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Long COVID: pathogenesis, diagnosis and clinical management

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Published in
Frontiers in Medicine
Frontiers in Public Health

ISSN 1664-8714
ISBN 978-2-8325-6396-0
DOI 10.3389/978-2-8325-6396-0

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Long COVID: pathogenesis, diagnosis and clinical management

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Citation
Goldman, M., Mainous, A., Bao, S., eds. (2025). *Long COVID: pathogenesis, diagnosis and clinical management*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-6396-0

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frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 16 May 2025
DOI 10.3389/fmed.2025.1615692

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 21 April 2025
ACCEPTED 05 May 2025
PUBLISHED 16 May 2025

CITATION
Mainous AG III, Bao S and Goldman M (2025) Editorial: Long COVID: pathogenesis, diagnosis and clinical management. *Front. Med.* 12:1615692. doi: 10.3389/fmed.2025.1615692

Editorial: Long COVID: pathogenesis, diagnosis and clinical management

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KEYWORDS

COVID, Long COVID, clinical management, diagnosis, mortality

Editorial on the Research Topic
Long COVID: pathogenesis, diagnosis and clinical management

Five years have passed since Coronavirus disease 2019 (COVID-19) rapidly spread worldwide, causing the biggest public health crisis in 21st Century (1, 2). While acute severe damages caused by the SARS-CoV-2 virus COVID-19 were eventually controlled with vaccines, public health measures and surveillance systems, the long-term effects of the infection are yet to be fully understood. The medical community now has a new battle to confront: long COVID, also known as Post COVID Condition or Post Acute Sequelae of COVID-19. The public health impact of Long COVID is huge with millions of people affected and major economic and societal consequences. Indeed, Long COVID is estimated to affect more than 400 million people worldwide with the estimated prevalence of long COVID in the US adult population being 7.5% (3, 4). Long COVID has been linked to an increase in both hospitalizations and death from a variety of causes (5, 6). Less severe outcomes associated with long COVID are significant activity limitations and even increased work days missed due to illness (7, 8).

From a clinical standpoint, long COVID is not a homogeneous disease. It should be viewed as a multisystemic syndrome which persists for at least 3 months after acute COVID-19 (1, 2). It might cause a wide range of symptoms so that its differentiation from other conditions is very challenging, as further underlined in several articles of this series which provide additional insight into different aspects of Long COVID (9).

The influence of smoking and obesity on risk of hospitalization was addressed by Fernández-Pedruelo et al. In an analysis of medical records of a sample of patients diagnosed with COVID-19 in Spain, the results showed that patients with obesity had a significantly higher risk of post acute sequelae, namely memory disorders, from COVID-19. Importantly, smoking was not directly related as a long COVID complication. Neither of these factors was associated with an increased risk of hospitalization. This study points to the importance of different long COVID complications and factors that may increase the risk for one type of complication but not another.

The prevalence of long COVID and corresponding risk factors was investigated in several studies (Aldhawyan et al.; Saloma et al.). The value of these studies showed that long COVID is a world wide problem. As we gain more knowledge about long COVID

it is important to keep in mind that to appropriately address long COVID we need to adopt a global viewpoint. Saloma et al. provided new information on the impact of new variant, Theta, of SARS-CoV-2 on the prevalence of long COVID. Ruiyin et al. focused on long COVID from the Omicron variant. These studies highlight the influence of different SARS-CoV-2 variants in different parts of the world and their resulting long COVID. The need for long-term monitoring of long COVID is apparent as well as the impact on human health and the need for our health systems to adopt policy response strategies.

Similar to a need for a global view on prevalence of long COVID, several studies focused on the more extreme complication of long COVID, mortality (Grippo et al.; Won et al.). Studies from Italy and South Korea showed that long COVID complications can be very severe. Although this effect was shown in the US it is important to add these additional international studies to our body of knowledge (5). Strategies to identify the population at risk of severe long-term consequences of SARS-CoV-2 infection and interventions aimed at reducing this risk must be developed.

Several review articles were also included in this Research Topic (Ranque and Cogan; Dietz and Brondstater). These reviews bring to the forefront current strategies for managing and preventing long COVID. A particular value of these reviews is that they show what we know and what we don't know. Further, they point to promising new strategies and underutilized modalities.

A study that focused on a much different aspect of our toolbox for long COVID was the study by Sperl et al.. This study on long COVID focused on the psychometrics involved in the translation and adaption of the COVID-19 Yorkshire Rehabilitation Scale for a German patient population. Activity limitations and complications like dyspnea are not uncommon in long COVID. As might be expected there were some modifications both in terms of translation and cultural references needed to make the English version work for German populations. This study reinforces that long COVID is a global problem and we need to pull information learned in one country to help other countries more successfully deal with the problem.

Finally, this Research Topic of articles included a series of case reports on the commonly reported long COVID complication of fatigue (Morelli-Zaher et al.). Patients with excessive daytime sleepiness was assessed for objective central hypersomnia. This series of case reports shows that methylphenidate was a promising treatment for these patients. This leads to the conclusion that the long COVID complication of central hypersomnia needs to be included in the physicians' differential diagnosis because it may be a treatable condition.

In conclusion, this group of articles points to the global impact of long COVID as well as the varied complications from the condition. As the focus on COVID-19 wanes in the popular press, it is incumbent upon us all to ensure that long COVID is handled as a major public health priority requiring additional research on its pathogenesis and treatment.

Author contributions

AM: Writing – review & editing, Writing – original draft. SB: Writing – review & editing. MG: Writing – review & editing.

Conflict of interest

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

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

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Case Report
PUBLISHED 14 February 2024
DOI 10.3389/fneur.2024.1349486

OPEN ACCESS

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RECEIVED 04 December 2023
ACCEPTED 29 January 2024
PUBLISHED 14 February 2024

CITATION
Morelli-Zaher C, Vremaroiu-Coman A, Coquoz N, Genecand L, Altarelli M, Binkova A, Frésard I, Bridevaux P-O and Gex G (2024) Post-COVID central hypersomnia, a treatable trait in long COVID: 4 case reports. *Front. Neurol.* 15:1349486. doi: 10.3389/fneur.2024.1349486

Post-COVID central hypersomnia, a treatable trait in long COVID: 4 case reports

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Introduction: Fatigue is the most commonly reported post-COVID symptom. A minority of patients also report excessive daytime sleepiness, which could be a target for treatment.

Methods: Among 530 patients with a post-COVID condition, those with excessive daytime sleepiness were systematically assessed for objective central hypersomnia, with exclusion of all cases not clearly attributable to SARS-CoV-2 infection.

Results: Four cases of post-COVID central hypersomnia were identified, three fulfilling the criteria of the 3rd International Classification of Sleep Disorders for idiopathic hypersomnia, and one for type II narcolepsy. We report here their clinical history, sleep examination data and treatment, with a favorable response to methylphenidate in three cases and spontaneous resolution in one case.

Conclusion: We highlight the importance of identifying cases of post-COVID central hypersomnia, as it may be a treatable trait of a post-COVID condition.

KEYWORDS

idiopathic hypersomnia, central hypersomnia, narcolepsy, long COVID, post-COVID condition, treatment, methylphenidate, SARS-CoV-2

1 Introduction

Fatigue is the most commonly reported symptom of post-COVID condition (PCC) and affects more than 40% of all patients, with repercussions in work and daily life several months after infection (1, 2). With several 100 million people infected worldwide, post-COVID fatigue has a significant impact on physical and psychological health of many individuals with important social and economic consequences. Unfortunately, there is still no pharmaceutical treatment for this condition. Post-COVID central hypersomnia is rarely reported and only few data on sleep studies are available (3). In contrast to fatigue, treatments are available for central hypersomnia, in particular when they meet the diagnostic criteria for idiopathic hypersomnia and narcolepsy. We present the clinical history and detailed sleep studies of four patients with proven central hypersomnia triggered by SARS-CoV-2 infection (three idiopathic hypersomnia and one with type II narcolepsy), including the evolution under medication. We then discuss the question of whether SARS-CoV-2 could be added to the viruses possibly involved in the still unclear pathogenesis of idiopathic hypersomnia.

2 Methods

From May 2021 to January 2023, 530 patients were referred for evaluation to our post-COVID clinic, which covers a population of around 300,000 inhabitants. Patients complaining of excessive sleepiness were first assessed and treated for a psychiatric disorder, sleep insufficiency, or sedative medications. If sleepiness persisted, they were offered a sleep study, consisting of a polygraphy if there was a high probability of sleep apnea syndrome, if not a polysomnography (PSG). If the mean daily total sleep time estimated by sleep diary was more than 11 h, a 48 h sleep laboratory assessment was proposed, consisting of a 24 h *ad libitum* sleep PSG, a second night PSG, and a multiple sleep latency test (MSLT). If the total sleep time was <11 h, but the daytime sleepiness was judged severe enough to evoke narcolepsy, we performed a PSG and a MSLT.

By systematically following this diagnostic process (Figure 1), we identified eight patients with objective central hypersomnia. In order to select only cases formally confirmed as due to SARS-CoV-2 infection, we excluded four cases due to potential confounding factors (two sleep apnea syndromes, one reclassified as a depressive disorder, and one with a questionable temporal relationship between symptom onset and SARS-CoV-2 infection). The remaining four patients linked the onset of sleepiness to their SARS-CoV-2 infection, which were all confirmed by polymerase chain reaction testing and treated in an ambulatory care unit. Of these, three met the International Classification of Sleep Disorders Third Edition (ICSD-3) criteria for idiopathic hypersomnia and one for type II narcolepsy. Drug, psychoactive medication, sleep insufficiency, a psychiatric disorder, and other causes of sleepiness were ruled out by a thorough anamnesis, physical assessment, actigraphy, biological workup, PSG, and brain nuclear magnetic resonance imaging. All patients gave informed and written consent to the present publication.

3 Case descriptions

3.1 Patient 1

Patient 1 was a previously healthy 18-year-old male student who presented a SARS-CoV-2 infection in November 2020. Before COVID-19, his usual sleep duration was about 8–9 h per day. After the infection, he experienced excessive daytime sleepiness and a significant increase in his sleep requirements, up to 12–14 h per day. Five months later, he was still unable to return to school due to difficulty wakening up for early morning classes, as well as falling asleep in class. The 48 h sleep studies and tests performed 10 months after the initial SARS-CoV-2 infection are reported in Table 1. The diagnosis of idiopathic hypersomnia was made according to ICSD-3 criteria. A sleep onset rapid eye movement period (SOREMP) was observed at the 9 a.m. nap, which is common at this age.

As the attentional deficit related to sleepiness had a major impact on the patient, he was prescribed methylphenidate 40 mg/d, which was effective on sleepiness, fatigue, and concentration in class. His sleep requirements decreased back to 8–9 h/day and he was able to return to school with complete resolution of drowsiness, lateness and absences. A trial to stop methylphenidate failed after 4 months (13 months after his infection) with a resurgence of hypersomnia (sleep duration more than 11 h per day). Three years after the infection, he continues taking this medication.

3.2 Patient 2

Patient 2 was a previously healthy 38-year-old female who suffered from a SARS-CoV-2 infection in October 2020. Before COVID-19, her usual sleep duration was about 9 h per day. Approximately 4–6 weeks after infection, she developed excessive daytime sleepiness and increased sleep requirements, resulting in absences from work. Eight months after the infection, she still had major difficulties concentrating and an irresistible need for afternoon naps. An actigraphy documented a mean nocturnal sleep time of over 11 h per night on weekdays and about 14 h per night on weekends. Due to the major disability related to sleepiness and actigraphy data, we started methylphenidate at that point. With 20 mg/d, she was able to return to work.

A 48 h sleep laboratory workup was performed about 1 month later, i.e., 9 months after infection. She stopped methylphenidate 5 days before the test to enable interpretation. Results are shown in Table 1. The diagnosis of idiopathic hypersomnia was made according to ICSD-3 criteria on the basis of the symptoms and the aforementioned actigraphy. The borderline MSLT results (mean sleep latency 8.1 min) were attributed to the finally favorable evolution. Indeed, we were able to taper the methylphenidate to 10 mg/d just after the sleep tests and stop it gradually after 2 months with no recurrence of hypersomnia.

3.3 Patient 3

Patient 3 was a 54-year-old male treated for hypertension and sleep apnea syndrome for several years who was referred to our clinic by his general practitioner. A SARS-CoV-2 pneumonia was diagnosed in May 2021, but did not require hospitalization. Two months after infection, he was suffering from dyspnea and irrepressible bouts of sleepiness leading to daytime naps. He reported an increase in nocturnal sleep duration from 6 to 7 h per day before SARS-CoV-2 infection to 9–10 h per day afterwards, in addition to one or two naps during the day. Naps were restorative before the rapid reappearance of sleepiness. He also described dizziness, memory, and attention disorders and irritability. He reported no sleep hallucination, sleep paralysis, or cataplexy. There was no evidence of narcolepsy before COVID-19. Continuous positive airway pressure (CPAP) adherence was good (6 h 45

Abbreviations: BMI, body mass index; CPAP, continuous positive airway pressure; HADS, hospital anxiety and depression scale; ICSD-3, international classification of sleep disorders, third cersion; MLST, multiple sleep latency test; ODI, oxygen desaturation index; PLM, periodic limb movement; PSG, polysomnography; RERA, respiratory Effort related arousal; SF-36, 36-item short form health survey; SOREMP, sleep onset REM period; TST, total sleep time; WASO, wakefulness after sleep onset.

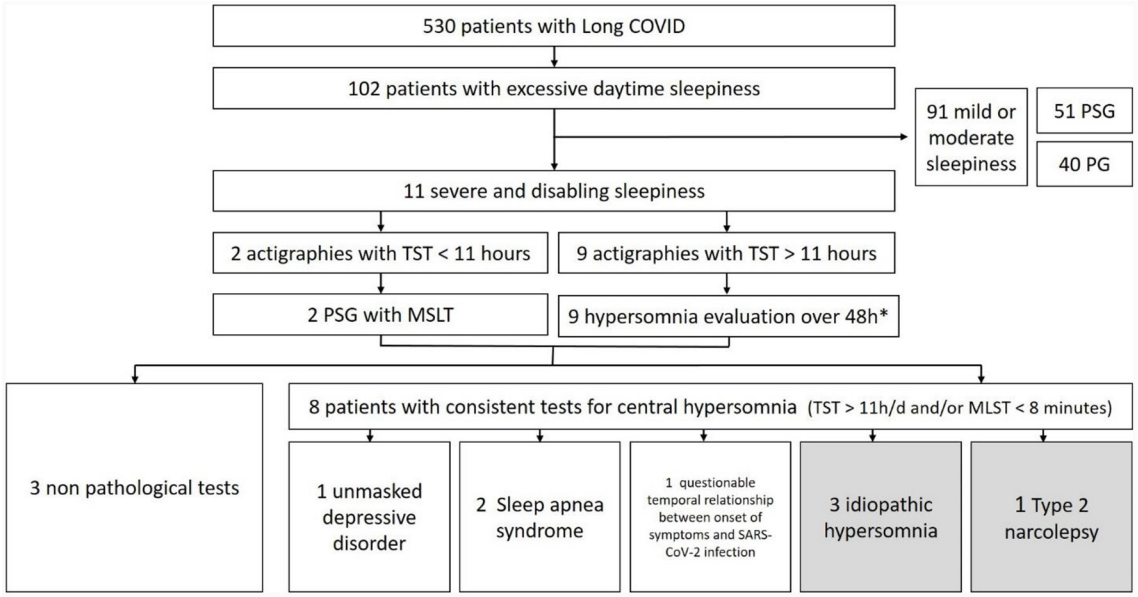

FIGURE 1
Flow chart of diagnostic trajectories. PSG, polysomnography; PG, polygraphy; TST, total sleep time; MSLT, multiple sleep latency test. *See text for details.

min/night before infection) and effective (no residual fatigue; apnea-hypopnea index, 3.4/h according to built-in software).

The work-up included a cardiopulmonary exercise test that found dysfunctional breathing with hyperventilation. A dedicated respiratory rehabilitation program improved dyspnea. However, attacks of daytime sleepiness persisted and led to a 48 h sleep laboratory workup 17 months after infection (Table 1). These examinations confirmed the effective treatment of sleep apnea syndrome by CPAP. The MLST found a mean sleep latency of 7 min 42 s with three sleep onset rapid eye movement periods, leading to the diagnosis of type II narcolepsy. We proposed modafinil to the patient, which he declined as he felt a slow trend toward the spontaneous improvement of symptoms and was reluctant take any psychotropic medication. He confirmed an improvement 3 months later (20 months after SARS-CoV-2 infection) and we stopped the follow-up.

3.4 Patient 4

Patient 4 was an 18-year-old female student with a recent history of infectious mononucleosis in July 2020, with full remission after 1 month. Following her first SARS-CoV-2 infection in November 2020, she gradually developed fatigue with excessive daytime sleepiness and increased sleep requirements. She barely managed to maintain her studies, but sleepiness gradually improved over the year 2021. In January 2022, she presented with a second SARS-CoV-2 infection, which led to a significant recurrence of hypersomnia, including an irrepressible need to sleep in front of her schoolmates. The results of the 48 h sleep laboratory assessment performed in November 2022 are reported in Table 1. We retained the diagnosis of idiopathic hypersomnia according to ICSD-3 criteria. We prescribed methylphenidate 10 mg/three times daily, which is the first-line reimbursed treatment in Switzerland. She takes it only on days when her work requires more concentration (about 3 times/week), with a good effect on sleepiness.

4 Discussion

Among 530 patients living with PCC, we identified four cases of objective central hypersomnia. Of these, three met ICSD-3 criteria for idiopathic hypersomnia and one for type II narcolepsy, whereas these pathologies are excessively rare in the general population. The clear temporal link between the onset of symptoms and SARS-CoV-2 infection, together with the exclusion of other causes of central hypersomnia, strongly suggests a causal link between infection and central hypersomnia in these four cases, which could be named "post-COVID central hypersomnia."

We prescribed methylphenidate in three of the four patients described, which had a very positive effect on excessive daytime sleepiness and daytime functioning. Methylphenidate is generally recommended as a second-line treatment in idiopathic hypersomnia, modafinil being the first line. However, in Switzerland, reimbursement of modafinil is only possible after failure of methylphenidate. Furthermore, as methylphenidate not only has a dopaminergic, but also an adrenergic effect, we postulated that its effect would be broader than modafinil on the cognitive dysfunctions associated with Long COVID. Indeed, these dysfunctions go beyond the wakefulness regulation system and also concern the functions of attention, working memory and cognitive flexibility, which are improved by increased levels of norepinephrine.

The prevalence of central hypersomnia in PCC is probably underestimated in our cohort as we did not report cases of

TABLE 1 Clinical data and results of sleep studies and sleep latency tests.

	Case 1	Case 2	Case 3	Case 4
Gender and age (years)	M, 18	F, 38	M, 54	F, 18
BMI, kg/m^2	19.0	23.7	22.6	20.3
Time from acute COVID, weeks	45	40	76	108
Epworth sleepiness scale	21	11	11	15
HADS	11	17	11	10
SF-36	95	92	106	102
Sleep onset latency, min	3.8	9.7	0.5	6.9
WASO, min	38.1	13.5	93.5	15
Sleep efficiency, %	92	98	82	98
Slow-wave sleep, %	22	22	21	19
REM sleep, %	14	27	28	17
Micro-arousals index,/h	20	17	17	8
AHI/h	0.6	1.8	4.7	0.5
RERA/h	2.2	2.8	4.7	0.7
ODI,/h	0.1	1.2	3.7	0.1
Mean SpO2, %	95.0	94.9	95.5	95.3
PLM index/h	1	9	4	0
TST over 24 h *ad libitum* sleep, h:min	12:26	10:28	NA	14:32
Mean sleep latency on 5 naps-MSLT, min	7.2	8.1	7.7	8.2
SOREMP, *n*	1	0	3	0

Polysomnography results refer to the first night of the 48 h workup. M, male; F, female; BMI, body mass index; HADS, hospital anxiety and depression scale; SF-36, 36-item short form health survey; WASO, wakefulness after sleep onset; AHI, apnea hypopnea index; RERA, respiratory effort-related arousal; ODI, oxygen desaturation index; PLM, periodic limb movement; NA, not available; TST, total sleep time; MLST, multiple sleep latency test; SOREMP, sleep onset rapid eye movement period.

hypersomnia with a more rapid evolution, which resolved before the somnological assessment could be carried out. In addition, we excluded four patients with a potentially questionable link to the infection, even though these patients were profoundly convinced of the responsibility of their viral infection. Regarding the prevalence of post-COVID central hypersomnia in the general population, a minimal prevalence of 1.3/100,000 inhabitants could be suggested as the population covered by our clinic is around 300,000, but it should be emphasized that our study design is not adequate for determining a prevalence, which is obviously subject to numerous biases.

Central hypersomnia may be one of the many neurological impairments described in PCC, whose pathophysiology remains unclear (1, 3). Several hypotheses have been proposed, including neurological damage, immune system dysregulation, autonomic nervous system dysfunction and a persistent viral presence (4). These mechanisms could explain a prolonged dysfunction of brainstem nuclei involved in sleep-wakefulness regulation (5). Although no routinely available paraclinical test can currently confirm the diagnosis of PCC, certain non-specific neuroimaging changes have been reported (6).

According to our observations, SARS-CoV-2 could be added to the viruses possibly involved in the still unclear pathogenesis of the so-called "idiopathic" hypersomnia, such as Epstein Barr virus and SARS-CoV-1 (7, 8). Moldofsky and Patcar (7) showed an association between myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and SARS-CoV-1 infection, with five of 22 patients showing excessive sleepiness confirmed by MLST. To date, two cases of narcolepsy triggered by SARS-CoV-2 infection have also been described (9, 10). Viral components used in vaccines may also trigger central hypersomnia, similar to the increased risk of narcolepsy shown with H1N1 vaccination (10), or the reported recurrence of severe hypersomnia after a SARS-CoV-2 vaccine in a patient previously treated for post-Epstein-Barr virus hypersomnia (11). Similarly, SARS-CoV-2 infection triggered an exacerbation of Kleine-Levin syndrome in 2 cases (12, 13). These data suggest a potential common immunological action of different viruses on the function of brainstem nuclei involved in sleep-wakefulness regulation.

Retornaz et al. (14) found high clinical and biological similarities between long COVID and ME/CFS. However, central hypersomnia is a clearly distinct entity as excessive sleepiness is not a classical symptom of ME/CFS. This was illustrated by Neu et al. (15) who reported MSLT in 16 ME/CFS patients, with a MSLT within the norm.

Our study has some limitations. First, the causal link between SARS-CoV2 infection and hypersomnia in our four cases is not formally proven. A causal link is certainly strongly suggested by the clear temporal relationship and the rigorous exclusion of other causes of hypersomnia, but there is currently no test that can formally attribute a symptom to PCC. Second, the prevalence of post-COVID central hypersomnia cannot be precisely estimated by our data as discussed above. Third, we only have one sleep laboratory assessment per case that was performed quite late after the onset of symptoms, which does not allow to describe the objective evolution of hypersomnia over time. Finally, the small number of cases limits the conclusions that can be drawn about the treatment and evolution of this condition. Although there was a clear improvement in sleepiness in two of four cases at around 12 and 20 months from symptom onset, this is insufficient to draw any general conclusions about the course of post-COVID central hypersomnia. Further research is therefore still needed in this area.

5 Conclusion

Fatigue is the most frequent symptom in patients with a PCC, yet without any effective treatment. We report four cases of post-COVID central hypersomnia, with a favorable response to methylphenidate in three patients. Therefore, it is important to identify central hypersomnia in these patients as it may be a treatable trait of long COVID. In addition, post-COVID central hypersomnia could also serve as a model to better understand post-infectious hypersomnia.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CM-Z: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. AV-C: Data curation, Formal analysis, Methodology, Writing – review & editing. NC: Writing – review & editing. LG: Writing – review & editing. MA: Writing – review & editing. AB: Writing – review & editing. IF: Writing – review & editing. P-OB: Methodology, Supervision, Writing – review & editing. GG: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

Funding

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

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 15 March 2024
DOI 10.3389/fpubh.2024.1377866

OPEN ACCESS

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RECEIVED 28 January 2024
ACCEPTED 06 March 2024
PUBLISHED 15 March 2024

CITATION
Ruiyin W, Qi J, Tingting W, Yuqin Y, Yan J and Kun P (2024) Long COVID outcomes following omicron wave in non-hospital population.
Front. Public Health 12:1377866.
doi: 10.3389/fpubh.2024.1377866

Long COVID outcomes following omicron wave in non-hospital population

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Background: The persistence of symptoms or the development of new symptoms following a diagnosis of SARS-CoV-2 has given rise to a multifaceted clinical condition referred to as "long COVID" (LC). The understanding of LC among China's non-hospitalized population continues to be insufficient. This investigation was designed to evaluate the protracted consequences amongst this demographic, as well as to identify the associated risk factors.

Methods: This research constitutes a prospective cohort study focusing on non-hospitalized individuals, aged between 18 and 59, who have been positively diagnosed with COVID-19. Each participant was subjected to a sequence of questionnaire-based surveys, designed to evaluate symptoms as well as the status of depression and anxiety. A logistic regression model, adjusted for multiple variables, was employed to scrutinize the correlation between demographic elements, lifestyle attributes, and health-related risk factors in relation to conditions and symptoms post COVID-19 infection.

Results: A total of 706 individuals participated in the 3 months follow-up, with 620 continuing on to the 6 months follow-up. The median age was 35 (28, 43) years, and 597 (85%) are female. Upon follow-up, Compared with patients without LC, patients with LC have a higher proportion of females (420 (87%) vs. 177 (79%); $p = 0.010$), were older (35 (29, 44) years vs. 33 (27, 41) years; $p = 0.010$) and have more comorbidities. Out of all participants, 483 (68.4%) reported experiencing at least one symptom at the 3 months mark, while 49.7% reported symptoms persisting at the 6 months mark. At the 3 months follow-up, the most prevalent persistent symptoms were cough (46%), fatigue (38%), and shortness of breath (34%). By the 6 months follow-up, fatigue (25%), shortness of breath (22%), and sleep disorders (16%) were the most commonly reported symptoms. Anxiety and depression were consistently reported as prevalent symptoms throughout the follow-up period. Most patient symptoms fade over time, with the quickest decreases observed in cough (from 46 to 9%), expectoration (from 26 to 6.3%), smell disorder (from 16 to 3.9%), and taste disorder (from 18 to 3.5%). Male and those possessing advanced educational qualifications exhibit a decreased susceptibility to the sustained incidence of coughing. Conversely, older age and the presence of comorbidities were identified as risk factors for persistent fatigue and shortness of breath.

