM as a cardinal symptom, GET and CBT are still suggested as effective treatment approaches in these guidelines (41). This is despite there currently being no research evidence of convincing effects of these approaches for ME/CFS patients with PEM (10, 33, 34, 65, 66) and despite the fact that several surveys actually reported that over half of the ME/CFS patients experience substantial deterioration after GET and usually do no benefit from CBT (67–69).

GET and curative CBT were seldom explicitly mentioned as applied method in both our hospital and rehabilitation surveys. Yet, many patients reported that they encountered elements of CBT and GET, such as being encouraged to believe their disease is not serious or physical, encouragement to increase activity levels, and disregarding symptoms. This usually happened in settings where PEM was not addressed. Some of the citations that the respondents had added in comments text fields in both surveys testify to this (see Table 6).

When evidence for curative treatments for ME/CFS is lacking, intervention should at least aim at educating the patient to optimize their ability to maintain function in everyday activities and reduce PEM. This may help to alleviate symptoms and increase quality of life (35, 36). Therefore, in updated clinical recommendations for ME/CFS, educational approaches are included. They typically aim at empowering the patient for self-management with a focus on pacing strategies to conserve energy and focus on coping with a disease with substantial function loss and symptom burden.

In the rehabilitation survey, applied intervention methods were not evaluated systematically, but the programs are usually multidisciplinary and patient education is often part of a rehabilitation program. In the case PEM was addressed in the rehabilitation, nearly three-quarters of respondents reported that they had learned a lot which they had benefited from afterward. This applied to less than a third of the patients if PEM had not been discussed.

In the hospital survey, a considerable portion of the respondents had received educational group courses as well. Some patients received educational courses that were aimed exclusively at ME/CFS patients, while others were included in courses aimed at patients with more general fatigue or health problems. Nearly all participants of ME/CFS-specific courses reported to have obtained information about PEM, but only one of seven participants of the less specific courses reported the same. Apparently, the focus on education, and counseling had been delivered from clinical settings with different explanatory approaches to ME/CFS. Not informing ME/CFS patients about their main disabling symptoms is both worrying and unacceptable and may lead to severe consequences for the patients. In our study, functional deterioration was reported by over seven out of 10 participants of the non-specific courses, but only by less than two out of 10 of the participants of the ME/CFS-specific education. Understandably, the perceived impact on health and functioning and rated care quality was associated with this. Half of the patients who had not received information about PEM during their hospital intervention, versus only one in each 20 patients who had received this, felt that they had been treated incorrectly.

TABLE 5 Distribution of degree of perceived care quality on several factors as reported by the respondents in the three types of care settings, stratified and tested by PEM-focus. Measures for internal consistencies calculated of all variables, including PEM-focus, are presented as well.

	Survey 1—hospital PEM-focus in consultation				Survey 1—hospital PEM-focus in intervention				Survey 2—rehabilitation PEM-focus in rehabilitation			
	n	no-PEM 49 (56%)	PEM+ 38 (44%)	*P*-value	*n*	no-PEM 31 (35%)	PEM+ 58 (65%)	*P*-value	*n*	no-PEM 414 (53%)	PEM+ 374 (48%)	*P*-value
		Test statistics				*Test statistics*				*Test statistics*		
Healthcare provider ME/CFS knowledge	86	$\rho = 0.62$		<0.001	89	$\rho = 0.74$		<0.001	786	$\rho = 0.56$		<0.001
Very little	11	22.4%	0.0%		18	51.6%	3.4%		125	28.4%	2.1%	
Not much	10	18.4%	2.7%		9	25.8%	1.7%		115	23.3%	5.1%	
Both	17	28.6%	8.1%		17	19.4%	19.0%		125	19.2%	12.3%	
Good	16	16.3%	21.6%		23	3.2%	37.9%		228	21.1%	37.6%	
Very good	32	14.3%	67.6%		22	0.0%	37.9%		193	8.0%	42.8%	
Symptom acknowledgment	86	$\rho = 0.60$		<0.001	88	$\rho = 0.55$		<0.001	784	$\rho = 0.48$		<0.001
Not at all	10	20.4%	0.0%		12	30.0%	5.2%		73	16.8%	1.1%	
To a small degree	9	18.4%	0.0%		9	23.3%	3.4%		72	14.1%	3.8%	
To some degree	13	22.4%	5.4%		17	23.3%	17.2%		84	16.1%	4.8%	
To a great degree	17	18.4%	21.6%		26	20.0%	34.5%		275	36.0%	34.0%	
To a very great degree	37	20.4%	73.0%		24	3.3%	39.7%		280	17.0%	56.3%	
Suitability of intervention					89	$\rho = 0.61$		<0.001	785	$\rho = 0.46$		<0.001
Not at all					17	45.2%	5.2%		161	34.2%	5.4%	
To a small degree					10	22.6%	5.2%		127	18.9%	13.1%	
To some degree					22	22.6%	25.9%		113	17.7%	10.7%	
To a great degree					24	6.5%	37.9%		243	22.3%	40.5%	
To a very great degree					16	3.2%	25.9%		141	6.8%	30.3%	
Completed intervention					78	$\rho = 0.26$		0.021	784	$\rho = 0.06$		0.12
No					12	27.6%	8.2%		104	15.0%	11.3%	
Yes					66	72.4%	91.8%		680	85.0%	88.7%	
Cronbach's alpha		0.89				0.89				0.80		

Spearman's rank correlation coefficient (Spearman's rho: ρ) as a measure of association with PEM-focus. Cronbach's alpha as a measure of internal consistency (with the full scale of PEM-focus).

Generally, in intervention effect studies, clinical effectiveness is evaluated. Unfortunately, as reported in our study, even when PEM was addressed in the therapeutic approach, clinical improvements were generally absent. Due to the nature of the disease, some deterioration can be expected after out-of-home interventions, particularly among patients with higher disease degrees. The combined burden of travel, social interaction, coping with time schedules, etc. will often be far beyond the patients' day-to-day activity level.

Compared to our study, higher improvement rates were reported following specialist ME/CFS services in England (70). At 1-year follow-up, 28% reported overall improvement, and only 8% worsened health. One reason might be that the specialist services are indeed better tailored to this specific patient group. Other reasons might be that the evaluated patients had a shorter duration of ME/CFS and were only mildly affected (70). Our data did not cover treatment at a specialist ME/CFS service.

4.2 Is addressing PEM related to the explanatory view of me/CFS?

The PEM phenomenon challenges existing medical assumptions of the health benefits of exercise and other physical and mental activity and sensory stimuli (71). As knowledge and understanding of PEM are crucial for diagnosis and maintaining optimal functioning in ME/CFS, early screening and explaining explicitly about PEM are essential in clinical consultations where ME/CFS is suspected (14, 35). Failure to recognize ME/CFS and PEM may result in poor management in daily life and in the clinical approach, which may hamper recovery potential and aggravate the disease (62, 72).

Only two out of five respondents had noticed that PEM had been addressed in the clinical consultations. The main reason for not discussing PEM in a clinical consultation is probably that the clinician does not acknowledge PEM as an essential feature in ME/CFS. The

TABLE 6 Illustrating citations of the respondents of both underlying surveys (freely translated from Norwegian) (57, 58).

Psychosomatic approach
"The doctor said it should not be called ME but rather 'BE' because it is Between the Ears."
"We were met by a psychologist who claimed that if you felt exhaustion coming over you, you should think of something pleasant and that 'feeling' would go away!."
"There was a great deal of focus on stress management and stuck-thought- patterns."
"I felt that ME was not taken very seriously; all forms of exhaustion seemed to be taken under the same umbrella."
"PEM and exhaustion were seen as complaints and depression, and as an excuse not to exercise."
Sustained arousal hypothesis
"The doctor believed that I could recover completely with their approach; a sustained stress response, which is cured with the right mind-set and individually adapted training."
"They were only concerned with the body's stress response."
Consequences of opposing explanatory models of ME/CFS
"Because of their perception that ME comes from a biopsychosocial model of explanation, I was never able to become fully comfortable with them. I have a completely different experience of the disease and they focused far too much on the psychological side."
Poor disease understanding among healthcare providers
"The healthcare providers barely knew anything about ME/CFS, but they tried their best. The stay was too much. Just being there. It took many years for me to get back to the same level I was before I left."
Ignoring symptoms
"I told them about all the symptoms, but was then told that we had too much focus on symptoms."
"It was just about not thinking about the symptoms, that you get well as long as you increase your activity and think positively."
"The (rehabilitation) stay is based on CBT and GET, the patient himself must be well aware of his own limits, otherwise it can become too much."
Addressing PEM perceived as more positively
"It was a very nice stay and it was nice to meet more people like me. I did not get any better, but I brought home some tips on everyday life that make it a little easier."
"The first time I met healthcare providers who believed in me and took my illness into account"
"If you could not handle an activity, they said, 'It's great that you are taking care of yourself!"
Failure to acknowledge PEM may cause potential iatrogenic harm
"Became bedridden for 1 year after rehabilitation because I had to exercise four times a day on weekdays. It was not adapted to ME at all. The basic philosophy at the center was that one could become healthy through exercise."
"Now, 4 months later, I am still worse than when I went to the rehabilitation institution. But the place is very good; one just has to be healthier than I was to benefit from the stay."
New knowledge and strategies may take time before potential benefit is recognized
"It took a long time, approximately 6 months, before there was an effect of the changes I made."

applied explanatory model in the various clinical settings was not explicitly evaluated in the surveys. However, not acknowledging PEM as a key phenomenon, which in this study was associated with little focus on the patients' symptoms and poor specific suitability of intervention, is in our opinion an obvious indication of a psychosomatic view. Some of the citations confirm an apparent psychosomatic approach at some of the evaluated healthcare services (see Table 6).

One of the assumptions derived from a biopsychosocial perspective is the sustained arousal hypothesis (73), based on 'the cognitive activation theory of stress' (CATS) (74). According to CATS, the sustained stress responses may originate from different precipitating factors (interacting with predisposing factors (genetic traits, personality) and learned expectations (classical and operant conditioning)). Although this theory has not been confirmed, the sustained arousal hypothesis has strong support in Norway, including in some of the evaluated departments, as mirrored in some of the comments (see Table 6).

Because of the presence of a strong psychosomatic network in Norway (3), and the equivocal explanatory view and recommendations for approaching ME/CFS of both the National Advisory Unit on CFS/ME and the Norwegian CFS/ME guidelines (41), it was not surprising to meet a psychosomatic view in several of the specialist healthcare services evaluated in our study.

The respondents' own underlying assumptions explaining their symptoms had not been assessed. However, for majority of the ME/CFS patients, a predominantly biomedical explanation of their disease usually fits their experiences better than a psychosomatic approach (32, 75, 76). Generally, many ME/CFS patients feel that the doctors psychologize too much, trivialize the symptoms, or tell them that their symptoms are psychosomatic (43, 77–79). If patients meet an opposing explanatory model in healthcare practice, negative patient experiences and dissatisfaction with received care may arise (75, 79). In our study, failure to address PEM led to ineffective, harmful healthcare and respondents reported poor disease understanding of ME/CFS among healthcare providers and a lack of validation of their illness experiences (see also Table 6). This has also been reported in previous studies (42, 43, 45, 79, 80). The high internal consistency of not addressing PEM and a reported approach that was poorly customized to ME/CFS suggests that these elements may measure a similar notion of viewing ME/CFS (58).

Illnesses that lack clear pathophysiology, that has inconsistent diagnostic criteria, inadequate research focus, and lack of proper training, seem frequently to be related to negative consequences or iatrogenesis for the patient (80–82). As in our study, Geraghty and Blease (32) recognized several modalities of iatrogenesis in ME/CFS such as high levels of patient dissatisfaction, challenges to the patients' narratives and experiences, and negative responses to therapy. In addition, other modalities were identified, such as difficulties in reaching an acceptable diagnosis of ME/CFS and access to medical care and social support.

4.3 Methodological issues, strengths, and limitations

To our knowledge, this is the first study to evaluate the significance of addressing PEM in the clinical approach to ME/CFS patients in naturalistic settings of specialist healthcare practice. The evaluation of PEM-focus was in fact not the primary outcome of the initial surveys. This may have reduced respondent bias because they were unaware of the aim of the present analyzes of assessing the significance of acknowledging the PEM phenomenon with regard to their health and perceived care quality.

The inclusion of two comparable surveys, together covering specialist healthcare for ME/CFS patients in Norway, and the large sample size from a large geographical area in the rehabilitation survey were also strengths of this study. Another key feature of this study is the focus on intervention-induced 'deterioration' versus 'no-deterioration' instead of evaluating clinical effectiveness. This seems especially relevant in the evaluation of 'real-life' interventions for ME/CFS because of general limited improvement in health status. Instead, exacerbations are frequently described in patient surveys but usually ignored or camouflaged in the presentation of average scores.

In the analyzes of our study, the occurrences of provided healthcare are in fact the main study focus and not the individual respondents. Therefore, in the hospital survey, some respondents assessed their experiences from more than one department. These have been analyzed as independent occurrences. We considered this as acceptable since ME/CFS is a chronic disease with very limited recovery potential (35, 72, 83), the provided healthcare could cover a time frame of 5 years and the order in which the setting was evaluated was random. Notably, each respondent could evaluate each department only once. The patients' view concerning PEM-focus and outcome seemed independent of order and number of assessed settings.

This current study has some limitations, mainly concerning methodological issues. The low sample size of the hospital survey may have reduced the statistical power and the chance of detecting true consequences. This might especially concern the analyzes concerning the impact of the interventions on health. In addition, it limited the opportunity to conduct analysis more specific per clinical specialty. Furthermore, the limited diversity of potential covariates in the available data reduced the number of possible factors of interest to adjust for in the regression analyzes.

As a consequence of performing non-prespecified analyzes based on an exploration of two retrospective surveys, some applied measures and scales were not optimal and inconsistent. This applied also to the assessment of PEM-focus that was operationalized with different wording and different scales for the three types of healthcare settings. However, we do not expect this to be a major drawback. Additionally, we were not able to assess the actual focus on PEM in the clinical settings. We were dependent on patients' perception of its acknowledgment and recall bias may have occurred. This may also have affected the outcome measures that assessed satisfaction and impact on functioning and health status. The retrospective design, however, might have been a methodological plus as the participants gained the opportunity to put their experiences into a longer-term perspective. It may take time to implement new knowledge and learned strategies in daily life before the potential benefit is recognized (see Table 6). Psychosomatic approaches may aim at influencing how patients interpret and report their health state and thus may easily bias subjective outcome measures immediately after the intervention.

A strength of recruiting respondents outside the healthcare settings and collecting anonymous feedback is a better chance of obtaining objective opinions. Patients may hesitate to share negative experiences with healthcare providers because they fear they will appear unmotivated and non-cooperative. This could negatively affect the approval of health benefit allowances.

The recruitment method with open online surveys may, however, have affected the representativeness of the study population. Because of the anonymity, diagnoses could not be verified. ME/CFS status was self-reported by the respondents, therefore is misclassification possible (53). We have limited descriptive data on the respondents, and we have no insight into the population of eligible patients who have visited the hospitals or rehabilitation institutions in the studied period. Invitation of participation to the surveys was shared online among groups that are interested in ME/CFS. However, subjects who are active on social media or are members of the Norwegian ME Association may be overrepresented. Former ME/CFS patients had the possibility to participate in the hospital survey as well. However, none had selected the diagnostic alternative 'had a fatigue illness before but not now'. In the rehabilitation survey, 20 respondents (0.9%) were excluded because they were neither a patient nor a relative. Some might have been former patients.

Notably, patients with a severe or very severe degree of the disease are poorly represented. An obvious reason is that this group of patients might be less active on social media and has limited energy to answer a questionnaire. They are also less likely to have obtained secondary healthcare because their severe disease status might hamper access to specialist healthcare. In the region of the hospital survey, ambulant healthcare services are not available for this patient group. Challenges in obtaining adequate healthcare have been confirmed in a recent Norwegian study where this was the case for around seven out of ten ME/CFS patients with a severe or very severe sickness degree (84). Some respondents reported that they no longer dared to have contact with healthcare providers due to frequent negative experiences with various healthcare providers.

The hospital survey had aimed at including long COVID patients as well but did not succeed in this. Only two long COVID patients with PEM are part of the study population. Although a relatively high proportion of long COVID patients are expected to develop ME/CFS (47, 85–87), this was not common knowledge at the beginning of 2022, and many long COVID patients with ME/CFS symptoms may not have identified themselves as an ME/CFS patient.

4.4 Implications for research and clinical practice

Quality of healthcare is typically described in terms of clinical effectiveness, patient safety, and patient experience. This study evaluated 'real-life' experiences of ME/CFS with routine specialist healthcare service in a country with generally high-quality healthcare. The quality of care services delivered to ME/CFS patients seemed strongly related to the acknowledgment of the disease and its cardinal symptom PEM in particular. Ignoring PEM in the approach of ME/CFS appears as a reckless maltreatment of patients.

The findings seem relevant for long COVID as well. Alertness to the possibility of the development of COVID-induced PEM and ME/CFS is, therefore, essential in patients with post-COVID symptoms.

In patients with (suspected) ME/CFS or long COVID, early identification and management of PEM may be a cost-effective and the most important method for stabilizing symptoms and improving prognosis and patients' quality of life (10, 35, 87–89).

In general, ME/CFS-specific knowledge seems limited in many healthcare providers (80, 81, 90–93) and usually ignored in their education (93). The reported iatrogenesis may be traced back to this but also to the fact that at present, ME/CFS is not covered by a defined clinical specialty. As seen from our study, patients had been referred to several medical specialties, both for clinical consultations and intervention. Although ME/CFS is regarded as a multisystem disease, with a neuroimmunological base, often proceeded by an infection, neither the disciplines of infectious diseases, immunology, nor neurology has claimed 'ownership' over the diagnosis. This 'orphaned' position may have significant implications for whether medical specialists feel an interest or obligation to keep up to date in the field. This might be a reason that still, among many healthcare providers, skepticism is established about whether the disease is primarily 'physical' (80, 81, 90, 91). This affects care quality. It has been demonstrated that health providers' view of ME/CFS being a psychosomatic disorder is associated with worse outcomes than views of ME/CFS as a physical illness (38). Immediate large-scale investment in updated education of (future) healthcare providers about the management of ME/CFS, long COVID, and PEM is essential. In our study, the inter-variability between the departments of how patients rated PEM-focus and related care quality was substantial. This provides opportunities to learn from each other's clinical practice if interested and open-minded about alternative approaches to ME/CFS.

In healthcare, there is a growing need and recognition of patient experiences as an important aspect of evidence-based practice. Patient experiences as described in our study may contribute to the improvement of the quality of specialist healthcare practice for ME/CFS. The significance of acknowledging the PEM phenomenon for outcome and healthcare quality in ME/CFS or long COVID has not been studied systematically before. It seems unethical to study this in an experimental design, therefore evaluating this in pragmatic settings seems most appropriate. The analyzes and findings presented here can be considered exploratory. Further well-designed research is needed to validate these findings and investigate the value of acknowledging PEM in the approach of ME/CFS and long COVID.

5 Conclusion

Despite the inclusion of PEM as a core symptom of ME/CFS in updated diagnostic criteria sets, and the biomedical evidence of the existence of the phenomenon, PEM is still not always accepted and taken into consideration in specialist healthcare practice in Norway.

PEM was not addressed in more than half of the evaluated consultations and rehabilitation stays, and one-third of the hospital interventions. Not addressing PEM doubled the probability of a decline in health and functioning following the intervention and was strongly associated with reduced perceived care quality, satisfaction, and benefit. Acknowledgment of PEM by the healthcare provider was correlated with a more positive rating by the patients of the healthcare providers' recognition of patient's symptoms, level of ME/CFS knowledge, and suitability of the intervention to their condition.

This study confirmed the significance of acknowledging the PEM phenomenon in the clinical approach of ME/CFS patients in specialist healthcare practice. When disregarding the PEM phenomenon, healthcare for ME/CFS patients can be described as ineffective, harmful, and of poor quality. In this respect, it seems essential to raise awareness among healthcare providers in specialist healthcare about ME/CFS and PEM.

Data availability statement

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

Ethics statement

Ethical approval was not required for the studies involving humans because the study was based on the anonymous replies on two online surveys. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements because the study was based on anonymous replies.

Author contributions

MW conceptualized and designed the study, conducted the hospital survey and the analyzes related to the hospital survey, and wrote the first draft of the manuscript. SR conducted the analyzes related to the rehabilitation survey and contributed to the final draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

MW was employed by one of the evaluated hospitals.

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

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Significant burden of post-COVID exertional dyspnoea in a South-Italy region: knowledge of risk factors might prevent further critical overload on the healthcare system

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Background: Exertional dyspnoea in post-COVID syndrome is a debilitating manifestation, requiring appropriate comprehensive management. However, limited-resources healthcare systems might be unable to expand their healthcare-providing capacity and are expected to be overwhelmed by increasing healthcare demand. Furthermore, since post-COVID exertional dyspnoea is regarded to represent an umbrella term, encompassing several clinical conditions, stratification of patients with post-COVID exertional dyspnoea, depending on risk factors and underlying aetiologies might provide useful for healthcare optimization and potentially help relieve healthcare service from overload. Hence, we aimed to investigate the frequency, functional characterization, and predictors of post-COVID exertional dyspnoea in a large cohort of post-COVID patients in Apulia, Italy, at 3-month post-acute SARS-CoV-2 infection.

Methods: A cohort of laboratory-confirmed 318 patients, both domiciliary or hospitalized, was evaluated in a post-COVID Unit outpatient setting. Post-COVID exertional dyspnoea and other post-COVID syndrome manifestations were collected by medical history. Functional characterization of post-COVID exertional dyspnoea was performed through a 6-min walking test (6-mwt). The association of post-COVID exertional dyspnoea with possible risk factors was investigated through univariate and multivariate logistic regression analysis.

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Results: At medical evaluation, post-COVID exertional dyspnoea was reported by as many as 190/318 patients (59.7%), showing relatively high prevalence also in domiciliary-course patients. However, functional characterization disclosed a 6-mwt-based desaturation walking drop in only 24.1% of instrumental post-COVID exertional dyspnoea patients. Multivariate analysis identified five independent predictors significantly contributing to PCED, namely post-COVID-fatigue, pre-existing respiratory co-morbidities, non-asthmatic allergy history, age, and acute-phase-dyspnoea. Sex-restricted multivariate analysis identified a differential risk pattern for males (pre-existing respiratory co-morbidities, age, acute-phase-dyspnoea) and females (post-COVID-fatigue and acute-phase-dyspnoea).

Conclusion: Our findings revealed that post-COVID exertional dyspnoea is characterized by relevant clinical burden, with potential further strain on healthcare systems, already weakened by pandemic waves. Sex-based subgroup analysis reveals sex-specific dyspnoea-underlying risk profiles and pathogenic mechanisms. Knowledge of sex-specific risk-determining factors might help optimize personalized care management and healthcare resources.

KEYWORDS

post-COVID syndrome, healthcare burden, healthcare capacity, post-COVID exertional dyspnoea, fatigue

Introduction

Post-COVID-19 syndrome is a multisystem disease developing in patients with prior SARS-CoV-2 infection, characterized by a wide range of persistent clinical symptoms, occurring in hospitalized as well as in patients with relatively mild acute-phase illness (1–3). According to recent epidemiologic estimates, such an emerging condition is thought to affect 65–144 million individuals worldwide (4–6).

Since a notable portion of subjects affected by post-COVID syndrome reports lingering and debilitating symptoms (7, 8), such as dyspnoea and exertional intolerance (9), often associated with impairment of daily life activities (10), this new chronic health condition is expected to result in a considerable societal impact, potentially leading to economically relevant consequences, in terms of days off from work and utilization of healthcare resources and management (2, 6, 11). Appropriate management strategies specifically addressed to target post-COVID patients with clinically significant exertional dyspnoea should be established by healthcare systems and policymakers (1, 12–14). However, the limited capacity of healthcare systems would represent a paramount critical issue, in light of the significant restrictions and resource redirection from the usual chronic to acute healthcare settings, during the pandemic peaks (6, 15).

Furthermore, such a scenario is expected to become particularly challenging in those socioeconomic and/or geographic areas already facing shortages of medical equipment and care facilities. Many of Southern Italy's regions were subjected to considerable cuts and healthcare restrictions to chronic respiratory disease management in the last decade, with consequent vulnerability to saturation of healthcare facilities (16, 17). When subjected to this additional strain, after the already-devastating pandemic waves, such healthcare systems might be led close to the risk of collapse (15–17). Knowledge of predictors for severe post-COVID syndrome-related dyspnoea might help identify high-risk patients and potentially relieve healthcare service from overload (1, 18).

However, the risk factors underlying dyspnoea associated with post-COVID syndrome are yet to be elucidated (1, 2, 19). Remarkably, an apparent lack of concordance between the presence of subjective exertional intolerance and results of pulmonary functional or radiological investigations has been observed in several studies (1, 18, 20), in that up to 35–65% of patients complained of dyspneic symptomatology despite normal pulmonary function test and chest CT imaging profile (14, 21–23). This study aimed to characterize a large cohort of post-COVID patients in Apulia, Italy, in the setting of a multi-disciplinary dedicated post-COVID Unit, to estimate the frequency of new or persistent dyspnoea in the post-acute-COVID-19-episode phase, in both hospital- and domiciliary-management patients, and to investigate predictors of post-COVID dyspnoea and reasons for lack of return to baseline health status at follow-up.

Materials and methods

Study design

This study was carried out in the Respiratory Post-COVID-19 Syndrome outpatient specialist service, specifically established at the Pulmonology Unit of the University Policlinico Hospital of Bari (Apulia, Italy). The Post-COVID-19 Syndrome clinical service project is an ongoing initiative developed by the University Policlinico Hospital of Bari aimed to evaluate the long-term impact of COVID-19 on the respiratory system and offer healthcare to patients (> 16 years

Abbreviations: PCED, Post-COVID Exertional Dyspnoea; 6-mwt, 6-min-walking-test.

old) residents in the Italian Apulia Region and potentially needing management for Post-COVID Exertional Dyspnoea (PCED). Service setting up included a first assessment protocol scheduled at 3 months post-acute-SARS-CoV-2-infection and a subsequent follow-up protocol after the first consultation depending on the grade of severity and persistence of symptoms. The service was available for all post-COVID patients, regardless of symptoms or acute-phase healthcare setting.

The study was designed as a retrospective cross-sectional observational survey. Patients attended the clinical service for Post-COVID Syndrome assessment throughout the pandemic period. Results of the 3-month post-acute-SARS-CoV-2-infection assessment are reported herewith (recruitment period January 2021–August 2021).

Appropriate information about the use of personal data was given to all patients cared for in the clinic and also regarded the possible use of collected data for publication. In the information, it was clarified that data will be used according to Italian law about the protection of personal data. Signed informed content was obtained from each participant.

The study was conducted in accordance with the principles of the 1964 Declaration of Helsinki.

The protocol of the study was communicated to the Puglia Observatory for Epidemiology.

Study population

All patients had received molecular/antigen-based laboratory confirmation of SARS-CoV-2 infection by nasal/oral swab-based analysis. At the time of the evaluation, all patients had received recovery confirmation by achieving molecular/antigen SARS-CoV-2 swab test negativization.

Data collection

The assessment protocol included medical history collecting both remote pre-COVID-19 clinical conditions and information on acute-phase-COVID-19 episodes (both respiratory and non-respiratory clinical symptoms, domiciliary/hospitalization course, hospitalization setting when applicable, need for respiratory/ventilatory support, medications). Clinical severity during the COVID-19 acute phase was classified as follows: (1) domiciliary course; (2) hospitalization in a General Medicine setting; (3) hospitalization in a Pulmonology/Semi-Intensive Care setting; (4) ICU admission. (24, 25). Careful clinical evaluation of Post-COVID-related medical history included both current respiratory (self-reported PCED, coughing, chest pain/breathing discomfort) and non-respiratory (fatigue, joint/muscle pain, gustative sensory impairment, olfactory sensory impairment, fever, cephalalgia/headache/cognitive fog, tachycardia, alopecia, anxiety/depression) clinical symptoms (9, 26, 27). Clinical symptoms were collected upon semi-structured interview-based specific questions during clinical examination, by the visiting physician. Medical evaluation of respiratory health status included signs of peripheral desaturation, resting room pulse-oximetry, and walking drop during 6mwt.

Instrumental physical evaluation

Instrumental characterization of PCED was carried out through a 6-min-walking-test (6-mwt) and measuring distance run, completed/interrupted 6-mwt, difference pre-post 6-mwt in subjective perceived exertion using the Borg-Category-Ratio-10 (a scale ranging from 0 to 10, in which 10 represents extreme intensity of activity), and pre-post 6-mwt peripheral $SatHbO_2$ walking drop. A 6-mwt test interruption and/or shorter distance run indicate worse performance. Instrumental PCED was defined as a 6-mwt-induced increase of $\geq$2 units in Borg-Category-Ratio-10 (DeltaBorgScale$\geq$2) and/or 6-mwt test interruption. Instrumental PCED was also compared to self-reported PCED in medical history. To gain insights into the pathogenic mechanism underlying Post-COVID dyspnoea, instrumental PCED-suffering patients were classified according to peripheral $SatHbO_2$ walking drop during 6-mwt (DeltaSatHbO$_2$ $\leq -2\%$ indicating presumably dyspnoea-underlying respiratory dysfunction, otherwise indicate presumably other dyspnoea-underlying mechanisms).

Statistical analysis

Descriptive statistics were used to describe clinical features of the study population according to pre-existing clinical conditions, acute-phase-COVID-19 symptoms, and post-COVID-related manifestations. Continuous variables were expressed as mean ± SD. Categorical variables were expressed as frequencies by absolute value and percentage (%) of the total. Differences in the population subsets were assessed by the Mann–Whitney U-test for continuous variables and Fisher's z-Exact Test for categorical variables. For each post-COVID syndrome-related clinical manifestation, persistence rate and new-onset rate are reported. Persistence rate is reported as a ratio between the number of patients showing each single symptom at 3-month follow-up divided by the number of patients showing the same symptom in the acute phase. New-onset rate is reported as a ratio between the number of patients showing each single symptom at 3-month follow-up divided by the number of patients lacking the same symptom in the acute phase. For each value of persistence rate and new-onset rate, 95% CI was reported, assuming a binomial distribution. Differences in persistent rate and new-onset rate for each post-COVID syndrome-related clinical manifestation were analyzed by the McNemar test.

To identify predictors of PCED, a multivariate logistic regression model was established. Acute-phase dyspnoea, PCED, acute-phase fatigue, and post-COVID fatigue were used as outcome variables of the model, respectively. Variables were included as covariates in the model according to their clinical significance and/or their significant difference in the univariate analysis (fully adjusted multivariate logistic regression model). Furthermore, for each of the predictor variables, partial multivariate logistic regression analysis was also performed by including only sex and age as covariates. Furthermore, multivariate logistic regression analysis was refined by splitting up the study cohort according to sex. All analyses were performed using SPSS software (version 23.0, SPSS Inc., Chicago, IL, United States). The statistical significance threshold was set at 0.05.

TABLE 1 Characteristics of post-COVID syndrome cohort.

Cohort	Hospitalized (N = 79)	Domiciliary (N = 239)	Total cohort (*N* = 318)	*p-value*
Patients' characteristics (n = 318)				
Age, years (mean ± SD) [Range]	61.66 ± 12.83 [31;87]	51.67 ± 14.36 [16;89]	54.17 ± 14.63 [16;89]	0.000
Age distribution <55 yrs., # (%)	25/79 (31.6)	147/239 (61.5)	172/318 (54.1)	0.000
Female Sex, # (%)	27/79 (34.1)	132/239 (55.2)	159/318 (50.0)	0.002
Duration of Disease (Onset-to-negativization), days (mean ± SD) [Range]	35.39 ± 16.13 [4;95]	30.55 ± 12.91 [3;94]	31.78 ± 13.93 [3;95]	0.014
Length of Follow-up (from Disease Onset, days) (mean ± SD) [Range]	127.24 ± 67.136 [35–398]	111.62 ± 59.092 [14–458]	115.53 ± 61.47 [14–458]	0.061
Clinical symptomatology (n = 318)				
At least one Symptom, # (%)	79 (100)	234	313 (98.4)	0.337
None (Asymptomatic), # (%)	0	5	5 (1.6)	
Symptomatic before swab-test diagnosis, # (%)	76	218	294 (92.4)	0.217
Asymptomatic before swab-test diagnosis, # (%)	3	21	24 (7.5)	
Dyspnoea, # (%)	61	137	198 (62.3)	0.002
Fatigue, # (%)	57	158	215 (67.6)	0.336
Fever, # (%)	63	170	233 (73.3)	0.145
Coughing, # (%)	41	143	134 (42.1)	0.238
Dyspnoea and/or Respiratory insufficiency, # (%)	79	137	216 (67.9)	0.000

Healthcare setting in acute phase, hospitalization ward (*n* = 318)	Hospitalized	Domiciliary	Total cohort
Nr,# (%)	**79 (24.8)**	**239 (75.2)**	**318 (100)**
General Medicine care, # (%)	43 (13.5)		
Semi-Intensive care, # (%)	21 (6.6)		
Intensive care, # (%)	15 (4.7)		

Demographic and clinical data are reported according to the healthcare setting (Hospitalized vs. Domiciliary) during the acute infection phase.

Results

Cohort

A total of 318 consecutive patients attended the Post-COVID-19 outpatient service (age 54.17 ± 14.63 years, range 16–89 yrs.; female sex ratio: 159/318, 50.0%). The mean period of follow-up (from disease onset) was 115.53 ± 61.466 days (Table 1). No sex-related statistically significant differences were found in age distribution (54.30 ± 14.13 vs. 54.03 ± 15.17 in males vs. females, respectively, $p = 0.886$), diagnostic pathway, acute disease duration, and follow-up length. Conversely, older patients had a significantly longer acute disease duration ($p = 0.004$) and length of follow-up ($p = 0.033$). A total of 311/318 patients (97.8%) had at least one symptom during the acute infection phase. Fever was the commonest reported symptom (233/318 patients, 73.3%), followed by fatigue and dyspnoea (215/318, 67.9%, and 198/318, 62.3%, respectively). The number of patients suffering from respiratory insufficiency was up to 216/318 (67.6%).

During the acute phase, 79/318 patients (24.8%) needed hospitalization-based care and suffered from respiratory insufficiency needing hospitalization during the acute phase, whereas the remaining 239 patients displayed domiciliary management (Table 1). Hospitalized patients were significantly older (61.66 ± 12.839 vs. 51.67 ± 14.364, $p = 0.001$), had a significantly longer acute-disease duration (35.39 ± 16.13 vs. 30.55 ± 12.91 days, $p = 0.014$) and had a greater frequency of acute-phase dyspnoea (61/79, 77.2% vs. 137/239, 57.3%, $p = 0.002$) compared to domiciliary patients, respectively. Clinical manifestations in the acute phase displayed a typical sex-related pattern, with fever mostly affecting male patients and olfactory impairment, chest pain, cephalalgia, and diarrhea more frequently reported by female patients However, no sex-related statistically significant differences were found in age distribution, diagnostic pathway, acute disease duration, and follow-up length. Furthermore, male patients had an increased risk for unfavorable evolution requiring hospitalization (52/159, 32.7%, vs. 27/159, 17%, respectively, $p = 0.002$).

TABLE 2 Clinical data of Post-COVID Syndrome cohort, at 3 months follow-up.

Clinical symptomatology. Post-COVID at 3 months follow-up (n = 318)	
Symptom	# (%)
At least one Post-COVID Syndrome-related Symptom	243 (76.4)
Post-COVID exertional dyspnoea (PCED)	190 (59.7)
Fatigue	96 (30.2)
Joint/Muscle Pain	40 (12.6)
Gustative sensory impairment	19 (6.0)
Olfactory sensory impairment	24 (7.5)
Fever	3 (0.9)
Cephalalgia/Headache/Cognitive Fog	19 (6.0)
Coughing	55 (17.3)
Breathing Discomfort/Chest Pain	32 (10.1)
Tachycardia	9 (2.8)
Alopecia	12 (3.8)
Anxiety/Depression	9 (2.8)
At least one Post-COVID Syndrome-related respiratory symptom	206 (64.8)
At least one Post-COVID Syndrome-related non-respiratory symptom	143 (45.0)
Multiple (≥2) Post-COVID Syndrome-related symptoms	141 (44.3)

The frequency of each manifestation reported in the Post-COVID phase is shown. PCED: Post-COVID exertional dyspnoea.

Post-COVID manifestations

At least one Post-COVID Syndrome clinical manifestation at follow-up was reported by 243/318 patients (76.4%). The commonest reported feature was by far exertional dyspnoea, complained of by 190/318 patients (59.7%), followed by fatigue (96/318, 30.2%) and coughing (55/318 patients, 17.3%). At least one Post-COVID-Syndrome-related respiratory symptom was reported by 206/318 patients (64.8%). A large proportion of patients showed multiple concomitant respiratory or non-respiratory manifestations, with 141 (44.3%) individuals reporting ≥2 symptoms. Results are shown in Table 2.

Clinical burden of post-COVID exertional dyspnoea

The presence of PCED showed no significant relationship with clinical settings during the acute phase, as it was reported in a similar percentage in hospitalized vs. domiciliary patients (50/79, 63.3% vs. 140/239, 58.6%, respectively; $p = 0.503$). Interestingly, the frequency of exertional dyspnoea was significantly higher in Post-COVID-fatigue-suffering vs. fatigue-free patients (68/96, 70.8% vs. 122/222, 54.9%, respectively, $p = 0.009$), whereas no such increase is evident concerning patients suffering from fatigue during acute phase infection (133/215, 61.9% vs. 57/103, 55.3%, $p = 0.274$), thus suggesting that Post-COVID fatigue contributes to PCED, likely through a mechanism independent from acute-phase dyspnoea. Age turned out to be a significant risk factor for the frequency of exertional dyspnoea, which was reported significantly more often by old patients compared to young patients ($p = 0.021$). Nonetheless, the clinical burden of PCED was not specific for older adult patients only, since a notable portion (57/190, 30.0%) of PCED-reporting patients were < 50 yrs., most of which characterized by a domiciliary course (54/57, 94.7%), a scenario being consistent across patients with both persistent dyspnoea and new-onset dyspnoea.

Persistence and new-onset rate

Although the majority of PCED-reporting patients had suffered from subjective dyspnoea during the acute infection phase as well (143/190, 75.3%) or desaturation during hospitalization (11/190, 5.8%), which were consistent with the definition of "persistent dyspnoea", a significant proportion of them (36/190, 18.9%) was negative for subjective dyspnoea/respiratory insufficiency throughout the acute infection phase ("new-onset dyspnoea"). Therefore, when globally considered, 36/318 patients of our cohort (11.3%) displayed new-onset PCED at 3-month follow-up. The persistence rate of each post-COVID symptom was variable, with a high rate for some symptoms such as fatigue, joint/muscle pain, and coughing, as well as for exertional dyspnoea, to a very low rate for fever and gustative sensory impairment. Likewise, fatigue and joint/muscle pain, as well as exertional dyspnoea, showed a considerable new-onset rate, whereas for other symptoms new-onset rate was negligible (Table 3).

Sex-related effect

Noteworthy, female patients reported Post-COVID-Syndrome-related symptoms more frequently than male patients, as only 29/159 female patients were symptom-free, compared to 46/159 male patients ($p = 0.034$). The greater predominance of Post-COVID Syndrome to affect female sex was evident in both respiratory and non-respiratory symptoms (0.013 and 0.001, respectively). Several single symptoms displayed a statistically significant increase in female vs. male patients,

TABLE 3 Post-COVID syndrome at 3 months follow-up ($n = 318$).