Conclusion: In the after of COVID-19, it has been observed that the majority of patient symptoms tend to decrease over time. The primary residual symptoms noticed after a 6 month follow-up were fatigue, dyspnea, and sleep disturbances. However, it's noteworthy that the risk factors associated with these symptoms exhibit subtle variations. Furthermore, psychological sequelae, namely depression and anxiety, are frequently reported among COVID-19 survivors.

KEYWORDS

long COVID, PASC, omicron, non-hospital population, risk factor

Introduction

Long COVID (LC), or post-acute sequelae of SARS-CoV-2 infection (PASC), has become a substantial public health issue. LC is a term frequently employed to delineate symptoms that persist or manifest subsequent to an acute diagnosis of SARS-CoV-2, extending beyond the initial four-week period (1). This condition, frequently experienced by patients who have recovered from acute SARS-CoV-2 infection, is characterized by lingering symptoms such as fatigue, muscular weakness, dyspnea, arthralgia, and neurological complications (2, 3). The prevalence of LC remains uncertain; however, conservative estimates suggest that it affects approximately 10% of non-hospitalized survivors, with a higher proportion among hospitalized individuals (4, 5), this condition significantly deteriorates the quality of life and imposes a considerable economic burden (6).

Regarding the long-term consequences of the Omicron variant, preliminary evidence suggests a trend towards less severity and shorter duration compared to the Delta variant and other strains. Arjun's et al. research in India indicates an 8.2% risk of LC following an Omicron infection, markedly lower than the risk associated with the Delta variant (7). Consistently, Antonelli et al. reported a lower incidence of LC in Omicron cases (4.8%) than in Delta cases (10.8%) (8). In China, the first wave of the Omicron variant occurred in December 2022, yet the long-term effects on non-hospitalized individuals remain largely undetermined.

Therefore, it is imperative to evaluate the enduring repercussions of COVID-19 in non-hospitalized patients and to identify potential risk factors. This will equip healthcare providers with the necessary information to effectively manage LC and its impact on patients and their families. Additionally, it will contribute to the growing body of knowledge regarding LC in non-hospitalized populations.

Methods

Study design and participants

In this prospective cohort study, non-hospitalized patients confirmed with COVID-19 infection through reverse transcriptase polymerase chain reaction (RT-PCR) or COVID-19 antigen testing were recruited from Longfu Hospital in Beijing, China. The study population comprises hospital staff, encompassing both permanent and contingent employees, together with police department personnel who collaborate with the medical institution. The inclusion criteria encompassed individuals aged between 18 and 59 years. Subjects were excluded if they declined participation, failed follow-up, were unable to articulate their symptoms, or experienced COVID-19 reinfection during the follow-up period. The data collection spanned from December 2022 to August 2023. The study received approval from the Research Ethics Commission of Beijing Longfu Hospital (LFYYLL-2023-01), and written informed consent was obtained from all participants.

Data management and outcome measurement

The acute phase data incorporated demographics (including age, gender, body mass index (BMI), educational background, and smoking and drinking habits), symptoms, comorbidities, and chest computed tomography. Subsequent clinical follow-ups of all study participants were conducted via telephone consultations and in-person appointments at 3- and 6 months intervals after diagnosis. During each encounter, the Long-term Follow-up Case Report Form (CRF), based on the World Health Organization's CRF for post-COVID conditions, was utilized to gather information regarding the patient's current health status and any lingering symptoms. The Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) were employed to assess the prevalence and intensity of depressive and anxious symptoms. All follow-up information was ultimately compiled into Microsoft Excel for streamlined storage and efficient management.

Statistical analysis

We undertook descriptive statistical analysis to assess the baseline characteristics and enduring health implications of COVID-19. Both continuous and categorical variables were represented as median (interquartile range (IQR)) and frequency (percentage), respectively. For group comparisons, we deployed the Chi-squared test or Fisher's exact test in conjunction with the Wilcoxon rank-sum test. A p-value below 0.05 was deemed statistically significant.

To explore and ascertain the odds ratios (ORs) and 95% confidence intervals (CIs) for associations between demographic attributes, comorbidities, and persistent symptoms, univariable and multivariable logistic regression analyses were conducted. Our final analysis incorporated all participants for whom the variables of interest were accessible, excluding the imputation of missing data. All statistical evaluations were executed using R software, version 4.0.2.[1]

Results

In this study, a cohort of 744 patients, diagnosed with mild to moderate COVID-19, was observed from December 1, 2022, through July 30, 2023. However, the sample size was eventually reduced to 706 due to the exclusion of 38 patients. These exclusions were a result of a lack of follow-up participation: 12 patients voluntarily opted out, 24 were unreachable, and 2 withdrew due to miscellaneous reasons. After the 3 months follow-up period, all 706 participants remained in the study. However, at the 6 months mark, only 620 participants were

1 https://cran.r-project.org

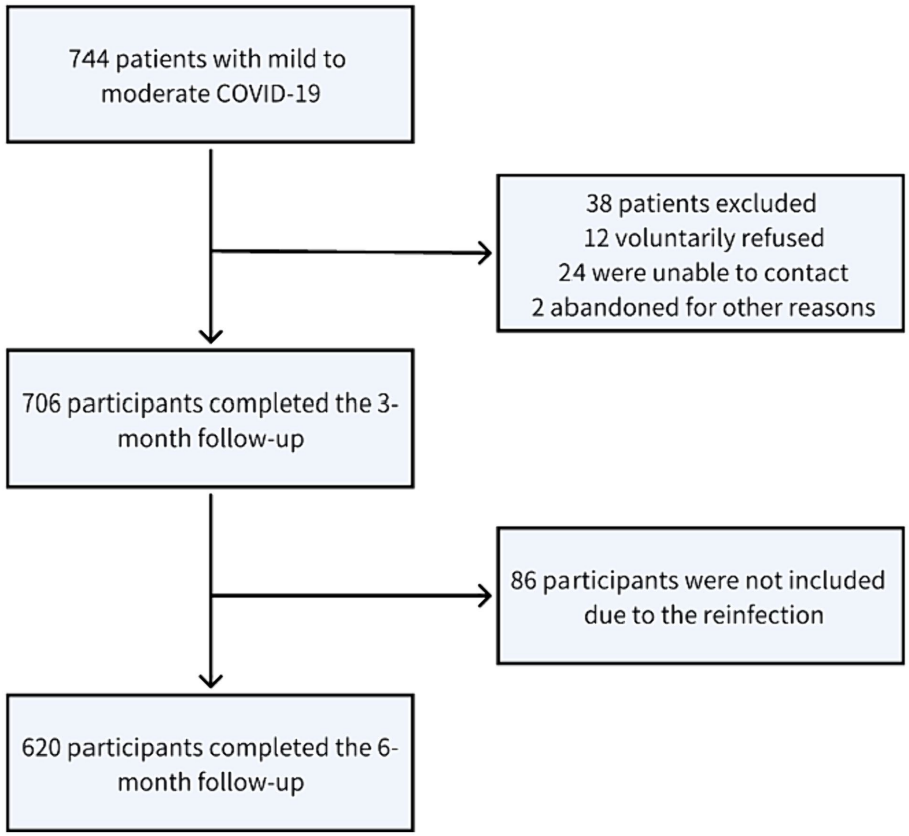

FIGURE 1
Flow chart of patients diagnosed with mild to moderate COVID-19 between December 1 and July 30, 2023.

included in the data analysis. The decrease in participant count was due to the exclusion of 86 individuals who experienced COVID-19 reinfection during the observation period. These demographic and participation details are illustrated in Figure 1.

Table 1 delineates the demographic and clinical attributes of participants, segregated based on the 3 months and 6 months follow-up data. The median participant age stands at 35 years (interquartile range: 28, 43 years), with an age range of 21 to 59 years. The gender distribution is predominantly female (85% in participants).

In terms of educational attainment, the majority (58%) hold a university degree, trailed by individuals with education level below college (25%). The prevalence of underlying health conditions is relatively low, with only 5.8% of the participants having three or more such conditions. Allergic rhinitis tops the list of comorbidities (84 participants, 12%), succeeded by hypertension (66 participants, 9.3%), and osteoarthritis (64 participants, 9.1%).

Upon comparing COVID-19 patients with and without long-term sequelae during the 3 months follow-up, it was noted that the group with LC had a higher proportion of females (87% versus 79%; $p = 0.010$), older median age (35 years versus 33 years; $p = 0.010$), and greater comorbidity prevalence. However, there were no significant differences in BMI, educational background, and substance use habits such as smoking and drinking.

The 6 months follow-up for LC mirrored these findings. Notable differences in osteoarthritis, depression, and anxiety were observed between the 3 months and 6 months follow-ups. As the duration progressed, other conditions like asthma ($p = 0.024$), gastrointestinal issues ($p = 0.015$), and oncological conditions ($p = 0.038$) appeared to influence the long-term effects of COVID-19.

In the follow-up interview, 68.4% (483) of the participants reported experiencing at least one symptom after 3 months, while 49.7% (308) reported persistent symptoms after 6 months. The most prevalent symptoms at the 3 months mark were coughing (46%), fatigue (38%), and shortness of breath (34%). By the 6 months mark, the most frequent symptoms were fatigue (25%), shortness of breath (22%), and sleep disorders (16%). Anxiety and depression emerged as the most common symptoms during the follow-up period, particularly among participants with higher education levels and those with multiple comorbidities. Over time, most symptoms exhibited a declining trend, with the most notable reductions observed in coughing (from 46 to 9%), expectoration (from 26 to 6.3%), smell disorders (from 16 to 3.9%), and taste disorders (from 18 to 3.5%) (Figure 2).

In the multivariable regression analysis (Figure 3), the risk is lower for male and higher for female in 3 months (OR 0.58, 95% CI 0.36–0.94) and in 6 months (OR 0.49, 95% CI 0.29–0.83). In addition, participants with three or more comorbidities demonstrated an elevated risk in 3 months (OR 2.94, 95% CI 1.10–7.87) and in 6 months (OR 3.98, 95% CI 1.66–9.57). Factors such as age, BMI, level of education, and lifestyle habits like smoking and drinking did not significantly impact the risk of LC.

10.3389/fpubh.2024.1377866

TABLE 1 Characteristics of enrolled patients.

Characteristic	Long COVID3				Long COVID6			
	Overall, $N = 706$[a]	NO, $N = 223$[a]	Yes, $N = 483$[a]	p-value[b]	Overall, $N = 620$[a]	NO, $N = 303$[a]	Yes, $N = 317$[a]	p-value[b]
Gender				0.010				0.026
Female	597 (85%)	177 (79%)	420 (87%)		522 (84%)	245 (81%)	277 (87%)	
Male	109 (15%)	46 (21%)	63 (13%)		98 (16%)	58 (19%)	40 (13%)	
Year	35 (28, 43)	33 (27, 41)	35 (29, 44)	0.010	35 (28, 44)	34 (28, 43)	36 (29, 45)	0.036
BMI	22.9 (20.8, 25.7)	22.7 (20.6, 25.8)	23.0 (20.9, 25.7)	0.388	23.0 (20.7, 25.8)	23.0 (20.7, 25.8)	22.9 (20.7, 25.8)	0.774
Culture				0.701				0.623
College lower	176 (25%)	52 (23%)	124 (26%)		160 (26%)	75 (25%)	85 (27%)	
College	413 (58%)	131 (59%)	282 (58%)		360 (58%)	175 (58%)	185 (58%)	
College higher	117 (17%)	40 (18%)	77 (16%)		100 (16%)	53 (17%)	47 (15%)	
Smoke_and_Drink				0.462				0.347
Both	25 (3.5%)	11 (4.9%)	14 (2.9%)		23 (3.7%)	12 (4.0%)	11 (3.5%)	
Drink	29 (4.1%)	11 (4.9%)	18 (3.7%)		24 (3.9%)	10 (3.3%)	14 (4.4%)	
None	634 (90%)	196 (88%)	438 (91%)		556 (90%)	276 (91%)	280 (88%)	
Smoke	18 (2.5%)	5 (2.2%)	13 (2.7%)		17 (2.7%)	5 (1.7%)	12 (3.8%)	
Basic_disease				0.027				0.001
No	464 (66%)	159 (71%)	305 (63%)		403 (65%)	212 (70%)	191 (60%)	
One	152 (22%)	44 (20%)	108 (22%)		136 (22%)	65 (21%)	71 (22%)	
Two	49 (6.9%)	15 (6.7%)	34 (7.0%)		44 (7.1%)	19 (6.3%)	25 (7.9%)	
Three or above	41 (5.8%)	5 (2.2%)	36 (7.5%)		37 (6.0%)	7 (2.3%)	30 (9.5%)	
Hypertension				0.178				0.538
NO	640 (91%)	207 (93%)	433 (90%)		558 (90%)	275 (91%)	283 (89%)	
Yes	66 (9.3%)	16 (7.2%)	50 (10%)		62 (10%)	28 (9.2%)	34 (11%)	
Diabetes				0.412				0.319
NO	674 (95%)	215 (96%)	459 (95%)		590 (95%)	291 (96%)	299 (94%)	
Yes	32 (4.5%)	8 (3.6%)	24 (5.0%)		30 (4.8%)	12 (4.0%)	18 (5.7%)	
Heart diseases				0.446				0.069
NO	698 (99%)	222 (100%)	476 (99%)		612 (99%)	302 (100%)	310 (98%)	
Yes	8 (1.1%)	1 (0.4%)	7 (1.4%)		8 (1.3%)	1 (0.3%)	7 (2.2%)	
Haematological conditions				>0.999				0.374
NO	701 (99%)	222 (100%)	479 (99%)		615 (99%)	302 (100%)	313 (99%)	
Yes	5 (0.7%)	1 (0.4%)	4 (0.8%)		5 (0.8%)	1 (0.3%)	4 (1.3%)	
COPD				>0.999				0.616
NO	703 (100%)	222 (100%)	481 (100%)		617 (100%)	301 (99%)	316 (100%)	
Yes	3 (0.4%)	1 (0.4%)	2 (0.4%)		3 (0.5%)	2 (0.7%)	1 (0.3%)	
Allergic rhinitis				0.714				0.575
NO	622 (88%)	195 (87%)	427 (88%)		550 (89%)	271 (89%)	279 (88%)	
Yes	84 (12%)	28 (13%)	56 (12%)		70 (11%)	32 (11%)	38 (12%)	
Asthma				0.387				0.024
NO	688 (97%)	219 (98%)	469 (97%)		605 (98%)	300 (99%)	305 (96%)	
Yes	18 (2.5%)	4 (1.8%)	14 (2.9%)		15 (2.4%)	3 (1.0%)	12 (3.8%)	
Gastrointestinal problems				0.075				0.015

(Continued)

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TABLE 1 (Continued)

Characteristic	Long COVID3				Long COVID6			
	Overall, $N = 706$[a]	NO, $N = 223$[a]	Yes, $N = 483$[a]	p-value[b]	Overall, $N = 620$[a]	NO, $N = 303$[a]	Yes, $N = 317$[a]	p-value[b]
NO	689 (98%)	221 (99%)	468 (97%)		604 (97%)	300 (99%)	304 (96%)	
Yes	17 (2.4%)	2 (0.9%)	15 (3.1%)		16 (2.6%)	3 (1.0%)	13 (4.1%)	
Oncological conditions				0.164				0.038
NO	691 (98%)	221 (99%)	470 (97%)		606 (98%)	300 (99%)	306 (97%)	
Yes	15 (2.1%)	2 (0.9%)	13 (2.7%)		14 (2.3%)	3 (1.0%)	11 (3.5%)	
Thyroid disease				0.090				0.099
NO	677 (96%)	218 (98%)	459 (95%)		593 (96%)	294 (97%)	299 (94%)	
Yes	29 (4.1%)	5 (2.2%)	24 (5.0%)		27 (4.4%)	9 (3.0%)	18 (5.7%)	
Kidney problems				>0.999				0.499
NO	704 (100%)	223 (100%)	481 (100%)		618 (100%)	303 (100%)	315 (99%)	
Yes	2 (0.3%)	0 (0%)	2 (0.4%)		2 (0.3%)	0 (0%)	2 (0.6%)	
Immune system diseases				>0.999				>0.999
NO	703 (100%)	222 (100%)	481 (100%)		617 (100%)	302 (100%)	315 (99%)	
Yes	3 (0.4%)	1 (0.4%)	2 (0.4%)		3 (0.5%)	1 (0.3%)	2 (0.6%)	
Osteoarthrosis				0.042				0.043
NO	642 (91%)	210 (94%)	432 (89%)		562 (91%)	282 (93%)	280 (88%)	
Yes	64 (9.1%)	13 (5.8%)	51 (11%)		58 (9.4%)	21 (6.9%)	37 (12%)	

[a]*n* (%); Median (IQR).
[b]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

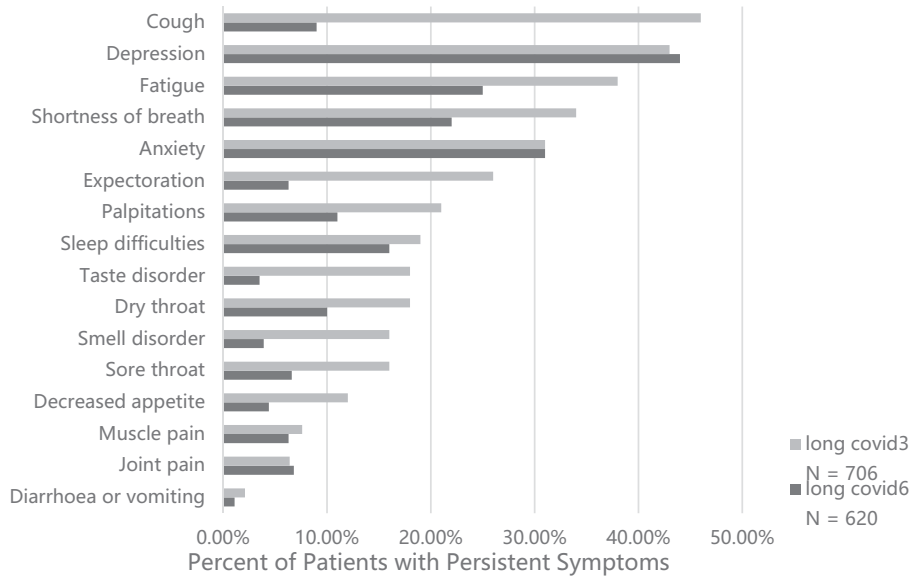

FIGURE 2
Outcomes of persistent symptoms 3- to 6 months after non-hospital patients admitted for acute COVID-19.

Common symptoms such as cough, fatigue, and shortness of breath were further examined using multivariate regression analysis. Males exhibit a reduced incidence of coughing over a 3 months observation period (OR 0.57, 95% CI 0.35–0.92), however, this

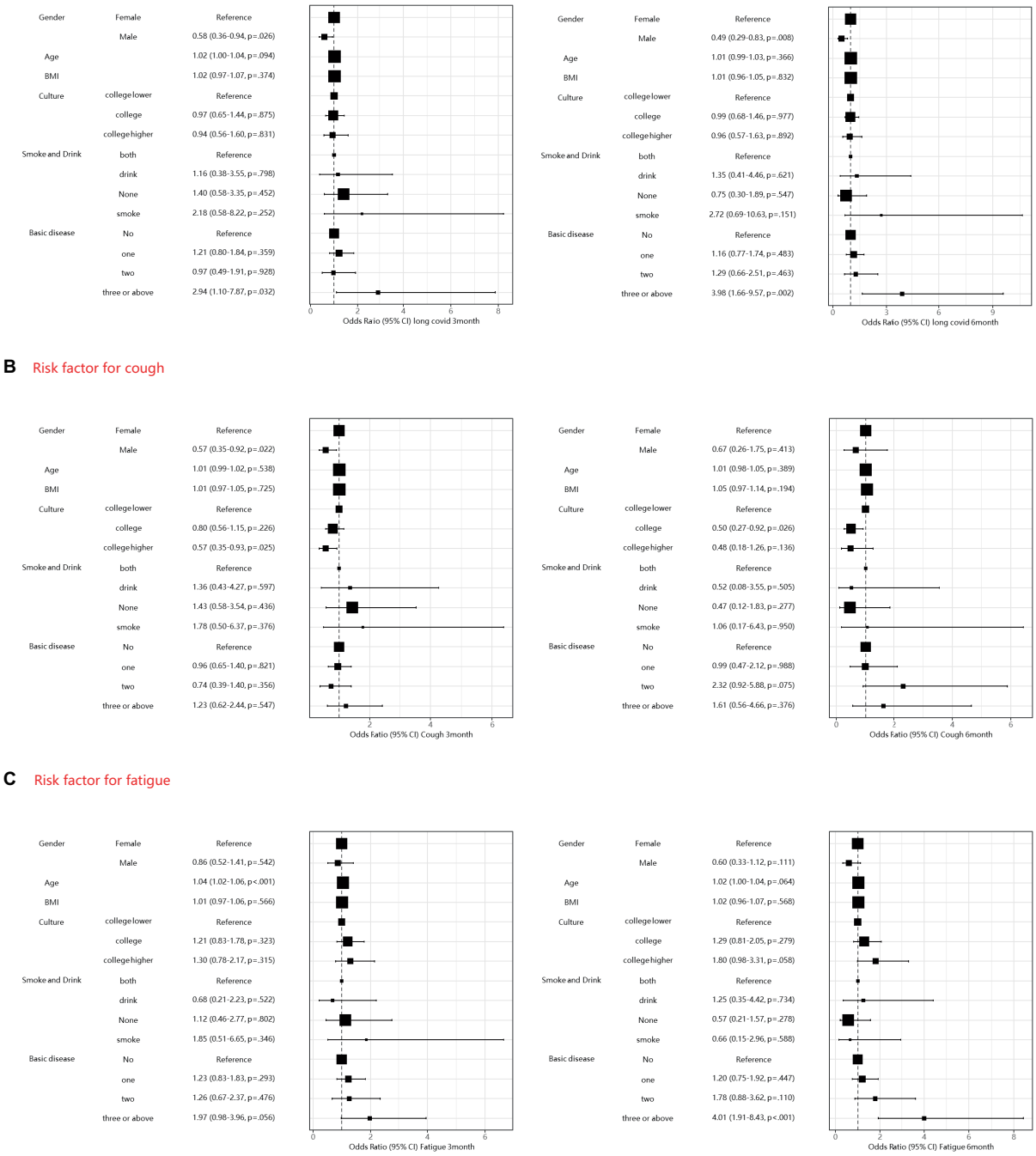

FIGURE 3 (Continued)

difference effect dissipated after 6 months. Similarly, for males, experiencing fatigue or shortness of breath does not confer any advantages.

Compared to individuals with lower education levels, individuals with higher education levels are less likely to experience cough related symptoms within 3 months (OR 0.57, 95% CI 0.35–0.93). Correspondingly, compared to individuals with higher education levels and those with lower education levels, individuals with college levels have a lower risk of developing cough related symptoms within 6 months (OR 0.50, 95% CI 0.27–0.92). Age was identified as a risk factor for fatigue during the three-month follow-up (OR 1.04, 95% CI 1.02–1.06), while the presence of three or more comorbidities became more pronounced at the 6 months (OR 4.01, 95% CI 1.91–8.43).

With regard to shortness of breath, both two and three or more comorbidities were associated with an increased risk at both the 3 months and 6 months follow-ups.

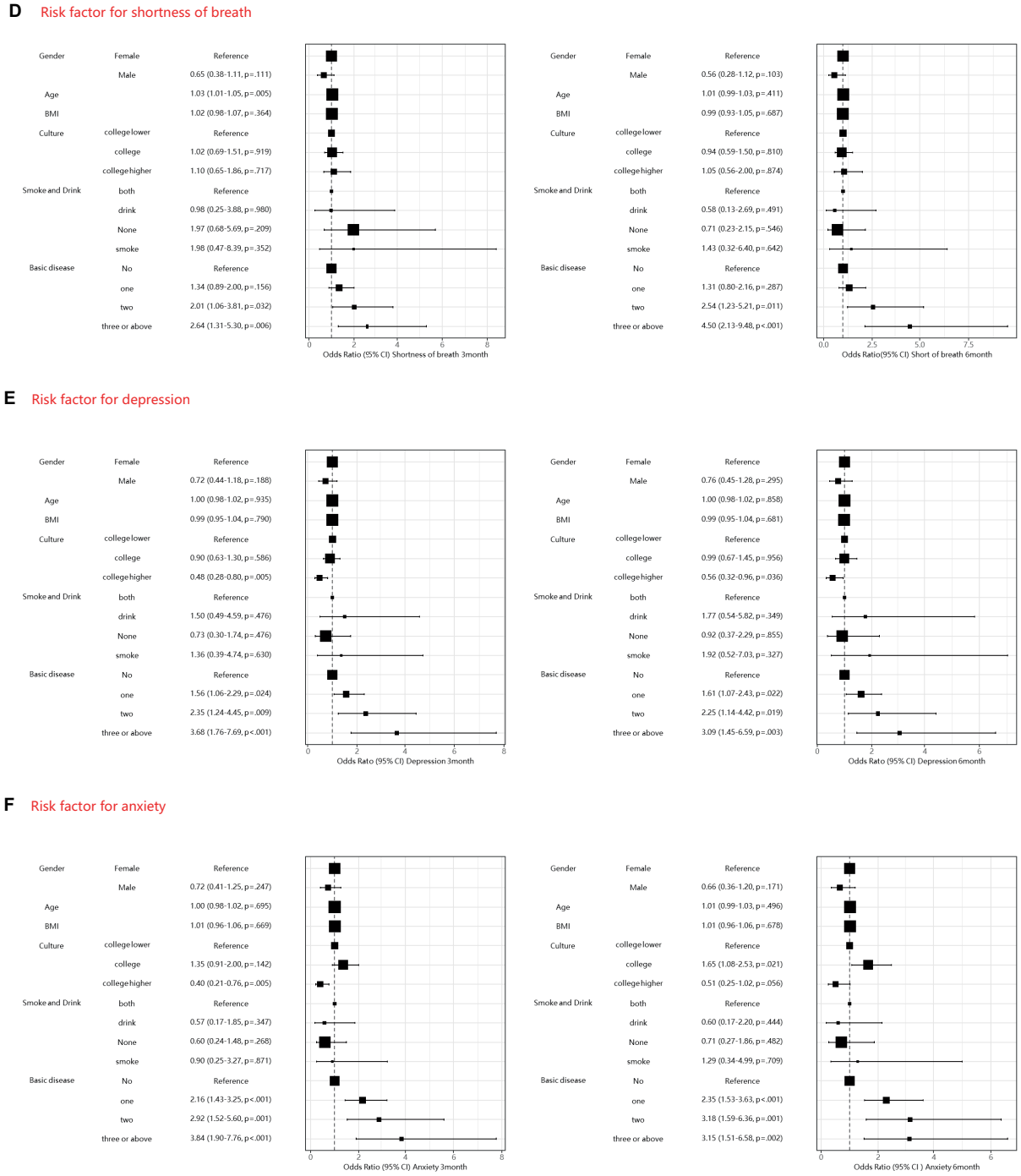

FIGURE 3
Multivariable logistic regression model to identify pre-existing risk factors for long COVID **(A)**, cough **(B)**, fatigue **(C)**, short of breath **(D)**, depression **(E)** and anxiety **(F)** in 3 months and 6 months.