Post-COVID at 3 months follow-up ($n = 318$). Persistence rate and new-onset rate						
	# (%)	Persistence Rate		New onset rate		*p*-value
At least one post-COVID syndrome-related symptom	243 (76.4)					
Post-COVID exertional dyspnoea (PCED)	190/318 (59.7)	143/198*	0.72 (0.65–0.78)	47/120*	0.39 (0.30–0.48)	0.488
		154/216**	0.71 (0.65–0.77)	36/102**	0.35 (0.26–0.45)	0.022
Fatigue	96/318 (30.2)	74/215	0.34 (0.28–0.41)	22/103	0.21 (0.14–0.31)	0.000
Joint/Muscle pain	40/318 (12.6)	29/175	0.16 (0.11–0.23)	11/143	0.08 (0.04–0.14)	0.000
Gustative sensory impairment	19/318 (6.0)	16/131	0.12 (0.07–0.19)	3/187	0.02 (0.00–0.05)	0.000
Olfactory sensory impairment	24/318 (7.5)	22/136	0.16 (0.11–0.24)	2/182	0.01 (0.00–0.04)	0.000
Fever	3/318 (0.9)	3/233	0.01 (0.00–0.04)	0/85	0.00 (0.00–0.05)	0.000
Cephalalgia/Headache/Cognitive Fog	19/318 (6.0)	13/90	0.14 (0.08–0.24)	6/228	0.05 (0.02–0.10)	0.000
Coughing	55/318 (17.3)	43/184	0.23 (0.18–0.30)	12/134	0.09 (0.05–0.15)	0.000
Breathing discomfort/Chest pain	32/318 (10.1)	10/56	0.18 (0.09–0.30)	22/262	0.08 (0.05–0.12)	0.005

Persistence rate and new-onset rate of each single manifestations. Persistence rate is reported as a ratio between number of the patients showing each single symptom at 3-month follow-up divided by number of patients showing the same symptom in the acute phase. New-Onset Rate is reported as a ratio between number of patients showing each single symptom at 3-month follow-up divided by the number of patients lacking the same symptom in the acute phase.
*Compared to self-reported dyspnoea as a baseline in acute-phase manifestations (198/318 patients); **Compared to respiratory insufficiency, with or without symptomatic dyspnoea, during acute phase infection as a baseline manifestation (216/318 patients).

such as coughing ($p = 0.003$), fatigue (61/159, 38.4%, vs. 35/159, 22.0%, $p = 0.002$), and alopecia ($p = 0.001$), while other symptoms, such as exertional dyspnoea, did not reach statistical significance, albeit showing a clear trend towards higher frequency in female patients compared to male patients (103/159, 64.8% vs. 87/159, 54.7%, respectively $p = 0.086$). Interestingly, after the removal of hospitalized patients, who had an increased male-to-female ratio, the female-*vs*-male greater frequency of exertional dyspnoea reached statistical significance (85/132, 64.6%, vs. 55/107, 51.4%, respectively; $p = 0.048$).

Functional investigation

As part of the clinical evaluation of the post-COVID-19 protocol of our outpatient service, an investigation by functional 6-mwt was carried out. Instrumental 6-mwt PCED and self-reported PCED in medical history were then compared. Data from the 6-mwt investigation were available for 175 of 318 patients (Table 4). Age and sex distribution were not significantly different between patients subjected to 6-mwt vs. patients with unavailable 6-mwt (data not shown). The mean run distance was 515.41 ± 142.36) mt. Instrumental PCED was reported by 133/175 (76.0%) patients, a greater proportion if compared to self-reported PCED-suffering patients (114/175 patients, 65.1%). Furthermore, among the 133 instrumental dyspneic patients, 18 patients did not complete the 6-mwt, due to the onset of severe exertional dyspnoea (and/or thoracic/respiratory symptoms). No significant difference in terms of either basal SpO_2 (97.91 vs. 98.29), or post-6mwt SpO_2 (97.23 vs. 97.69) was observed in dyspneic vs. non-dyspneic patients, whereas 6-mwt run distance was only marginal reduced in dyspneic vs. non-dyspneic patients (507.15 vs. 540.95, respectively, $p = 0.632$), although such differences approached significant threshold when patients were stratified and compared with respect to self-reported PCED. When we tried to more deeply characterize the 133 instrumental PCED-affected patients, with respect to presence of acute-phase dyspnoea/respiratory insufficiency, we found that Post-COVID dyspnoea could be classified as persistent dyspnoea in 100/133 patients (75.2%) and as new-onset dyspnoea in 33/133 (24.8%) cases, thus showing an overlapping scenario with results obtained on basis of self-reported PCED. To gain better insight into the etiology of the PCED, we investigated the intrinsic respiratory contribution to exercise intolerance. Our results disclosed that most dyspneic patients had no evident functional respiratory deficit, since only 32/133 patients (24.1%) with instrumental PCED had 6-mwt-based desaturation walking drop ($DeltaSatHbO_2 \leq -2\%$). Noteworthy, post-COVID fatigue was present at a higher rate, namely 44/133 (33.3%). Accordingly, the presence of instrumental 6-mwt-based PCED was not significantly correlated with the frequency of 6-mwt-based desaturation signs ($p = 0.84$), whereas it showed a statistically significant correlation with the frequency of post-COVID fatigue ($p = 0.02$).

Pre-existing co-morbidities and dyspnoea

With the aim to identify pre-existing clinical conditions as possible predictors of Post-COVID Syndrome clinical manifestations, we collected information on the remote clinical history of recruited patients (Table 5). Some of the co-morbidities showed non-overlapping distribution according to sex, namely dys-metabolic co-morbidities, smoking, and cardiovascular co-morbidities which were more frequent in male patients, whereas the presence of allergy showed a non-significant trend towards a greater prevalence in female patients.

Self-reported PCED was significantly associated with pre-COVID-19 respiratory co-morbidities ($p = 0.001$) and a history of

TABLE 4 Results of functional 6-mwt on patients with available 6mwt data ($n = 175$ patients).

Post-COVID exertional dyspnoea (PCED). Results of functional 6-mwt	
Patients with 6-mwt-Characteristics ($n = 175$)	
Sex – Female ratio, # (%)	**86 (49.1)**
Age, Mean (SD), yrs	53.28 ± 14.503
Hospitalized, # (%)	**44 (25.1)**
Self-reported Post-COVID exertional dyspnoea (PCED), # (%)	114 (65.1)
Post-COVID Fatigue, # (%)	50 (28.6)
Instrumental results	
Completed Test, # (%)	157
Interrupted Test, # (%)	18
Basal 6mwt $HbSatO_2$ fraction, Mean (SD)	98.0 ± 1.38
Post-test 6mwt $HbSatO_2$, Mean (SD)	97.3 ± 2.40
6mwt run distance, Mean (SD)	515.41 ± 142.36
Instrumental Post-COVID exertional dyspnoea (PCED), # (%)[a]	133 (76.0)
Instrumental 6-mwt-based peripheral $HbSatO_2$ desaturation	32/133 (24.1%)
Post-COVID Fatigue	44/133 (33.3%)

[a]Instrumental exertional dyspnoea is defined as completing 6mwt with ≥2 DeltaBorg Units increase and/or 6mwt interrupted test due to onset of severe exertional dyspnoea and/or thoracic pain. Post-COVID exertional dyspnoea (PCED).

TABLE 5 Pre-existing co-morbidities in the Post-COVID cohort.

Pre-existing condition	# (%)
Comorbidities (any)	191/242 (78.9)
Respiratory Comorbidities	57/242 (23.6)
COPD	15/242 (6.2)
Asthma	24/242 (9.9)
Cardiovascular Comorbidities	100/242 (41.3)
Dis-metabolic Comorbidities	67/242 (27.7)
Diabetes/Obesity Comorbidities	27/242 (11.2)
Smoking	120/243 (49.4)
Allergy	89/243 (36.6)
Non-Asthmatic Allergy	68/242 (27.9)
Allergy (inhalants)	42/243 (17.3)
Allergy (other)	46/243 (18.9)

Clinical manifestations related to pre-COVID infection were collected by medical history, at time of 3-month Post-COVID follow-up.

allergy ($p = 0.039$). However, despite self-reported PCED being more frequent in patients with pre-COVID-19 respiratory co-morbidities, a notable proportion of young patients (<50 yrs) had mute history for pre-COVID-19 respiratory diseases (38/46, 82.6%). No association was found with other co-morbidities or smoking. Conversely, fatigue revealed no significant association with any of the considered clinical predictors, except for the previously mentioned female sex.

Multivariate analysis

To better identify predictors of PCED, we established a multivariate logistic regression model. As shown in Table 6, the model identified five predictor variables providing independent statistically significant contributions to the risk of PCED, namely Post-COVID fatigue, pre-existing respiratory co-morbidities, history of non-asthmatic allergy, age, and acute-phase dyspnoea. Conversely, predictors of acute-phase dyspnoea displayed a different pattern (Table 6), with only one common significant predictor with PCED (pre-existing respiratory co-morbidities), and three other independent predictors specific for acute-phase dyspnoea (pre-existing cardiovascular co-morbidities, acute-phase fatigue, and hospitalization). Despite showing several sex-related differences in univariate analysis, the female sex seems to play no significant effect in multivariate analysis, on either acute-phase dyspnoea or PCED. Therefore, we decided to refine the regression analysis according to the two sex-based subgroups.

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TABLE 6 Multivariate logistic regression analysis on the whole cohort ($n = 318$ patients).

Covariate		B	OR	95%CI		p
(A) Outcome: Post-COVID exertional dyspnoea (PCED)						
Age^	*Unadjusted*	0.551	1.735	1.097	2.744	0.018*
	Fully Adjusted	0.812	2.251	1.092	4.640	0.028*
	Partially Adjusted	0.559	1.749	1.103	2.773	0.017*
Pre-existing Respiratory Comorbidities	*Unadjusted*	1.231	3.426	1.631	7.198	0.001*
	Fully Adjusted	1.132	3.103	1.362	7.073	0.007*
	Partially Adjusted	1.129	3.092	1.454	6.577	0.003*
History of non-asthmatic allergy	*Unadjusted*	0.546	1.727	0.941	3.169	0.078
	Fully Adjusted	0.965	2.625	1.282	5.376	0.008*
	Partially Adjusted	0.544	1.723	0.921	3.224	0.089
Acute-Phase Dyspnoea	*Unadjusted*	1.396	4.038	2.497	6.531	0.000*
	Fully Adjusted	1.443	4.233	2.207	8.120	0.000*
	Partially Adjusted	1.406	4.079	2.497	6.665	0.000*
Post-COVID Fatigue	*Unadjusted*	−0.688	0.502	0.301	0.839	0.009*
	Fully Adjusted	0.903	2.466	1.194	5.094	0.015*
	Partially Adjusted	0.624	1.866	1.098	3.174	0.021*
(B) Outcome: Acute-Phase Dyspnoea						
Pre-existing Respiratory Comorbidities	*Unadjusted*	0.671	1.957	1.000	3.831	0.046*
	Fully Adjusted	0.881	2.414	1.132	5.146	0.023*
	Partially Adjusted	0.574	1.776	0.898	3.511	0.046*
Pre-existing Cardiovascular Comorbidities	*Unadjusted*	0.815	2.259	1.289	3.961	0.004*
	Fully Adjusted	0.964	2.621	1.264	5.435	0.010*
	Partially Adjusted	0.821	2.272	1.213	4.255	0.010*
Domiciliary Management	*Unadjusted*	−0.925	0.396	0.221	0.711	0.002*
	Fully Adjusted	−0.987	0.373	0.173	0.804	0.012*
	Partially Adjusted	−0.907	0.404	0.219	0.745	0.004*
Acute-Phase Fatigue	*Unadjusted*	0.490	1.633	1.011	2.637	0.045*
	Fully Adjusted	0.726	2.066	1.122	3.806	0.020*
	Partially Adjusted	0.478	1.613	0.994	2.615	0.046*

(A): Stepwise regression analysis was performed by using Post-COVID exertional dyspnoea (PCED) as outcome variable and the following parameters as covariates: Age ≥ 55 yrs. ^, Female Sex, Pre-existing Respiratory Comorbidities, Pre-existing Cardiovascular Comorbidities, Pre-existing Dis-metabolic Comorbidities, Smoking, History of non-asthmatic allergy, Domiciliary Management, Acute-Phase Dyspnoea, Post-COVID Fatigue.

(B): Stepwise regression analysis was performed by using Acute-Phase Dyspnoea as outcome variable and the following parameters as covariates: Age ≥ 55 yrs. ^, Female Sex, Pre-existing Respiratory Comorbidities, Pre-existing Cardiovascular Comorbidities, Pre-existing Dis-metabolic Comorbidities, Smoking, History of non-asthmatic allergy, Domiciliary Management, Acute-Phase Fatigue.

Results of logistic regression analysis are reported according to unadjusted analysis (univariate), multivariate analysis for multiple confounders (Fully Adjusted) and sex- and age- adjusted multivariate analysis (Partially Adjusted). Only variables showing statistically significance are shown. ^= For the purpose of statistical analysis, cut-off for age was set up at 55 yrs, which represents the median age of our cohort. * = statistically significant.

When the analysis was restricted to female patients (Table 7), only two independent significant predictors were identified by regression analysis as contributors to PCED, namely, acute-phase dyspnoea (OR: 3.085; 95%CI: 1.056–9.012, $p = 0.007$) and Post-COVID fatigue (OR: 4.069; 95%CI: 1.458–11.354, $p = 0.039$). On the other hand, when the same analysis was restricted to male patients (Table 7), the regression analysis disclosed four independent significant predictors, namely acute-phase dyspnoea, pre-existing respiratory co-morbidities, age, and history of non-asthmatic allergy. The predictive effect of history of non-asthmatic allergy on PCED in male patients is not completely clear, since it displays a statistically significant contribution in the multivariate analysis, while falling below the statistical threshold in univariate analysis. Noteworthy, sex-based subgroup analysis reveals that post-COVID fatigue represents a female-specific risk factor for

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TABLE 7 Multivariate logistic regression analysis after splitting up the cohort according to sex.

Covariate		B	OR	95%CI		*p*
(A) Outcome: Post-COVID exertional dyspnoea - Female only (n = 159)						
Acute-Phase Dyspnoea	*Unadjusted*	1.521	4.577	2.281	9.185	0.000*
	Fully Adjusted	1.403	4.069	1.458	11.354	0.007*
	Partially Adjusted	1.556	4.738	2.347	9.565	0.000*
Post-COVID Fatigue	*Unadjusted*	0.923	2.518	1.227	5.165	0.012*
	Fully Adjusted	1.126	3.085	1.056	9.012	0.039*
	Partially Adjusted	0.893	2.443	1.186	5.030	0.015*
(B) Outcome: Post-COVID exertional dyspnoea - Male only (n = 159)						
Age^	*Unadjusted*	0.926	2.525	1.320	4.833	0.005*
	Fully Adjusted	1.088	2.969	1.062	8.303	0.038*
	Partially Adjusted	0.834	2.304	1.090	4.867	0.029*
Pre-existing Respiratory Comorbidities	*Unadjusted*	1.487	4.423	1.560	12.540	0.005*
	Fully Adjusted	1.504	4.499	1.357	14.921	0.014*
	Partially Adjusted	1.365	3.915	1.358	11.285	0.012*
History of non-asthmatic allergy	*Unadjusted*	0.774	2.168	0.909	5.170	0.081
	Fully Adjusted	1.189	3.283	1.176	9.166	0.023*
	Partially Adjusted	0.953	2.595	1.045	6.444	0.040*
Acute-Phase Dyspnoea	*Unadjusted*	1.312	3.714	1.891	7.297	0.000*
	Fully Adjusted	1.456	4.289	1.755	10.479	0.001*
	Partially Adjusted	1.296	3.654	1.821	7.330	0.000*

In both models, stepwise regression analysis was performed by using Post-COVID exertional dyspnoea (PCED) as outcome variable and the following parameters as covariates: Age ≥ 55 yrs. ^, Pre-existing Respiratory Comorbidities, Pre-existing Cardiovascular Comorbidities, Pre-existing Dis-metabolic Comorbidities, Smoking, History of non-asthmatic allergy, Domiciliary Management, Acute-Phase Dyspnoea, Post-COVID Fatigue. **(A)**: Female only. **(B)**: Male only. Results of logistic regression analysis are reported according to unadjusted analysis (univariate), multivariate analysis for multiple confounders (Fully Adjusted) and age-adjusted multivariate analysis (Partially Adjusted). Only variables showing statistically significance are shown. ^= For the purpose of statistical analysis, cut-off for age was set up at 55 yrs, which represents the median age of our cohort.
* = statistically significant.

PCED. Accordingly, when we set up a similar logistic regression model with Post-COVID Fatigue as the outcome variable, the sex female arose as an independent statistically significant variable (OR: 2.169; 95%CI: 1.162–4.048; $p = 0.015$), by univariate analysis (not shown). Hence, these results suggest that PCED seems to display a different pattern of underlying risk factors in female and male patients.

Discussion

In the present study, we report a snapshot of the clinical features of a large cohort of patients referring to an outpatient service, specifically established for follow-up of Post-COVID Syndrome manifestations. At 3-month follow-up, patients displayed a wide range of clinical features, spanning from mild symptoms with little clinical relevance, or complete recovery, to the detection of long-term symptoms of considerable clinical significance. Our results evidenced that Post-COVID Syndrome, at 3-month post-infection remission, actually involved at least one reported clinical manifestation in a conspicuous portion of patients, with respiratory symptoms playing a pivotal role, as exertional dyspnoea revealed to be the commonest reported feature. PCED is a debilitating condition requiring targeted management, including frequent follow-up consultations and other-than-respiratory specialist evaluation (4, 12, 28, 29). A proper ongoing outpatient service is then needed in the appropriate healthcare setting, in the framework of a holistic multi-disciplinary approach, including pulmonary functional investigations, respiratory rehabilitation facilities (1, 15), and invasive and non-invasive imaging examinations (30–35). Such dedicated service would mitigate the post-COVID disease trajectory, thus potentially preventing the worsening of daily life and/or professional impairment, as well as avoiding future hospitalizations (15, 34).

Due to the high variability of PCED, comprehensive management cannot be achieved according to a "one-size-fits-all care" model (36). Rather, optimal care organization requires a personalized fashion, thus addressing different dyspnoea manifestations, severity degrees, and eventual co-morbid conditions (4, 6, 15). In this framework, it could be reasonable to think that PCED mainly develops in people with older age, with pre-existing respiratory conditions, or with acute-phase hospitalization courses (37–39). Although self-reported PCED was more frequent in patients with pre-COVID-19 respiratory co-morbidities in this cohort, our results suggest that a notable portion (57/190, 30.0%) of PCED-reporting patients were relatively young (under 50 yrs), most of whom were never admitted but remained at home and had an unremarkable medical history for pre-COVID-19 respiratory diseases (82.6%). Post-COVID multi-professional service should then sustain growing

healthcare needs posed by different patients' subsets, ranging from individuals with pre-existing respiratory conditions (whose potentially already altered lung parenchyma likely contributed to worsening acute-phase lung inflammation and consequent persistence of the exertional dyspnoea in post-COVID phase (40, 41)), to a considerable amount of relatively young and healthy dyspnoea-affected patients, who are expected to ask for increasing demand for adequate medical attention. Given their long life expectancy, the importance of ensuring adequate ongoing long-term outpatient post-COVID assistance in the latter patients' subgroup is crucial (42, 43). Policymakers need to be aware that adequate supplies are required to potentiate healthcare delivery for PCED patients. However, expansion of healthcare capacity may be hard to achieve in those areas with resource limitations (44). In the last decade, the Apulia Region, Southern Italy, was subjected to diminished healthcare provision, reorganization of bed allocation, limitation of medical/healthcare personnel units, and reduction of respiratory rehabilitation infrastructures, with pandemic waves imparting further unprecedented strain, with consequent impaired capacity to sustain healthcare overload (16, 17).

As underlined in the results, an acute-phase hospitalization course is not a significant predictor of PCED. Furthermore, the persistence of acute-phase dyspnoea cannot fully account for the presence of PCED, since a notable portion of Post-COVID dyspneic subjects (19%) reported new-onset exertional dyspnoea, despite unremarkable acute-phase respiratory history. Our findings provide evidence that PCED is a heterogeneous nosological entity, with likely multiple underlying aetiologies. In the present study, instrumental characterization of respiratory function, based on 6-mwt, disclosed a high prevalence of PCED, even higher than subjectively reported dyspnoea, potentially due to either a higher sensitivity of instrumental 6-mwt-based approach or patients' under-reporting during the medical interview. Noteworthy, we did not detect any statistically significant correlation between Post-COVID instrumental 6-mwt-based PCED and signs of actual pulmonary dysfunction, in terms of desaturation signs ($DeltaSatHbO_2 \leq -2\%$), thus indicating that PCED should not be regarded as a condition mainly involving lung damage or impairment. Rather, we found a statistically significant correlation between instrumental 6-mwt-based PCED and the frequency of post-COVID fatigue. Several studies also suggest that PCED is a wide-range disease, potentially encompassing several potential underlying conditions (6, 19, 43). Accordingly, at least two different phenotypes/mechanisms underlying PCED arise from our results. In a portion of individuals, PCED may represent a sequela associated with marked functional pulmonary involvement/damage and manifesting in the post-COVID phase as a walking drop in peripheral oxygenation. Such respiratory impairment might be primarily explained as chronic lung damage or, alternatively, as dysregulated inflammatory cytokine response in chest respiratory muscles or persistent pulmonary microvascular thrombosis and altered alveolar diffusion (37, 38, 42). Another subset of patients in our study had no detectable peripheral desaturation, thus clearly suggesting a different pathogenic mechanism. Accordingly, a number of recent reports described PCED as a consequence of decreased peripheral oxygen delivery or muscular consumption/deconditioning, in the absence of oxygen supply limitations (1, 20, 21). Several underlying mechanisms have been evoked, such as systemic microclotting/thromboinflammation, reduced metabolic oxidative capacity, virus-induced alterations in muscle tissue, and inactivity-induced muscle loss (18, 36, 45–49). Previous studies showed that a substantial proportion of Post-COVID Syndrome-affected patients with exertional dyspnea display radiological evidence of pulmonary interstitial disease, with heterogeneous aetiologies, such as pulmonary fibrosis conditions induced by the initial COVID-19 episode, previously identified interstitial fibrosis showing SARS-CoV-2-associated worsening/deterioration, as well as previously undiagnosed interstitial fibrosis unraveled by SARS-CoV-2 infection (50, 51). Furthermore, persistent interstitial disease and pulmonary embolism-related sequelae are also part of the dyspnea-associated spectrum post-COVID-related disease (33, 52, 53). It can be surmised that a fraction of dyspneic patients and 6-mwt-associated desaturation events might have been secondary to signs of a residual thin scattered area of the lung parenchyma involved by interstitial disease, although we could not test such an assumption since the radiological thoracic examination was not routinely part of our clinical protocol and data of chronic lung affection was not collected systematically in our cohort. Indeed, despite some chest CT abnormalities (ground-glass opacities, reticulations, interstitial thickening, fibrosis, and bronchiectasis) may persist 3 months after SARS-CoV-2 infection, only a weak correlation has been reported between abnormalities observed on "resting" investigations, such as imaging, and post-COVID exertional dyspnea (51–54).

Previous studies investigating risk factors behind PCED showed conflicting results (19, 55). In the present study, we set up a multivariate regression analysis, which disclosed a quite different risk profile between acute-phase dyspnoea and exertional dyspnoea in the post-COVID phase. Post-COVID fatigue, pre-existing respiratory co-morbidities, history of non-asthmatic allergy, age, and acute-phase dyspnoea emerged as independent statistically significant contributors to PCED, whereas hospitalization did not seem to play a significant role and only represented a risk factor for acute-phase dyspnoea, thus confirming findings of univariate analysis. Similarly, a clinical history of pre-existing cardiovascular co-morbidities represents a determinant for acute-phase dyspnoea, not for PCED, since it is well known that systemic hyper-inflammatory dysregulation in COVID acute phase is mainly responsible for rapid clinical deterioration in heart-disease patients, whereas it can be surmised that such condition will not play a major role in Post-COVID phase, characterized by a likely resolution of pro-inflammatory imbalance. In order to better characterize the risk factor profile, we also set up a sex-specific analysis. Our results showed a typical sex-oriented clinical profile in COVID, with increased risk of severe disease and hospitalization risk displayed by males during the acute phase, and greater frequency of long-lasting complaints occurring in females during the Post-COVID phase, in striking accordance with the literature (56–59). Sex-restricted multivariate regression analysis reveals a partially different risk profile underlying PCED, with post-COVID fatigue representing a female-specific risk factor, whereas pre-existing respiratory co-morbidities, age, and history of non-asthmatic allergy arose as male-specific determinants. Hence, considering the two

above-described different aetiologies for PCED, the pulmonary-driven mechanism seems to display a male-to-female predominance. On the opposite, fatigue-driven PCED seems to be the predominant scenario in female patients, in both univariate and multivariate analysis. In accordance, fatigue is a manifestation that is typically more frequent in female patients, both hospitalized and at home, as shown in our study and previous studies (56). Female-to-male fatigue-driven increased risk of PCED seems to involve a relatively low pulmonary impairment, but likely represents a hallmark of Post-COVID Syndrome. A potential explanation for this female increased predominance finding could be related to potential hormonal influence (57–60). Based on the results reported in the present study, which disclosed the sex-specific independent predictors underlying dyspneic symptoms, we advocate that an optimization strategy should be deployed for personalized Post-COVID Syndrome exertional dyspnoea follow-up, according to a sex-specific protocol. In primary care settings for male patients with post-COVID dyspnoea, careful attention is needed for the presence of previous respiratory conditions, which should then prompt a higher priority toward specialty-care pulmonology management. In second-level pulmonary care, an appropriate work-up should include more invasive radiological and functional thoracic surveillance for these patients' subgroups, in light of the male-specific greater risk of worsening previous respiratory diseases. On the other hand, since Post-COVID fatigue emerged as a major contributor to PCED in female patients, particular concern on this symptom is warranted by primary care physicians, aimed to activate higher priority scores for rapid evaluation in specialty-care settings, which would then be mainly focused on thorough investigation of fatigue in a female-specific protocol. In this framework, a comprehensive assessment of fatigue by a multi-professional healthcare team should consider functional muscle-weakness investigation, neuropsychological management, and non-invasive cardiopulmonary exercise testing, aside from standard pulmonology care.

Finally, our results are based on a cohort of patients infected during the first pandemic peaks characterized by the dominance of Alpha or Delta SARS-CoV-2 variants, whereas most recent pandemic waves (with the Omicron variant and its sublineages becoming dominant) displayed attenuated acute illness and mortality but increased spreading rate (61, 62). Despite more recent SARS-CoV-2 variants seeming to be associated with a reduced odd risk of post-COVID sequelae (63) compared to earlier variants, the high absolute numbers of infected people are expected to impose a non-negligible clinical burden and a considerable concern on healthcare organizations (64). Future studies are needed to assess the degree of overlap between the risk profiles for post-COVID in the different SARS-CoV-2 variants. Interestingly, a very recent inquiry highlighted female gender as the main post-COVID-underlying risk determinant independent of the viral strain (65), which would support a strategy based on sex-specific work-up protocol as a promising approach, not only for post-COVID management of people infected by initial-SARS-CoV-2 variants, but also for individuals suffering from long-term sequelae of more recent, or currently emerging, SARS-CoV-2 variants.

Our study has some limitations. Clinical data from the acute infection phase were retrospectively collected through medical history, which could lead to recall bias. Although the post-COVID service was available for all Post-COVID-Syndrome patients, regardless of symptoms or acute-phase healthcare setting, we cannot exclude potential referral bias toward dyspnea-affected patients as expected in a pulmonology clinical setting. Instrumental data are only based on 6-mwt technique, which mirrors an overall functional capacity and may potentially be affected by several confounders and was performed in a cross-sectional manner, thus resulting in an inevitably lacking pre-COVID assessment. It was not possible to systematically collect radiologic examinations in the recruited patients, which prevented us from more characterization of different phenotypic PCED clusters. Hence, most results are based on subjective patients' reported outcomes, rather than objective assessment, since the observational nature of the study prevented us from carrying out a deeper investigation on metabolic aerobic fitness with a mainly experimental technique such as cardiopulmonary exercise testing.

Conclusion

Post-COVID exertional dyspnoea was revealed to be the commonest reported feature, potentially associated with a relevant clinical burden. A proper management strategy needs to be established by healthcare system institutions and policymakers, to sustain requirements for healthcare delivery and mitigate evolution towards chronicity. However, such growing healthcare demand will probably overload the insufficient capacity of the public health service in Italy and the Apulia Region, previously weakened by resource limitations and pandemic bursts. Knowledge of sex-specific risk-determining factors might help optimize personalized care management and healthcare resources.

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 humans were approved by Puglia Observatory for Epidemiology. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ER: Conceptualization, Investigation, Writing – original draft. ECu: Conceptualization, Data curation, Methodology, Writing – original draft. PP: Data curation, Methodology, Validation, Writing – review & editing. CC: Conceptualization, Data curation, Investigation, Writing – review & editing. VS: Conceptualization, Data curation, Writing – review & editing. CS: Conceptualization, Methodology, Writing – review & editing. CP: Data curation, Formal analysis, Methodology, Writing – review & editing. FB: Data curation, Methodology, Writing – review & editing. MC: Data curation,

Methodology, Writing – review & editing. MT: Data curation, Investigation, Methodology, Writing – review & editing. ECa: Data curation, Investigation, Methodology, Writing – review & editing. SL: Data curation, Investigation, Methodology, Writing – review & editing. LM: Data curation, Investigation, Supervision, Writing – review & editing. ST: Conceptualization, Supervision, Writing – original draft. OR: Conceptualization, Methodology, Writing – review & editing. GL: Conceptualization, Data curation, Formal analysis, Project administration, Writing – review & editing, Writing – original draft.

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Conflict of interest

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Prevalence, predictors, and patient-reported outcomes of long COVID in hospitalized and non-hospitalized patients from the city of São Paulo, Brazil

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Background: Robust data comparing long COVID in hospitalized and non-hospitalized patients in middle-income countries are limited.

Methods: A retrospective cohort study was conducted in Brazil, including hospitalized and non-hospitalized patients. Long COVID was diagnosed at 90-day follow-up using WHO criteria. Demographic and clinical information, including the depression screening scale (PHQ-2) at day 30, was compared between the groups. If the PHQ-2 score is 3 or greater, major depressive disorder is likely. Logistic regression analysis identified predictors and protective factors for long COVID.

Results: A total of 291 hospitalized and 1,118 non-hospitalized patients with COVID-19 were included. The prevalence of long COVID was 47.1% and 49.5%, respectively. Multivariable logistic regression showed female sex (odds ratio [OR] = 4.50, 95% confidence interval (CI) 2.51–8.37), hypertension (OR = 2.90, 95% CI 1.52–5.69), PHQ-2 > 3 (OR = 6.50, 95% CI 1.68–33.4) and corticosteroid use during hospital stay (OR = 2.43, 95% CI 1.20–5.04) as predictors of long COVID in hospitalized patients, while female sex (OR = 2.52, 95% CI 1.95–3.27) and PHQ-2 > 3 (OR = 3.88, 95% CI 2.52–6.16) were predictors in non-hospitalized patients.

Conclusion: Long COVID was prevalent in both groups. Positive depression screening at day 30 post-infection can predict long COVID. Early screening of depression helps health staff to identify patients at a higher risk of long COVID, allowing an early diagnosis of the condition.

KEYWORDS

long COVID, mental health, depression screening, quality of life, middle income countries

1 Introduction

The World Health Organization (WHO) defines long COVID as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. Long COVID impacts various population groups, leading to a diverse array of signs and symptoms. Over 200 different symptoms have been reported that can have an impact on daily life activities (1). It poses a growing medical challenge due to the complexity and diversity of its long-term effects. The presence of respiratory, motor, cardiovascular, or psychological sequelae heightens the demand for physical rehabilitation services and psychosocial support. Consequently, long COVID is increasingly burdening the healthcare system. Apart from strengthening the primary healthcare system and its multidisciplinary teams, there is a need to enhance specialized care. Considering that middle-income countries may have limited access to healthcare systems with fewer resources compared to high-income countries, it is crucial to investigate the prevalence of long COVID in these middle-income countries.

The majority of studies on long COVID have been carried out in Europe and North America, focusing on patients who were hospitalized and later discharged (2, 3). The United States produced the largest number of related publications, followed by the United Kingdom. The top ten most frequent keywords cited in these publications are "fatigue," "depression," and "inflammation" (2). Long COVID appears to be more common among women, older adult individuals, and those with existing comorbidities and higher body mass index (BMI) (2). However, limited research has been conducted on the long-term predictors in patients from middle-income countries comparing hospitalized and non-hospitalized patients. A systematic literature review published in 2021 showed that the number of publications had the following geographic distribution: Europe (62%, 24/39), followed by Asia (23%, 9/39), North America (8%, 3/39) and the Middle East 8% (3/39) and none of the included studies were carried out in low-middle-income countries (4). Furthermore, another systematic literature review and meta-analysis comprising 139 studies, highlighted a limitation of the geographic homogeneity. Over 50% of publications originated from Europe, with, less than 5% representing studies in long COVID from Africa, Oceania and South America. This underscores the need for more data from low-middle income countries (5). The study postulates that the prevalence of long COVID may exhibit variations between hospitalized and non-hospitalized COVID-19 patients in middle-income countries. Additionally, specific demographic and clinical factors, including patient-reported outcomes variables, including aspects of mental health, may serve as predictors of long COVID. The relationship between depression and long COVID is still an ongoing area of research and results are not conclusive.

The primary objective of this research is to assess the prevalence of long COVID among both hospitalized and non-hospitalized patient cohorts. Furthermore, the study seeks to identify predictive and protective factors influencing the development of long COVID within these groups. This investigation also endeavors to evaluate the impact of long COVID on the quality of life among afflicted individuals in Brazil.

2 Materials and methods

2.1 Population under study, study design, criteria of eligibility

This was a single center, retrospective cohort study, which included all the hospitalized and non-hospitalized adult patients (with a confirmed diagnosis of COVID-19 at Hospital Israelita Albert Einstein (HIAE) from February 12, 2021 to July 25, 2022. The Brazilian Israelite Society Albert Einstein is a nonprofit healthcare, educational, and research organization, with headquarters in the city of São Paulo, managing diverse services from primary to tertiary care, in the public and private healthcare sectors. It operates 40 healthcare units, mainly in the state of São Paulo. In 2022, the private sector HIAE had 344,000 emergency department visits, 495,000 outpatient visits, and 62,000 hospital discharges. The institution manages a diverse healthcare system ranging from primary healthcare to tertiary care services in the public and private sectors.

Any hospitalized and non-hospitalized adult patients (18 or more years of age) with a laboratory-confirmed COVID-19 were included. The laboratorial confirmation was performed using RT-PCR on specimens obtained via naso-pharyngeal swab, according to the protocol instituted at HIAE.

2.2 Long COVID definition

Long COVID was defined according to WHO criteria as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection. The signs and symptoms included in long COVID were general signs and symptoms (fatigue), respiratory and cardiac symptoms (dyspnea, cough, chest pain), neurological symptoms (memory loss, headache, sleep problem), and other symptoms (anosmia, ageusia, motor problems and difficulties with activities of daily living). We collected data on the first SARS-CoV-2 infection recorded in our system and excluded patients who were subsequently diagnosed with re-infection documented in the electronic medical record.

2.3 Follow Up

All the hospitalized patients with COVID-19 were followed through telephone interviews run by a trained professional 30 days and 90 days after hospital discharge, If the subject was unreachable at first call, three attempts were made. Non-hospitalized patients were followed 30 days and 90 days after COVID-19 confirmation date, via text message or email.

2.4 Data collection and measures

Data were collected using an electronic medical record, and patient reported questionnaires. At baseline, demographic characteristics including age, sex, and BMI, and clinical information including symptoms on admission, disease duration from onset of symptoms and underlying comorbidities were collected. Intensive care unit admission, use of mechanical ventilation, length of hospital stay,

and drug therapy (i.e., steroids, antibiotics, and remdesivir) were also collected for hospitalized patients.

At 30-day and 90-day follow-up, symptoms and the PHQ-2 questionnaire were collected in both groups, and the EuroQol-5D3L quality of life questionnaire and EuroQol visual analog scale (EQ-VAS) were collected only in the hospitalized patient group.

2.4.1 Structured questionnaires

The EuroQol-5D3L is a generic instrument for measuring health-related quality of life which generates an EQ-5D index score from 1 (full health) to 0 (a state as bad as being dead). The EQ-VAS is a 0–100 scale where patients are asked to indicate their overall health, where the higher the value, the better. Patients with and without long COVID were analyzed according to change in the EQ-5D index score and EQ-VAS scale from 30 days to 90 days. Three categories were defined: improvement, no change and worsening (6).

The PHQ-2 addresses the frequency of depressed mood and anhedonia in the last two weeks and can be used as a first approach for diagnosing depression. If the score is 3 or greater, major depressive disorder is likely (7).

2.5 Period of COVID-19 variants

As only a small number of positive samples among our cases were sequenced, all individuals were classified according to the most prevalent variant. Due to the low number of Alpha cases, it was combined with the Gamma cases to form a single time period. The time period between February 12, 2021, to August 5, 2021 was considered the "Alpha/Gamma era"; August 6, 2021 to December 16, 2021 the "Delta era"; and December 17, 2021 to July 25, 2022, the "Omicron era" (8).

2.6 Statistical analysis

To compare the demographic characteristics of hospitalized and non-hospitalized patients among COVID-19 variant eras, the Pearson's Chi-square and Fisher's exact test were used for categorical variables and were summarized as counts and percentages (9). In addition, normality assumptions were tested by the Anderson-Darling normality test. If this test provided evidence against a normal distribution for a given continuous variable, the Wilcoxon-Mann–Whitney U test was used instead. Both were expressed as medians with IQR (Interquartile Range).

A logistic regression model was used to investigate which factor, either at baseline or follow-up day 30, was associated with long COVID at day 90 in the two groups (hospitalized and non-hospitalized patients). The variables selected to enter the multivariate model were those with significant associations on univariate analysis ($p < 0.05$). Dichotomous intervals for continuous variables such as age (≥60 years or < 60 years) and length of stay (≥21 days or < 21 days) were created for the models. For the purposes of logistic regression, the PHQ-2 response on day 30 was used. Some variables did not have full information for all observations, for instance PHQ2 ≥ 3 (n = 6) and obesity (n = 4) had a total of 281 patients (long COVID = 131 and no long COVID = 150) and these variables were removed from the hospitalized long COVID prediction model. Predictors for both models did not present variance inflation factors (VIF >10), indicating that collinearity was not a problem. Receiver Operating Characteristic (ROC) curve analysis was employed to evaluate the performance of the predictive model. The Area Under the ROC Curve (AUC) was calculated to assess the discriminatory ability of the model in distinguishing between long COVID and no long COVID. All results with $p < 0.05$ were considered statistically significant. Data was manipulated in Knime Analytics Software[1] and all statistical analyses were performed in R (4.2.0 version)[2] programming language. The R packages used in the analyses are described in Supplementary Data 1.

2.7 Ethics approval

The study was approved by the HIAE Research Ethics Committee, protocol number 6.204.804, CAAE: 69689123.2.0000.0071, and the National Commission for Research Ethics.

3 Results

3.1 Demographic and clinical characteristics of hospitalized and non-hospitalized patients

During the study period, 1,409 patients with confirmed COVID-19 were included, of which 291 (20.65%) were hospitalized patients and 1,118 (79.35%) non-hospitalized patients (Figure 1).