Depression and anxiety are prevalent conditions among individuals with long COVID, and their prevalence does not significantly alter over time. During follow-up periods at 3 and 6 months, it has been observed that individuals with higher levels of education and those experiencing complications are at a greater risk of developing anxiety and depression. Conversely, factors such as age, gender, smoking habits, and alcohol consumption do not influence the occurrence of these mental health conditions.

Discussion

In our research, we examined the enduring clinical consequences in non-hospitalized adult demographics following Omicron infection, while simultaneously scrutinizing alterations in symptom profiles and predisposing factors. Our findings revealed that a majority, exceeding half of the afflicted individuals, exhibited persistent symptoms. The most prevalent of these included cough, fatigue, dyspnea, and insomnia. Factors such as gender – specifically being female – and the

presence of comorbidities (9–11) amplified the likelihood of developing post-COVID-19 conditions. Our analysis demonstrated that the risk of numerous health outcomes in the aftermath of mild to moderate COVID-19 infection became increasingly conspicuous within the initial 3 months post-infection, subsequently declining. The data also indicated that this risk fluctuated across different symptom spectra and evolved over time.

The prevailing symptoms observed amongst individuals include fatigue and shortness of breath, aligning with prior research (12–15). A meta-analysis has established that COVID-19 infection markedly elevates the likelihood of enduring fatigue and shortness of breath, with risk factors of 1.72 and 2.60 respectively, when assessed 4 weeks or more following initial infection, relative to a non-infected control cohort (16). This implies that regardless of the virus's mutation or hospitalization status, chronic fatigue and shortness of breath persist as significant detriments impacting individuals' quality of life. We further noted that while the severity of fatigue and shortness of breath diminished over time, the rate of decrease was gradual. Risk factors correlated with age and multiple comorbidities, but no significant relationship with gender was found. In our research, we did not explore the foundational mechanisms at play. However, contemporary scholarly work suggests that these mechanisms are likely complex and might encompass cerebral targeting, skeletal muscle impairment, as well as compromised erythrocyte functionality. Recent studies (17) reveal elevated levels of brain-reactive autoantibodies against MBP, MOG, tubulin, CP2, and synaptophysin in patients suffering from protracted COVID-19, suggesting a possible involvement of neuroautoimmune pathophysiology. Post-infection structural changes in skeletal muscle microvasculature due to immune response, such as reduced capillary density, thickened capillary basement membrane, and an increased number of CD169+ macrophages, may contribute to fatigue (18). Romy Kronstein-Wiedemann et al. (19) reported that long-term COVID-19 patients exhibited hindered oxygen-hemoglobin binding and enhanced carbon monoxide binding, indicating that persistent fatigue might be associated with compromised erythrocyte function in patients with prolonged coronavirus infection. Metabolic alterations in fatigued patients, including lactate, fumaric acid, symmetric dimethylarginine, and asymmetric dimethylarginine, could potentially serve as therapeutic targets (20, 21). Our findings also suggest a correlation between long-term COVID-19 and osteoarthrosis, implying possible involvement of the musculoskeletal system. This insight could aid in formulating rehabilitation strategies for managing post-COVID-19 fatigue (22).

During the course of a COVID-19 infection, numerous individuals reported symptoms such as coughing, expectoration, fatigue, shortness of breath, palpitations, and insomnia. However, it has been observed that the prevalence of these symptoms has exhibited a consistent decline over time. The most rapidly diminishing symptom appears to be coughing. This suggests that the manifestation of 'Long-COVID' symptoms tends to gradually diminish over time, which aligns with prior research on the progression of COVID-19 (23). In the current investigation, empirical data indicates that 30 days post onset or admission due to COVID-19, the estimated prevalence of cough was 18.6% (95% CI 10.6 to 30.7; 9 studies, $n = 1{,}829$). This figure saw a decrease to 8.6% (95% CI 5.3 to 13.7; 8 studies, $n = 8{,}219$) after a period of 90 days (24). A related study conducted by Osmanov et al. (25) revealed a decrease in fatigue levels in children from 15.8% at the time of discharge, to 8.8% seven months later. Furthermore, the percentage of sleep disturbances reported experienced a drop from 7.5 to 5.8%. Extensive research has suggested that gender significantly influences the clinical presentation and outcomes of various diseases, including those affecting respiratory functions. Our analysis of the available data delineates a robust correlation between gender and persistent post-COVID-19 cough, with females exhibiting a higher propensity towards experiencing this symptom as compared to males. Concurrently, our study also unearthed individuals boasting higher education levels demonstrated a reduced likelihood of suffering from a persistent cough, thereby suggesting that education might serve a protective role against this symptom (26). Intriguingly, our research did not unearth any significant correlation between smoking habits and the occurrence of a persistent cough. Despite the fact that smoking can unquestionably exacerbate respiratory health, it seemingly bears minimal influence on the persistence or severity of a cough specifically associated with COVID-19. This insinuates the possibility of unique mechanisms triggering coughs caused by this virus. The heightened activity of transient receptor potential (TRP) channels, which are expressed on the C fibers of the vagal nerve and mediate cough responses, as well as laryngeal hypersensitivity and dysfunction accompanied by abnormal vocal cord movement could potentially explain this phenomenon (27). Additionally, mast cells, known for expressing female sex hormone receptors, may shed light on the cause of persistent cough in females.

An exhaustive examination of accessible data unveils a significant prevalence of anxiety and depression amongst individuals suffering from long COVID, corroborating prior research (28–31). These psychiatric manifestations may endure well beyond the resolution of the disease's acute phase, resulting in considerable distress and compromised functionality (32). Elements such as ambiguity associated with long COVID, physical manifestations, and social segregation contribute to the inception and intensification of anxiety and depression within this demographic. Intriguingly, our investigation underscores a significant correlation between elevated education levels and heightened incidence of anxiety and depression amongst long COVID patients. Despite education typically providing individuals with superior tools to tackle health-related adversities, it may also precipitate excessive introspection, escalated health apprehension, and an illusion of control over health consequences. The impetus to excel acadically can amplify pre-existing psychological susceptibilities. These observations emphasize the need for custom-made interventions targeting individuals with advanced education to cater to their distinct mental health requirements. Our analysis further delves into the repercussions of multiple medical complications on anxiety and depression amongst long COVID patients. Individuals with co-morbidities or a history of numerous complications are at an escalated risk for the development of psychological distress. The obligation of managing intricate medical conditions, confronting ambiguity regarding recuperation, and grappling with an extended illness trajectory can contribute to exacerbated anxiety and depression. This insight underscores the indispensability of comprehensive care that addresses both physical and mental health dimensions for long COVID patients with multiple complications.

Limitations

This cohort study possesses several inherent limitations. Primarily, it is important to note the disproportionate representation of women

in the COVID-19 lifeline cohort which may introduce selection bias, compared to the broader lifeline population. Secondly, the absence of a control group, composed of healthy adults unaffected by COVID-19, restricts the comparative scope of our study the third limitation arises from potential comorbidities or complications that some patients might encounter during the follow-up period. These additional health issues could potentially influence both their overall health status and the persistence and prevalence of COVID-19 symptoms. The fourth limitation pertains to the subjective nature of patient-reported outcomes, such as fatigue, anosmia, and dysgeusia. These self-reported symptoms may not be as precise or consistent as a physician's clinical diagnosis. Lastly, we cannot disregard the possibility of behavioral and environmental disparities between infected and uninfected individuals. Such differences could potentially inflate the calculated incidence rate among those infected with COVID-19.

Conclusion

Following the COVID-19 pandemic, it was observed that the majority of patients' symptoms gradually subsided, with cough, expectoration, olfactory disturbance, and gustatory disorder showing the most rapid decline. However, after a 6 months observation period, nearly half of the affected individuals continued to exhibit at least one symptom. Predominantly, fatigue, dyspnea, and sleep disturbances were the most frequently reported post-illness conditions. The risk factors associated with these residual symptoms varied slightly. For instance, cough was predominantly observed in women, establishing gender as a principal risk factor for this symptom. Age and pre-existing health conditions were more frequently linked to fatigue and shortness of breath. Furthermore, psychological disorders such as depression and anxiety were prevalent among the post-COVID-19 conditions. Currently, the mechanisms underlying these diverse post-COVID-19 symptoms remain elusive. Future research should aim to devise treatment strategies tailored to these specific symptoms to enhance therapeutic efficacy.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of Beijing Longfu Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WR: Writing – original draft. JQ: Writing – review & editing. WT: Writing – review & editing. YY: Data curation, Writing – original draft. JY: Data curation, Writing – original draft. PK: Methodology, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The research presented herein has been generously supported by the Dongcheng District Research Fund, as indicated by Dongwei Jianyan [2023]-5.

Acknowledgments

Our heartfelt gratitude extends to all patients and their respective families who have willingly participated in this study. Furthermore, we extend our appreciation to the entire team (Dawei Huang, Yue Wu, Hongyan Wan, Lei Guo) involved in the longitudinal research study for their unwavering dedication and commitment.

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.2024.1377866/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Mini Review
PUBLISHED 14 June 2024
DOI 10.3389/fmed.2024.1430444

OPEN ACCESS

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RECEIVED 09 May 2024
ACCEPTED 04 June 2024
PUBLISHED 14 June 2024

CITATION
Dietz TK and Brondstater KN (2024) Long COVID management: a mini review of current recommendations and underutilized modalities.
Front. Med. 11:1430444.
doi: 10.3389/fmed.2024.1430444

Long COVID management: a mini review of current recommendations and underutilized modalities

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Long COVID is a condition that develops in a subset of patients after COVID-19 infection comprising of symptoms of varying severity encompassing multiple organ systems. Currently, long COVID is without consensus on a formal definition, identifiable biomarkers, and validated treatment. Long COVID is expected to be a long-term chronic condition for a subset of patients and is associated with suffering and incapacity. There is an urgent need for clear management guidelines for the primary care provider, who is essential in bridging the gap with more specialized care to improve quality of life and functionality in their patients living with long COVID. The purpose of this mini review is to provide primary care providers with the latest highlights from existing literature regarding the most common long COVID symptoms and current management recommendations. This review also highlights the underutilized interventions of stellate ganglion blocks and low-dose naltrexone, both with well-established safety profiles demonstrated to improve quality of life and functionality for patients suffering with some symptoms of long COVID, and encourages prompt referral to interventional pain management.

KEYWORDS

long COVID, chronic COVID-19, post-acute sequelae of SARS-CoV-2, post COVID, management, low-dose naltrexone, stellate ganglion block

1 Introduction

The recent Coronavirus disease 2019 (COVID-19) pandemic elicits many challenges in healthcare. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 infection (1, 2). SARS-CoV-2 utilizes angiotensin-converting-enzyme 2 (ACE2) to bind with spike protein (S-protein) to enter the cell (2). ACE2 is found in several body tissues such as the heart, lungs, kidneys, and gastrointestinal system (3). Most people infected by COVID-19 make a full recovery however, there are varying estimates from 0 to 93% of those infected developing a long-term condition comprised of often severe symptoms affecting multiple organ systems known as long COVID (1, 2, 4, 5). These estimate are highly varied based on several factors such as the definition of long COVID, settings such as hospital-based versus outpatient, reporting methods such as medical records versus self-report, and vaccination status (5, 6). In a subset of patients, long COVID is expected to be a chronic illness with high impacts to healthcare utilization, workforce and employment. The long COVID burden is estimated to be $2.6 trillion per year in the USA (7). The pandemic united the world in a global effort for rapid development and delivery of COVID vaccinations but the lack of sufficient data and recommendations for managing long COVID complications remain.

There are no current validated biomarkers or validated treatments for long COVID making management difficult for providers and frustrating for patients already living with long COVID. Due to the lack of sufficient data many recommendations for managing long COVID are based on expert opinion thus there is urgent need for more research. Patients living with long COVID experience varying severity of debility. Many current strategies include self-management and rehabilitation. Proposed treatments include: apheresis (8), nirmatrelvir/ritonavir (Paxlovid) (9), antihistamines such as loratadine (10), fexofenadine, and famotidine (11), anticoagulants such as apixaban (10) and antiplatelet agents such as aspirin and clopidogrel (12). Thrombolytics such as nattokinase, serrapeptase, lumbrokinase, and bromelain have also been proposed as potential treatments for long COVID (13).

Missed opportunities for intervention are imputable to the paucity of randomized controlled trials. Long COVID patients are more likely to utilize services from their primary care providers to seek further care for their new chronic disease. The aim of this mini review is to provide primary care providers the latest highlights from existing literature regarding current recommendations and feature two safe and underutilized interventions that may be helpful in improving functionality and quality of life for their patients already suffering with some symptoms of long COVID with an emphasis on prompt referral to interventional pain management.

2 Background

COVID-19 was declared a pandemic on March 11, 2020 and as of March 2024, the World Health Organization reports over 775 million cases of COVID-19 worldwide; 103 million cases are in the United States alone (14). The prevalence of long COVID may be underestimated due to the breadth and variability of symptoms (15). There is consistent evidence that women are more likely to report symptoms of long COVID and have a diagnosis compared to men (6, 16–18). An analysis of repeat cross-sectional data collected by US Census Bureau from June 2022 to June 2023 determined the highest prevalence of long COVID and prevalence of associated significant activity limitation was found in adults 35–44 years of age (19). This group encompasses the largest portion of the US workforce as the median age of the labor force is 41.8 (20).

Long COVID pathophysiology remains unclear. Current hypotheses underlying pathophysiology include: Post-viral immune dysregulation triggering multi-organ inflammation, reactivation of latent pathogens, autoimmunity, and formation of microclots (21, 22).

Long COVID is without specific biomarkers for detection and without validated effective treatments (4, 18, 23). Over 200 symptoms encompassing multiple organ systems have been reported and severity varies from mild and reversible to moderate or severe and persistent (18). Long COVID is expected to be a long-term chronic condition for a subset of patients that may last months to years and is associated with suffering and incapacity highlighting an urgent need for clearer management guidelines and interventions.

3 Long COVID definitions

Long COVID has also been referred to as post COVID conditions (PCC), post-acute sequelae of SARS-CoV-2 infection (PASC), and long-haul COVID (7, 24, 25). In 2021, long COVID condition was assigned an International Classification of Diseases, Tenth Revision (ICD-10) code, U90.9 (26).

There is not an established definition for long COVID, though sometimes it includes symptom duration or clusters of symptoms and may not always be straightforward (27, 28). Raveendran (28) proposes clinical and essential criteria to facilitate categorizing long COVID into four categories: confirmed, probable, possible, or doubtful. The National Institute for Health and Care Excellence (NICE) defines long COVID as "signs and symptoms that continue or develop after acute COVID-19" and "includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)" (29). The National Institutes of Health (NIH) Researching COVID to Enhance Recovery (RECOVER) Initiative program defines long COVID as "ongoing, relapsing, or new symptoms, or other health effects occurring after the acute phase of SARS-CoV-2 infection (i.e., present four or more weeks after acute infection)" (22).

A Delphi process conducted in partnership between the World Health Organization (WHO) Clinical Case Definition Working Group on Post-COVID-19 Condition and an international panel of patients, providers, researchers and WHO staff, provides the following definition for long COVID: A condition occurring in individuals with SARS-CoV-2 infection history at least 3 months post-acute infection with persistent symptoms of at least 2 months duration in which an alternative diagnosis cannot be obtained (30). The US Centers for Disease Control and Prevention (CDC), defines long COVID as new onset or persistent symptoms of at least 4 weeks' duration from acute infection (31). Commonalities in the definition of long COVID is comprised of signs and symptoms occurring 3 months after acute COVID infection and persistent for at least 2 months. Differences in the timelines defining long COVID have significant effects on comparing research among these studies. Several studies note that long COVID symptoms change over time from predominantly respiratory towards neuropsychiatric symptoms.

4 Preliminary workup

Diagnosing long COVID is difficult with over 200 associated/related symptoms. Long COVID is not exclusively associated with severe acute COVID infections. Many studies focus on hospitalized COVID patients thus there is an underrepresentation of non-hospitalized COVID patients (32). The most commonly reported long COVID symptoms include: fatigue, dyspnea, cognitive impairment, myalgias and arthralgias, headache, cough, chest pain, smell and taste alterations (17, 26, 33, 34). No specific biomarkers exist to detect long COVID (4, 15, 18) although proposed biomarkers include: C-reactive protein (35), interferon gamma (36), interleukin-6 (35, 37), and tumor necrosis factor alpha (38). Antibodies do not facilitate the retrospective diagnosis of infection in patients with long COVID. Antibodies are only found in about 80% of patients that seroconvert and these levels decrease over time and are undetectable at 3 months (26). Most studies measured spike antibodies, which are no longer relevant post-vaccination. Anti-nucleocapsid protein antibodies also diminish over 6 months in 50% of patients hospitalized with COVID-19 (39).

Assessment of patients with high suspicion for long COVID should include a comprehensive evaluation with collection of a

TABLE 1 Long COVID intervention recommendations by symptom.

	Self-management[a]	Physical exercise rehabilitation	Pulmonary rehabilitation	SGB	LDN
Cardiopulmonary symptoms					
Fatigue	X	X[b]		X	X
Dyspnea			X	X	
CVD: Chest Pain, Palpitations, Fatigue, Brain Fog		X[b]		X	X
Neuropsychiatric symptoms					
Depression		X	X	X	
Anxiety		X	X	X	
Sleep disturbances	X	X		X	X
Parosmia				X	
Cognitive impairment		X		X	

[a]Self-management strategies include rest, good sleep hygiene, energy pacing, diet control, and distraction.
[b]Prior to physical exercise rehabilitation initiation, rule out conditions such as post-exertional malaise (PEM) and postural orthostatic tachycardia syndrome (POTS).
CVD, cardiovascular dysautonomia; SGB, stellate ganglion block; LDN, low-dose naltrexone.

thorough history. Physical examination should include baseline vital signs and bloodwork such as complete blood count, electrolytes, creatinine, random blood glucose, hemoglobin A1c, thyroid panel, and an electrocardiogram (EKG) (40). Tools such as the World Health Organization (WHO) Post-COVID-19 Functional Status (PCFS) Scale and the Montreal Cognitive Assessment (MOCA) test may be helpful to assess for resolution of acute COVID symptoms, recurrence of symptoms, and/or development of new symptoms within the first year following acute COVID infection (41). After thorough work-up to exclude other alternative diagnoses and referrals to appropriate specialists when indicated, management comprises of symptom control and interventions for treatable characteristics.

5 Management

Current and recommended management strategies differ widely across the literature. Strategies consist primarily of supportive care or based on system involvement. Current care recommendations include multidisciplinary rehabilitation, self-management and self-pacing (42–44). Self-management approaches include appropriate rest, practicing good sleep hygiene, energy pacing methods, diet control, and distraction (41, 42, 45). Pacing strategies are aimed at coping with inconsistent and decreased energy levels by adapting or adjusting efforts to different activities (43). This may include energy conservation which integrates activity prioritization, task delegation, assistive device utilization, and alternating between activity and rest to complete daily activities, and activity pacing which incorporates activity goals and gradual increase of activity levels (43). Higher pacing adherence is associated with higher rates of recovery and improvement (43).

Described hereafter are management recommendations for the most common long COVID presentations that cause the most morbidity and disability. Management recommendations by symptom is presented in Table 1.

5.1 Cardiopulmonary symptoms

Fatigue and dyspnea are two of the most common complaints in patients with long COVID (41, 42, 46–51). Fatigue screening may be achieved by utilizing validated tools such as the Fatigue Assessment Scale (FAS), Visual Analogue Fatigue Scale (VAFS), or Fatigue Severity Scale (FSS) (41, 43). Objective testing for fatigue may be performed using tests such as the 6-min walk test (6MWT) and the Timed Up and Go (TUG) Test (41). Dyspnea is associated with poor sleep, mood, life quality and strength particularly at 12 months post-COVID (52). Dyspnea and depressive symptoms at 3 months post-COVID are predictors of severity of dyspnea 12 months post-COVID and may be screened with standardized dyspnea and mood questionnaires (52). Assessment of dyspnea may include pulmonary function tests (PFTs), transthoracic echocardiogram (TTE), and the 6-min walk test (6MWT) (41). Patients with pre-existing cardiac history should have regular monitoring of troponin and inflammatory panels, electrocardiogram, chest x-ray, echocardiogram, holter-EKG and spirometry (18).

Cardiovascular dysautonomia symptoms include chest pain, palpitations, fatigue, and brain fog due to deficient function of the autonomic nervous system (ANS) (52). The most prevalent type is postural orthostatic tachycardia syndrome (POTS) (52, 53). POTS may be screened and assessed through utilization of orthostatic vital signs and tilt table testing (41, 53). Symptom management for patients with confirmed POTS may include compression stockings, hydration, and behavioral modification (41, 53). Pharmacological management may also be employed based on target symptom. For example, to reduce tachycardia and improve exercise or orthostatic intolerance, beta-blockers may be utilized (53).

Physical exercise rehabilitation has also been shown to provide improvement of fatigue but it is essential to rule out conditions such as post-exertional malaise (PEM) and POTS as exercise may exacerbate symptoms and be harmful (41, 48, 51). A randomized controlled trial (RCT) examined functional versus aerobic exercise telerehabilitation programs in combination with breathing techniques to improve long COVID symptoms and demonstrated both improved quality of life and stress symptoms (54). However, functional exercise exhibited more significant results improving fatigue and functional performance (54). Physical exercise rehabilitation should be performed in a clinical setting with direct supervision to ensure patient safety (51, 55).

Pulmonary rehabilitation has positive effects on dyspnea, physical function, quality of life, anxiety and depression, however not as significant

on fatigue (56, 57). Face-to-face rehabilitation and telerehabilitation both demonstrate improved outcomes with face-to-face delivery faring slightly better in terms of improved quality of life (57).

5.2 Neuropsychiatric symptoms

The most common neuropsychiatric symptoms in long COVID include depression, anxiety, sleep disturbances, parosmia, and cognitive impairment (58, 59). "Brain fog" is a term used by patients to describe their cognitive impairment experience and may include any of the following: concentration difficulty, feelings of confusion, cognitive slowing, mental fuzziness, forgetfulness, word finding, mental fatigue (45, 59).

Neuropsychiatric screening may include formal psychological assessment, testing for autonomic dysfunction, and cognitive impairment screening with the MOCA test (26, 41). Sleep quality and mental health should also be assessed (41). Autonomic dysfunction may be screened with the Composite Autonomic Symptom Scale-31 (COMPASS 31) and diagnosis may be facilitated through evaluation of beat-to-beat blood pressure and heart rate variability (HRV) (26). Dysautonomia symptoms that are also components of long COVID include changes to smell and taste, headaches, and hypoxia (26).

Utilization of psychological aides such as cognitive behavioral therapy and antidepressants for mental health conditions associated with long COVID may provide benefit (26).

Parosmia is a sense of smell distortion and negatively impacts quality of life as a significant number of patients report associated weight loss, reductions in enjoyment of food, and depression (60). For persistent parosmia, management includes olfactory training, nasal corticosteroid sprays, and/ or vitamin A drops (41, 60).

Exercise based rehabilitation is also recommended to manage long COVID mental health and sleep-related problems once other conditions such as POTS and PEM have been ruled out (41, 48, 56).

5.3 Underutilized modalities

Long COVID symptoms contribute to social and economic hardship for individuals and their families highlighting the urgent need for interventions to provide relief (61). The following highlights two underutilized interventions with well-established safety profiles that may improve functionality and quality of life in patients suffering with long COVID.

5.3.1 Stellate ganglion block

Overactivity in the sympathetic nervous system coupled with underactivity in the vagus nerve may contribute to the persistent inflammation found in long COVID (62). This persistent inflammation unsettles the sympathetic and parasympathetic nervous systems' balance and likely contributes to the characteristic symptoms of long COVID (62). A safe and underutilized intervention to target the autonomic nervous system to potentially relieve long COVID symptoms is the stellate ganglion block (SGB). SGBs have been a treatment modality for nearly a century, particularly for several sympathetically mediated conditions such as complex regional pain syndrome (CRPS), postherpetic neuralgia, and refractory cardiac arrhythmias (32, 63). SGBs are considered an emergent modality in conditions such as anosmia, chronic fatigue syndrome, and anxiety and depression in PTSD (64).

SGBs are performed with imaging guidance while patients are in the supine position, head turned opposite from the procedure side, and with the head of the bed slightly elevated to reduce risk of adverse events such as pneumothorax or injury of adjacent structures (62, 64). This positioning also facilitates decompression of the subclavian vessels and reduces the distance of the stellate ganglion from the needle entry point (62).

Complications that may occur after SGB delivery include systemic or local adverse events. Systemic adverse events include the most common complaints of hoarseness and lightheadedness, followed by cough, dyspnea, migraine headaches, or ptosis (65). Local adverse events include hematoma formation, dural puncture, and local infection (two cases with patients on either concomitant oral or system steroids potentially increasing infection risk during the peri-procedure period) (65). While most complications are transient, these potential adverse events must be weighed against the patient's personal symptom burden prior to SGB recommendation.

Parosmia is associated with poor quality of life and significant weight loss (60). In a study comparing interventions for parosmia, while SGBs had the lowest utilization in comparison to oral steroids and smell training, it had the highest reported percentage improvement among participants with maintained benefit (60). The classic protocol as designed by Hummel et al. for smell training, or olfactory training, involves patients sniffing four odors for at least 10 s, twice daily, for at least 3 months (66, 67).

A retrospective cohort study of 41 participants evaluated the use of SGBs for long COVID symptoms and initial symptoms included: fatigue (85%), brain fog (80%), post-exertional malaise (66%), mood changes (51%), taste or smell changes (44%), shortness of breath (41%), sleep problems (34%), tachycardia or palpitations (22%) (62). Reduction of at least one symptom was reported in 86% and relief of all presenting initial symptoms was reported in 61% of participants (62). Most patients reported symptom improvement within 15-min of SGB delivery while other symptoms that could not be evaluated immediately such as fatigue or brain fog, improvement was reported over 1–2 weeks from delivery (62). At 9-to-12-month follow-up, only 2 patients reported return of symptoms (62). Long term follow-up studies of long COVID patients after SGB are recommended to evaluate duration of benefit. Pearson et al. (62) urge for prompt consideration of SGBs to treat long COVID symptoms as diminished response has been observed in other chronic post-viral diseases such as Lyme disease or myalgic encephalopathy and is theorized to be attributed to time-critical neuroadaptive changes.