Table 1 summarizes the demographic and clinical characteristics of the eligible population in the two study groups (hospitalized and non-hospitalized) stratified by COVID-19 eras. Patients who were hospitalized were more likely to be older (median age 53.0 vs. 43.0 years old, $p < 0.01$) than non-hospitalized patients, regardless of variant, and had higher BMI (27.9 vs. 25.7 kg/m^2, $p < 0.01$) in the Alpha/Gamma era. Hospitalized patients also had more comorbidities and the predominant symptoms on admission were cough (35.7% vs. 28.2%, $p = 0.01$), fever (55.7% vs. 20.5%, $p < 0.01$), myalgia (30.6% vs. 19.7%, $p < 0.01$), fatigue (32.0% vs. 25.1%, $p = 0.02$) and dyspnea (19.9% vs. 5.4%, $p < 0.01$) when compared to non-hospitalized patients. Regarding the clinical course among hospitalized patients, 42.3% required admission to the ICU, 9.6% received mechanical ventilation, 59.5% antibiotics, 69.8% steroids and 12.4% remdesivir. Patients admitted during the Alpha/Gamma era received proportionally more mechanical ventilation (14.6%, $p = 0.01$) and corticosteroids (93.4%, $p < 0.01$) (Supplementary Table 1).

3.2 Long COVID prevalence and its characteristics

The prevalence of long COVID was found to be 47.1% among hospitalized patients and 49.5% among non-hospitalized patients at 90 days. Among hospitalized patients, the prevalence of long COVID varied across different eras, with rates of 58.3% during the Alpha/Gamma era, 46.7% during the Delta era, and 33.6% during the Omicron era. Among non-hospitalized patients, the prevalence of

1 https://www.knime.com/knime-analytics-platform

2 https://www.r-project.org/

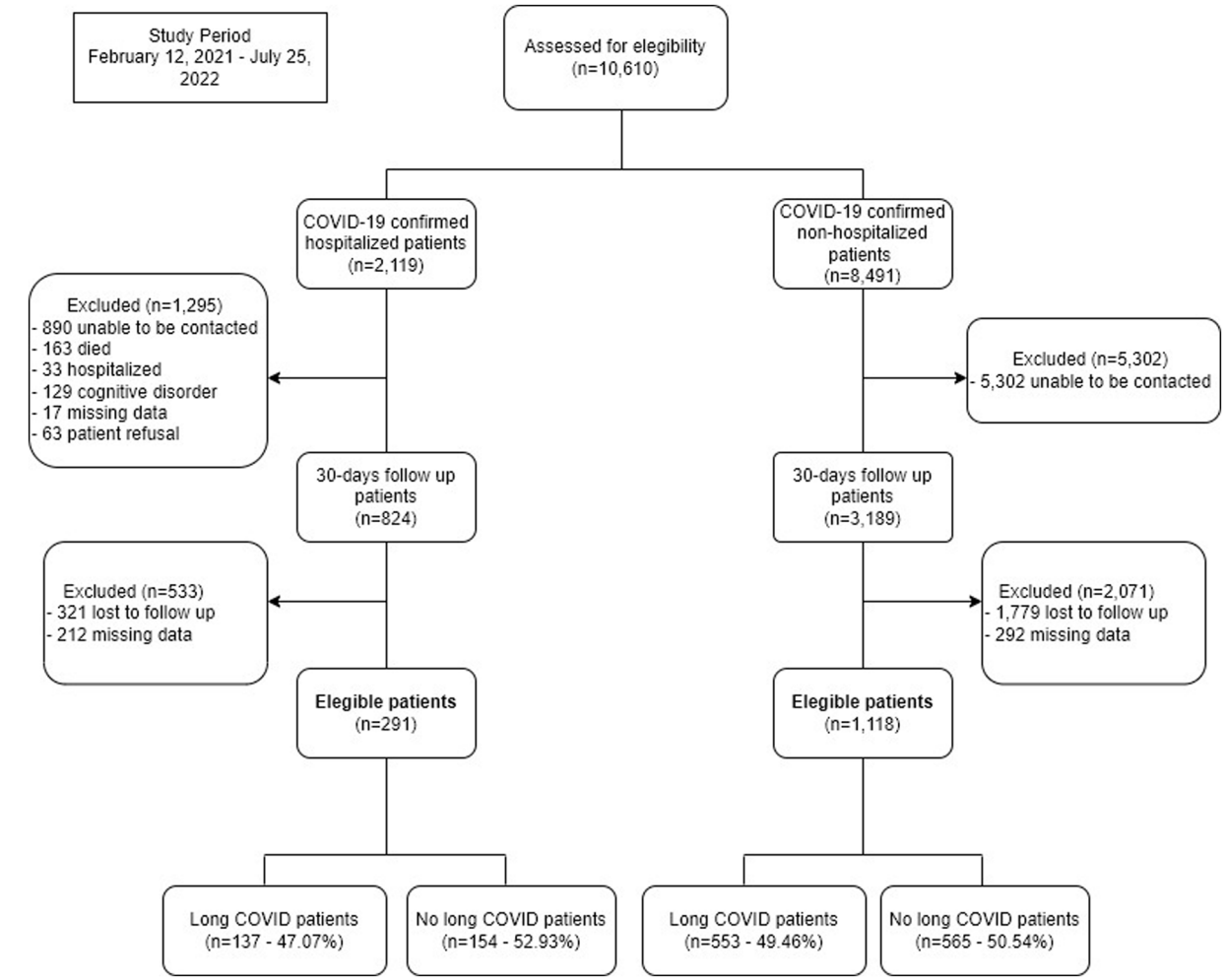

FIGURE 1
Study flowchart.

long COVID was 50.83% during the Alpha/Gamma era, 63.16% during the Delta era, and 48.26% during the Omicron era. In hospitalized patients diagnosed with long COVID, the most common symptoms reported were memory loss (33.6%) and fatigue (30.7%). Among non-hospitalized patients, the prevalent symptoms included memory loss (45.8%), fatigue (46.5%), sleep disorders (32.4%) and headache (30.7%) (Supplementary Figure 1 provides further details).

The analysis of the change in the EQ-5D index score from 30 days to 90 days showed that patients with long COVID have a higher rate of worsening over time than those without long COVID (33.8% vs. 11.3%, $p < 0.01$) (Figure 2A). There was no significant difference for the EQ-VAS variation score in the same period ($p = 0.45$) (Figure 2B), however, the EQ-VAS score at 90 days was lower among patients with long COVID compared to those without this condition (Supplementary Figure 2).

3.3 Predictive and protective factors of long COVID

Multivariable logistic regression showed that predictors of long COVID among hospitalized patients were female sex (odds ratio [OR] = 4.50, 95% confidence interval (CI): [2.51–8.37]), hypertension (OR = 2.90 [1.52–5.69]), PHQ-2 ≥ 3 (OR = 6.50 [1.68–33.4]) and corticosteroid treatment during hospital stay (OR = 2.43 [1.20–5.04]) and a protective factor was Omicron era (OR = 0.40 [0.19–0.83]) (Table 2). Among non-hospitalized patients, predictors were female sex (OR = 2.52 [1.95–3.27]) and PHQ-2 > 3 (OR = 3.88 [2.52–6.16]) and a protective factor was age ≥ 60 years old (OR = 0.68 [0.48–0.97]) (Table 3).

The ROC curve was employed to analyze the predictive power of the variables for the classification of long COVID. For the group of hospitalized patients, the analyzed variables were gender, age (> = 60 years), hypertension, PHQ2, and corticosteroid use, resulting in an area under the curve (AUC) value of 0.759 and a 95% confidence interval between 0.704 and 0.815. Regarding the group of outpatient patients, the available variables were gender, age (> = 60 years), and PHQ2, yielding an AUC value of 0.667 and a 95% confidence interval between 0.638 and 0.696 (Supplementary Figures 3, 4).

4 Discussion

This study revealed that the prevalence of long COVID among hospitalized patients and non-hospitalized patients was 47.1 and 49.5%, respectively, at the 90 days after initial SARS-CoV-2 infection in a middle-income country. The prevalence of long COVID varied

TABLE 1 Demographic and clinical characteristics of the eligible population by COVID-19 era.

Characteristic	Overall			Alpha/Gama			Delta			Omicron		
	Hospitalized N = 291	Non-Hospitalized N = 1,118	*p*-value*	Hospitalized N = 151	Non-Hospitalized N = 303	*p*-value†	Hospitalized, N = 15	Non-Hospitalized N = 38	*p*-value‡	Hospitalized N = 125	Non-Hospitalized N = 777	*p*-value*
Sex, n (%)												
Male	187 (64.26%)	427 (38.19%)	**<0.01**	107 (70.86%)	127 (41.91%)	**<0.01**	6 (40.00%)	17 (44.74%)	0.75	74 (59.20%)	283 (36.42%)	**<0.01**
Age, Median (P25-P75)	53.00 (43.00–67.00)	43.00 (36.00–53.00)	**<0.01**	47.00 (40.00–55.00)	43.00 (37.00–53.00)	**<0.01**	59.00 (42.00–73.00)	42.73 (38.41–49.41)	**<0.01**	66.00 (51.00–77.00)	42.82 (35.53–53.50)	**<0.01**
BMI, Median (P25-P75)§	27.31 (24.72–29.98)	25.99 (23.31–29.40)	**<0.01**	27.85 (25.62–30.94)	25.72 (23.41–29.39)	**<0.01**	24.92 (22.89–28.09)	26.84 (24.97–30.21)	0.15	26.30 (24.01–29.39)	25.99 (23.23–29.40)	0.42
Missing	4	461		0	211		1	16		3	234	
Rhinorrhea, n (%)	52 (17.87%)	308 (27.55%)	**<0.01**	24 (15.89%)	47 (15.51%)	0.92	1 (6.67%)	10 (26.32%)	0.15	27 (21.60%)	251 (32.30%)	**0.02**
Cough, n (%)	104 (35.74%)	315 (28.18%)	**0.01**	51 (33.77%)	48 (15.84%)	**<0.01**	8 (53.33%)	9 (23.68%)	0.05	45 (36.00%)	258 (33.20%)	0.54
Fever, n (%)	162 (55.67%)	229 (20.48%)	**<0.01**	94 (62.25%)	38 (12.54%)	**<0.01**	6 (40.00%)	10 (26.32%)	0.34	62 (49.60%)	181 (23.29%)	**<0.01**
Sore Throat, (%)	60 (20.62%)	344 (30.77%)	**<0.01**	18 (11.92%)	36 (11.88%)	0.99	0 (0.00%)	9 (23.68%)	**0.05**	42 (33.60%)	299 (38.48%)	0.30
Myalgia, (%)	89 (30.58%)	220 (19.68%)	**<0.01**	53 (35.10%)	37 (12.21%)	**<0.01**	0 (0.00%)	7 (18.42%)	0.17	36 (28.80%)	176 (22.65%)	0.13
Headache, n (%)	62 (21.31%)	267 (23.88%)	0.35	36 (23.84%)	49 (16.17%)	**0.05**	4 (26.67%)	11 (28.95%)	1.00	22 (17.60%)	207 (26.64%)	**0.03**
Fatigue, n (%)	93 (31.96%)	281 (25.13%)	**0.02**	45 (29.80%)	49 (16.17%)	**<0.01**	6 (40.00%)	10 (26.32%)	0.34	42 (33.60%)	222 (28.57%)	0.25
Dyspnea, n (%)	58 (19.93%)	60 (5.37%)	**<0.01**	30 (19.87%)	16 (5.28%)	**<0.01**	4 (26.67%)	1 (2.63%)	**0.02**	24 (19.20%)	43 (5.53%)	**<0.01**
Anosmia, n (%)	16 (5.50%)	120 (10.73%)	**<0.01**	9 (5.96%)	45 (14.85%)	**<0.01**	1 (6.67%)	17 (44.74%)	**<0.01**	6 (4.80%)	58 (7.46%)	0.28
Dysguesia, n (%)	18 (6.19%)	102 (9.12%)	0.11	10 (6.62%)	37 (12.21%)	0.07	1 (6.67%)	14 (36.84%)	**0.04**	7 (5.60%)	51 (6.56%)	0.68
Nausea, n (%)	28 (9.62%)	55 (4.92%)	**<0.01**	9 (5.96%)	10 (3.30%)	0.18	1 (6.67%)	5 (13.16%)	0.66	18 (14.40%)	40 (5.15%)	**<0.01**
Diarrhea, n (%)	6 (2.06%)	90 (8.05%)	**<0.01**	2 (1.32%)	15 (4.95%)	0.06	0 (0.00%)	4 (10.53%)	0.57	4 (3.20%)	71 (9.14%)	**0.03**
Hypertension, n (%)	74 (25.43%)	90 (8.05%)	**<0.01**	32 (21.19%)	11 (3.63%)	**<0.01**	3 (20.00%)	2 (5.26%)	0.13	39 (31.20%)	77 (9.91%)	**<0.01**
Diabetes, n (%)	46 (15.81%)	37 (3.31%)	**<0.01**	15 (9.93%)	4 (1.32%)	**<0.01**	1 (6.67%)	0 (0.00%)	0.28	30 (24.00%)	33 (4.25%)	**<0.01**
Obesity, n (%)	71 (24.74%)	153 (23.29%)	0.63	47 (31.13%)	22 (23.91%)	0.23	1 (7.14%)	6 (27.27%)	0.21	23 (18.85%)	125 (23.02%)	0.32
Missing	4	461		0	211		1	16		3	234	
COPD, n (%)‖	19 (6.53%)	29 (2.59%)	**<0.01**	6 (3.97%)	5 (1.65%)	0.19	1 (6.67%)	0 (0.00%)	0.28	12 (9.60%)	24 (3.09%)	**<0.01**
Cancer, n (%)	8 (2.75%)	5 (0.45%)	**<0.01**	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)		8 (6.40%)	5 (0.64%)	**<0.01**

*Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test. †Pearson's Chi-squared test; Wilcoxon rank sum test; Welch Two Sample t-test; Fisher's exact test. ‡ Pearson's Chi-squared test; Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test. § BMI = Body Mass Index. ‖ COPD = Chronic Obstructive Pulmonary Disease. * Pearson's Chi squared test; Wilcoxon rank sum test; Fisher's exact test | † Pearson's Chi-squared test; Wilcoxon rank sum test; Welch Two Sample t-test; Fisher's exact test | ‡ Pearson's Chi-squared test; Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test | § BMI = Body Mass Index | || COPD = Chronic Obstructive Pulmonary Disease. Values in bold are statistically significant ($p < 0.05$).

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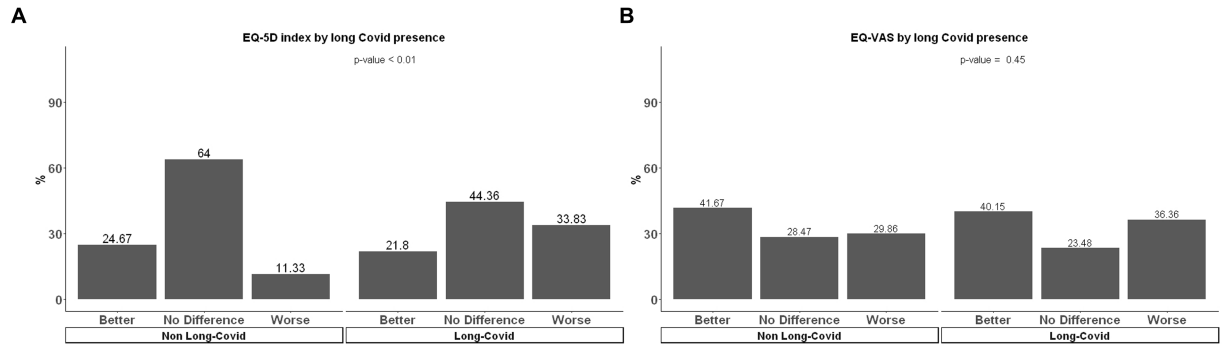

FIGURE 2
(A) EQ-5D index and **(B)** EQ-VAS change from 30 days to 90 days follow up for long COVID and no long COVID of hospitalized patients.

across different variant eras with the lowest prevalence seen in the Omicron era. Memory loss and fatigue were the most common symptoms for both groups. The factors associated with long COVID were female gender and positive screening for depression (PHQ-2 score) in both groups. The presence of hypertension also showed a risk for the development of long COVID among hospitalized patients while Omicron era infection was associated with a lower risk. Additionally, hospitalized patients with long COVID had a higher percentage of worsening quality of life measured by the EQ-5D index score at 90 days when compared to patients without long COVID.

A surveillance report of the European Centre for Disease Prevention and Control (ECDC), through a systematic review study and meta-analysis revealed a higher incidence of long COVID in patients admitted to the ICU. In this report overall prevalence of any post COVID-19 condition symptom was estimated at 51% in the community setting; 67% in the hospital setting; and 74% in the ICU setting (3). More recently, another systematic review signaled that the prevalence estimates of long COVID were significantly influenced by the severity of acute infection and being hospitalized (10). However, our results showed similar overall prevalence among non-hospitalized patients and hospitalized patients.

Interestingly, our study showed that the prevalence of long COVID was lowest during the Omicron era in hospitalized patients. A recent systematic review demonstrated that patients infected with the Omicron variant may have a lower risk of developing long COVID than those infected with other variants (11). However, the Omicron era was not shown to be a protective factor in non-hospitalized patients and further research is needed to understand the specific mechanisms underlying this observation and to determine if it holds true across different populations and settings.

Limited research exists on long COVID among hospitalized and non-hospitalized patients in middle-income countries. In Malaysia, common symptoms observed in both outpatients and inpatients include fatigue, brain fog, depression, anxiety, insomnia, and joint or muscle pain (12). However, in India, a single-center prospective observational cohort study highlighted fatigue, dyspnea, and weight loss as the predominant symptoms among hospitalized patients (13). A study in China found that at 6-month follow-up, fatigue or muscle weakness and sleep difficulties were the main symptoms observed in COVID-19 patients who had recovered. Patients with more severe illness had reduced lung function and a higher risk of psychological complications like anxiety and depression (14). In line with these findings and following similar results in high-income countries (2, 3, 15, 16), our study identified fatigue and memory loss as the most prevalent symptoms among both hospitalized and non-hospitalized patients. These results underscore the wide range of symptoms and the potential impact on various patient populations affected by long COVID.

Previous literatures showed that symptoms due to long COVID have a strong impact on quality of life of affected patients (17, 18). While our study found no difference in the EQ-VAS visual analog scale between patients with and without long COVID at 90 days compared to 30 days after COVID-19, the long COVID group exhibited a lower quality of life score according to the EuroQol-5D3L questionnaire. This contrasts with findings from a high-income country, where a Japanese report indicated that participants with long COVID had lower average scores on both the EQ-VAS and EuroQol-5D3L compared to those without long COVID (19). Gaspar et al. (20) in a study conducted in Portugal showed an association between the presence of long COVID and the deterioration of quality of life, assessed through the EQ-5D index, at 3-, 6-, and 9-months post-discharge. Further research is needed to better understand the long-term effects of COVID-19, including how it affects the quality of life of those with persistent symptoms.

Previous studies, including those conducted in low-and middle-income countries, have established a link between female gender and long COVID (12, 13, 21–23), However, it has not been previously reported that a positive depression screening at day 30 using a validated questionnaire could be a risk factor for diagnosing long COVID at day 90 (24, 25). Additionally, few studies have examined depression as a risk factor for COVID-19 or long COVID (26, 27). Taquet et al. showed a bidirectional association between COVID-19 and psychiatric disorder. Adults with a history of COVID-19 diagnosis have an approximately doubled risk of being newly diagnosed with a psychiatric condition than those without SARS-CoV-2 infection. On the other hand, having a diagnosis of psychiatric disorder in the year before the COVID-19 pandemic was associated with a 65% increased risk of COVID-19 (28). More recently, an investigation of factors associated with psychiatric outcomes in long

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TABLE 2 Multivariate analysis of predictors for long COVID in hospitalized patients.