For patients suffering with long COVID, consider timely referral to interventional pain management for SGB consideration.

5.3.2 Low-dose naltrexone

Another underutilized intervention with an established safety profile for a variety of conditions is the pharmacological agent naltrexone. Naltrexone is a non-selective opioid antagonist currently approved by the US Food and Drug Administration (FDA) for the treatment of alcohol and opioid dependence and is prescribed at 50–150 mg daily (68, 69). At doses below 5 mg, it is considered low-dose naltrexone (LDN), exhibits anti-inflammatory and analgesic properties, and has been used off-label to reduce severity of symptoms in conditions such as fibromyalgia, multiple sclerosis, complex regional pain syndrome, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and

Crohn's disease (69–71). LDN is widely available with a prescription, also at a low cost, and is associated with minimal side effects (69). LDN has been associated with improvement of several clinical symptoms related to long COVID such as fatigue, poor sleep quality and pattern, brain fog, post-exertional malaise, headache, and demonstrated reduction of symptoms and improvement of functionality (70). In patients living with long COVID presenting with neuropsychiatric symptoms, fatigue, or exertional intolerance, consider utilization or adjunct therapy with LDN.

5.4 Prevention

There is general agreement across the literature stating the most effective way to prevent long COVID is to prevent COVID-19 infection with appeals for strong vaccination efforts (15, 18, 72). Vaccination may decrease prevalence of long COVID among US adults by almost 20.9% with at least two-dose vaccination associated with lower risk of persistent fatigue and pulmonary complaints (72, 73). Vaccination reduces the risk of long COVID (40, 41, 46, 74, 75). Several studies demonstrate protective effects of vaccination against long COVID (46, 76–79). Additionally, vaccination alleviates the severity of long COVID symptoms (26, 41, 80–82).

6 Conclusion

Long COVID is an emerging condition without formal consensus on its definition, diagnostic tools, or validated treatments. In a subset of patients, long COVID is likely a chronic disease with long-term disability which will contribute to rising healthcare utilization, and decreased workforce and productivity. There is an urgent need for more knowledge regarding long COVID identification, treatments, and outcomes to direct management guidelines particularly for primary care providers who serve as the gap to more specialized care for patients living with long COVID. Multidisciplinary rehabilitation is the most recommended course of care for patients with long COVID (2, 18). However, it is not recommended for patients with irreversible lung damage (70), ME/CFS (32), or POTS (18).

ME/CFS and long COVID have many overlapping symptoms and features making it difficult to distinguish one from another. Most notable differences include: changes to smell and taste, rash and loss of hair more likely in long COVID compared to ME/CFS (83). Higher inflammatory response reflected by stronger cytokine levels has been demonstrated in ME/CFS compared to long COVID however larger scale studies are needed to confirm (84). Employ caution with physical exercise rehabilitation recommendations as exercise may exacerbate symptoms and be detrimental for conditions such as PEM and POTS (41, 48, 51). In ME/CFS patients, NICE guidelines have recommendations for pacing methods for these patients as to not overexert themselves or aggravate their symptoms (32). Long COVID symptoms can be debilitating to its sufferers and impact not only patients but their families. In addition to multidisciplinary rehabilitation, consider early referral to interventional pain management for consideration of SGB or initiation of LDN to alleviate long COVID symptoms. Vaccination not only reduces the risk of and is protective against long COVID, but also alleviates the severity of long COVID symptoms (26, 40, 41, 46, 74–77, 80–82).

Primary care providers are at the forefront of care for their patients living with long COVID. With this up-to-date information, they will be able to identify the most common symptoms and presentation, validate patients' experiences, provide care recommendations to improve quality of life and functionality, and coordinate future long-term supportive care.

Author contributions

TD: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. KB: Writing – review & editing.

Funding

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

Acknowledgments

A special thank you to KB (Shenandoah University, Winchester) for her unwavering support, invaluable guidance, and constructive feedback during the development of this article. All opinions, omissions, and errors remain my own.

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 03 July 2024
DOI 10.3389/fmed.2024.1401602

OPEN ACCESS

EDITED BY
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RECEIVED 15 March 2024
ACCEPTED 18 June 2024
PUBLISHED 03 July 2024

CITATION
Grippo F, Minelli G, Crialesi R, Marchetti S, Pricci F and Onder G (2024) Deaths related to post-COVID in Italy: a national study based on death certificates.
Front. Med. 11:1401602.
doi: 10.3389/fmed.2024.1401602

Deaths related to post-COVID in Italy: a national study based on death certificates

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Introduction: SARS-CoV-2 infection has been associated with the onset or persistence of symptoms in the long-term after the acute infection is resolved. This condition known as Post-COVID, might be particularly severe and potentially life-threatening. However, little is known on the impact of post-COVID condition on mortality. Aim of the present study is to assess and quantify Post-COVID deaths in Italy in years 2020 and 2021, based on an analysis of death certificates.

Methods: Data from the Italian National Cause of Death Register were analyzed. ICD-10 code U09.9, released by the World Health Organization in September 2020, was used to identify the 'Post-COVID' condition. Numbers of post-COVID deaths from October 2020 to December 2021 were analyzed. Rates of post-COVID deaths were calculated for the year 2021.

Results: Between October 2020 and December 2021, 4,752 death certificates reporting post-COVID condition were identified. Of these, 14.9% ($n = 706$) occurred between October and December 2020 and 85.1% ($n = 4,046$) in 2021. In 46.0% of post-COVID-related deaths, the underlying cause of death was COVID-19. Other frequent underlying causes were heart disease (14.3% of cases), neoplasms (9.2%), cerebrovascular diseases (6.3%) and Alzheimer's disease and other dementias (5.5%). The mortality rate related to post-COVID conditions in year 2021 was 5.1 deaths per 100 thousand inhabitants and it increased with increasing age. Men showed a higher mortality rate than women (4.3 deaths per 100 thousand in women and 6.0 deaths per 100 thousand in men).

Discussion: Post-COVID conditions contributed to a substantial number of deaths in Italy. Strategies to identify the population at risk of severe long-term consequences of SARS-CoV-2 infection and interventions aimed at reducing this risk must be developed.

KEYWORDS

long-COVID, post-COVID, mortality, death certificates, morbidity

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused numerous deaths worldwide. International data show that since the beginning of SARS-CoV-2 epidemic more than 7 million persons died because of Coronavirus disease (COVID-19) worldwide (1). In particular, SARS-CoV-2 infection can cause an acute respiratory syndrome associated with high mortality rate particularly in old and frail persons and in those with a high multimorbidity burden (2, 3).

SARS-CoV-2 infection has also been associated with the onset or persistence of symptoms in the long-term, weeks or months after the acute infection is resolved. This condition known as Post-COVID is defined as the persistence of symptoms due to SARS-CoV-2 infection for more than 12 weeks after the start of acute symptoms (4, 5). The post-COVID condition was officially recognized by the World Health Organization (WHO) in 2020 by the definition in the International Classification of Diseases, 10th Revision (ICD–10) of mortality code U09.9 for coding and reporting Post-COVID conditions linked with preceding acute COVID-19 (6). According to a meta-analysis of 194 studies including 735,006 individuals, 45% of SARS-CoV-2 infection survivors experienced at least one unresolved condition at a mean follow-up of 4 months (7). Post-COVID has also been associated with poor quality of life and with a high utilization healthcare services, including outpatient visits, diagnostic tests and hospitalizations (8, 9). Female sex, older age, pre-existing comorbidities were found to be significantly associated with its development (10).

Although some Post-COVID conditions affecting the neurological, cardiocirculatory, respiratory and endocrine system might be particularly severe and potentially life-threatening (11, 12), little is known on the impact of Post-COVID condition on mortality. A study, performed by the Center for Disease Control (CDC) in the United States (US) and based on death certificates analysis, showed that post-COVID played a part in 3,544 deaths in the US from January 2020 through the end of June 2022 (13). However, this study was based on literal text search of death certificates, due to the fact that the code U09.9 was not implemented in the United States in the period considered in the analysis, leading potentially to an underestimation of Post-COVID deaths. Aim of the present study is to assess and quantify Post-COVID deaths in Italy in years 2020 and 2021 (those associated with the strongest impact of COVID-19 on mortality in Italy) (14), based on an analysis of codes reported in death certificates.

Methods

Data source

Analyses were performed based on the Italian National Cause of Death Register (15), managed by the Italian National Institute of Statistics (ISTAT), which collects information on the cause of death and demo-social variables (sex, age, residence, citizenship, etc.) for all deaths occurring in Italy. Causes of death are provided by physicians who report the sequence of causes directly leading to death and other relevant morbid conditions that may have contributed to death. All conditions reported are classified according to the International Classification of Diseases, 10th Revision (ICD-10) of the World Health Organization (WHO) (16). From the coded information, the underlying cause (UC) of death, defined as the disease or injury that initiated the sequence of morbid events leading directly to death, and other relevant conditions contributing to death are extracted. The coding and the selection of the UC is performed by means of the worldwide used software Iris.[1] Certificates reporting COVID-19 have been coded according to the instructions issued by WHO which are incorporated also in the software Iris (6, 17). The available national data concerns deaths occurring in Italy until December 2021.

Post-COVID and COVID-19 definitions

Since the beginning of the pandemic, the WHO has progressively activated the emergency ICD-10 codes for COVID-19 related conditions (see Table A1 in the Appendix). In addition to the mortality codes for COVID-19, the code U09.9, indicating late effects or prolonged course, was introduced in September 2020, using the neutral wording 'Post-COVID' (6, 18). WHO specified that 'This term does not pre-empt any etiopathological links, and leaves space for linking any condition to a preceding acute COVID' (6). The code U09.9 is not used for the UC and if the code U09.9 was reported as UC, according WHO provision, the death was attributed to COVID-19.

Numbers of Post-COVID deaths presented in this study refer to deaths occurring from October 2020 (after the code U09.9 for Post-COVID condition was made available by WHO) till December 2021, for which the code U09.9 is reported anywhere on the death certificate. Rates of Post-COVID deaths refer only to deaths occurring in year 2021. Confirmed cases of COVID-19 presented in the manuscript were obtained from the National Institute of Health (19).

Data analyses

The distribution of Post-COVID deaths by UC is presented according to ICD-10 codes. Age-standardized mortality rates were computed by the direct method, using five-year age-group specific rates, except for the 0, 1–4 age groups and the upper age group 95 years and more. Age-specific rates were calculated using mid-year population in 2021. The European standard population was used for weighing the rates (20). We calculated age-standardized mortality rates for Italy as a whole and by sex and age groups (i.e., <50, 50–64, 65–79, and ≥ 80 years).

Results

Between 1st October 2020 and 31st December 2021, 4,752 death certificates reporting Post-COVID condition were identified in the Italian National Cause of Death Register, 0.43% of the over 1.1 million deaths observed in the same period (Table A2 in the Appendix). Of these, 14.9% ($n = 706$) occurred between October and December 2020

1 www.iris-institute.org

and 85.1% ($n = 4,046$) in 2021. Overall, 46.0% of deaths were observed in men and 54.0% in women. Concerning the age distribution, 65.0% of deaths were aged 80 years or more, 26.4% 65–79 years, 7.0% 50–64 years and 1.5% were 0–49 years.

Table 1 reports the distribution of cases according to the UC of death. In 46.0% of Post-COVID related deaths, the UC was COVID-19. Other frequent UC were heart disease (14.3% of cases), neoplasms (9.2%), cerebrovascular diseases (6.3%), Alzheimer disease and other dementias (5.5%) and diseases of digestive system (2.6%). This distribution was slightly different between men and women: in men, COVID-19 and neoplasms were more commonly observed as an UC of death, while women showed a higher proportion of heart disease, cerebrovascular disease and Alzheimer and other dementias. The proportion of deaths reporting COVID-19 as UC varied by age: from 53.4% in 0–49 years old group, to 48.1% in 50–64 years, 48.6% in 65–79 years and 44.6% in 80 years and more groups.

Figure 1B shows the distribution of Post-COVID deaths by month from Febrary 2020 to December 2021 in comparison with the monthly numbers of Sars-CoV-2 positive tests. The monthly trend of Post-COVID related deaths followed the same pattern of the number of cases with a slightly lag time for each wave of the pandemic. Post-COVID related deaths showed a peak (644 cases, the maximum monthly number) in January 2021 following the November 2020 peak of positive tests (two months lag time). A second peak of deaths occurred in April 2021 (506 cases) following the March 2021 peak of positive tests, and the third in October 2021 (173 cases) after the August peak of positive tests. A similar pattern was observed when Post-COVID related deaths were compared with COVID-19 deaths (Figure 1A).

In 2021, the standardized mortality rate related to Post-COVID condition was 5.1 deaths per 100 thousand inhabitants (Figure 2) while the mortality rate for all causes was 898.5 (Table A2 in the Appendix). Based on mortality rates, Post-COVID condition accounts for 0.6% of total mortality. Mortality rate of Post-COVID condition progressively increased with increasing age, reaching 59.2 deaths per 100 thousand inhabitants in the population aged 80 years or older. In addition, men showed 40% higher value of mortality rates than women (in 2021 the rate was 4.3 deaths per 100 thousand in women and 6.0 deaths per 100 thousand in men). Gender differences were higher in younger age groups and tended to disappear only at older ages: the rate ratio male/female was 2.3 in 0–49 years old group, 2.2 in the 50–64 years group, 2.0 in the 65–79 years group and 1.1 in over-80 years group.

Post-COVID mortality rates vary across geographical areas within the Country (Table A2 in the Appendix), with decreasing gradient from North to south. Mortality rates range from 3.0 deaths per 100

TABLE 1 Underlying causes of post-COVID deaths in Italy in 2020 and 2021.

Underlying cause of death		Number			Percent		
ICD10 codes	Description	Men	Women	Total	Men	Women	Total
U071, U072	COVID-19	1,075	1,112	2,187	49.2	43.3	46.0
I10-I25, I30-I51	Heart diseases	272	408	680	12.4	15.9	14.3
	of which:						
I20-I25	Ischemic heart disease	135	117	252	6.2	4.6	5.3
I10-I15	Hypertensive heart diseases	49	137	186	2.2	5.3	3.9
I30-I51	Other heart diseases	88	154	242	4.0	6.0	5.1
C00-D48	Neoplasms	244	191	435	11.2	7.4	9.2
I60-I69	Cerebrovascular diseases	121	179	300	5.5	7.0	6.3
G30, F01-F03	Alzheimer disease and other dementias	75	187	262	3.4	7.3	5.5
K00-K99	Diseases of the digestive system	63	62	125	2.9	2.4	2.6
N00-N99	Diseases of the genitourinary system	42	42	84	1.9	1.6	1.8
E10-E14	Diabetes	48	50	98	2.2	1.9	2.1
V00-X59	Accidental deaths	21	53	74	1.0	2.1	1.6
A00-B99	Infectious and parasitic diseases	26	40	66	1.2	1.6	1.4
G20-G21	Parkinson disease	38	28	66	1.7	1.1	1.4
	Other causes	160	215	375	7.3	8.4	7.9
	Total	2,185	2,567	4,752	100.0	100.0	100.0

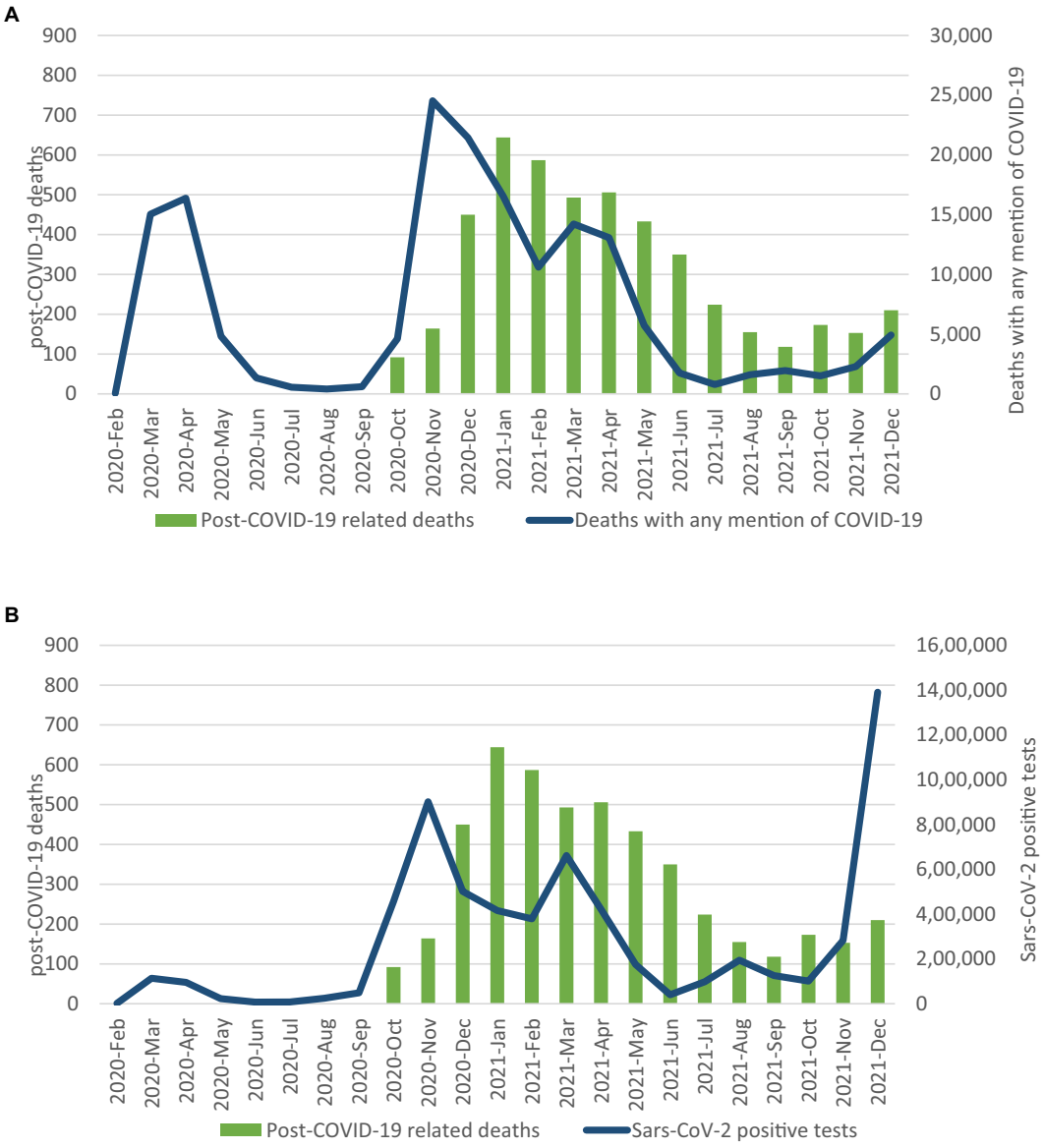

FIGURE 1
Post-COVID-19 deaths and SARS-CoV-2 positive tests by month **(A)** and post-COVID-19 and COVID-19 deaths by month **(B)**.

thousand in the Island area (0.3% of overall mortality rate) and 6.8 (0.8% of overall mortality rate).

Discussion

This is one of the first national studies quantifying, in terms of mortality, the burden of Post-COVID condition. Italy, in particular, faced significant challenges during the early stages of the pandemic, reporting approximately 6 million cases and over 140 thousand deaths from February 2020 (1), but the impact of long-term consequences of COVID-19 on mortality where not estimated so far. The study shows that in 2020 and 2021, Post-COVID contributed to more than 4,700 deaths in Italy. COVID-19 was identified as the leading cause of death in about half of these cases, but also heart disease, neoplasms, cerebrovascular diseases and Alzheimer disease and other dementias were commonly associated with these deaths. Older persons and men seemed at higher risk for Post-COVID related death. Post-COVID mortality is higher in the northern area of Italy and decreases in the South, following the distribution of the COVID-19 cases and deaths in the Country (19).

The overall number of deaths and mortality rate in the Italian population seems substantially higher as compared with what described in a recent study performed in the US (13). These differences can be due to the different methodology adopted in the two studies. As mentioned, in the study performed in the US, the identification of Post-COVID deaths was based on literal text search of death certificates, since the ICD-10 code to identify this condition was not implemented in the period considered in the analysis, leading potentially to an underestimation of Post-COVID deaths. At the opposite the Italian National Institute of Statistics (ISTAT) adopted this code and made it available for use in death certificates from September 2020, allowing for a more careful coding of Post-COVID condition.

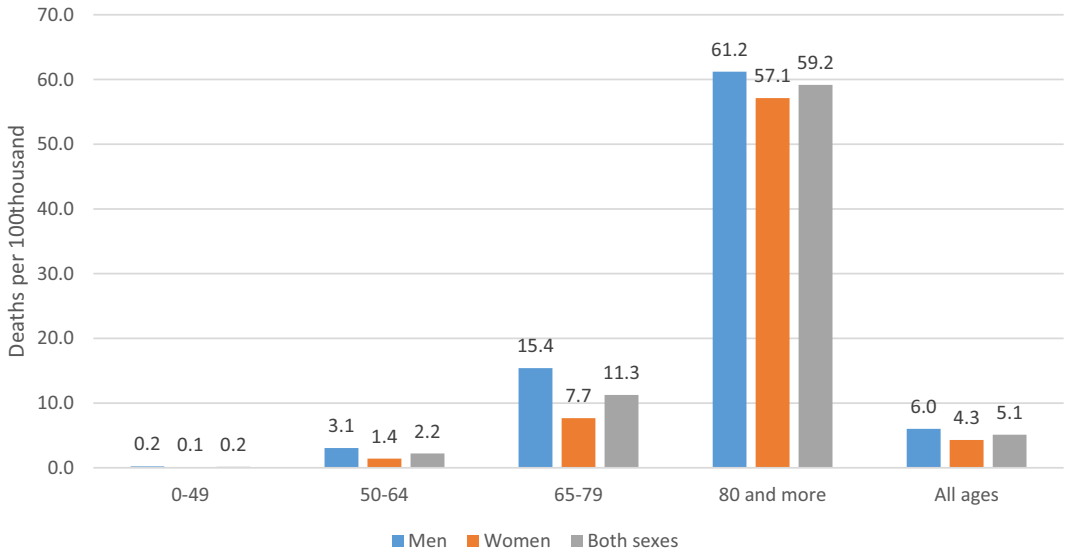

FIGURE 2
Standardized mortality rates of post-COVID condition by sex and age group. Year 2021 (deaths per 100 thousand inhabitants).

Post-COVID condition was poorly known at the beginning of the epidemic and the first study recognizing and reporting this condition in the Italian population was published in July 2020 (21). First guidelines on this condition were published between the end of 2020 and beginning of 2021 (17, 22). In addition, poor availability of diagnostic tools for COVID-19 in the first 2 months of the epidemic in Italy (March and April 2020) may have limited the ability to diagnose not only COVID-19 but also its long-term consequences in 2020 (23). Therefore, a misclassification of Post-COVID related deaths, particularly in 2020 is possible and for this reason only mortality rates for year 2021 are presented in this study.

Long term consequences of COVID-19 can substantially impact on health outcomes. In a cohort study performed on more than 600,000 adults in Italy, patients suffering from COVID-19 had a 2-fold higher rates of outpatient visits and hospitalizations and nearly 3-fold higher rates of instrumental diagnostic procedures in the 6-month after acute the infection (9). Similarly, in a cohort study performed in the US on more than 100,000 patients, SARS-CoV-2 infection was associated with a 4% increase in healthcare utilization over a 6-month period, mainly for emergency department visits (24). COVID-19 has been associated with onset of acute conditions that can increase mortality in the long term (i.e., stroke or myocardial infarction) or it can lead to progressive onset of severe and potentially life-threatening in the long-term, such as myocarditis or dementia (7, 8).

Noticeably, in almost half of the cases of Post-COVID related deaths the underling cause of death was represented by a chronic condition, including heart disease, neoplasms, cerebrovascular disease and Alzheimer dementia. This finding underlines the fact that COVID-19 can interact with pre-existing conditions, leading to increase long-term mortality due to these conditions (25). The interplay between COVID-19 and pre-existing health conditions can lead to increased mortality rates by exacerbating underlying health issues, compromising organ function, and impairing the body's ability to fight off the infection.

Interestingly men and older adults have the highest mortality rate for post-COVID condition. This finding mirrors what was observed for acute COVID-19 mortality, suggesting a common pathway leading to increased mortality related to acute and long-term consequences of SARS-CoV-2 infections, in persons with these characteristics (2, 3, 26). Advanced age is associated with the presence of multiple chronic conditions and with frailty, which can increase the susceptibility to negative health consequences related to COVID-19 and Post-COVID (3). Several factors can explain gender differences in COVID-19, which can be generalized to post-COVID (27, 28). Biological factors can make men more susceptible to severe outcomes from certain infections, including COVID-19, while women generally present a stronger immune response. Men have a higher prevalence of underlying health conditions, including cardiovascular disease, hypertension, and diabetes, which increase the risk of severe COVID-19 outcomes. Finally, hormonal differences could play a role in the immune response to infections.

The present study has several limitations. First, the ICD-10 code identifying post-COVID conditions was implemented at a national level on September 2020 and therefore deaths associated with this condition occurring before this date may have been underestimated. Second, we can not link Post-COVID related deaths with SARS-Cov-2 infection and therefore it is not possible to measure the time interval between SARS-CoV-2 infection and Post-COVID related deaths and to assess how infection characteristics (i.e., infection severity or variant) impacts on mortality. Indeed, the onset and time course of conditions largely varies across individuals and by type of condition (7, 8, 29). Neurological conditions often have a delayed onset of weeks to months and several neurocognitive symptoms can worsen over time. Similarly, cardiovascular and respiratory complications of COVID-19 infection can progressively worsen over time, leading to increased mortality in the long-term. Third, data presented apply to the Italian population and cannot be generalizable to other countries or regions with different healthcare systems, demographic profiles or varying degrees of SARS-COV-2 infection spread. In this context, we described substantial differences in Post-COVID-related mortality between Italy and the US. Further analyses from death registries of additional countries may

be necessary to comprehensively address this topic. Finally, while death certificates can provide valuable information for epidemiological research, they may have not captured the full complexity or nuances of post-COVID conditions. This could be attributed to the limited knowledge on the numerous potential long-term consequences of COVID-19, particularly during the early phases of the epidemic, and the possibility that some conditions leading to long-term mortality from COVID-19 may not have been accurately diagnosed as related to the infection.