Characteristic	No longCOVID, N = 150	Long COVID, N = 131	Univariate analysis		Multivariate analysis	
			OR (95% CI)*	*p*-value	OR (95% CI)*	*p*-value
Era, n (%)						
Alpha/Gamma	63 (42.00)	87 (66.41)	—		—	
Delta	8 (5.33)	6 (4.58)	0.54 (0.17–1.64)	0.28	0.57 (0.15–2.01)	0.38
Omicron	79 (52.67)	38 (29.01)	0.35 (0.21–0.57)	**<0.01**	0.40 (0.19–0.83)	**0.01**
Sex, n (%)						
Female	38 (25.33)	64 (48.85)	2.82 (1.71–4.69)	**<0.01**	4.50 (2.51–8.37)	**<0.01**
Age, n (%)						
> = 60 years	62 (41.33)	36 (27.48)	0.54 (0.32–0.89)	**0.02**	0.59 (0.30–1.15)	0.12
ALOS, n (%)†						
> = 21 days	15 (10.00)	17 (12.98)	1.34 (0.64–2.84)	0.43		
Intensive Care Unit, n (%)						
Yes	63 (42.00)	54 (41.22)	0.97 (0.60–1.56)	0.89		
Mechanical ventilation, n (%)						
Yes	13 (8.67)	14 (10.69)	1.26 (0.57–2.82)	0.57		
Hypertension, n (%)						
Yes	31 (20.67)	41 (31.30)	1.75 (1.02–3.02)	**0.04**	2.90 (1.52–5.69)	**<0.01**
Diabetes, n (%)						
Yes	27 (18.00)	17 (12.98)	0.68 (0.35–1.30)	0.25		
COPD, n (%)‡						
Yes	12 (8.00)	7 (5.34)	0.65 (0.24–1.67)	0.38		
CKD, n (%)§						
Yes	7 (4.67)	4 (3.05)	0.64 (0.17–2.18)	0.49		
Cancer, n (%)						
Yes	5 (3.33)	2 (1.53)	0.45 (0.06–2.13)	0.34		
Hypothyroidism, n (%)						
Yes	6 (4.00)	7 (5.34)	1.35 (0.44–4.31)	0.59		
Obesity, n (%)						
Yes	31 (20.67)	39 (29.77)	1.63 (0.95–2.82)	0.08		
Dyslipidemia, n (%)						
Yes	8 (5.33)	12 (9.16)	1.79 (0.72–4.71)	0.22		
PHQ2 ≥ 3, n (%)						
Yes	3 (2.00)	12 (9.16)	4.94 (1.53–22.1)	**0.02**	6.50 (1.68–33.4)	**0.01**
Remdesivir, n (%)						
Yes	20 (13.33)	14 (10.69)	0.78 (0.37–1.60)	0.50		
Antibiotics, n (%)						
Yes	82 (54.67)	83 (63.36)	1.43 (0.89–2.32)	0.14		
Corticosteroids, n (%)						
Yes	90 (60.00)	107 (81.68)	2.97 (1.73–5.22)	**<0.01**	2.43 (1.20–5.04)	**0.02**

*OR = Odds Ratio, CI = Confidence Interval. †ALOS = Average length of stay. ‡ COPD = Chronic Obstructive Pulmonary Disease. §CKD = Chronic Kidney Disease. Values in bold are statistically significant ($p < 0.05$).

COVID was published and it was shown that patients with long COVID are at increased risk for psychiatric disease, including depression, compared with those without long COVID (29). Conversely, Wang et al. found a strong association between symptoms of depression and anxiety, worry about COVID-19, loneliness, and perceived stress with the risk of long COVID. They note that their results should not be misinterpreted as being supportive of the hypothesis that symptoms of long COVID are psychosomatic since a

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TABLE 3 Multivariate analysis of predictors for long COVID in non-hospitalized patients.

Characteristic	No long COVID, N = 565	Long COVID, N = 553	Univariate analysis		Multivariate analysis	
			OR (95% CI)*	*p*-value	OR (95% CI)*	*p*-value
Era, n (%)						
Alpha/Gamma	149 (26.37)	154 (27.85)	—			
Delta	14 (2.48)	24 (4.34)	1.66 (0.84–3.40)	0.15		
Omicron	402 (71.15)	375 (67.81)	0.90 (0.69–1.18)	0.45		
Sex, n (%)						
Female	283 (50.09)	408 (73.78)	2.80 (2.18–3.61)	**<0.01**	2.52 (1.95–3.27)	**<0.01**
Age, n (%)						
≥60 years	109 (19.29)	60 (10.85)	0.51 (0.36–0.71)	**<0.01**	0.68 (0.48–0.97)	**0.04**
Hypertension, n (%)						
Yes	49 (8.67)	41 (7.41)	0.84 (0.55–1.30)	0.44		
Diabetes, n (%)						
Yes	15 (2.65)	22 (3.98)	1.52 (0.79–3.02)	0.22		
COPD, n (%)†						
Yes	13 (2.30)	16 (2.89)	1.27 (0.60–2.70)	0.53		
CKD, n (%)‡						
Yes	2 (0.35)	3 (0.54)	1.54 (0.25–11.7)	0.64		
Cancer, n (%)						
Yes	4 (0.71)	1 (0.18)	0.25 (0.01–1.72)	0.22		
PHQ2 ≥ 3, n (%)						
Yes	28 (4.96)	105 (18.99)	4.49 (2.95–7.07)	**<0.01**	3.88 (2.52–6.16)	**<0.01**

*OR = Odds Ratio, CI = Confidence Interval. †COPD = Chronic Obstructive Pulmonary Disease. ‡CKD – Chronic Kidney Disease. Values in bold are statistically significant ($p < 0.05$).

significant number of patients without mental illness also develop long COVID (30).

The association between depression and long COVID may be explained by several factors. Inflammation and activation of the hypothalamic–pituitary–adrenal axis, which can lead to chronic immune suppression, can be generated by distress. Additionally, depression may lead to changes in the brain and nervous system, which could contribute to long COVID symptoms such as fatigue and cognitive impairment (31). This suggests that recommending mental health screening to support these patients might be warranted. The PHQ-2 is a simple and effective screening tool that can be used to assess depression symptoms. Early identification and treatment of depression may help prevent the development of long COVID and improve overall health outcomes.

While hypertension is known to increase the risk of severe COVID-19 illness, the underlying mechanisms are not fully understood (32). Hypertension may contribute to the development of long COVID by affecting cardiovascular health and immune function. Initially, there was a suggested link between the use of renin-angiotensin-aldosterone system (RAAS) inhibitors and mortality in severe SARS-CoV-2 infection due to interactions with the bradykinin pathway. However, subsequent evidence has not confirmed this hypothesis (33–37). Other studies have indicated that hypertension's association with known risk factors such as advanced age, obesity, diabetes, cardiovascular disease, and chronic kidney disease could explain its role as a risk factor (38, 39). Limited research has been conducted on the role of hypertension as a predictor of long COVID and the impact of RAAS inhibitors on long-term symptoms. A recent study involving 414 patients indicated that hypertension appears to play a significant role in the persistence of long COVID symptoms. Among these individuals, 39.6% reported symptoms extending beyond 6 weeks post-infection. The study found that long COVID was notably higher in patients over 65 years old and those with various comorbidities, including Type II diabetes mellitus, dyslipidemia, coronary artery disease, asthma, and cancer. Specifically, hypertension showed an odds ratio of 2.59 and was statistically significant ($p = 0.001$), indicating a notable association with prolonged symptoms post-infection (40).

Similar to a study conducted in Italy, our results indicate that the severity of acute COVID-19 (ICU admission, prolonged length of stay, and use of mechanical ventilation) did not exert a substantial influence on the development of long-term COVID-19 (41). Interestingly, our findings showed that patients who received steroids during hospitalization were at greater risk of developing this condition. Likewise, a study from Southeastern Italy also demonstrated that corticosteroid therapy administered in the acute phase of COVID-19 might be associated with an increased risk of long COVID. One plausible hypothesis posited by the authors is that the administration of corticosteroids during the acute phase of illness may potentially contribute to the persistence of the virus within non-respiratory system among some patients reservoirs (24). To ascertain the potential

association between corticosteroid utilization and an increased risk of prolonged COVID-19, along with its dependence on factors such as dosage, type, or duration of in-hospital steroid therapy, further comprehensive investigations are warranted.

The Omicron era was found to be associated with a lower risk of developing long COVID among hospitalized patients while age ≥ 60 years old was a protective factor among non-hospitalized patients, similar to that reported by Reme et al. (42). The findings of a study published in 2022 demonstrated that the mean number of post-COVID-19 symptoms was higher in patients infected with the Wuhan variant than in those infected with the Alpha or Delta variant (43). Meanwhile a correspondence published in the same year found a reduction in the odds of long COVID with the Omicron variant versus the Delta variant (44). This intriguing finding suggests that the emergence of different COVID-19 variants may influence the clinical course and outcomes of this disease, including the likelihood of experiencing long-term symptoms. Understanding the role of the new COVID-19 variants in long COVID may aid in tailoring treatment approaches and public health interventions to mitigate its long-term burden. This study has several strengths. Its innovative approach focuses on exploring long COVID within the context of a middle-income country, specifically in Brazil. By comparing occurrences and predictive factors between hospitalized and non-hospitalized patients, the study provides crucial insights into how the severity of the initial illness influences the manifestation and impact of long COVID on individuals. Moreover, the study delves into the use of patient-reported outcome measures and their long-term effects on conditions such as COVID, examining their influence on both quality of life and mental health.

Our study sheds light on the prevalence of long COVID in distinct patient groups and identifies potential predictors, including gender, underlying health conditions, and depression screening. These findings offer crucial information for comprehending, predicting, and managing long COVID in diverse patient cohorts. By focusing on a middle-income country, the research contributes to a more comprehensive understanding of long COVID by incorporating data from varied socioeconomic backgrounds.

4.1 Limitations

This study has limitations due to its single institution setting and limited timeframe. The generalizability of the findings to broader populations may be limited. The reliance on clinical data and lack of exploration of certain factors, such as pre-existing conditions, especially presence of depression or mood disorder, may contribute to variations in outcomes and the prevalence of long COVID. Variables related to comorbidities were collected from the medical records; however, the Charlson Comorbidity Index was not routinely measured, so we did not use this information in our analysis. Socioeconomic data were not collected for this study. Additionally, the study's retrospective nature and reliance on self-reported symptoms introduce biases and variability in reporting. Furthermore, the study did not thoroughly examine the impact of treatment regimens other than remdesivir, or vaccination status. Due to the sensitive nature of personal information within vaccination data, access to this information in national databases is limited under the General Data Protection Law established in 2020 in Brazil. Consequently, these data was not included in the analyses. As of July 2022, at the conclusion of the Omicron wave, approximately 90% of the population of the State of São Paulo had received the first dose of the COVID-19 vaccine. We believe this fact may have contributed to the protective outcome during the Omicron wave in the multivariate analysis. Moreover, our study did not specifically address the characteristics of patients diagnosed with the COVID variants (Alpha/Gamma, Delta, and Omicron). Given the evolving nature of the virus and the emergence of new variants, it is essential to recognize that the dynamics of long COVID may be influenced by factors specifically to each variant. Therefore, extrapolation of our findings to populations affected by more recent variants should be approached with caution, and further research is warranted to understand the implications of these variants on the manifestation and impact of long COVID.

Future research with larger cohorts and prospective designs is needed to validate these findings, explore the underlying mechanisms, and address these limitations for a more comprehensive understanding of long COVID.

5 Conclusion

In conclusion, approximately half of both hospitalized and non-hospitalized patients in Brazil developed long COVID 90 days after their initial COVID-19. The prevalence of long COVID differed among different strain eras, with fatigue and memory loss being the most frequently reported symptoms. We identified a significant association between a positive depression screening at day 30 and an increased risk of developing long COVID at day 90. These findings may highlight the importance of integrating depression screening into regular COVID-19 follow-ups at primary care clinics.

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 humans were approved by Ethics Committee of Hospital Israelita Albert Einstein – CEP/Einstein. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the waiver of the use of informed consent is based on: i) being a retrospective observational study that utilized only medical records, institutional information systems, and/or other sources of data and clinical information available within the institution without the use of biological material

anticipated; ii) because all data were handled and analyzed anonymously, without nominal participant identification; iii) because the study results will be presented in an aggregated manner, preventing individual participant identification; and iv) because it is a non-interventional study (without clinical interventions) and without alterations/influences in the participant's routine/treatment, consequently posing no additional risks or harm to their well-being. Additionally, we will be unable to obtain consent from all participants in this research.

Data sharing agreement

De-identified individual study data reported in this article can be requested upon application to investigator board via the corresponding author.

Author contributions

DMa: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing. SB-P: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. KP: Writing – original draft, Methodology, Formal analysis. JP: Conceptualization, Investigation, Writing – original draft. EP: Data curation, Formal analysis, Validation, Visualization, Writing – original draft. DMe: Data curation, Methodology, Project administration, Supervision, Writing – original draft. CA: Data curation, Project administration, Writing – original draft. BP: Data curation, Writing – original draft. VL: Writing – original draft. SA: Data curation, Validation, Writing – original draft. PT: Writing – review & editing. CL: Writing – review & editing. MN: Writing – review & editing. SK: Writing – review & editing. VT: Conceptualization, Resources, Writing – review & editing. TK: Writing – review & editing. ME: Writing – review & editing. AM: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1302669/full#supplementary-material

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Social determinants of health predict readmission following COVID-19 hospitalization: a health information exchange-based retrospective cohort study

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Introduction: Since February 2020, over 104 million people in the United States have been diagnosed with SARS-CoV-2 infection, or COVID-19, with over 8.5 million reported in the state of Texas. This study analyzed social determinants of health as predictors for readmission among COVID-19 patients in Southeast Texas, United States.

Methods: A retrospective cohort study was conducted investigating demographic and clinical risk factors for 30, 60, and 90-day readmission outcomes among adult patients with a COVID-19-associated inpatient hospitalization encounter within a regional health information exchange between February 1, 2020, to December 1, 2022.

Results and discussion: In this cohort of 91,007 adult patients with a COVID-19-associated hospitalization, over 21% were readmitted to the hospital within 90 days (n=19,679), and 13% were readmitted within 30 days (n=11,912). In logistic regression analyses, Hispanic and non-Hispanic Asian patients were less likely to be readmitted within 90 days (adjusted odds ratio [aOR]: 0.8, 95% confidence interval [CI]: 0.7–0.9, and aOR: 0.8, 95% CI: 0.8–0.8), while non-Hispanic Black patients were more likely to be readmitted (aOR: 1.1, 95% CI: 1.0–1.1, p=0.002), compared to non-Hispanic White patients. Area deprivation index displayed a clear dose–response relationship to readmission: patients living in the most disadvantaged neighborhoods were more likely to be readmitted within 30 (aOR: 1.1, 95% CI: 1.0–1.2), 60 (aOR: 1.1, 95% CI: 1.2–1.2), and 90 days (aOR: 1.2, 95% CI: 1.1–1.2), compared to patients from the least disadvantaged neighborhoods. Our findings demonstrate the lasting impact of COVID-19, especially among members of marginalized communities, and the increasing burden of COVID-19 morbidity on the healthcare system.

KEYWORDS

COVID-19, social determinants of health, epidemiology, clinical outcomes, infectious disease, healthcare utilization, health disparities, hospitalization

1 Introduction

Since February 2020, over 104 million people in the United States have been diagnosed with SARS-CoV-2 infection, or COVID-19, with over 8.5 million, or 28,812 per hundred thousand population, reported in the state of Texas (1). The risk of SARS-CoV-2 exposure, progression to clinical disease, and severe outcomes such as hospitalization and death depend on both individual and societal factors (2–6). However, there is increasing recognition of significant rates of severe COVID-19 outcomes and post-acute syndromes, including long COVID, among populations previously thought to be 'low-risk' (7–9). Furthermore, the absolute risk of outcomes, such as hospitalization and death, have changed over time as novel SARS-CoV-2 variants emerged, vaccinations increased, and public health policies adapted to local epidemic dynamics (10–12).

As the pandemic progressed, social determinants of health, including demographic, financial, and social factors, emerged as significant contributors to adverse COVID-19 outcomes. Investigations have highlighted the risk of SARS-CoV-2 exposure among low-income, minority, and immigrant populations (13), and the impracticality of quarantine and isolation guidelines in high-density housing and other communal settings (14). Additionally, disparities in healthcare utilization among members of different socioeconomic groups were well documented before and during the COVID-19 pandemic (15–17). Hospital visits, especially unplanned readmissions, are important metrics not only of patient health, but also of healthcare practices, population health, and care costs (18, 19).

While increasing age and comorbidity burden have been identified as independent risk factors for COVID-19-related hospitalization and readmission, the relationship between readmission across healthcare systems and social determinants of health in the United States has been described in only a few studies (4, 20, 21). Therefore, the current study aimed to investigate 30, 60, and 90-day readmission outcomes among patients with a COVID-19-associated inpatient hospitalization encounter identified within a regional health information exchange between February 1, 2020, to December 1, 2022.

2 Methods

2.1 Health information exchange

Greater Houston Healthconnect (GHH) is the regional health information exchange (HIE) for Southeast Texas. GHH collects prospective and retrospective health data from approximately 15.5 million unique patients from more than 75 Texas counties and 40 Louisiana parishes through partnerships with more than 150 member hospitals, over 2,000 ambulatory practices, and several local public health departments. In practice, HL7 version 2 real-time feeds and Consolidated Continuity of Care Documents (C-CDA) are converted to a relational database with individual patients' longitudinal electronic health data. While the primary objective of any HIE is to facilitate clinical care by supporting the efficient exchange of clinical information, these large EHR datasets are increasingly being utilized for treatment, payment, and operations-related research (22, 23).

2.2 Identification of COVID-19 cases

COVID-19 cases were defined as any patient with either: A COVID-19 diagnosis identified through ICD-10 or SNOMED CT codes (see Supplementary 1 for the codeset); A positive diagnostic laboratory test for SARS-CoV-2, including nucleic acid amplification tests and antigen tests (antibody tests were excluded); And a case report documented by local public health departments. Patients for whom a COVID-19 identification date could not be determined were excluded.

2.3 Study population

The study area for this investigation covered most of Southeast Texas and included Brazoria, Burleson, Chambers, Fort Bend, Galveston, Grimes, Hardin, Harris, Jasper, Jefferson, Liberty, Madison, Matagorda, Montgomery, Nueces, Orange, Polk, San Jacinto, San Patricio, Walker, Waller, and Wharton counties, where a high proportion of hospitals are GHH members. Patients' residential addresses were extracted at the time of the initial data pull (December 2022). Patients with an 'inpatient' encounter beginning within 7 days (+/−) of any COVID-19 identification date who resided within the study area were eligible for inclusion in the COVID-19 inpatient cohort. 'Emergency Room' type encounters were not included in the inpatient cohort.

2.4 Exclusion criteria

Pediatric patients (<18 years of age), patients who were pregnant or delivering at their index encounter, patients who expired during their index encounter, and patients residing outside of the study area were excluded from readmission analyses. Pregnant patients were excluded from readmission analyses due to the likelihood of subsequent hospital encounters unrelated to COVID-19, i.e., labor and delivery encounters.

2.5 Study outcomes

The primary outcome was all-cause readmission, defined as any subsequent inpatient hospital encounter beginning within 90 days from discharge from the index encounter. Patients for whom readmission status could not be determined (e.g., a post-discharge encounter that was not clearly a readmission) were excluded from this analysis.

2.6 Study exposures

Patient demographics, including age at index encounter admission, sex, race, and ethnicity, were extracted directly from the EHR. The Charlson Comorbidity Index (CCI) was calculated as a measure of overall comorbidity burden (24, 25); individual CCI components were extracted by searching ICD-10-CM (26) and SNOMED CT (27) diagnosis codes associated with the index encounter as well as up to 3 years prior to the index encounter. Peaks in Texas COVID-19 incidence were used to categorize COVID-19 admissions to further reflect local epidemic dynamics (28).