Conclusion

In conclusion, we show that Post-COVID condition contributed to a substantial number of deaths in Italy. Strategies to identify the population at risk of severe long-term consequences of SARS-CoV-2 infection and interventions aimed at assessing this population and reducing this risk must be developed.

Data availability statement

The analyses presented in the paper are based on aggregated data. Requests for access to the causes of death dataset should be addressed to the Istat contact centre (https://contact.istat.it/s/?language = en). The datasets presented in this article are not readily available because the data analysis used in this study complies with the European General Data Protection Regulation (GDPR EU 2016/679). The Italian Data Protection Authority has authorised the processing of personal data on causes of death by the Italian Institute of Statistics.

Author contributions

FG: Data curation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. GM: Methodology, Supervision, Writing – review & editing, Writing – original draft. RC: Supervision, Writing – review & editing. SM: Methodology, Supervision, Writing – review & editing. FP: Supervision, Writing – review & editing. GO: Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The study was nested in the project analysis and strategies of response to the long-term effects of COVID-19 infection (Long-COVID) funded by the National Center for Disease Prevention and Control of the Italian Ministry of Health in 2021 and approved by the Ethics Committee of the ISS (ref. PRE-BIO CE 01.00 0015066, 2022). The study sponsor had no role in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

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

Publisher's note

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Appendix

TABLE A1 Emergency ICD-10 codes for COVID-19 and post-COVID.

Codes	Description	Positions in death certificates
U07.1	Confirmed diagnosis of COVID-19	Underlying cause
U07.2	Clinical or epidemiological diagnosis (suspected or probable) of COVID-19	Underlying cause
U10.9	Multisystem inflammatory syndrome associated with COVID-19, unspecified	Other causes
U09.9	Post COVID-19 condition	Other causes

The underlying cause of death is defined as 'the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury'. Codes U10.9 and U09.9 cannot be used for the underlying causes of death and if reported as underlying causes of death, according to WHO provision, the death was attributed to COVID-19.

TABLE A2 Deaths and standardized mortality rates (deaths per 100 thousand inhabitants) of Post-COVID condition and all causes by sex and area (Nuts1) of residence (Year 2020 and 2021).

Nuts1 Area	Deaths						Standardized mortality rates		
	2020			2021			2021		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
Post-COVID-19 condition									
North-west	112	160	272	540	659	1,199	6.3	4.5	5.3
North-east	67	106	173	496	610	1,106	7.9	5.7	6.8
Center	57	65	122	371	420	791	5.8	3.9	4.8
South	52	45	97	340	362	702	5.1	3.8	4.4
Islands	19	20	39	123	113	236	3.8	2.3	3.0
Nonresidents, missing	2	1	3	6	6	12			
Italia	309	397	706	1,876	2,170	4,046	6.0	4.3	5.1
All causes of death									
North-west	54,541	57,620	112,161	90,640	97,177	187,817	1,082.1	696.1	854.9
North-east	37,062	40,719	77,781	65,084	70,194	135,278	1,060.2	689.1	844.7
Centre	38,012	40,758	78,770	69,369	74,951	144,320	1,089.4	722.8	877.1
South	41,418	41,275	82,693	77,937	80,503	158,440	1,198.8	820.2	984.9
Islands	20,806	20,651	41,457	38,579	39,898	78,477	1,201.8	818.4	983.5
Nonresidents, missing	961	570	1,531	1,734	903	2,637			
Italia	192,800	201,593	394,393	343,343	363,626	706,969	1,117.2	738.8	898.5

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 10 July 2024
DOI 10.3389/fpubh.2024.1403153

OPEN ACCESS

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RECEIVED 18 March 2024
ACCEPTED 26 June 2024
PUBLISHED 10 July 2024

CITATION
Won J-H, Hong Y, Kim S and Lee H (2024) One-year post-acute COVID-19 syndrome and mortality in South Korea: a nationwide matched cohort study using claims data. *Front. Public Health* 12:1403153. doi: 10.3389/fpubh.2024.1403153

One-year post-acute COVID-19 syndrome and mortality in South Korea: a nationwide matched cohort study using claims data

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Background: Current understanding of post-COVID-19 syndrome in South Korea is primarily based on survey studies or research targeting specific patient groups, such as those hospitalized. Moreover, the majority of relevant studies have been conducted in European and North American populations, which may limit their applicability to the South Korean context. To address this gap, our study explores the one-year outcomes of COVID-19, focusing on the potential post-acute syndrome and all-cause mortality in South Korea.

Methods: This retrospective cohort study used nationwide claims data in South Korea, including adults aged >18 with records between January 20, 2020, and February 25, 2021. Patients were classified into COVID-19 and non-COVID-19 groups and matched 1:1 based on propensity scores. Primary outcomes were 12-month post-acute COVID-19 syndrome and all-cause mortality.

Results: The study involved 34,802 matched patients. The COVID-19 group had significantly elevated risks of coagulopathies (OR = 2.70 [2.24, 3.28]; $p < 0.001$), chronic lower respiratory diseases (OR = 1.96 [1.80, 2.14]; $p < 0.001$), symptoms of the circulatory and respiratory systems (OR = 1.91 [1.80, 2.04]; $p < 0.001$), mood disorders (OR = 1.67 [1.51, 1.86]; $p < 0.001$), cardiac diseases (OR = 1.39 [1.21, 1.59]; $p < 0.001$), and symptoms of cognition, perception, emotional state, and behavior (OR = 1.15 [1.04, 1.27]; $p = 0.005$). All-cause mortality was higher in the COVID-19 group during the 6 months (OR = 1.34 [1.06, 1.69]; $p = 0.015$), but gradually decreased, reaching an OR of 0.996 ([0.83, 1.19]; $p = 0.964$) at 1 year.

Conclusion: In South Korea, the 12-month post-acute COVID-19 syndrome includes coagulopathies, respiratory issues, mood disorders, and cardiac diseases. The risk of all-cause mortality post-COVID-19 is heightened for up to 6 months, then significantly decreases and resolves within a year.

KEYWORDS

COVID-19, post-acute sequelae of COVID-19, mortality, South Korea, cohort studies

1 Introduction

Post-acute COVID-19 Syndrome is characterized by a range of new, recurring, or persistent symptoms or conditions that COVID-19 survivors experience beyond the acute phase (1). The prevalence of post-acute COVID-19 syndrome ranges from 5 to 50%, depending on factors such as the definition used, the population studied, and the time period observed (2). Health complications associated with post-acute COVID-19 Syndrome include, but are not limited to, thromboembolic disorders, neuropsychiatric issues, and chronic fatigue syndrome (3).

Although progress has been made in understanding the long-term effects of COVID-19 up to one-year post-infection, knowledge gaps still remain. For example, previous investigations have been studied in specific patient groups such as hospitalized, or were conducted predominantly in European and American countries, with relatively few studies focusing on Asian populations, especially in South Korea (4–7). Furthermore, much of the existing research in Asia focused only on subjective findings based on survey or narrowly targeted specific medical conditions (8–12).

Motivated by the knowledge gap, we investigated the one-year consequences of COVID-19, focusing on the potential post-acute COVID-19 syndrome and all-cause mortality in South Korea. Leveraging the wide coverage of a nationwide population-based claims database in South Korea (13–15), we aim to understand how COVID-19 affects the general population across all demographics and varying COVID-19 severities. To this end, we identified diseases, symptoms and all-cause mortality experienced by individuals who contracted COVID-19 *prior to* the initiation of the COVID-19 vaccination in South Korea. We then evaluated whether the diseases, symptoms and all-cause mortality happened more frequently or less in individuals who were infected with COVID-19 than in those not in the same period.

2 Materials and methods

2.1 Data source

We used a nationwide claims database named the HIRA Covid-19 OMOP database, provided by the Health Insurance Review & Assessment Service (HIRA) in South Korea, standardized according to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM, version 5.3) (13). Maintained by the governmental institute in South Korea, the HIRA Covid-19 OMOP database contains information about COVID-19 diagnosis, managed by the Korea Disease Control and Prevention Agency, and all-cause mortality data, linked with the national death registry of Statistics Korea (13). All COVID-19 diagnoses during our study period were confirmed only by reverse transcription polymerase chain reaction (RT-PCR) testing (13).

This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (SNUH), Seoul, South Korea. Due to the retrospective and de-identified nature of this study, the SNUH IRB waived the requirement for obtaining informed consent from study participants (IRB No: E-2207-022-1337).

2.2 Study population

Eligible patients were adults aged >18 years old and had at least one visit record in the HIRA CDM database between January 20, 2020 and February 25, 2021. These two dates were the day when the first case of COVID-19 was confirmed in South Korea and the day when the COVID-19 vaccination program started in South Korea, respectively. Eligible patients were divided into two groups based on the presence or absence of a COVID-19 diagnosis record during the study period: *COVID-19* and *non-COVID-19 groups*, respectively.

The index date was the date of the first recorded COVID-19 diagnosis or the initial visit date within the study period for the COVID-19 and the non-COVID-19 groups, respectively. To ensure covariate balance, eligible patients were matched 1:1 based on propensity scores derived from a logistic regression model incorporating age, sex, Charlson Comorbidity Index (CCI), and index month/year. Baseline covariates were matched using data from 1 year prior to the index date to account for pre-existing conditions. We utilized the OHDSI adaptation of the CCI, which employs SNOMED CT coding and has been validated across major studies for its comparable performance to the Quan adaptation. Propensity score matching was performed using the open-source OHDSI Cohort Method packages in R (16).

2.3 Outcomes

The primary outcomes of interest were the potential 12-month post-acute COVID-19 syndrome, defined as the occurrence of pre-specified diseases and symptoms (Supplementary Table S1) observed between one-month and a year after the index date, and all-cause mortality within a year after the index date. Pre-specified diseases and symptoms were chosen based on their possible association with post-acute COVID-19 syndrome (3). We categorized potential 12-month post-acute COVID-19 syndrome according to the Korean Standard Classification of Diseases and Causes of Death, 8th edition (KCD-8). Outcomes related to external causes (e.g., injury, poisoning) or congenital anomalies were excluded from the pre-specified diseases and symptoms. The temporal trends in the primary outcomes were also assessed over a year divided into three periods: the acute phase (between the index date and 1 month after an index date), the 6-month post-acute phase (between 1 and 6 months after an index date), and the 12-month post-acute phase (between 1 and 12 months after an index date).

2.4 Statistical analyses

We estimated an odds ratio (OR) of the primary outcomes between the COVID-19 and non-COVID-19 groups using a multiple logistic regression, which incorporated age at the index date, sex, CCI, and index month/year as covariates. Kaplan–Meier Survival curves were used to visually compare the differences in survival probability between the two groups. Furthermore, we analyzed temporal trends in ORs for the primary outcomes using linear regression, where OR and numerically encoded time

10.3389/fpubh.2024.1403153

periods were the dependent and independent variables, respectively. All statistical analyses were performed using R (version 3.5.1; R Foundation, Vienna, Austria).

3 Results

3.1 Study population

A total of 18,278 and 5,501,604 patients initially met the eligibility criteria for the COVID-19 and non-COVID-19 groups, respectively. After 1:1 propensity score matching, the study population consisted of 34,802 patients with both the COVID-19 and non-COVID-19 groups accounting for half of the total patients (i.e., $n = 17,401$) (Table 1). Baseline characteristics were adequately balanced, with the average age of the study population at 49 years, and females constituting 48%. The average Charlson Comorbidity Index (CCI) score in the COVID-19 group was 1.65, slightly lower than that in the non-COVID-19 group (1.768).

3.2 12-month post-acute COVID-19 syndrome

The COVID-19 group had significantly higher risks of coagulation defects, purpura, and other hemorrhagic conditions (OR = 2.70 [2.24, 3.28]; $p < 0.001$), chronic lower respiratory diseases (OR = 1.96 [1.80, 2.14]; $p < 0.001$), symptoms related to the circulatory and respiratory systems (OR = 1.91 [1.80, 2.04], $p < 0.001$), mood disorders (OR = 1.67 [1.51, 1.86]; $p < 0.001$), ischemic heart diseases and other forms of heart disease (OR = 1.39 [1.21, 1.59]; $p < 0.001$), and symptoms related to cognition, perception, emotional state and behavior (OR = 1.15 [1.04, 1.27]; $p = 0.005$) (Figure 1). Conversely, the risks of

TABLE 1 Baseline characteristics of the COVID-19 and non-COVID-19 groups before and after propensity score matching.

	Before PS matching (overall group)			After PS matching*		
	COVID-19 ($N = 18,278$)	Non-COVID-19 ($N = 5,501,604$)	aSD	COVID-19 ($N = 17,401$)	Non-COVID-19 ($N = 17,401$)	aSD
Age, years	50.0	51.2	0.068	48.8	48.6	0.016
Charlson Comorbidity Index	1.923	1.523	0.194	1.650	1.768	0.055
Sex (%)						
Male	47.4%	49.5%	0.043	47.6%	47.5%	0.003
Female	52.6%	50.5%	0.043	52.4%	52.5%	0.003
Index date (%)						
February 2020–May 2020	18.0%	47.8%	0.298	18.9%	20.1%	0.012
June 2020–September 2020	17.3%	49.6%	0.323	18.0%	17.8%	0.020
October 2020–February 2021	66.8%	5.3%	0.615	65.3%	64.3%	0.010

Values are numbers (percentages) unless stated otherwise. PS, propensity score; aSD, absolute standardized difference.
*Balance in covariate distribution between two groups was assessed using the absolute standardized mean difference.

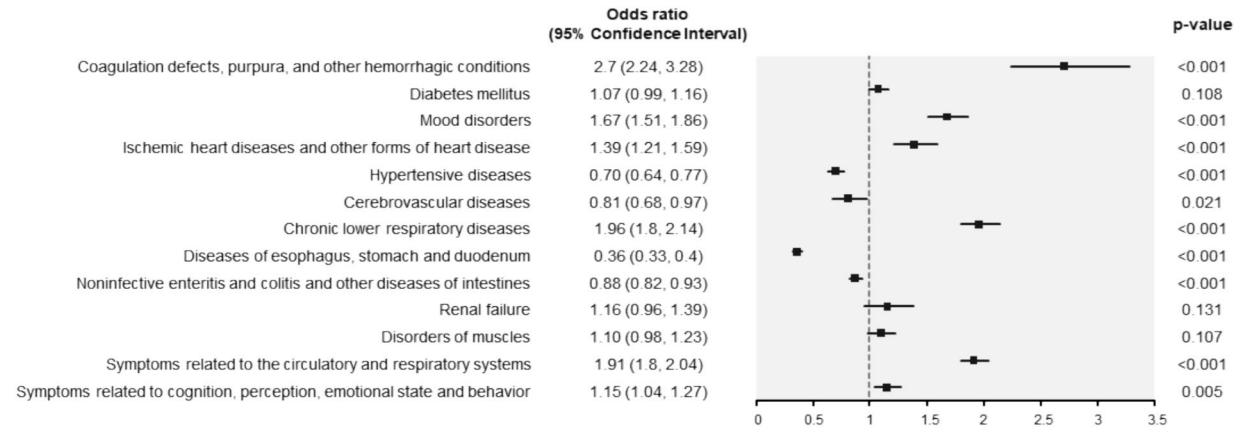

FIGURE 1
Odds ratio (OR) of 12-month post-acute COVID-19 syndrome. An OR greater than one indicates a higher risk of post-acute COVID-19 syndrome in the COVID-19 group than in the non-COVID-19 group.

noninfective enteritis and colitis (OR = 0.88 [0.82, 0.93]; $p < 0.001$), cerebrovascular diseases (OR = 0.81 [0.68, 0.97]; $p < 0.001$), hypertensive disorders (OR = 0.70 [0.64, 0.77]; $p < 0.001$), and diseases of esophagus, stomach, and duodenum (OR = 0.36 [0.33, 0.40]; $p < 0.001$) were significantly lower in the COVID-19 group than in the non-COVID-19 group. On the other hand, the risks of diabetes mellitus (OR = 1.07 [0.99, 1.16]; $p = 0.108$), muscular disorders (OR = 1.10 [0.98, 1.23]; $p = 0.107$), and renal failure (OR = 1.16 [0.96, 1.39]; $p = 0.131$) did not differ significantly between the two groups.

3.3 All-cause mortality

In the acute phase, the COVID-19 group had significantly higher odds of all-cause mortality than the non-COVID-19 group (OR = 1.74 [1.17, 2.61]; $p = 0.007$, Figure 2A). However, this increased risk disappeared by a year after the index date (OR = 0.996 [0.83, 1.19]; $p = 0.964$), with a statistically significant 0.6-fold decrease in the ORs over a year (Supplementary Table S3). While the COVID-19 group had a slightly lower survival probability than the non-COVID-19 group (Figure 2B), this difference was not statistically significant and the largest observed difference in survival probability between the two groups was 0.33 percentage points at day 82.

3.4 Temporal changes in post COVID-19 syndrome

Although statistically not significant, consistent increases in the ORs were noted for disorders of muscles (3.5-fold increase), cerebrovascular diseases (2.1-fold increase), symptoms related to cognition, perception, emotional state and behavior (1.4-fold increase), diabetes mellitus (1.3-fold increase) and renal failure (1.3-fold increase) (Figure 3; Supplementary Table S3). Conversely, a significant decrease in OR was observed for chronic lower respiratory diseases (0.6-fold decrease). Furthermore, consistent but statistically insignificant decreases in the ORs for mood disorders (0.7-fold decrease), coagulation defects, purpura, and other hemorrhagic conditions (0.6-fold decrease).

4 Discussion

Using a nationwide claims database in South Korea, we identified several diseases that were more frequently experienced by patients contracted with COVID-19 than those not, which could be collectively referred to as post-acute COVID-19 syndrome. Notably, the COVID-19 group had a significantly higher risk of developing coagulation defects, purpura, and other hemorrhagic conditions for a year post-infection (OR = 2.70 [2.24, 3.28], $p < 0.001$). A probable

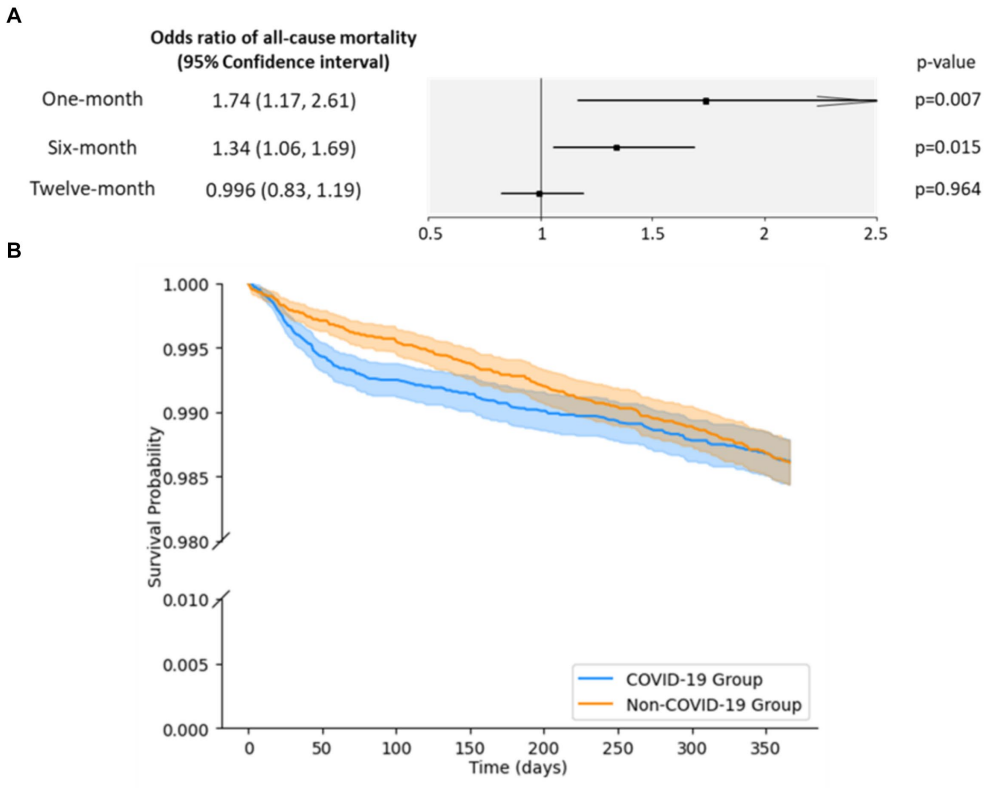

FIGURE 2
Odds ratio (OR) and survival probabilities for all-cause mortality. **(A)** ORs of all-cause mortality by period. An OR greater than one indicates a higher risk of all-cause mortality in the COVID-19 group than in the non-COVID-19 group. **(B)** Kaplan–Meier survival curves for all-cause mortality. The curves represent the survival probabilities in days for the COVID-19 group (blue) and the non-COVID-19 group (orange). The shaded regions correspond to the lower and upper 95% confidence bounds.

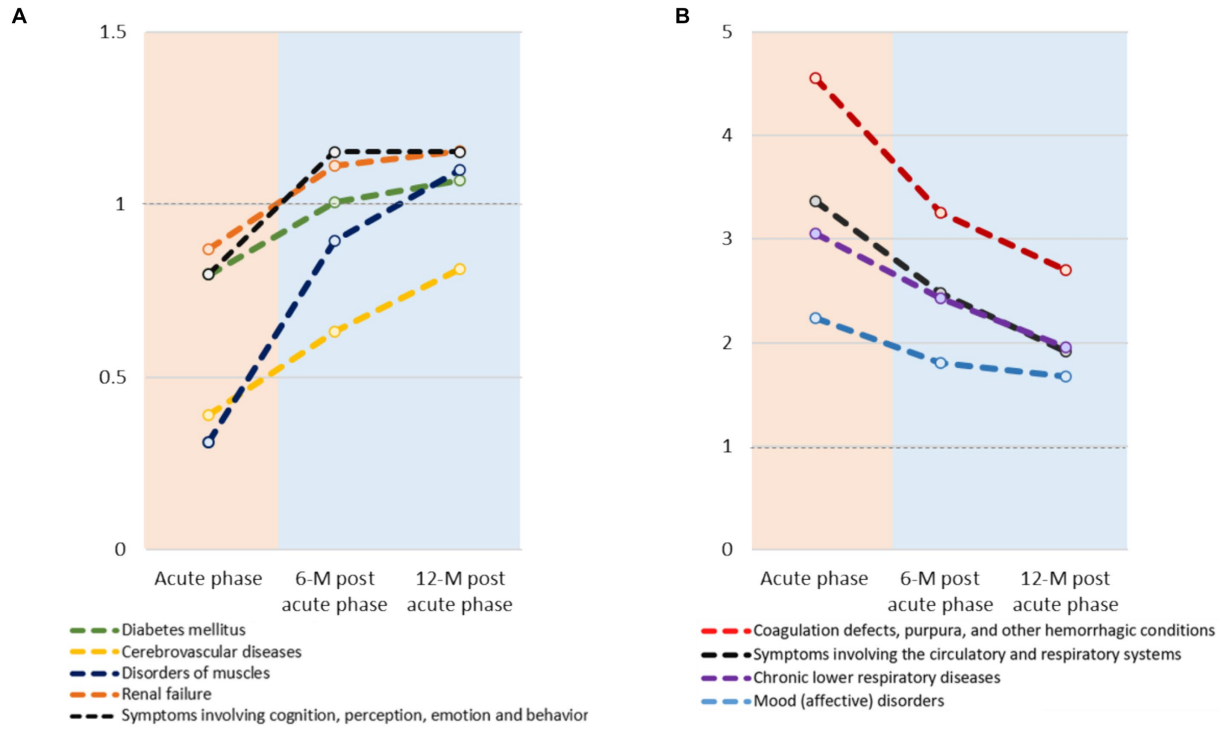

FIGURE 3
Temporal trends in odds ratios (OR) of post COVID-19 syndrome over a year between COVID-19 and non-COVID-19 groups: **(A)** increasing trend and **(B)** decreasing trend. Only those with a difference of OR ≥ 0.2 between the acute and 12-month post-acute phases, and a fold change in OR of ≥1.2 or ≤0.7 between these phases are shown.

mechanism for the heightened risk of hemorrhagic conditions is the cytokine storm triggered by the SARS-CoV-2 virus (17–21). Furthermore, the interaction of SARS-CoV-2 with endothelial cells in the lung, particularly those with overexpressed angiotensin-converting enzyme 2 (ACE2), could exacerbate the risk of coagulopathies by inducing a pro-coagulative and inflammatory state (17–21). Moreover, we noted a significantly higher risk of ischemic heart diseases and other forms of heart diseases in the COVID-19 group (OR = 1.39 [1.21, 1.59], $p < 0.001$). Our findings suggest that the impact of SARS-CoV-2 on hematological and inflammatory functions extends beyond the acute phase, with potential long-term implications, including the development of cardiovascular diseases such as ischemic heart diseases (22–24).

A significantly elevated risk of chronic lower respiratory diseases (OR = 1.96 [1.80, 2.14], all $p < 0.001$) was observed in COVID-19 patients, potentially exacerbated by the virus-induced inflammatory environment, which may accelerate the progression and worsen symptoms of pre-existing conditions such as chronic obstructive pulmonary disease (COPD) (25–28). These findings underscore the long-term respiratory implications of COVID-19, contributing to the emergence of new chronic respiratory diseases and aggravating existing conditions. Likewise, there was a sustained increase in the risk of mood disorders among COVID-19 patients for up to a year (OR = 1.67 [1.51, 1.86], $p < 0.001$). Factors such as pandemic-induced stress, uncertainty, and strict quarantine measures, including social distancing and isolation, highlight the necessity for comprehensive, long-term mental health care strategies for COVID-19 survivors (29–31).

Moreover, COVID-19 patients had a higher risk of all-cause mortality during both the acute phase (OR = 1.74 [1.17, 2.61], $p = 0.007$) and at 6 months (OR = 1.34 [1.06, 1.69], $p = 0.015$), which diminished by 1 year (OR = 0.996 [0.83, 1.19], $p = 0.964$). Supporting these observations, another study demonstrated that the COVID-19 pandemic did not significantly affect the overall national mortality rate in South Korea (32). Furthermore, South Korea has maintained a low COVID-19 death rate at 0.7 (per 100,000) since the start of the pandemic (0.2 since May 2020; 0.2 since June 2020), which was much lower than that in other countries such as the United States, i.e., 60.3 since the start of the pandemic; 36.9 since May 2020; 27.2 since June 2020 (33). Several factors contribute to this low mortality rate, including South Korea's robust public health preparedness, effective management protocols, and the demographic characteristics of our study population.

South Korea was ranked as the fifth best country globally for disaster preparedness and management protocols aimed to reduce COVID-19 mortality (34). In addition, the government provided COVID-19 diagnoses and treatments free of charge to all COVID-19 patients supporting patient recovery (29, 35). These comprehensive healthcare and public health strategies in South Korea may have mitigated the long-term mortality risks associated with COVID-19. Moreover, the demographic characteristics of the study population, with an average age of 48.8 years and a moderate comorbidity burden (CCI score of 1.65), may have influenced the observed all-cause mortality. While these factors collectively contribute to our findings, the precise reasons for the low mortality in COVID-19 patients in South Korea remain unclear.

However, the risk for diseases of the digestive system remained significantly lower in the COVID-19 group over a year than in the non-COVID-19 group (noninfective enteritis and colitis, OR = 0.88 [0.82, 0.93]); diseases of esophagus, stomach, and duodenum (OR = 0.36 [0.33, 0.40]; all $p < 0.001$) in the COVID-19 group than in the non-COVID-19 group. This observation may be attributed to the paradoxical dual role of the ACE2 receptor in the digestive system, where its overexpression increases susceptibility to SARS-CoV-2 but its anti-inflammatory effects could potentially protect against severe digestive complications (36, 37). Additionally, many physicians in South Korea often prescribe gastrointestinal medications such as rebamapide and famotidine along with other drugs, particularly in patients with common respiratory illness (38–40). This prescription practice, which became more widespread after the South Korean government began covering the full cost of medications for COVID-19 patients (40), could have contributed to the lower risks for diseases of the digestive system in the COVID-19 group in our findings. On the other hand, several studies have proposed potential therapeutic advantages of gastrointestinal medications as COVID-19 treatments (41–43). However, the direct impact of these medications on digestive diseases in COVID-19 patients remains unclear.

This study had two major limitations. First, potential confounders such as socioeconomic status and vaccination status that could have affected health outcomes were not fully adjusted (35). However, we adjusted for various factors to minimize the impact of potential confounders. Additionally, by using nationwide data, our study ensured a broad and representative sample. Furthermore, we included only those study participants whose index dates were before the start of the COVID-19 vaccination program in South Korea (35). In addition, it is unlikely, if not impossible, that our study population included patients vaccinated during the follow-up period. Although the COVID-19 vaccination program in South Korea began on February 26, 2021, its roll-out has been seriously hampered by the failure in securing a sufficient number of vaccine doses to cover the population until the end of 2021. Therefore, the early vaccination program in South Korea was strictly prioritized to people over 70 years old. Additionally, those confirmed with COVID-19 (all testing results were PCR-based) were excluded from the vaccination program at least until mid-2022. Given the average age of our study population was 50 and the one-year follow-up period ends February 2022, it is unlikely, if not impossible, that our study population included patients vaccinated during the follow-up period.

Secondly, the utilization of claims data may have introduced bias in disease reporting and diagnosis. The claims database in South Korea includes primary and additional diagnoses that are recorded as the main reasons for treatment or prescription. However, claims data often prioritize specific diagnoses for billing purposes, potentially overlooking other health issues. This issue was particularly pronounced during the COVID-19 pandemic, when there was heightened attention on reporting severe respiratory illnesses and commonly prioritized illnesses related to COVID-19. Consequently, this may have led to an underreporting of less severe or secondary conditions not closely associated with COVID-19, skewing our understanding of the prevalence and diversity of health conditions (44–46).

We observed a slightly lower risk of hypertensive disorders (OR = 0.70 [0.64, 0.77], $p < 0.001$) and cerebrovascular diseases (OR = 0.81 [0.68, 0.97], $p = 0.021$) in the COVID-19 group compared to the non-COVID-19 group. This finding differs from other studies that reported insignificant associations between COVID-19 and these conditions (47–49). This discrepancy may have been caused by the underreporting or deprioritization of those conditions by physicians in South Korea, particularly during the peak of the COVID-19 pandemic.

Additionally, changes in public behavior during the COVID-19 pandemic may explain the lower odds ratios for certain diseases. For example, healthcare utilization for hypertension increased among the general population in South Korea during the pandemic (50, 51). This suggests that while COVID-19 patients might have experienced delays in care for certain conditions, non-COVID-19 patients continued to seek and receive care, possibly to address health concerns proactively before any healthcare service disruptions could occur. Therefore, the lower risk of certain conditions in the COVID-19 patients observed in this study should not be misconstrued as a protective effect of COVID-19. Instead, it is more likely to reflect changes in healthcare utilization and physician reporting patterns during the pandemic, which differently impacted access to healthcare and the management of COVID-19 and non-COVID-19 patients. Conversely, diseases that showed an increased risk in the COVID-19 group may have actually had a lower risk, influenced by similar biases.

While we used comprehensive list of predefined diseases and symptoms covered a wide range of health conditions to reduce the risk of missing less common health issues, further studies using electronic medical records (EMR), which provide a more accurate and details of patient health status and clinical outcomes with physician-confirmed diagnoses and laboratory details, may further validate our findings. Such studies could also address potential biases introduced by the prioritization of specific diagnoses during the pandemic.

In conclusion, post-acute COVID-19 syndrome in South Korea comprises coagulopathies, lower respiratory diseases, mood disorders, and ischemic heart diseases. All-cause mortality is also increased after infection with COVID-19 for up to 6 months, after which the risk significantly decreases and eventually resolves within a year. However, these results should be interpreted with caution, considering the changes in healthcare delivery and reporting biases specific to the Korean healthcare system during the pandemic.

Data availability statement

This study was conducted using anonymized data in a retrospective analysis, adhering to the guidelines set by the Institutional Review Board (IRB). In compliance with IRB regulations, the anonymized data used in this study cannot be shared. This restriction is in place to uphold the privacy and confidentiality standards required by the IRB.

Ethics statement

The studies involving humans were approved by the Institutional Review Board (IRB) of Seoul National University Hospital (SNUH), Seoul, South Korea (IRB No: E-2207-022-1337). The studies were conducted in accordance with local legislation and institutional requirements. Written informed consent for participation was not required from the participants or their legal guardians/next of kin because the database was fully anonymized.

Author contributions

J-HW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft. YH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing, Funding acquisition. SK: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. HL: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was supported by the BK21FOUR Program of the National Research Foundation of Korea (NRF) funded by the Ministry of Education (5120200513755).

Acknowledgments

This study used an OMOP-CDM data provided by the Health Insurance Review & Assessment Service (HIRA), South Korea (i.e., HIRA CDM). The views expressed in this paper are solely those of the author(s) and none of the HIRA or the Korea Ministry of Health and Welfare (MOHW), South Korea.

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.2024.1403153/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 30 August 2024
DOI 10.3389/fmed.2024.1401491

OPEN ACCESS

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RECEIVED 15 March 2024
ACCEPTED 16 August 2024
PUBLISHED 30 August 2024

CITATION
Sperl L, Stamm T, Mosor E, Ritschl V, Sivan M, Hoffmann K and Gantschnig B (2024) Translation and cultural adaptation of the COVID-19 Yorkshire Rehabilitation Scale into German.
Front. Med. 11:1401491.
doi: 10.3389/fmed.2024.1401491

Translation and cultural adaptation of the COVID-19 Yorkshire Rehabilitation Scale into German

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Background: Experts estimate that in up to 10% of the infected, SARS-CoV-2 would cause persistent symptoms, activity limitations and reduced quality of life. Referred to as long COVID, these conditions might, in the future, specifically impact German-speaking countries due to their higher rates of unvaccinated people compared to other Western countries. Accurate measurement of symptom burden and its consequences is needed to manage conditions such as long COVID, and several tools have been developed to do so. However, no patient-reported instrument existed in the German language at the time of writing.

Objective: This study, therefore, aimed to develop a German version of the COVID-19 Yorkshire Rehabilitation Scale (C19-YRS).

Methods: We conducted a translation and qualitative evaluation, including cultural adaptation, of the C19-YRS and assessed its face validity. After creating a preliminary version, 26 individuals (14 women [53%]) participated in cognitive interviews (January 2022 to March 2022). Using cognitive debriefing interviews, we ensured the content's comprehensibility. The matrix-framework method guided the qualitative data analysis.

Results: Compared to the original English version, adaptations were necessary, resulting in changes to the introductory text, while the items for recording persistent symptoms were hardly changed.

Conclusion: The German version of the C19-YRS is expected to support standardized long COVID care.

KEYWORDS

long-COVID, long-term consequences, post-acute sequelae of SARS-CoV-2 (PASC), rehabilitation, patient-reported outcomes

1 Introduction

Experts estimate that in up to 10% of the infected, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) causes persistent symptoms, activity limitations and reduced quality of life (1, 2). Literature refers to these conditions as long COVID and defines them as a combination of manifestations such as fatigue, exhaustion, decreased physical endurance, post-exertional malaise, breathing difficulties, anxiety, depression, posttraumatic stress disorder or pain, lasting for more than 4 weeks after the infection (3–9). Long COVID can affect people of all ages, regardless of whether they had a severe or mild course of disease (5, 9, 10). Vaccination tends to lead to a risk reduction regarding long COVID symptoms (1, 11–13), whereas reinfections seem to cumulatively increase the risk (14).

Long COVID could particularly impact German-speaking countries in Europe, where the number of unvaccinated people is high (15) as well as reinfection rate due to the lack of primary prevention since spring 2023. Accurate measurement of symptom burden and its impact on people's daily lives is needed to manage this condition effectively, and rapid assessment is necessary to fully assess patients' problems and enable targeted multidisciplinary intervention (16). To date, the C19-YRS is the only tool that provides exemplary ideas for patient-centered management and interventions based on the severity of problems reported in the screening tool (17). Completing the C19-YRS over time provides a comprehensive overview of a patient's progress, whether their condition is improving, worsening or fluctuating, which then also supports goal setting and the planning of patient-centered therapeutic interventions. Translating and adapting a multi-professional, COVID-19-specific assessment tool such as the C19-YRS can facilitate comprehensive assessment and intervention counseling, potentially improving standardized care for people with persistent symptoms after acute COVID-19 infection (17). No patient-reported instrument existed in the German language at the time of writing. Therefore, this study aimed to develop a German version of the COVID-19 Yorkshire Rehabilitation Scale (C19-YRS).

2 Materials and methods

We conducted a translation and qualitative evaluation, including cultural adaptation, of the C19-YRS into German and assessed its face validity.

2.1 COVID-19 Yorkshire Rehabilitation Scale (C19-YRS)

The COVID-19 Yorkshire Rehabilitation Scale is a 22-item patient-reported outcome measure for assessing and monitoring long COVID symptoms and was the first long COVID-specific scale reported in the literature (18). Considering psychometric properties, the English version of the C19-YRS showed good internal consistency, and scaling and targeting assumptions were satisfied (19).

Information collected includes 16 symptoms (including shortness of breath, persistent cough, fatigue, pain or discomfort, cognitive problems, anxiety, depression, symptoms of posttraumatic stress disorder [PTSD], palpitations, dizziness, weakness, and sleep problems) as well as their impact on five areas of activities and participation (including communication, mobility, personal care, activities of daily living, and social life) (see Supplementary Appendix 1). The patient is asked to rate each symptom or functional ability on a scale from 0 to 10 (0 being not present and ten being most severe and life-disturbing) (18). The C19-YRS is recommended for initial assessment, at 6 weeks, and at 6 months for follow-up and includes a self-report version. In a self-reported screening tool, outcomes are reported directly without interference from clinicians or health professionals (20), which supports people's active participation in the decision-making process regarding their health care (21). For this reason, it was decided to first translate the self-reported version of the C19-YRS within the scope of this paper.

2.2 Translation and cross-cultural adaptation

First, the authors contacted the team of developers of the original C19-YRS, who granted permission to translate the self-report version of the C19-YRS into German (Austria). The translation process followed five steps according to the guideline established by Beaton et al. (22) namely (1) initial translation, (2) synthesis of translations, (3) back translation, (4) expert committee, and (5) review of preliminary version. In the first step (1), two translators each produced a German version of the C19-YRS (T1&T2). In a second step (2), a third person, who also has expertise in research and translation processes, helped synthesis these translations (T1&T2) into a new version (T12). At this point, the translation team added a step to Beaton's guideline, as a person who is not a native German speaker reviewed the synthesized version to ensure that it was easy to understand. Then, in the third step (3), two English first language translators who were not familiar with the screening tool worked from the T12 translation and produced two back translations (BT1&BT2). In the fourth step (4), an expert committee (methodologist [TS], linguist [LD], translators) reviewed all reports to reach a consensus and jointly produced a preliminary version. Beaton et al. (22) suggest that individuals from the target group should subsequently complete the preliminary version to test understanding of the items. For this purpose, the authors then decided to apply cognitive interviewing methods in the last step of the translation and adaptation process (5) (23). In addition, the cross-cultural adaptation of a health status screening instrument usually involves assessing validity and reliability (24). In the context of this study, an initial aspect of content, validity face validity, which assesses the extent to which a measurement instrument adequately reflects the construct being measured (25), was chosen.

2.3 Participants and sampling

For the cognitive interviews, the first author purposively recruited patients from Austrian rehabilitation centers

participating in the Austrian long COVID registry. Participation was open to people who had been diagnosed with COVID-19 infection, who were experiencing long-term symptoms following a COVID-19 infection, who were at least 18 years old, who understood and spoke sufficient German and who agreed to participate. This study involving human participants was reviewed and approved by the ethics committee of the Medical University Vienna as part of the Austrian Long COVID registry Project (EK 1591/2021). Written informed consent to participate in this study was provided by participants.

The Austrian long COVID registry is a nationwide registry, supported by Gesundheit Österreich GmbH, the Ministry of Health, Medical University of Vienna, Austria Health Insurance Fund, Danube University Krems and two Ludwig Boltzmann Institutes. The overall aim of the registry is to assess the disease course of post/long-COVID-19, evaluate its impact on quality of life on functional capacity, and, e.g., assess the interventions offered (26). Individuals who are referred to one of the participating centers - from primary care centers to rehabilitation centers - and who meet the above inclusion criteria will be asked to complete an online questionnaire covering the above objectives in self-report form and will then be registered in this way.

2.4 Data collection

The authors chose the two most common cognitive interviewing techniques for data collection, thinking aloud and probing (27). The interviews were conducted by the first author and took place either in person at the rehabilitation center or by telephone. Participants were instructed to express what came to their mind ("thinking aloud") while concurrently completing the C19-YRS (23), and in addition they answered probes retrospectively (28) (see Supplementary Appendix 3).

Typically, 10 to 50 interviews are conducted and analyzed in cognitive interviewing studies (29). Since no further new aspects emerged after 26 interviews, the author ended the data collection at this point as she assumed that thematic saturation was reached. Thematic saturation is achieved when further observations and analyzes do not yield any newer topics (30).

2.5 Data analysis

The authors used a method of analysis called framework, a matrix-based approach to manage qualitative data (31, 32). They entered summaries of individual interviews into a series of grids. Domains of inquiry, in this case, each question and text of the C19-YRS were in the same order as in the test questionnaire. This approach allowed the authors to review the data collected systematically (33).

2.5.1 Descriptive analysis

Next, the authors conducted a descriptive analysis to understand how participants interpreted the test questions and identified factors that influenced interpretation and responses. Familiarity with the data was ensured by reading the matrices and taking notes at each step to record ideas that emerged and were considered helpful for moving forward. The range of responses for each question was noted and then categorized in the next step to identify similarities and differences as participants may have interpreted to test questions differently (34).

2.5.2 Explanatory analysis

Then, the authors conducted an explanatory analysis to understand how these potential problems arose. First, they identified patterns in the data, and then these patterns were linked to, for example, participant understanding or response, which helped identify mechanisms by which problems emerged. The next step was to develop explanations for the patterns, which relied on participants' accounts captured in the cognitive interviews, whether through individual utterances or observations (34). The authors assessed whether the problem could potentially affect the quality of the data extracted from the Screening tool and made the necessary changes to the preliminary version of the C19-YRS (34).

During translation and cultural adaptation, translators wrote a report for each step they were involved. The expert committee then produced a preliminary version for the first author to use for pre-testing in the target population. All translators tried to stay close to the original version in this translation and adaptation process, but some changes were also necessary due to cultural differences. After completing the descriptive and explanatory analysis, the preliminary version was revised and sent to two health professionals experienced in working with people suffering from persistent symptoms after acute COVID-19 infection. Similar to peer-reviewing, their comments were then incorporated when creating the final Austrian-German version of the C19-YRS.

3 Results

First, the translators decided to expand the subtitle to "Self Report Version" to make the objective of the screening tool sufficiently clear from the outset, although the original English title of the C19-YRS, "COVID-19 Yorkshire Rehabilitation Scale (C19-YRS)", was retained. Therefore, they decided to expand the subtitle to "Self-Assessment Questionnaire for the Assessment of Persistent COVID-19 Symptoms". Second, the original introductory text stated, "Your answers will be recorded in your clinical record". The translators recognized they could not generally claim that the data collected would be recorded in clinical records, so this was deleted. Third it states, "If you can't remember, just indicate "don't know" Since there was no box for "don't know" where this could have been written, this was erased because the translators felt it could be misleading and confusing.

The first author then used this preliminary version to conduct the cognitive interviews. Twenty-six participants agreed to take part in the cognitive interviews. All of these participants were still suffering from persistent symptoms at the time of recruitment and thus constituted the target population of the C19-YRS. Characteristics of the study population are presented in Table 1.

Cognitive interviews lasted from 20 to 30 min, whether the interviewer conducted the interviews via telephone (n = 10) or on site (n = 16), while participants were filling out the pre-final version of the C19-YRS. The results of the interviews were primarily based on statements made by participants during the

10.3389/fmed.2024.1401491

TABLE 1 Characteristics of participants.

Characteristics		*n* = 26 (100%)
Sex, *n*	Female, *n* (%)	14 (53.8%)
	Male, *n* (%)	12 (46.2%)
Native in German	Yes, *n* (%)	21 (80.8%)
	No, *n* (%)	5 (19.2%)
Age, years	Mean (± SD)	51.5 (±10.7)
	Median [25–75%]	51.0 [43.8 – 60.0]
1. COVID-19 infection	October 2020, *n* (%)	3 (11.5%)
	November 2020, *n* (%)	3 (11.5%)
	December 2020, *n* (%)	1 (3.8%)
	January 2021, *n* (%)	1 (3.8%)
	February 2021, *n* (%)	1 (3.8%)
	March 2021, *n* (%)	4 (15.4%)
	April 2021, *n* (%)	3 (11.5%)
	May 2021, *n* (%)	1 (3.8%)
	September 2021, *n* (%)	2 (7.7%)
	October 2021, *n* (%)	2 (7.7%)
	November 2021, *n* (%)	5 (19.2%)
2. COVID-19 infection	January 2022, *n* (%)	1 (3.8%)
	February 2022, *n* (%)	1 (3.8%)
	No second Infection, *n* (%)	24 (92.3%)
Months since 1. COVID-19 infection	Mean (± SD)	10.54 (±4.81)

think aloud process, supported by the probes administered, as well as observations made from the interviewer. Observations were limited in telephone interviews, however, think aloud was more sufficient on the telephone as the participants appeared to talk the interviewer through each question more than those on site. The sample size of 26 seems appropriate, as no new topics emerged.

Questions 1-3

Q1 to 3 asked for the patient code, date and time, first under the heading. Fourteen of twenty-six participants skipped completing Q1 to 3 without further comment. The author observed that respondents were more likely to start with reading the introduction and therefore overlook these short questions. She suggested that these questions be listed after the introduction, and before the opening questions, and changed the location of Q1 to 3 accordingly.

Question 5 (Q5)

When completing Q5, which asked for health care services used for treatment of COVID-19 symptoms, eight participants wondered whether this question also meant specific health services such as rehabilitation centers and pulmonary physicians. They stated that the term "other health services" was not specific enough, therefore, the author decided to add other examples besides general practitioner (GP) that were mentioned by participants when thinking aloud (e.g., pulmonary physicians, 1450 Corona hotline in Austria). In addition, two participants asked whether Q5 meant the time of the acute infection or the time after, which could also have an influence on the answers, as the responses may vary depending on the requested time. It was clear from the outset of the original questionnaire that this question asked about treatment during the acute infection, so the author adjusted the translation accordingly.

Question 6 (Q6)

Eight out of twenty-six respondents were observed to complete Q6, which measures the extent of breathlessness, incorrectly because the answer to the question was misplaced. Three respondents additionally asked for help in completing it. The author observed that the visual representation of the question was misleading in this part of the questionnaire, as was the case with Q1 to 3, and therefore adapted this question to the visual appearance of the others (see Table 2).

Question 15 (Q15)

All participants agreed that Q15, which was screening post-traumatic stress disorder (PTSD), had to be read repeatedly to be understood while some also asked the interviewer for a verbal explanation. Four other participants interpreted the question as referring only to people who were in the hospital. The author concluded that the wording of the question was flawed and changed the question according to the verbal explanations she gave to the participants during the interviews, which were well understood.

Question 20 (Q20)

Nine participants indicated that Q20, evaluating the social role, was not easy to understand and required a verbal explanation from the author. Participants suggested that the question be reworded and Q20, like Q15 above, was rephrased according to the author's verbal explanation.

Question 21 (Q21)

Eight participants mentioned that Q21, requesting information on employment, was not clear, and they said that the answer choices provided did not correspond to the question asked. Therefore, the author tried to rephrase the original question to connect to the answers more appropriately.

According to every participant, the screening instrument has generally worked well for capturing their long COVID condition. Participants indicated that the C19-YRS was clear, feasible, user-friendly, and appropriate. Therefore, the authors would like to state that it appears that the face validity in the C19-YRS is good.

Following the results of the cognitive interview data analysis, the authors made changes to the preliminary version of the C19-YRS. The changes to the preliminary version were then proofread by two health professionals who work with patients with persistent symptoms after acute COVID-19 infection. After the authors incorporated their comments, which were mainly wording recommendations, a final version was prepared (see Supplementary Appendix 2). Table 3 illustrates the changes made from the preliminary to the final version, including feedback from both participants and health professionals.

4 Discussion

The present work is the first German version of the C19-YRS, a screening tool for long COVID. To date, this appears to be the only translation of a COVID-19-specific assessment or screening tool into German. Based on a rigorous translation and cross-cultural adaptation process that included 26 cognitive interviews with patients and feedback from health professionals working in the field of long COVID, as well as the evaluation of its face validity, a

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TABLE 2 Changes in the visual representation of Question 6.

C19-YRS Domain	Preliminary version			English version
1. Atemlosigkeit/ Kurzatmigkeit	Auf einer Skala von 0 bis 10, wie schwer würden Sie eine (eventuell vorhandene) Atemlosigkeit/ Kurzatmigkeit einschätzen? Bewerten Sie den Schweregrad dieses Problems (zwischen 0 - nicht vorhanden und 10 - schwerwiegend und Ihr Leben beeinträchtigend). (keine Antwort (k/a), wenn Sie die unten angeführten Tätigkeiten nicht ausüben)	Jetzt	Vor-Covid	On a scale of 0 to 10, how severe would you rate breathlessness/shortness of breath (if present)? Rate the severity of this problem (between 0 - nonexistent and 10 - severe and affecting your life). (no answer (N/A) if you do not perform the activities listed below).
	In Ruhe	0–10: ____	0–10: ____	At rest
	Beim Anziehen	0–10: ____ k/a ☐	0–10: ____ k/a ☐	On dressing yourself?
	Beim Treppen hinaufsteigen	0–10: ____ k/a ☐	0–10: ____ k/a ☐	On walking up a flight of stairs?
C19-YRS Domain	**Final version**			**English version**
1. Atemlosigkeit/ Kurzatmigkeit	Auf einer Skala von 0 bis 10, wie schwer würden Sie eine (eventuell vorhandene) Atemlosigkeit/ Kurzatmigkeit einschätzen? Bewerten Sie den Schweregrad dieses Problems (zwischen 0 - nicht vorhanden und 10 - schwerwiegend und Ihr Leben beeinträchtigend). (keine Antwort (k/a), wenn Sie die unten angeführten Tätigkeiten nicht ausüben)			On a scale of 0 to 10, how severe would you rate breathlessness/shortness of breath (if present)? Rate the severity of this problem (between 0 - nonexistent and 10 - severe and affecting your life). (no answer (N/A) if you do not perform the activities listed below).
		Vor-COVID	Jetzt	Pre-COVID / Now
	In Ruhe	0–10: ____	0–10: ____	At rest
	Beim Anziehen	0–10: ____ k/a ☐	0–10: ____ k/a ☐	While dressing
	Beim Treppen hinaufsteigen	0–10: ____ k/a ☐	0–10: ____ k/a ☐	When going up stairs

German version was created. Overall, this study emphasizes that the translated version of the C19-YRS appears suitable to assess persistent symptoms and to support establishment of standardized care in German speaking countries.

The final German C19-YRS has been carefully reviewed and compared with the original, as equivalence between the original and the translated version is considered important (35). No relevant differences were found that could affect the use of the C19-YRS in any way. Adjustments were necessary to adequately reflect the context in which the screening instrument is embedded. These inconsistencies primarily led to changes in the introductory text of the C19-YRS and the items recording the persistent symptoms were hardly affected.

However, instrument translation is usually accompanied by a change in context (25, 36). But compared to previous studies in which researchers reported that translation and cultural adaptation of assessments often lead to alteration in meaning and even deletion of items (37, 38), changes in the case of this study are marginal. Although the current work could be seen as an unproblematic adaptation process with only few changes, other explanations should also be discussed. As such, perhaps the premature state of current research on long COVID and the resulting limited knowledge of individuals affected and health professionals involved in their care (39) has actually restricted more critical examination of the C19-YRS. Widely varying descriptions and definitions of long COVID continue to appear in the literature, as well as in everyday language. With primary studies and reviews appearing at a rapid pace, current findings are inevitably associated with methodological differences and limitations. To improve our knowledge of long COVID, well-designed prospective studies are needed to establish long COVID definitions, accurate differentiation of symptoms, and appropriate treatment of this emerging condition (39). The increase in knowledge could then lead to a more critical review and adaptation process with the C19-YRS at a later date, possibly involving even greater significant changes.

The evaluation of the face validity was also rather superficial compared to other cross-sectional studies focusing on translation and cross-cultural adaptation (40, 41). Further investigation of psychometric properties, including internal consistency, already demonstrated in the original version (19), should be considered in future studies of the Austrian-German version of the C19-YRS.

5 Methodological considerations

The combination of different data sources and methods, as well as the involvement of numerous researchers in the translation process, in the sense of triangulation, enriched the data and reduced bias (42, 43). According to Collins (23), a sufficient number of participants were employed in this study, aiming to verify that the participants' understanding of the questionnaire items was in line with the intended meaning. The sample was balanced, such that the participants represented both genders, a variety of age groups, and both native speakers and non-native speakers. Peer review by health

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TABLE 3 Changes from the preliminary version to the final version of the C19-YRS.