2.7 Geographic information

COVID-19 patient hospitalization data were collected for the state of Texas from publicly available Department of State Health Services (DSHS) datasets.[1] Publicly available geographic information system (GIS) datasets were collected from the Texas Parks and Wildlife Department, the Texas Department of Transportation, the US Census repository, and DSHS. Ecological measures of socioeconomic disadvantage, including the Area Deprivation Index (ADI), which measures relative deprivation between all census block groups by state (29, 30) and the Social Vulnerability Index (SVI), which measures relative vulnerability to disaster among all census tracts in the state (31) were calculated from the geocoded patient-provided home addresses collated and analyzed December 2022. Heat maps were created by calculating kernel density estimates from patients' residential addresses; low-density values (<15th quantile) were truncated to preserve patient privacy. All geospatial analyses were performed on ArcGIS Pro version 3.1.1 (ESRI, Redlands, CA).

2.8 Statistical analyses

Demographic and clinical data were reported as frequencies and proportions for categorical variables and as the median and interquartile range (IQR) for continuous variables. Logistic regression modeling was performed to identify risk factors for readmission at 30, 60, and 90 days from discharge; crude and adjusted odds ratios and 95% confidence intervals are provided as estimates of risk for each outcome. Variable selection for the multivariable models was based on *a priori* clinical importance. For survival analyses, time zero was the date of discharge from the index encounter, event time was the date of first readmission, and data were censored at 90 days. All analyses were performed on Stata MP version 17.0 (StataCorp LLC, College Station, TX, United States). A p-value of <0.05 was considered nominally significant; a conservative, Bonferroni-corrected statistical significance threshold of 0.00625 was utilized in model-building.

2.9 Ethics statement

This retrospective registry-based study was approved by the Western Institutional Review Board as a quality improvement study and granted a waiver of informed consent (#1–1,053,411-1).

3 Results

3.1 Study population

From February 1, 2020, to December 1, 2022, 1,011,024 patients were identified as COVID-19 cases by diagnosis, laboratory testing, or local public health case reporting, of whom 133,298 (13%) had an inpatient hospital encounter within 7 days (+/−) of a COVID-19 identification date (Figure 1). Of these, 104,196 had a residential address within the study area, making-up the COVID-19 inpatient cohort (Figure 2). Of the inpatients, 80,253 were identified as COVID-19 cases during their index hospitalization. In this COVID-19 inpatient cohort, trends in inpatient admissions mirrored total COVID-19 incidence and total COVID-19 hospitalizations for the state of Texas (Figure 3). The median age at admission was 57.4 (IQR: 40.4–71.0), and 51,062 (49%) scored zero on the CCI (Table 1).

At their index hospital encounter, 21% of patients were privately insured, 47% were Medicare or Medicaid clients, and 27% had no payer information available (Table 1). Index inpatient encounters that noted the death of the patient occurred 4,875 (5%) times and were excluded from these readmission analyses. In total, 91,007 adult inpatients were included in these readmission analyses, of whom 11,912 (13%) were readmitted within 30 days of discharge from their index encounter (Figure 1). Additionally, 14,479 (74%) of readmitted patients returned to the same hospital, while 5,200 (26%) were admitted to a different hospital from their index encounter. Of the 19,679 patients who were readmitted within 90 days, 822 (4%) expired during their first readmission encounter. Diagnoses associated with index and readmission encounters are shown in Supplementary 2.

3.2 Readmission analyses

Univariable logistic regression analyses for 30, 60, and 90-day readmission are shown in Table 2, and Kaplan–Meier survival curves for time to readmission are shown in Figures 4, 5. Patients who expired during the observation period without a readmission (n = 2,499 patients) were excluded from Kaplan–Meier analyses. In multivariable logistic regression analysis, increasing age at encounter was significantly associated with 30, 60, and 90-day readmission (Table 3). Hispanic and non-Hispanic Asian patients were less likely to be readmitted within 90 days (aOR: 0.8, 95% CI: 0.7–0.9, and aOR: 0.8, 95% CI: 0.8–0.8), while non-Hispanic Black patients were more likely to be readmitted (aOR: 1.1, 95% CI: 1.0–1.1, p = 0.002), compared to non-Hispanic White patients. Living in neighborhoods with higher relative disadvantage was a significant risk factor in 30, 60, and 90-day readmission models. Increasing CCI scores were a risk factor in all readmission models. Medicare/Medicaid clients and patients without a named payor were more likely to be readmitted compared to patients with commercial insurance (aOR: 1.4, 95% CI: 1.3–1.5, and aOR: 1.3, 95% CI: 1.2–1.3), while patients with index encounters primarily covered by special COVID-19 funds were less likely to be readmitted within 90 days (aOR: 0.7, 95% CI: 0.5–0.8). Length of stay <2 days or ≥ 10 days were both risk factors for 90-day readmission compared to stays 4 to 5 days long (aOR: 2.0, 95% CI: 1.9–2.1, and aOR: 1.1, 95% CI: 1.0–1.1). To address the problem of competing risks of mortality and readmission and identify possible survivorship biases, we conducted additional analyses of 30-day mortality and readmission as a composite outcome (Supplementary 3). Receiver operating characteristic curves are displayed in Supplementary 4; area under the curve for each multivariable regression model are presented in the table legend (Figure 5).

4 Discussion

In this cohort of 91,007 adult patients with a COVID-19-associated hospitalization, over 21% were readmitted to the hospital

1 https://dshs.texas.gov/coronavirus

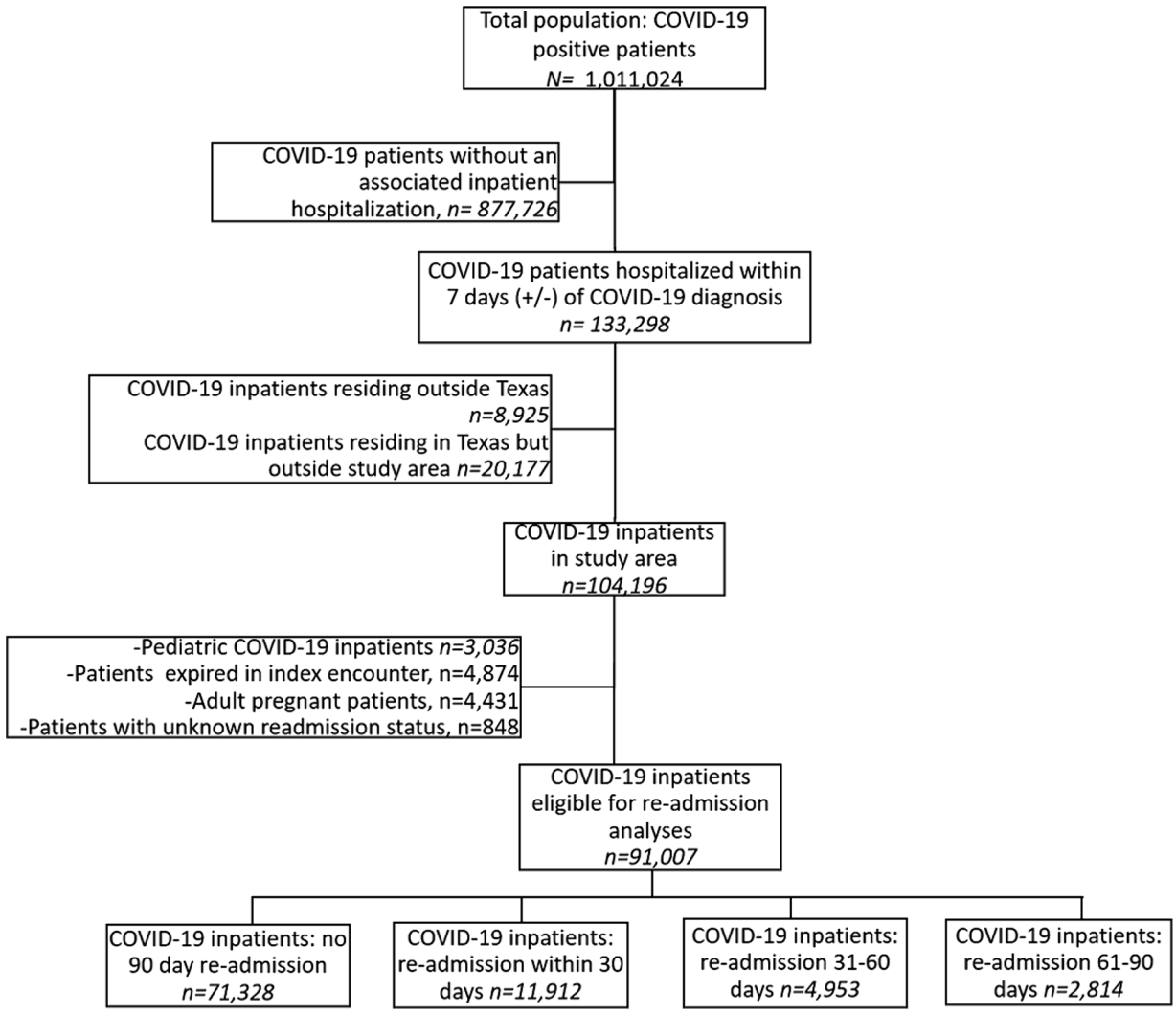

FIGURE 1
Study flowchart.

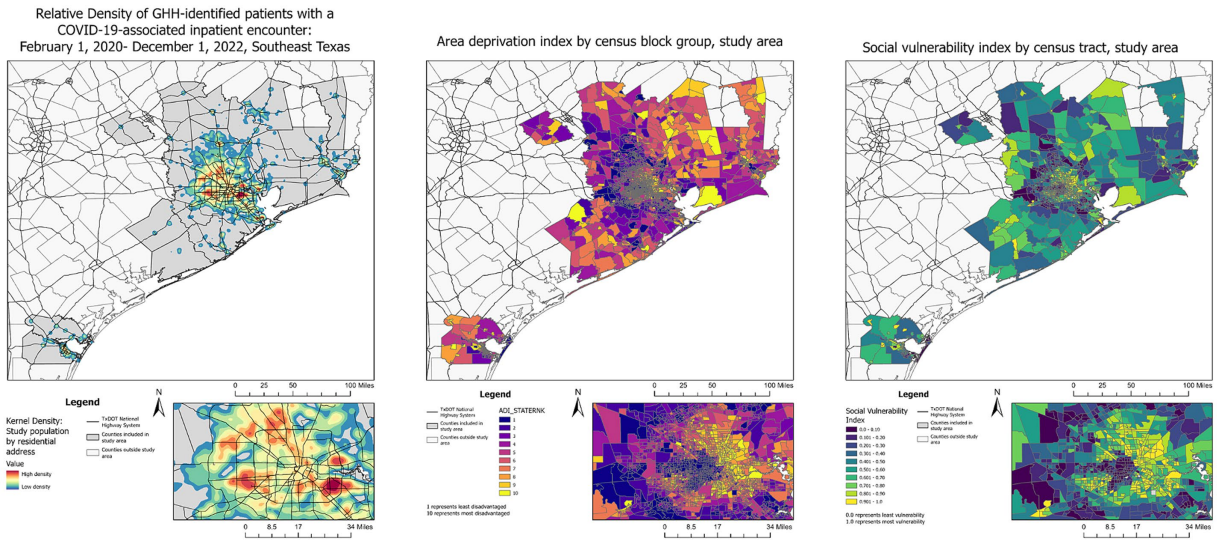

FIGURE 2
Relative density of GHH-identified patients with a COVID-19-associated inpatient encounter: February 1, 2020–December 1, 2022.

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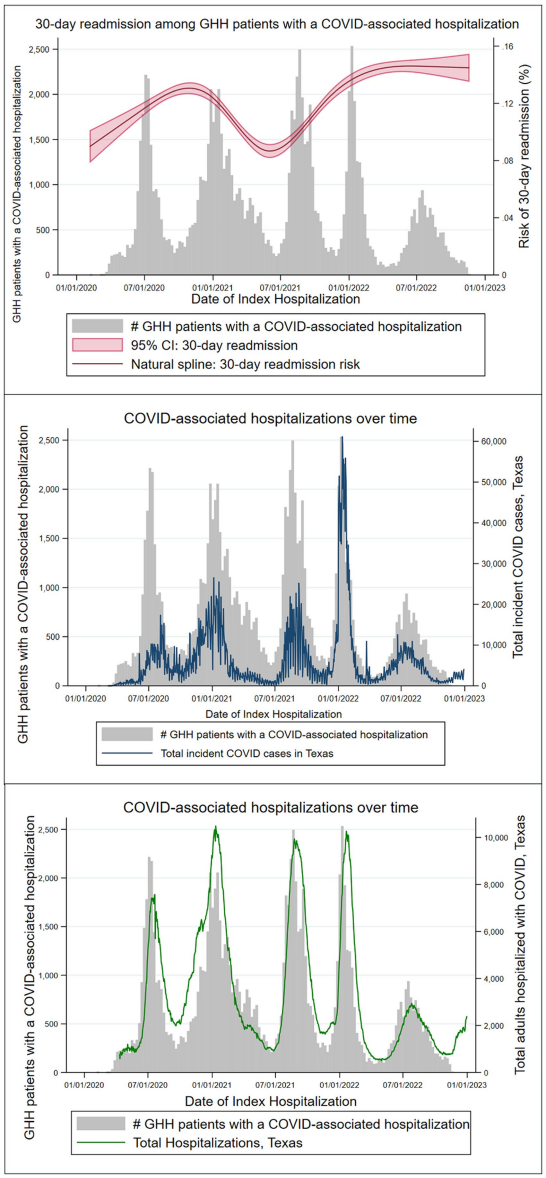

FIGURE 3
GHH patients with a COVID-19-associated hospitalization.

within 90 days of their initial visit ($n = 19,679$), and 13% were readmitted within the first 30 days ($n = 11,912$). While this study did not seek to determine the cause of admission or readmission, the relative frequencies of diagnoses such as pneumonia, acute respiratory failure, and hypoxia are characteristics of a population of patients with severe COVID-19. Total 30-day readmission risk varied significantly across time points, falling during the period of July 2021 through November 2021, when Delta was the dominant circulating variant and then peaking during the period of December 2021 to December 2022, as Omicron group variants became dominant.

The measured social determinants of health, including race/ethnicity, relative neighborhood disadvantage (ADI), and insurance status, were all associated with readmission risk. Non-Hispanic Black patients were more likely to be readmitted at 30, 60, and 90 days, while Hispanic patients were less likely to be readmitted at all time points, compared to non-Hispanic White patients. However, when mortality

TABLE 1 Characteristics of GHH patients with a COVID-19-associated inpatient hospitalization.

	Total
Characteristics	*N* = 104,196
Demographics	*n (%)*
Age (years)	
under 18	3,036 (2.9%)
18–29	9,945 (9.5%)
30–49	26,703 (25.6%)
50–69	36,521 (35.1%)
70+	27,991 (26.9%)
Sex	
Male	49,492 (47.5%)
Female, non-pregnant	50,027 (48.0%)
Pregnant female	4,534 (4.4%)
Unknown	143 (0.1%)
Race/Ethnicity	
Non-Hispanic White	46,071 (44.2%)
Non-Hispanic Black	19,664 (18.9%)
Non-Hispanic Asian	2,927 (2.8%)
Non-Hispanic American Indian/Alaska Native	371 (0.4%)
Non-Hispanic Native Hawaiian/ Pacific Islander	190 (0.2%)
Non-Hispanic Other	6,620 (6.4%)
Hispanic	27,040 (26.0%)
Missing	1,313 (1.1%)
Social vulnerability index	
1 (Least Vulnerable)	7,102 (6.8%)
2	8,327 (8.0%)
3	8,469 (8.1%)
4	10,364 (10.0%)
5	10,645 (10.2%)
6	9,513 (9.1%)
7	12,025 (11.5%)
8	13,057 (12.5%)
9	13,464 (12.9%)
10 (Most vulnerable)	11,146 (10.7%)
Missing	84 (0.1%)
Area deprivation index	
1 (Least disadvantaged)	7,523 (7.2%)
2	9,638 (9.2%)
3	10,499 (10.1%)
4	11,917 (11.4%)
5	11,690 (11.2%)
6	13,436 (12.9%)
7	12,600 (12.1%)
8	10,774 (10.3%)
9	9,450 (9.1%)

(Continued)

TABLE 1 (Continued)

Characteristics	Total N = 104,196
Demographics	*n (%)*
10 (Most disadvantaged)	5,952 (5.7%)
Missing	717 (0.7%)
Charlson Comorbidity Index, median (IQR)	1 (0–2)
Chronic pulmonary disease	11,936 (11.5%)
Cerebrovascular disease	3,729 (3.6%)
Dementia	4,255 (4.1%)
Diabetes without complications	22,160 (21.3%)
Diabetes with complications	5,239 (5.0%)
Congestive heart failure	10,111 (9.7%)
Hemiplegia	971 (0.9%)
Myocardial infarction history	4,899 (4.7%)
Mild liver disease	3,095 (3.0%)
Moderate to severe liver disease	805 (0.8%)
Mild to moderate renal disease	7,134 (6.8%)
Severe renal disease	4,332 (4.2%)
Peptic ulcer disease	608 (0.6%)
Peripheral vascular disease	3,011 (2.9%)
Rheumatic disease	1,387 (1.3%)
HIV infection	555 (0.5%)
HIV infection with complications	471 (0.5%)
Malignant neoplasm	5,072 (4.9%)
Solid tumor	849 (0.8%)
Date of index hospitalization	
February 1, 2020- September 15, 2020	18,347 (17.6%)
September 16, 2020- June 20, 2021	34,919 (33.5%)
June 21, 2021- November 20, 2021	23,319 (22.4%)
November 21, 2021- April 15, 2022	15,267 (14.6%)
April 16, 2022- November 30, 2022	12,344 (11.9%)
Length of stay (days), median (IQR)	4 (2–9)
Financial class (index hospitalization)	
Private insurance	21,729 (20.9%)
Medicare/Medicaid alone	25,542 (24.5%)
Medicare/Medicaid plus private insurance	23,533 (22.6%)
Self-Pay/Safety net	2,041 (2.0%)
Military or government	843 (0.8%)
COVID pay	1,479 (1.4%)
Other	436 (0.4%)
Unknown*	28,593 (27.4%)
Discharge disposition	
Home	47,318 (45.4%)
Transfer (facility)	653 (0.6%)
Expired	4,875 (4.7%)
Transfer (SNF/Nursing home)	3,467 (3.3%)
Transfer (Rehab/LTAC)	2,573 (2.5%)
Against medical advice	1,025 (1.0%)
Hospice	1,376 (1.3%)
Still patient	743 (0.7%)
Other	1,425 (1.4%)
Unknown	40,741 (39.1%)

*Unknown indicates insurance information was not reported, includes uninsured patients. NH, Non-Hispanic; IQR, Interquartile range; SNF, Skilled nursing facility; LTAC, long-term acute care.

and readmission were considered as a composite outcome, Hispanic patients were not at greater risk, which may indicate a survivorship bias among certain subgroups. Likewise, increasing neighborhood disadvantage displayed a clear dose–response relationship to readmission in age-adjusted time-to-event analysis and logistic regression models. While communities of color bore disproportionate COVID-19-related mortality early in the pandemic (32, 33), the demographic proportions of COVID-19 cases, hospitalizations, and deaths have varied widely across each wave of the pandemic (1). The observed associations between race, ethnicity, socioeconomic status, and poor health outcomes are unlikely biological in origin. As COVID-19 transitions into an endemic condition, further research is needed to elucidate the specific barriers to accessing quality, timely care for COVID-19 and to develop interventions to curb preventable readmissions within vulnerable communities.

The readmission rate demonstrated in this study is high relative to the extant literature, especially given the proportion of patients under 50 years of age (34%; 31,267/91,007) and patients with a zero score on the Charlson Comorbidity Index (47%; 42,413/91,007) (34, 35). This gap could be explained by the capacity of the health information exchange to identify encounters across institutions and hospital systems: 26% of readmission encounters were to a different hospital or hospital system from the index hospitalization encounter. Increasing length of stay is often used as a proxy of disease severity at the index encounter (36, 37), but in this study, the length of stay of the index encounter displayed a parabolic effect: readmission risk was highest in patients whose index encounter was either less than 2 days or 10 or more days. These results suggest some patients may have either been discharged prematurely or decompensated quickly after transitioning to outpatient care, possibly due to overburdened hospital and primary care facilities during epidemic peaks.

The breadth and depth of the HIE data facilitated accurate patient tracking across time and between facilities and enabled investigators to correctly determine readmission status, regardless of whether patients returned to the same hospital. Our analyses are further strengthened by the addition of neighborhood-level measures of disadvantage and encounter-specific insurance information. As we utilized neighborhood-level socioeconomic measures that have been normalized across United States national and state populations, our findings will be valuable in comparative analyses across regions.

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TABLE 2 Univariate logistic regression: readmission among patients with a COVID-19-associated inpatient hospitalization.

Univariate logistic regression, *N* = 91,007	30 day readmission		60 day readmission		90 day readmission	
Events	*n* = 11,912		*n* = 16,865		*n* = 19,679	
	OR (95% CI)	*p value*	*OR (95% CI)*	*p value*	*OR (95% CI)*	*p value*
Age (years)						
18–29	REF		REF		REF	
30–49	0.99 (0.91–1.08)	0.874	0.97 (0.90–1.05)	0.472	0.97 (0.91–1.04)	0.405
50–69	1.33 (1.23–1.44)	<0.001	1.35 (1.26–1.45)	<0.001	1.33 (1.25–1.42)	<0.001
70+	1.69 (1.55–1.83)	<0.001	1.80 (1.68–1.94)	<0.001	1.82 (1.70–1.94)	<0.001
Sex						
Male	REF		REF		REF	
Female, non-pregnant	1.02 (1.98–1.06)	0.358	1.06 (1.03–1.10)	0.001	1.09 (1.05–1.12)	<0.001
Race/Ethnicity						
Non-Hispanic White	REF		REF		REF	
Non-Hispanic Black	1.06 (1.00–1.11)	0.034	1.08 (1.04–1.13)	<0.001	1.08 (1.04–1.12)	<0.001
Non-Hispanic Asian	0.83 (0.74–0.94)	0.004	0.77 (0.69–0.86)	<0.001	0.73 (0.66–0.81)	<0.001
Non-Hispanic American Indian/Alaska Native	0.94 (0.68–1.29)	0.702	0.83 (0.62–1.10)	0.2	0.86 (0.66–1.12)	0.263
Non-Hispanic Native Hawaiian/ Pacific Islander	1.07 (0.69–1.65)	0.761	1.06 (0.73–1.55)	0.752	0.97 (0.67–1.40)	0.868
Non-Hispanic Other	0.75 (0.69–0.82)	<0.001	0.70 (0.65–0.76)	<0.001	0.69 (0.64–0.75)	<0.001
Hispanic	0.77 (0.73–0.81)	<0.001	0.72 (0.69–0.75)	<0.001	0.70 (0.67–0.73)	<0.001
Missing	0.15 (0.08–0.30)	<0.001	0.12 (0.07–0.22)	<0.001	0.14 (0.08–0.23)	<0.001
Social vulnerability index						
Quintile 1 (Least Vulnerable)	REF		REF		REF	
Quintile 2	1.07 (1.00–1.14)	0.063	1.07 (1.01–1.14)	0.024	1.08 (1.02–1.15)	0.005
Quintile 3	1.10 (1.03–1.18)	0.006	1.08 (1.02–1.14)	0.01	1.07 (1.01–1.13)	0.014
Quintile 4	1.23 (1.16–1.32)	<0.001	1.21 (1.14–1.28)	<0.001	1.22 (1.16–1.29)	<0.001
Quintile 5 (Most Vulnerable)	1.17 (1.10–1.25)	<0.001	1.14 (1.08–1.20)	<0.001	1.15 (1.09–1.21)	<0.001
Area deprivation index						
Quintile 1 (Least Disadvantaged)	REF		REF		REF	
Quintile 2	1.01 (0.95–1.08)	0.737	1.06 (1.00–1.12)	0.048	1.07 (1.02–1.13)	0.008
Quintile 3	1.10 (1.03–1.17)	0.004	1.13 (1.07–1.19)	<0.001	1.13 (1.07–1.19)	<0.001
Quintile 4	1.15 (1.08–1.22)	<0.001	1.17 (1.10–1.23)	<0.001	1.19 (1.13–1.25)	<0.001
Quintile 5 (Most Disadvantaged)	1.21 (1.13–1.30)	<0.001	1.23 (1.16–1.31)	<0.001	1.26 (1.19–1.33)	<0.001
Charlson Comorbidity Index	1.20 (1.19–1.21)	<0.001	1.24 (1.23–1.25)	<0.001	1.26 (1.25–1.27)	<0.001
Date of index hospitalization						
February 1, 2020-September 15, 2020	REF		REF		REF	
September 16, 2020- June 20, 2021	0.99 (0.94–1.05)	0.757	0.99 (0.94–1.04)	0.709	0.98 (0.93–1.02)	0.319
June 21, 2021- November 20, 2021	0.82 (0.77–0.87)	<0.001	0.82 (0.77–0.86)	<0.001	0.80 (0.76–0.84)	<0.001
November 21, 2021- April 15, 2022	1.37 (1.28–1.46)	<0.001	1.49 (1.40–1.57)	<0.001	1.54 (1.46–1.63)	<0.001
April 16, 2022- November 30, 2022	1.32 (1.23–1.42)	<0.001	1.48 (1.40–1.58)	<0.001	1.43 (1.35–1.52)	<0.001
Length of stay (index hospitalization)						
<2 days	2.05 (1.93–2.18)	<0.001	1.86 (1.76–1.96)	<0.001	1.74 (1.66–1.83)	<0.001
2–3 days	1.18 (1.11–1.26)	<0.001	1.10 (1.04–1.16)	0.001	1.07 (1.02–1.13)	0.007
4–5 days	REF		REF		REF	
6–7 days	1.03 (0.95–1.11)	0.487	1.07 (1.00–1.14)	0.039	1.08 (1.01–1.14)	0.016

(Continued)

TABLE 2 (Continued)

Univariate logistic regression, *N* = 91,007	30 day readmission		60 day readmission		90 day readmission	
Events	*n* = 11,912		*n* = 16,865		*n* = 19,679	
	OR (95% CI)	*p value*	*OR (95% CI)*	*p value*	*OR (95% CI)*	*p value*
8–9 days	1.18 (1.08–1.29)	<0.001	1.19 (1.10–1.28)	<0.001	1.16 (1.08–1.25)	<0.001
10+ days	1.23 (1.15–1.31)	<0.001	1.32 (1.25–1.39)	<0.001	1.28 (1.22–1.35)	<0.001
Financial class (index hospitalization)						
Private insurance	REF		REF		REF	
Medicare/Medicaid alone	1.61 (1.52–1.71)	<0.001	1.70 (1.62–1.79)	<0.001	1.76 (1.68–1.85)	<0.001
Medicare/Medicaid plus private insurance	1.39 (1.31–1.48)	<0.001	1.44 (1.37–1.52)	<0.001	1.47 (1.40–1.55)	<0.001
Self-Pay/Safety net	1.01 (0.86–1.18)	0.903	0.96 (0.84–1.11)	0.6	1.01 (0.88–1.14)	0.934
Military or government	1.12 (0.89–1.41)	0.35	1.23 (1.01–1.49)	0.036	1.23 (1.02–1.47)	0.029
COVID pay	0.69 (0.56–0.85)	0.001	0.52 (0.42–0.63)	<0.001	0.46 (0.38–0.56)	<0.001
Other	0.99 (0.70–1.39)	0.943	1.04 (0.78–1.39)	0.772	1.00 (0.76–1.32)	0.985
Unknown	1.37 (1.29–1.45)	<0.001	1.40 (1.33–1.47)	<0.001	1.41 (1.34–1.47)	<0.001

Children under 18, pregnant patients, and patients who expired at their index hospitalization were excluded from readmission analyses.
NH, Non-Hispanic; OR, odds ratio; CI, confidence interval.

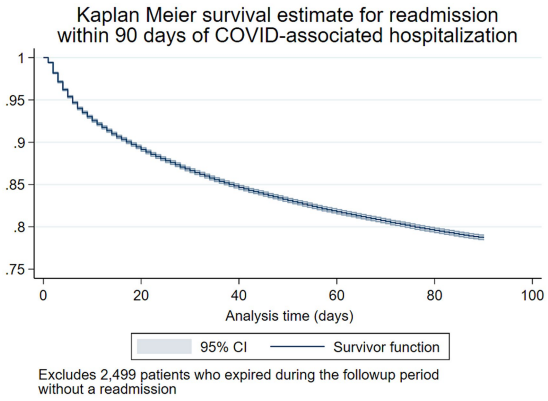

FIGURE 4
Kaplan–Meier survival estimate for 90-day readmission following COVID-19-associated hospitalization.

We chose to exclude pregnant patients from readmission analyses, as they likely represent a population of incidentally captured subclinical COVID-19 cases who are inherently at high risk for readmission. However, future studies are needed to investigate COVID-19-related maternal and fetal outcomes, as well as healthcare utilization among pregnant COVID-19 patients. The primary outcome was all-cause readmission; patients with readmissions due to causes unrelated to COVID-19 were likely included in this analysis. Additionally, due to a high number of index encounters with missing discharge disposition data, we analyzed readmission risk for living patients irrespective of discharge status, which may have resulted in the misclassification of some transfer encounters as readmissions. However, the proportion of transferred patients was relatively low (<7%) and consistent with other studies in the region (38, 39). As with all EHR-based research, events occurring outside of the healthcare system, including death outside of a hospital facility, are challenging to collect. While we were able to collect date of death from some patients who expired in the community, some patients who died after leaving their index encounter may have been classified as non-readmissions. Despite these limitations, our study adds to the growing body of evidence characterizing social determinants of COVID-19 healthcare utilization and disease outcomes throughout 3 years of the pandemic.

More than 20% of patients in this large, HIE-based cohort with a COVID-19-associated hospitalization were readmitted within 90 days of their index encounter, demonstrating the lasting impact of COVID-19 infection, especially among members of marginalized communities, and the increasing burden of COVID-19 morbidity on the healthcare system. Multiple investigations throughout the pandemic reported COVID-19 patients suffering substantial and long-lasting health changes, including decreased respiratory and cardiovascular function, ongoing symptoms requiring clinical intervention, and decreased quality of life in the months or even years following even apparently mild COVID-19 episodes (40–42). Our findings further illustrate the ongoing changes in patients' experiences of COVID-19 over 3 years of the pandemic and emphasize the need for transitional care for COVID-19 patients leaving the hospital. As growing numbers face the specter of long COVID, health authorities must ensure all patients have access to quality care, build trust in the health system among vulnerable populations, and ensure institutions have the capacity to provide care in the post-acute period.

Data availability statement

The datasets presented in this article are not readily available because clinical data cannot be shared publicly because of patient confidentiality concerns as imposed by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects. Requests to access de-identified data can be made to cphs@uth.tmc.edu which will be evaluated on a case by case basis in line with institutional policies. Requests to access the datasets should be directed to Committee for the Protection of Human Subjects: cphs@uth.tmc.edu.

TABLE 3 Multivariable logistic regression: readmission among patients with a COVID-19-associated inpatient hospitalization.

Multivariable logistic regression, *N* = 91,007	30 day readmission		60 day readmission		90 day readmission	
Events	*n* = 11,912		*N* = 16,865		*N* = 19,679	
	aOR (95% CI)	*p value*	*aOR (95% CI)*	*p value*	*aOR (95% CI)*	*p value*
Age (years)						
18–29	REF		REF		REF	
30–49	1.04 (0.95–1.13)	0.439	1.01 (0.93–1.09)	0.873	1.00 (0.93–1.08)	0.971
50–69	1.24 (1.14–1.35)	<0.001	1.20 (1.11–1.29)	<0.001	1.16 (1.08–1.25)	<0.001
70+	1.44 (1.32–1.57)	<0.001	1.42 (1.32–1.54)	<0.001	1.40 (1.30–1.50)	<0.001
Sex						
Male	REF		REF		REF	
Female, non-pregnant	0.99 (0.95–1.03)	0.609	1.03 (1.00–1.07)	0.071	1.06 (1.02–1.09)	0.001
Race/Ethnicity						
Non-Hispanic White	REF		REF		REF	
Non-Hispanic Black	1.06 (1.00–1.11)	0.047	1.08 (1.04–1.14)	<0.001	1.07 (1.02–1.12)	0.002
Non-Hispanic Asian	0.89 (0.79–1.01)	0.075	0.82 (0.73–0.92)	<0.001	0.77 (0.69–0.86)	<0.001
Non-Hispanic American Indian/Alaska Native	0.89 (0.65–1.24)	0.497	0.80 (0.60–1.07)	0.133	0.83 (0.63–1.10)	0.194
Non-Hispanic Native Hawaiian/ Pacific Islander	1.22 (0.79–1.90)	0.369	1.22 (0.83–1.80)	0.313	1.11 (0.76–1.62)	0.589
Non-Hispanic Other	0.85 (0.77–0.93)	<0.001	0.80 (0.74–0.86)	<0.001	0.79 (0.73–0.85)	<0.001
Hispanic	0.87 (0.83–0.92)	<0.001	0.82 (0.79–0.86)	<0.001	0.80 (0.77–0.84)	<0.001
Missing	0.15 (0.07–0.30)	<0.001	0.11 (0.06–0.21)	<0.001	0.13 (0.07–0.23)	<0.001
Area deprivation index						
Quintile 1 (Least Disadvantaged)	REF		REF		REF	
Quintile 2	1.02 (0.95–1.09)	0.612	1.06 (1.00–1.13)	0.035	1.08 (1.02–1.14)	0.005
Quintile 3	1.08 (1.01–1.15)	0.023	1.12 (1.05–1.18)	<0.001	1.12 (1.06–1.18)	<0.001
Quintile 4	1.12 (1.05–1.20)	0.001	1.15 (1.08–1.22)	<0.001	1.17 (1.11–1.24)	<0.001
Quintile 5 (Most Disadvantaged)	1.11 (1.04–1.20)	0.003	1.14 (1.07–1.21)	<0.001	1.16 (1.09–1.24)	<0.001
Charlson Comorbidity Index	1.19 (1.17–1.20)	<0.001	1.21 (1.20–1.22)	<0.001	1.23 (1.22–1.24)	<0.001
Date of index hospitalization						
February 1, 2020- September 15, 2020	REF		REF		REF	
September 16, 2020- June 20, 2021	0.88 (0.83–0.93)	<0.001	0.91 (0.86–0.96)	<0.001	0.91 (0.86–0.95)	<0.001
June 21, 2021- November 20, 2021	0.77 (0.72–0.83)	<0.001	0.79 (0.75–0.84)	<0.001	0.78 (0.74–0.82)	<0.001
November 21, 2021- April 15, 2022	1.09 (1.01–1.16)	0.018	1.19 (1.12–1.27)	<0.001	1.23 (1.16–1.30)	<0.001
April 16, 2022- November 30, 2022	1.03 (0.96–1.11)	0.391	1.17 (1.10–1.25)	<0.001	1.12 (1.05–1.19)	<0.001
Length of stay (index hospitalization)						
<2 days	2.31 (2.17–2.46)	<0.001	2.12 (2.00–2.24)	<0.001	1.98 (1.88–2.09)	<0.001
2–3 days	1.22 (1.14–1.30)	<0.001	1.14 (1.07–1.20)	<0.001	1.11 (1.05–1.17)	<0.001
4–5 days	REF		REF		REF	
6–7 days	0.98 (0.91–1.06)	0.616	1.03 (0.96–1.10)	0.439	1.06 (0.98–1.14)	0.346
8–9 days	1.08 (0.99–1.18)	0.101	1.09 (1.01–1.18)	0.031	1.06 (0.98–1.14)	0.152
10+ days	1.02 (0.96–1.09)	0.542	1.10 (1.04–1.16)	0.001	1.06 (1.00–1.11)	0.040
Financial class (index hospitalization)						
Private insurance	REF		REF		REF	
Medicare/Medicaid alone	1.31 (1.23–1.39)	<0.001	1.34 (1.27–1.42)	<0.001	1.38 (1.31–1.46)	<0.001
Medicare/Medicaid plus private insurance	1.19 (1.11–1.26)	<0.001	1.20 (1.14–1.27)	<0.001	1.22 (1.16–1.28)	<0.001
Self-Pay/Safety net	1.05 (0.90–1.24)	0.521	1.02 (0.89–1.18)	0.751	1.07 (0.93–1.22)	0.33
Military or government	0.99 (0.78–1.26)	0.951	1.05 (0.86–1.28)	0.637	1.05 (0.87–1.27)	0.621
COVID pay	0.94 (0.76–1.17)	0.578	0.73 (0.60–0.90)	0.003	0.65 (0.54–0.80)	<0.001
Other	0.98 (0.66–1.47)	0.942	1.08 (0.77–1.52)	0.639	1.07 (0.78–1.47)	0.691
Unknown	1.27 (1.19–1.34)	<0.001	1.28 (1.21–1.35)	<0.001	1.28 (1.22–1.35)	<0.001

Children under 18, pregnant patients, and patients who expired at their index hospitalization were excluded from readmission analyses. 30 day readmission model area under the receiver operating characteristic curve: 0.6539; 60 day readmission model area under the curve: 0.6648; 90 day readmission model area under the curve: 0.6692.
NH, Non-Hispanic; aOR, adjusted odds ratio; CI, confidence interval.

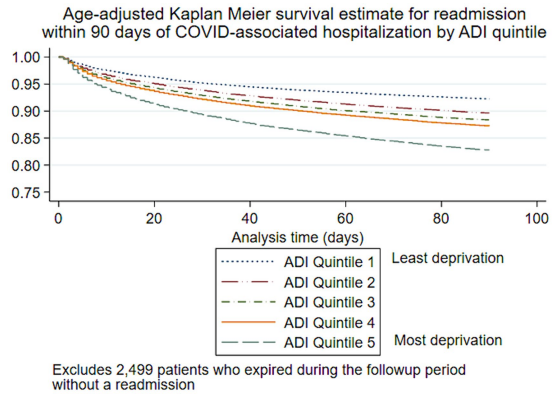

FIGURE 5
Age-adjusted Kaplan–Meier survival estimate for 90-day readmission following COVID-19-associated hospitalization by area deprivation index.

Ethics statement

The studies involving humans were approved by the Western Institutional Review Board as a quality improvement study and granted a waiver of informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MS: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. JM: Writing – review & editing, Validation, Data curation. MF: Writing – review & editing, Validation, Data curation. GT: Writing – review & editing, Validation, Data curation, Conceptualization. TC: Writing – review & editing, Supervision, Methodology, Formal analysis. RR: Writing – review & editing, Formal analysis. JH: Writing – review & editing, Supervision, Resources. EB: Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1352240/full#supplementary-material

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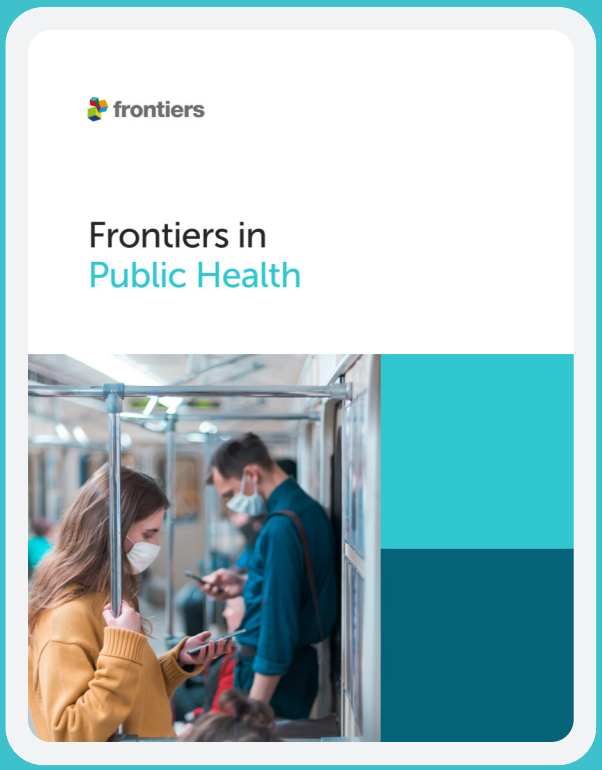

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