C19-YRS Domain	Preliminary version	Final version	English version
Q1, Q2, Q3	Patient*innen Code: Ausfülldatum (tt.mm.jjjj): Uhrzeit (hh:mm): (before introduction text)	Patient*innen ID: Ausfülldatum (tt.mm.jjjj): Uhrzeit (hh:mm): (after introduction text)	Patient ID: Date filled in (dd.mm.yyyy): Time (hh:mm): (after introduction text)
Q5	Haben Sie andere Gesundheitsdienstleistungen zur Behandlung von COVID-19 Symptomen in Anspruch genommen (z.B. Allgemeinmediziner*in/ Hausärzt*in)? Ja ☐ Nein ☐ Details:	Haben Sie andere Gesundheitsdienstleistungen zur Behandlung von COVID-19 Symptomen in Anspruch genommen (z.B. Hausärzt*in, Lungenfachärzt*in, 1450 Corona Hotline)? Ja ☐ Nein ☐ Könnten Sie diese bitte konkretisieren:	Have you used other health care services to treat COVID-19 symptoms (e.g., primary care physician*, pulmonary specialist*, 1450 Corona Hotline)? Yes ☐ No ☐ Could you please be more specific:
Q6	See Table 2	See Table 2	See Table 2
Q15	a) Hatten Sie irgendwelche ungewollten Erinnerungen an Ihre Krankheit oder Ihren Krankenhausaufenthalt, während Sie wach waren, also nicht im Schlaf? Ja ☐ Nein ☐ b) Hatten Sie unangenehme Träume über Ihre Krankheit oder Ihren Krankenhausaufenthalt? Ja ☐ Nein? c) Haben Sie versucht, Gedanken oder Gefühle über Ihre Krankheit oder die Aufnahme ins Krankenhaus zu vermeiden? Ja ☐ Nein ☐	a) Hatten Sie irgendwelche unangenehmen Erinnerungen an Ihre Krankheit oder Ihren Krankenhausaufenthalt, während Sie wach waren, also nicht im Schlaf? Ja ☐ Nein ☐ b) Hatten Sie unangenehme Träume über Ihre Krankheit oder Ihren Krankenhausaufenthalt? Ja ☐ Nein? c) Haben Sie versucht, Gedanken oder Gefühle über Ihre Krankheit oder die Aufnahme ins Krankenhaus zu vermeiden? Ja ☐ Nein ☐	Did you have any unwanted memories of your illness or hospitalization while you were awake, that is, not asleep? Yes ☐ No ☐ b) Did you have any unpleasant dreams about your illness or hospitalization? Yes ☐ No? c) Have you tried to avoid thoughts or feelings about your illness or hospital admission? Yes ☐ No ☐
Q20	Wie schwerwiegend sind auf einer Skala von 0 bis 10 die Probleme, die Sie bei der Betreuung von Familienmitgliedern und/oder im Kontakt mit Freund*innen haben, die mit Ihrer Krankheit zusammenhängen (und nicht auf die COVID-19 Maßnahmen zur sozialen Distanzierung/ Lockdown zurückzuführen sind)? 0 bedeutet keine Probleme, 10 bedeutet schwerwiegende Probleme	Wie schwerwiegend sind auf einer Skala von 0 bis 10 die Probleme, die Sie zum Beispiel im Kontakt mit Familienmitgliedern oder mit Freund*innen haben? Gibt es hier Einschränkungen in ihrem sozialen Leben, die mit Ihren anhaltenden Symptomen zusammenhängen (und nicht auf die COVID-19 Maßnahmen zur sozialen Distanzierung/ Lockdown zurückzuführen sind)? 0 bedeutet keine Probleme, 10 bedeutet schwerwiegende Probleme	On a scale of 0 to 10, how severe are the problems you have, for example, in contact with family members or friends? Are there any limitations in your social life that are related to your persistent symptoms (and not due to the COVID-19 social distancing/lockdown measures)? 0 means no problems, 10 means severe problems.
Q21	In welchem Beschäftigungsverhältnis stehen Sie? Hat Ihre Krankheit Ihre Fähigkeit beeinträchtigt, Ihrer üblichen Arbeit nachzugehen? Beruf: Beschäftigungsstatus vor der Covid-19 Pandemie: Beschäftigungsstatus vor Ihrer Covid-19 Erkrankung: Aktueller Beschäftigungsstatus:	Wie ist ihr aktueller Beschäftigungsstatus? Hat Ihre Krankheit Ihre Fähigkeit beeinträchtigt, Ihrer üblichen Arbeit nachzugehen? Beruf: Beschäftigungsstatus vor der Covid-19 Pandemie: Beschäftigungsstatus vor Ihrer Covid-19 Erkrankung: Aktueller Beschäftigungsstatus:	What is your current employment status? Has your illness affected your ability to perform your usual work? Occupation: Employment status before the Covid-19 pandemic: Employment status prior to your Covid-19 illness: Current employment status:

professionals was also beneficial, as their expertise was particularly helpful in adapting this comprehensive assessment.

Nevertheless, this is a report of a small-scale study. In comparison, Beaton et al. (22) suggests 30–40 participants for the pre-test. This study should be replicated in a bigger sample, including a population characterized by different treatment experiences. In this case, only individuals who were already assigned to a rehabilitation facility, that can currently be considered an essential part of treatment for long COVID in Austria, participated in this study. Also, the fact that the interviews were not recorded and transcribed could lead to a lower credibility of the results. The interviews were conducted by the first author and predominantly evaluated by her. As a control, interviews could have been conducted and evaluated by other researches as well. A high agreement would have been a sign for trustworthiness (44), as in the study of Friedli and Gantschnig (37). Content validity and internal consistency should be considered for further investigations (26),

as face validity, often giving a first impression without going into too much detail, is overall a very subjective assessment (45).

6 Conclusion

In conclusion, this study resulted in a German version of the C19-YRS. It is expected that the provision of this multi-professional screening tool will support the initial assessment of persistent symptoms, and the establishment of standardized care pathways in Austria. First, however, the psychometric properties should be further explored. Then, the efforts of the broader multi-professional rehabilitation team will be essential to ensure that this screening tool is successfully used in practice.

Data availability statement

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

Ethics statement

This study involving human participants was reviewed and approved by the Ethics Committee of the Medical University Vienna as part of the Austrian Long COVID registry. Participation was open to people who had been diagnosed with COVID-19 infection, who were experiencing long-term symptoms following a COVID-19 infection, who were at least 18 years old, who understood and spoke sufficient German and who agreed to participate.

Author contributions

LS: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review and editing. TS: Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review and editing. EM: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review and editing. VR: Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review and editing. MS: Resources, Supervision, Writing – review and editing. KH: Supervision, Writing – review and editing. BG: Methodology, Supervision, Writing – original draft, Writing – review and editing.

Funding

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

Acknowledgments

We would like to thank everyone involved for their help with the translations and also thank all the participants who took the time to participate in the cognitive interview process during their rehabilitation.

Conflict of interest

TS has received grant/research support from AbbVie and Roche, has been a consultant for AbbVie and Sanofi Genzyme, and has been a paid speaker for AbbVie, Novartis, Roche, Sanofi, and Takeda.

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

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1401491/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 02 October 2024
DOI 10.3389/fmed.2024.1455729

OPEN ACCESS

EDITED BY
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RECEIVED 27 June 2024
ACCEPTED 23 September 2024
PUBLISHED 02 October 2024

CITATION
Saloma CP, Ayes MEC, Taracatac PS and Asa MRQ (2024) Long-term COVID-19 sequelae by Theta and SARS-CoV-2 variants in a Philippine cohort.
Front. Med. 11:1455729.
doi: 10.3389/fmed.2024.1455729

Long-term COVID-19 sequelae by Theta and SARS-CoV-2 variants in a Philippine cohort

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Introduction: Millions have been infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) since its emergence in 2019, but most patients make a full recovery. The long-term consequences of the infection are anticipated to unravel in the succeeding years with reports of patients experiencing chronic, debilitating sequelae post-infection commonly referred to as Long COVID. Various Variants of Concern (VoCs) have emerged as the SARS-CoV-2 virus evolved displaying increased infectivity and immune evasiveness. We investigate whether the infecting VoCs affect the sequelae of Long COVID in a Philippine cohort.

Methods: SARS-CoV-2 cases confirmed using RT-PCR followed by Next Generation Sequencing were identified from selected regions of the Philippines and recruited through a retrospective-prospective cohort design. Participants were divided based on the initial infecting VoC or Variant of Interest (VoI) and were subsequently interviewed regarding the presence, intensity, and frequency of key Long COVID symptoms, and followed up on two more separate sessions at least three (3) months apart for a total of three (3) data collection points (S1, S2, S3) to document changes in symptoms throughout the year-long study period.

Results: Long COVID symptoms were reported in 88, 82, and 68% of participants in S1, S2, and S3, respectively, showing declining incidence with elapsed time since the first reported infection. General symptoms including headache, fatigue, and post-exertional malaise were the most frequently reported symptoms, while neuropsychiatric symptoms were the second most frequently reported symptoms. In all three (3) sessions, intermittent brain fog, fatigue, and headache were the most frequently reported symptoms in all SARS-CoV-2 variant cohorts. Factors such as age, sex, comorbidities, and disease severity influenced symptom frequency, providing insight into the risk factors that contribute to the prevalence of this disease.

Conclusion: A large proportion (>68%) of cases in this Philippine cohort previously infected with different SARS-CoV-2 variants presented with long-term complications of COVID-19 characterized by a highly heterogeneous set of debilitating symptoms. The study highlights the need for long-term monitoring of Long COVID and its impact on human health and the need for our health systems to adopt policy response strategies.

KEYWORDS

SARS-CoV-2, COVID-19, variants, Long COVID, genomic biosurveillance

1 Introduction

In March 2020, the disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), also known as Coronavirus disease (COVID-19), spread globally and quickly evolved into a worldwide health crisis that resulted in over 774 million infections and over 7 million deaths across 188 countries and 25 territories worldwide as of February 2024 (1). Apart from the original strain of SARS-CoV-2, variants of the virus bearing fitness-enhancing mutations began to emerge due to evolution and changes in the viral genome, which has implications on infectivity, clinical severity, and diagnostic accuracy (2–4).

Although most vaccinated individuals who contract COVID-19 go on to make a full recovery, there are many reports of patients experiencing chronic, debilitating sequelae post-infection – a phenomenon referred to variably as "Long COVID," "Long Haulers," or "Post COVID Syndrome" (5). As a multi-organ system illness, Long COVID encompasses a diverse range of symptoms that can persist for weeks, months, or even years beyond the acute phase of infection. Common manifestations include fatigue, body malaise, peripheral neuropathy or "pins-and-needles" sensation, tinnitus, dyspnea, muscle pain, joint pain or arthritis, gastrointestinal complications, insomnia, cognitive dysfunction, and mood disorders such as depression and anxiety (5, 6). Such symptoms can vary in intensity and frequency as some can be continuous or relapsing and remitting in nature (7). The highly heterogeneous nature of Long COVID underscores the complexity of its pathophysiology, which likely involves a combination of multiple factors such as viral persistence, dysregulated immune responses, neuroinflammation, complications related to comorbidities, and adverse effects of medications used (8).

Recent studies have shown that different SARS-CoV-2 variants may influence the clinical course and outcomes of COVID-19, which suggests that different variants may also have implications on the development of Long COVID (9, 10). While the impact of these variants on the severity of acute COVID-19 illness has been extensively studied, their association with Long COVID remains unclear (11). However, emerging evidence suggests that certain variants may be associated with long-term sequelae and distinct clinical phenotypes and patterns which thus raises concerns for the implications on clinical management and post-COVID recovery (10). This was of notable concern at the height of the pandemic when a newly identified Variant of Concern (VoC), dubbed "Theta" variant (P.3) was first identified and described in the Philippines (Figures 1A,B) (12–14).

Despite the growing recognition of Long COVID as a pressing public health concern, there is limited knowledge regarding the pathophysiology of this condition, especially across diverse geographic regions, particularly low- and middle-income countries. In addition, clinical definitions of the diagnosis and management of Long COVID vary between clinical reports since the pathophysiology of the disease is not well-defined, and specific treatments for the disease have yet to be reviewed (6). Thus, this study aims to document, profile, and compare the long-term sequelae of individuals previously infected with confirmed SARS-CoV-2 VoCs (Alpha, Beta, Delta, and Omicron) and the Theta variant in a Philippine cohort. Characterization of variant-specific long-term sequelae post-infection will help enhance post-COVID patient care by providing additional clinical insights for the effective identification of Long COVID and the holistic recovery of affected individuals.

2 Methods

2.1 Study population and sample

2.1.1 Inclusion criteria

The inclusion criteria for participant selection in the study encompassed individuals meeting the following criteria: aged 15 years and above; residing in the regions of Cebu, Metro Manila, Central Luzon, and West Visayas; confirmed to have tested positive for SARS-CoV-2 infection, specifically either the Theta variant or any other VoC; and whose samples were included in the Department of Health-Epidemiology Bureau (DOH-EB) COVID-19 Biosurveillance Program.

2.1.2 Sample collection and processing

Samples from the Department of Health Epidemiology Bureau (DOH-EB) SARS-CoV-2 Biosurveillance Program were collected as nasopharyngeal swabs from patients undergoing routine COVID-19 testing at any of the over 200 accredited testing centers across the country. The nasopharyngeal swabs were stored in refrigerated temperatures (4°C) pending transport to any of the 17 regional collection centers throughout the Philippine archipelago, after which the samples were forwarded to the University of the Philippines Philippine Genome Center in Quezon City under dry ice following a hub-and-spoke laboratory network setup. All samples were pre-screened and re-tested using SARS-CoV-2 RT PCR prior to whole genome sequencing following Illumina's COVIDSeq target enrichment protocol. Samples were deemed adequate for sequencing if the resulting Ct value in RT-PCR was lower than 30 in all gene targets. Average genome coverage of all samples sequenced either with NovaSeq 6,000, NextSeq 5,000 or MiSeq system of Illumina with this inclusion criteria was 98.93% (IQR 93.76–99.88).

2.1.3 Genomic sequencing and variant determination

SARS-CoV-2 whole genome sequencing (WGS) was performed at the DNA Sequencing Core Facility of the University of the Philippines Philippine Genome Center (PGC-DSCF). Manual RNA extraction using QIAamp viral RNA mini kit (3) or automated RNA extraction was performed either via the Magabio Plus Virus DNA/RNA Purification Kit or the 3DMed 96A Automated Viral RNA Purification Kit using the Thermo Scientific TMKingFisher TMFlex Purification System. Prior to library preparation, all samples were confirmed to be SARS-CoV-2 positive via RT-PCR as a quality control measure for viral gRNA integrity as evaluated by a clinical pathologist.

SARS-CoV-2 WGS performed at the PGC-DSCF followed COVIDSeq protocol of Illumina (Document # 1000000128490, version 3-January 2022) that was previously optimized by the DSCF team for use with the Illumina COVIDSeq Test (RUO) Kit (Part number 20043675) as previously described for the first detection of the B.1.1.7 variant in the Philippines (3) and the Theta variant (14). NovaSeq6000 was used to sequence samples in batches of 750 while fewer samples were run on NextSeq500 or MiSeq sequencing platforms.

Reference-based assembly, variant calling and lineage assignment were as previously described (14) and performed by the bioinformatics team at the UP PGC Core Facility for bioinformatics. Briefly, sequence reads were mapped to the reference SARS-CoV-2 genome sequence (NCBI accession no. NC_045512.2) using minimap2 v2.17 (15) and further processed using Samtools v1.10 (16) with consensus sequence

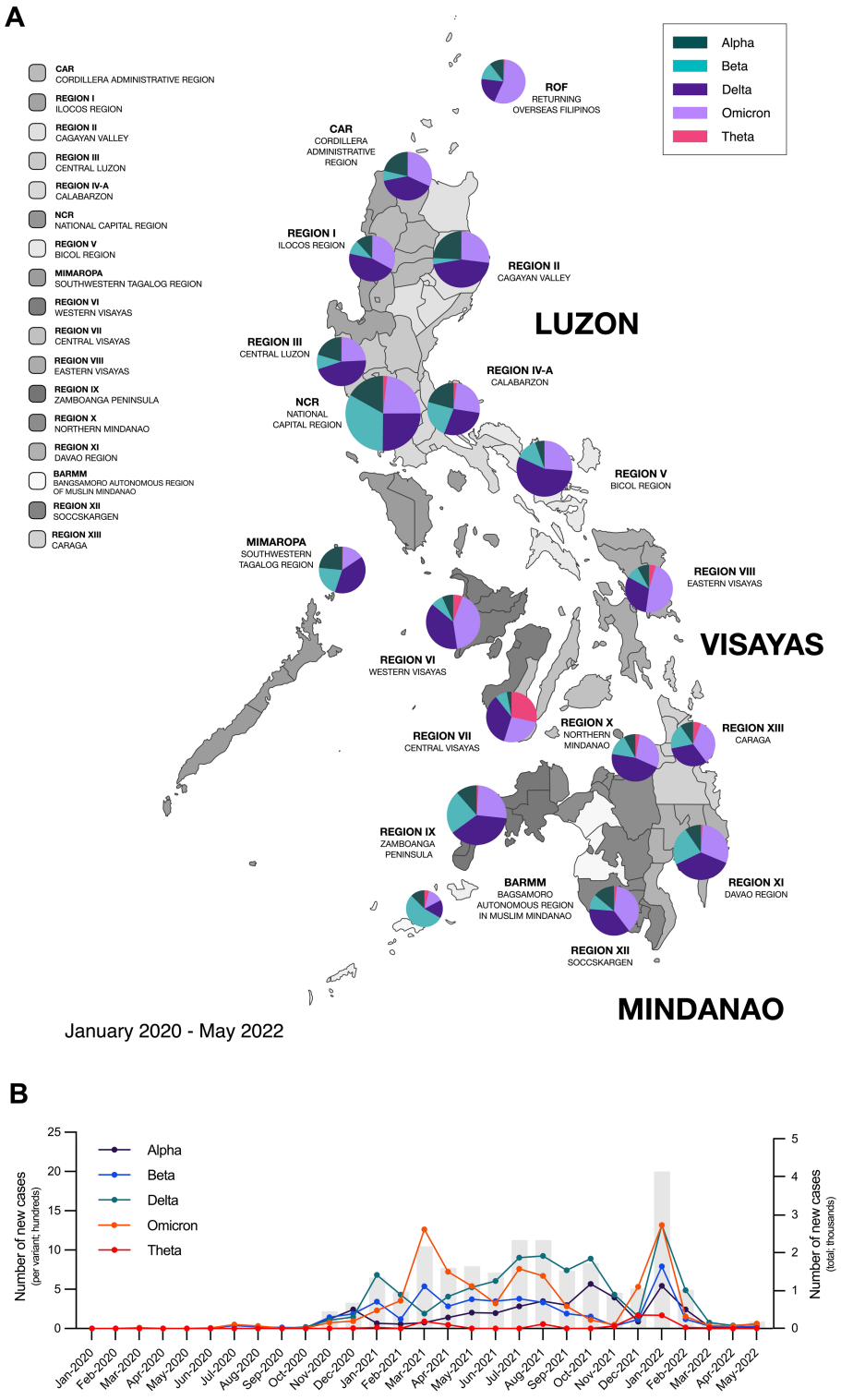

FIGURE 1
Different SARS-CoV-2 variants circulated throughout the Philippines from 2020–2022. **(A)** Map of the Philippines showing the distribution of circulating SARS-CoV-2 variants from January 2020 to May 2022 across the different regions in the country. **(B)** Epidemiological curve showing the number of new SARS-CoV-2 cases monthly in the Philippines and the incidence of different SARS-CoV-2 variants from January 2020 to May 2022. Bars represent the total number of new cases; data points on the line graph represent the number of new cases per variant; while pie charts show the percentage of circulating variants per region. Epidemiological data was provided by the Core Facility for Bioinformatics of the Philippine Genome Center.

generation and variant calling done using iVar v1.3 (17). SARS-CoV-2 lineages were assigned using pangolin v4.1.3 and its subsequent updates (18) and the tools MUMmer v4.0 (19) and RATT were used for variant annotation (20). SARS-CoV-2 phylogenetic trees were generated using CFB's local instance of the Nextstrain analysis platform (21). As of the end of July 2024, a total of 56,571 SARS-CoV-2 samples have been sequenced locally of which 3,737, 4,486, 8,800 and 608 were classified as alpha, Beta, Delta, and Theta variants, respectively.

2.1.4 Patient recruitment

Samples processed by the Philippine Genome Center between January 2021 to January 2022 were reviewed for eligibility with 4,739 potential respondents identified. From this pool, patients were selected via convenience sampling to be contacted for recruitment and interview after first being submitted to the DOH-EB for deanonymization (Figure 2). After the initial interview, participants were scheduled for two more separate sessions at a minimum three-month interval for a total of three data collection points (S1, S2, and S3).

From the pool of potential respondents, 460 patients were confirmed cases of COVID-19 due to the Theta variant. Initial sample size calculation yielded a target sample size of 134 patients per VoC cohort following assumptions of increased hospitalization rates in VoCs compared to non-VoCs of 20 and 7.5%, respectively, (22). Difficulties in establishing contact with historical cases and loss-to-follow up resulted in a final case recruitment rate of only 10% in the Theta variant cohort, yielding only 47 cases of Theta who ultimately agreed to enroll in the study. This was matched with at least 50 cases from each respective WHO-VoC cohort, resulting in a final recruitment of cases of Alpha ($n = 57$), Beta ($n = 56$), Delta ($n = 55$), Omicron ($n = 55$), and Theta ($n = 47$).

The following regions represent some of the main geographic locations where Theta was detected in the Philippines: The National Capital Region (NCR) – of which includes Metro Manila – Region IV-A, Region VI, and Region VII. Although Region III only accounted for 2% of the total Theta cases in the country, it was still considered in the study due to its proximity to the NCR. Within each region, key cities and provinces with the highest number of reported Theta cases were identified for recruitment into the study. Overall, 47 participants were recruited for the Theta variant: 13 from Region VII, 11 from Region VI, 11 from the NCR, 11 from Region IV-A, and one from Region III; while 223 participants were recruited for VoCs, all of which were from the NCR. Although a total of 270 participants were

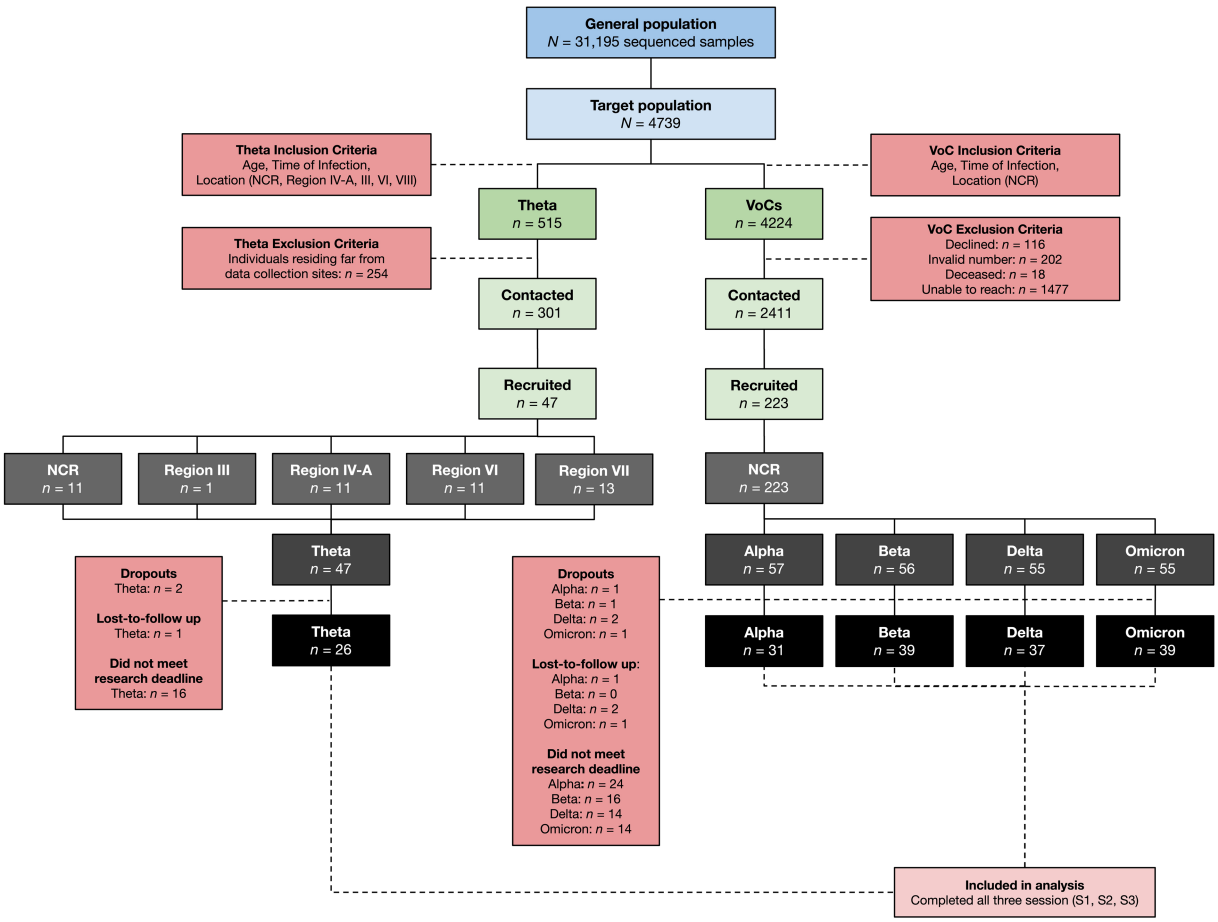

FIGURE 2
Research participant selection. SARS-CoV-2 cases from the NCR, Region III, Region IV-A, Region VI, and Region VII confirmed using Next Generation Sequencing from January 2021 to January 2022 were recruited into the study using an inclusion criteria based on location, time of infection, and age. Only data from those who completed the initial interview (S1) and both follow-up interviews (S2, S3) were included in the final analysis.

successfully recruited, not all were able to complete both follow-up interviews by the time of manuscript preparation, resulting in a smaller sample size for Alpha ($n = 31$), Beta ($n = 39$), Delta ($n = 37$), Omicron ($n = 39$), and Theta ($n = 26$).

2.2 Interview and data collection

Interviews were conducted at least one (1) year and eight (8) months from the time of infection, and interview questions focused on identifying and qualifying the presence, intensity, and frequency of long-term sequelae related to Long COVID based on the clinical definitions established through a Delphi consensus led by the World Health Organization (WHO) (23). Responses to the interview questions were recorded in a data collection form.

2.3 Ethics approval

As a multi-site study, ethics approval for the study was obtained from the Single Joint Research Ethics Board of the Department of Health (DOH-SJREB), University of the Philippines Manila Research Ethics Board (UPMREB/NCR), Vicente Sotto Memorial Medical Center Research Ethics Committee (VSMMC-REC/Region VII), Teresita L. Jalandoni Provincial Hospital Ethics Review Committee (TLJPH-ERC/Region VI), and West Visayas State University Ethics Review Committee (WVSU-ERC/Region VI) institutional review boards. The study was conducted in accordance with the local legislation and institutional requirements, and participants provided their written informed consent to participate in this study.

2.4 Statistical analysis

Categorical variables were described as frequencies and percentages, while continuous variables were described using the median and mean ± SEM. Categorical variables were compared using a Chi-squared test, while continuous variables were analyzed using parametric tests such as Paired *t*-test and one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test; and non-parametric tests such as Spearman's rank-order correlation, Mann–Whitney test, and Kruskal–Wallis test followed by Dunn's multiple comparisons test. All graphs were plotted using GraphPad Prism version 9.0 (GraphPad Software, La Jolla, CA, United States, https://www.graphpad.com/), R version 4.3.3, and RStudio software. All statistical analysis was done using GraphPad Prism version 9.0, and $p < 0.05$ was accepted as statistically significant in both the main analyses and *post hoc* tests.

3 Results

3.1 Baseline characteristics of SARS-CoV-2 cases recruited into the study

Baseline characteristics refer to the characteristics of participants recruited into the study and are summarized in Tables 1–3. The median age of each SARS-CoV-2 variant cohort was 28–35 years old. Across variant cohorts, the majority of Alpha (18 [58.1%]) and Delta (15 [40.5%]) cases were ages 20–29, while the majority of Beta (15 [38.5%]), Omicron (20 [51.3%]), and Theta (11 [42.3%]) cases belonged to ages 30–39. In terms of sex, the majority of Alpha (18 [58.1%]) cases were male, while the majority of Beta (23 [59.0%]), Delta (19 [51.4%]), Omicron (23 [59.0%]), and Theta (16 [61.5%]) cases were female. In terms of comorbidities, an equal number of participants (86 [50.0%]) reported having comorbidities or no comorbidities. Among those that did have underlying comorbidities, the majority reported having hypertension (20 [11.6%]), diabetes (19 [11.0%]), and allergies (31 [18.0%]) (Table 1). It is notable that the Philippines has the highest number of sequenced Beta cases at 4486 cases at the end of 2021 (Figure 1).

The Philippines utilized a highly heterogeneous set of primary SARS-CoV-2 vaccines during the pandemic, with a very high vaccination rate (>96% of the target population) in the National Capital Region (NCR), the main site of our study (24). In terms of vaccination status upon recruitment into the study, only two (1.16%) were unvaccinated while the majority of cases had at least one booster shot (153 [89.0%]). In particular, the majority of Alpha (14 [45.2%]) and Theta (14 [53.8%]) cases have had one booster shot, while the majority of Beta (18 [46.2%]), Delta (17 [45.9%]), and Omicron (23 [59.0%]) cases have had two booster shots. Across variant cohorts, the majority of cases took a heterologous vaccine combination (126 [73.3%]), with the remaining cases taking a homologous vaccine combination (44 [25.6%]). Among those who took a homologous vaccine combination, the majority of cases received an mRNA vaccine (i.e., Cominarty [Pfizer-BioNTech] and Spikevax [Moderna]) (32 [18.6%]). Among those who took a heterologous vaccine combination, the majority of Alpha (13 [41.9%]) and Omicron (16 [41.0%]), cases received a combination of an mRNA and viral vector vaccine, while the majority of Beta (15 [38.5%]), Delta (15 [40.5%]), and Theta (9 [34.6%]) cases took a combination of an inactivated whole virus and mRNA vaccine. In terms of the time elapsed since the most recent vaccination for each variant cohort, the median time elapsed prior to S1 ranged from 354 to 390 days; the median time elapsed prior to S2 ranged from 460 to 481 days; while the median time elapsed prior to S3 ranged from 561 to 591 days. Among those who were vaccinated prior to infection, the median time elapsed before infection ranged from 17 to 64 days, which is a period associated with optimal vaccine efficacy. We also accounted for those who were vaccinated post-infection, with the median time elapsed since their infection ranging from 104 to 194 days (Table 2).

In terms of total number of infections, the majority of cases reported having only one confirmed infection (i.e., from the variant of interest) (110 [64.0%]). At the time of infection, the majority of cases reported symptoms regardless of variant (163 [94.8%]). Symptomatic cases were further classified based on disease severity, wherein cases were categorized as mild if individuals experienced symptoms; moderate if they exhibited an oxygen saturation level below 95% and required supplemental oxygen; and severe if they were admitted to the intensive care unit (ICU) and required intubation. The majority of cases were classified as mild (139 [80.8%]), while only 22 (12.8%) and two (1.16%) cases were classified as moderate and severe, respectively. In terms of the time elapsed since infection with the variant of interest, the median time elapsed prior to S1 ranged from 700 to 736 days; the median time elapsed prior to S2 ranged from 806

TABLE 1 Demographics of SARS-CoV-2 cases recruited into the study.

Characteristic	Alpha (*N* = 31)	Beta (*N* = 39)	Delta (*N* = 37)	Omicron (*N* = 39)	Theta (*N* = 26)	*P*-value[†]
Age (years)						
Median (IQR)	28 (24–37)	33 (27–42)	31 (26–40)	35 (30–41)	31 (26–39)	0.2177
Age group, *n* (%)						
10–19	1 (3.2)	2 (5.1)	1 (2.7)	0 (0)	0 (0)	0.0858
20–29	18 (58.1)	10 (25.6)	15 (40.5)	8 (20.5)	10 (38.5)	
30–39	6 (19.4)	15 (38.5)	12 (32.4)	20 (51.3)	11 (42.3)	
40–49	3 (9.7)	8 (20.5)	2 (5.4)	9 (23.1)	4 (15.4)	
50–59	3 (9.7)	2 (5.1)	5 (13.5)	1 (2.6)	1 (3.8)	
60–69	0 (0)	2 (5.1)	2 (5.4)	1 (2.6)	0 (0)	
Sex, *n* (%)						
Male	18 (58.1)	16 (41.0)	18 (48.6)	16 (41.0)	10 (38.5)	0.5136
Female	13 (41.9)	23 (59.0)	19 (51.4)	23 (59.0)	16 (61.5)	
Number of comorbidities, *n* (%)						
Zero (0)	16 (51.6)	19 (48.7)	13 (35.1)	20 (51.3)	18 (69.2)	0.7020
One (1)	9 (29.0)	12 (30.8)	14 (37.8)	11 (28.2)	6 (23.1)	
Two (2)	4 (12.9)	6 (15.4)	6 (16.2)	6 (15.4)	2 (7.7)	
Three (3)	2 (6.5)	1 (2.6)	1 (2.7)	2 (5.1)	0 (0)	
Four (4)	0 (0)	1 (2.6)	3 (8.1)	0 (0)	0 (0)	
Comorbidities, *n* (%)						
Hypertension	4 (12.9)	6 (15.4)	5 (13.5)	5 (12.8)	0 (0)	0.7340
Diabetes	3 (9.7)	3 (7.7)	7 (18.9)	5 (12.8)	1 (3.8)	
Heart disease	0 (0)	1 (2.6)	1 (2.7)	2 (5.1)	1 (3.8)	
Lung disease	1 (3.2)	0 (0)	1 (2.7)	0 (0)	0 (0)	
Gastrointestinal	1 (3.2)	1 (2.6)	0 (0)	1 (2.6)	1 (3.8)	
Genito-urinary	0 (0)	1 (2.6)	0 (0)	1 (2.6)	0 (0)	
Neurological	0 (0)	0 (0)	2 (5.4)	0 (0)	1 (3.8)	
Cancer	1 (3.2)	1 (2.6)	0 (0)	2 (5.1)	1 (3.8)	
Allergies	6 (19.4)	10 (25.6)	10 (5.8)	4 (10.3)	1 (3.8)	
Asthma	3 (7.0)	2 (5.4)	5 (12.7)	6 (10.9)	0 (0)	
Skin disease	1 (3.5)	1 (1.8)	2 (5.5)	0 (0)	0 (0)	
Others	3 (9.7)	5 (12.8)	5 (13.5)	3 (7.7)	4 (15.4)	

[†]Statistically significant associations and differences were determined through Chi-Square test and Kruskal–Wallis test followed by Dunn's multiple comparisons test, respectively. After applying multiple corrections, the threshold for statistical significance was adjusted to $P < 0.05$ ($^*P < 0.05$).

to 827 days; while the median time elapsed prior to S3 ranged from 908 to 937 days (Table 3).

3.2 Long COVID symptoms are prevalent and predominantly fall under general and neuropsychiatric sequelae

In all three sessions, most participants reported experiencing sequelae post-infection regardless of variant (Figures 3A–C). In the first session (S1), Long COVID symptoms were reported in 88% of participants with more than 80% of each variant cohort reporting symptoms (Figure 3A). In the second session (S2) and third session (S3), the number of those reporting symptoms decreased to 82% (Figure 3B) and 68% (Figure 3C) of participants, respectively. From S1 to S2, only the Alpha and Beta cohorts consistently had at least 80% reporting symptoms. However, from S2 to S3, the number of those reporting symptoms remained unchanged in the Alpha cohort while the number decreased in the Beta cohort (Figure 3D). In contrast, the Delta, Omicron, and Theta cohorts exhibited a decrease in the number of those reporting symptoms from S1 to S3, although this was not statistically significant (Figure 3D). Across all variants, there was a significant increase in the number of symptomatic cases concurrent with the observed decrease in the number of asymptomatic cases from S2 to S3 (Figure 3E).

TABLE 2 Vaccination profile of SARS-CoV-2 cases recruited into the study.

Characteristic	Alpha (*N* = 31)	Beta (*N* = 39)	Delta (*N* = 37)	Omicron (*N* = 39)	Theta (*N* = 26)	*P*-value[†]
Vaccination status, *n* (%)						
Unvaccinated	0 (0)	1 (2.6)	0 (0)	0 (0)	1 (3.8)	0.5268
Complete primary series	5 (16.1)	4 (10.3)	4 (10.8)	1 (2.6)	3 (11.5)	
One booster shot	14 (45.2)	16 (41.0)	16 (43.2)	15 (38.5)	14 (53.8)	
Two booster shots	12 (38.7)	18 (46.2)	17 (45.9)	23 (59.0)	8 (30.8)	
Vaccine combination, *n* (%)						
Homologous	8 (25.8)	14 (35.9)	10 (27.0)	3 (7.7)	9 (34.6)	**0.0333**
Heterologous	23 (74.2)	24 (61.5)	27 (73.0)	36 (92.3)	16 (61.5)	
Vaccine type, *n* (%)						
Inactivated whole virus	2 (6.5)	0 (0)	3 (8.1)	0 (0)	3 (11.5)	**0.0294**
mRNA	4 (12.9)	14 (35.9)	6 (16.2)	2 (5.1)	6 (23.1)	
Viral vector	2 (6.5)	0 (0)	1 (2.7)	1 (2.6)	0 (0)	
Inactivated whole virus + mRNA	10 (32.3)	15 (38.5)	15 (40.5)	15 (38.5)	9 (34.6)	
Inactivated whole virus + viral vector	0 (0)	2 (5.1)	2 (5.4)	5 (12.8)	2 (7.7)	
mRNA + Viral vector	13 (41.9)	7 (17.9)	10 (27.0)	16 (41.0)	5 (19.2)	
Time elapsed since most recent vaccination (days), median (IQR)						
Time elapsed since vaccination and S1	390 (355–425)	390 (338–425)	387 (345–418)	376 (347–425)	354 (292–457)	0.9722
Time elapsed since vaccination and S2	478 (446–516)	481 (439–523)	481 (444–509)	474 (439–523)	460 (386–571)	0.9952
Time elapsed since vaccination and S3	565 (537–597)	591 (541–624)	570 (530–602)	565 (530–633)	561 (510–677)	0.8746
Time elapsed between pre-infection vaccination date and infection (days), median (IQR)	17 (13–49)	37 (5–69)	64 (39–109)	59 (33–167)	23 (13–101)	0.2124
Time elapsed between infection and post-infection vaccination date (days), median (IQR)	161 (111–222)	194 (140–238)	125 (74–151)	104 (69–223)	131 (90–208)	0.1846

[†]Statistically significant associations and differences were determined through Chi-Square test and Kruskal–Wallis test followed by Dunn's multiple comparisons test, respectively. After applying multiple corrections, the threshold for statistical significance was adjusted to $P < 0.05$ ($^*P < 0.05$). Bold values indicate statistically significant *P* values.

To systematically analyze and understand the breadth of Long COVID symptomatology, seven (7) main categories were identified based on the major organ systems affected by common Long COVID symptoms: general symptoms, cardiopulmonary symptoms, gastrointestinal symptoms, musculoskeletal symptoms, neuropsychiatric symptoms, dermatologic symptoms, and women-related symptoms.

In all three sessions, general and neuropsychiatric Long COVID symptoms represented the top two categories of the most frequently reported symptoms across all reports (Figures 4A–C). General symptoms represented the top category of the most frequently reported symptoms across all reports, accounting for over 35% of all reports in S1 (Figure 4A), 25% of all reports in S2 (Figure 4B), and 30% of all reports in S3 (Figure 4C). Neuropsychiatric symptoms represented the second top category of the most frequently reported symptoms across all reports, accounting for over 20% of all reports in S1 (Figure 4A), and over 15% of all reports in S2 (Figure 4B) and S3 (Figure 4C). Upon stratification of participants by variant, general and neuropsychiatric symptoms still represented the top two categories of the most frequently reported symptoms across all reports per variant (Figures 4D–F).

In each of the seven main categories, a comprehensive assessment was conducted to determine the presence of specific Long COVID symptoms in each cohort across the three sessions. General symptoms included headache, dizziness, fever, onset allergies, fatigue, post-exertional malaise, tinnitus, and peripheral neuropathy or "pins-and-needles" sensation; cardiopulmonary symptoms included dyspnea (difficulty breathing), palpitations, cough, and chest pain;

TABLE 3 Infection profile of SARS-CoV-2 cases recruited into the study.

Characteristic	Alpha (*N* = 31)	Beta (*N* = 39)	Delta (*N* = 37)	Omicron (*N* = 39)	Theta (*N* = 26)	*P*-value[†]
Total number infections						
One (1)	19 (61.3)	28 (71.8)	22 (59.5)	17 (43.6)	24 (92.3)	**0.0003**
Two (2)	11 (35.5)	10 (25.6)	15 (40.5)	15 (38.5)	2 (7.7)	
Three (3)	1 (3.2)	1 (2.6)	0 (0)	7 (17.9)	0 (0)	
Disease severity during acute infection						
Asymptomatic	2 (6.5)	1 (2.6)	3 (8.1)	2 (5.1)	1 (3.8)	0.5548
Mild	26 (83.9)	33 (84.6)	25 (67.6)	34 (87.2)	21 (80.8)	
Moderate	3 (9.7)	3 (7.7)	9 (24.3)	3 (7.7)	4 (15.4)	
Severe	0 (0)	2 (5.1)	0 (0)	0 (0)	0 (0)	
Time elapsed since infection (days), median (IQR)						
Time elapsed since infection and S1	736 (701–771)	736 (684–771)	733 (691–763)	722 (693–771)	700 (637–803)	0.9722
Time elapsed since infection and S2	824 (792–862)	827 (785–869)	827 (790–855)	820 (785–869)	806 (732–917)	0.9952
Time elapsed since infection and S3	911 (883–943)	937 (887–970)	916 (876–948)	911 (876–979)	908 (856–1,024)	0.8732

[†]Statistically significant associations and differences were determined through Chi-Square test and Kruskal–Wallis test followed by Dunn's multiple comparisons test, respectively. After applying multiple corrections, the threshold for statistical significance was adjusted to $P < 0.05$ ($^{***}P < 0.001$). Bold values indicate statistically significant *P* values.

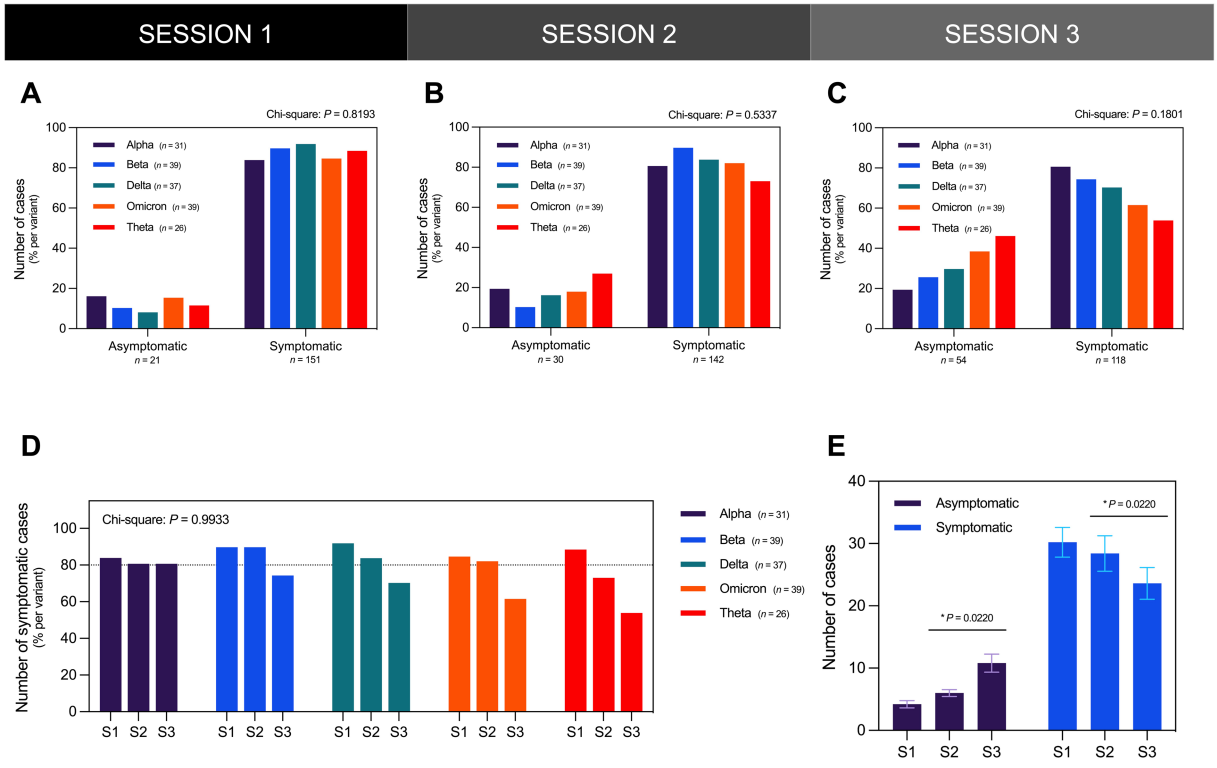

FIGURE 3
The majority of the participants presented as symptomatic for Long COVID in all three sessions regardless of infecting SARS-CoV-2 variant. The distribution of the number of asymptomatic and symptomatic cases did not vary significantly across different SARS-CoV-2 variants in **(A)** S1 (Chi-Square test; $P = 0.8193$), **(B)** S2 (Chi-Square test; $P = 0.5337$), and **(C)** S3 (Chi-Square test; $P = 0.1801$). **(D)** The distribution of the number of symptomatic cases per variant did not likewise vary significantly during the three interview sessions (Chi-Square test; $P = 0.9933$). **(E)** From interview sessions S2 to S3 which occurred 3 months apart, the number of asymptomatic cases significantly increased while the number of symptomatic cases significantly decreased (Paired *t*-test; $P = 0.0220$). Bars represent the percentage of cases per variant or mean ± SEM with statistically significant associations and differences determined through Chi-Square test and Paired *t*-test, respectively ($^{*}P < 0.05$, $^{ns}P > 0.05$).

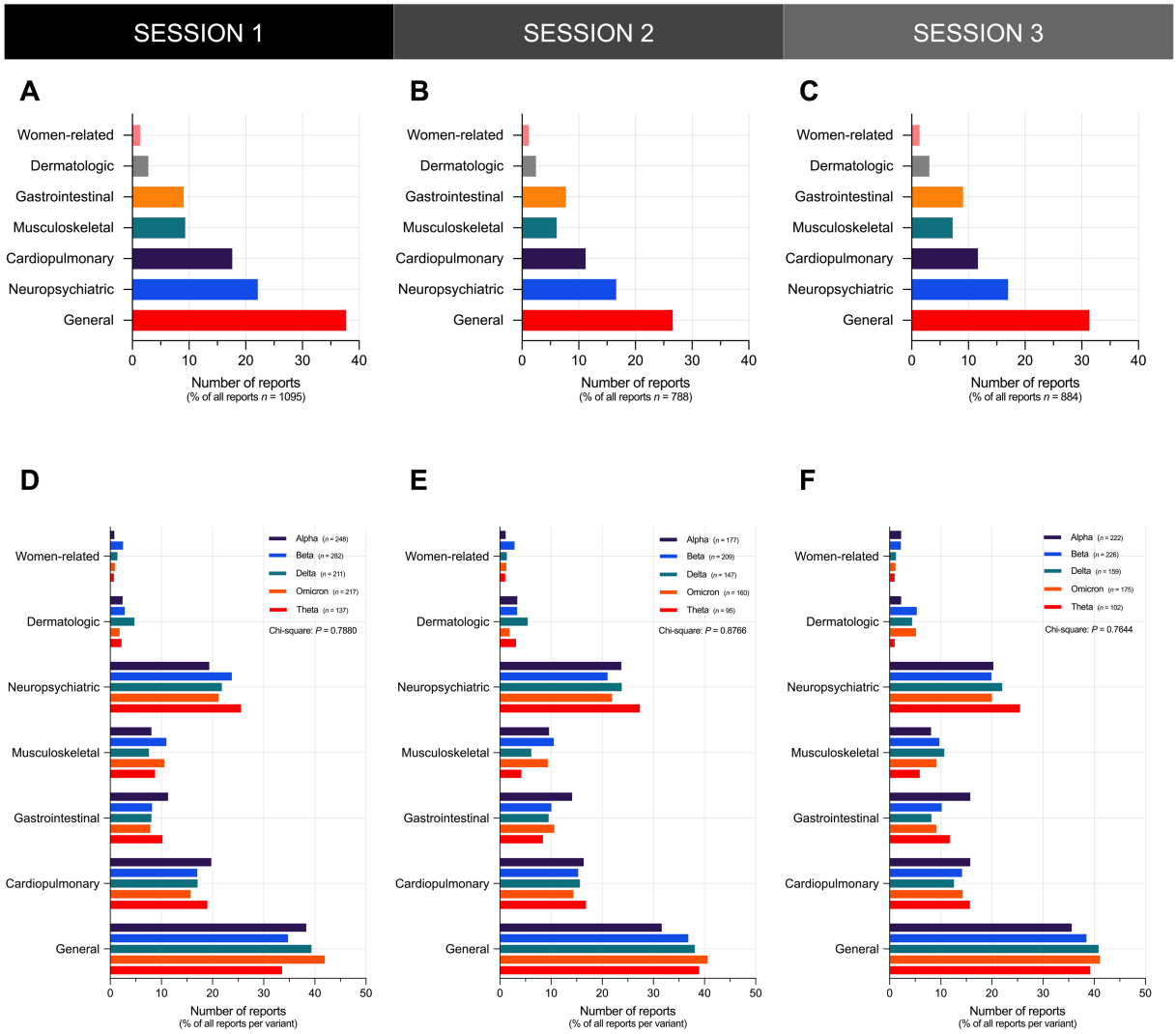

FIGURE 4
General and neuropsychiatric Long COVID symptoms represent the top two categories of the most frequently reported symptoms. Shown is the overall frequency of Long COVID symptoms reported by participants in **(A)** S1, **(B)** S2, and **(C)** S3. The distribution of the frequency of Long COVID symptoms reported by participants did not vary significantly across different SARS-CoV-2 variants in **(D)** S1 (Chi-Square test; $P = 0.7880$), **(E)** S2 (Chi-Square test; $P = 0.8766$), and **(F)** S3 (Chi-Square test; $P = 0.7644$). Bars represent the percentage of the total number of reports in the sample or the percentage of reports per variant with statistically significant associations determined through Chi-Square test ($^{*}P < 0.05$, $^{ns}P > 0.05$).

gastrointestinal symptoms included stomach pain, diarrhea, constipation, and acid reflux; musculoskeletal symptoms included muscle pain and joint pain; neuropsychiatric symptoms included brain fog (difficulty thinking or concentrating), sleep problems, mood changes, and changes in smell or taste; dermatologic symptoms included rashes and hair loss; and women-related conditions included changes in menstrual cycle.

In all three sessions, brain fog, fatigue, and headache, were the most frequently reported symptoms among participants (Figures 5A–C). Brain fog represented the most frequently reported symptom among participants in S1 (Figure 5A) and S2 (Figure 5B), and the second most frequently reported symptom in S3 (Figure 5C). Brain fog was reported in over 50% of participants in S1 (Figure 5A), 40% of participants in S2 (Figure 5B), and over 35% of participants in S3 (Figure 5C). Next to brain fog, fatigue and headache represented the second most frequently reported symptoms in S1 (Figure 5A) and S2 (Figure 5B), respectively, while the latter represented the most frequently reported symptom in S3 (Figure 5C). Fatigue was reported in over 55% of participants in S1 (Figure 5A), while headache was reported in over 35% of participants in S2 (Figure 5B) and S3 (Figure 5C). Notably, brain fog, fatigue, and headache manifested concurrently in more than 22% of participants in S1 (Figure 5D), over 10% of participants in S2 (Figure 5E), and approximately 16% of participants in S3 (Figure 5F).

Upon stratification of participants by variant, the most frequently reported symptoms did not vary significantly across all cohorts in all three sessions since brain fog, headache, and fatigue remained as some of the most frequently reported symptoms in all variant cohorts (Figures 5G–I). In S1, brain fog was the most frequently reported symptom in the Alpha (18 [58%]), Beta (27 [69%]), Omicron (17 [44%]), and Theta (11 [42%]) cohorts, and the second most frequently reported symptom in the Delta (17 [46%]) cohort (Figure 5G).

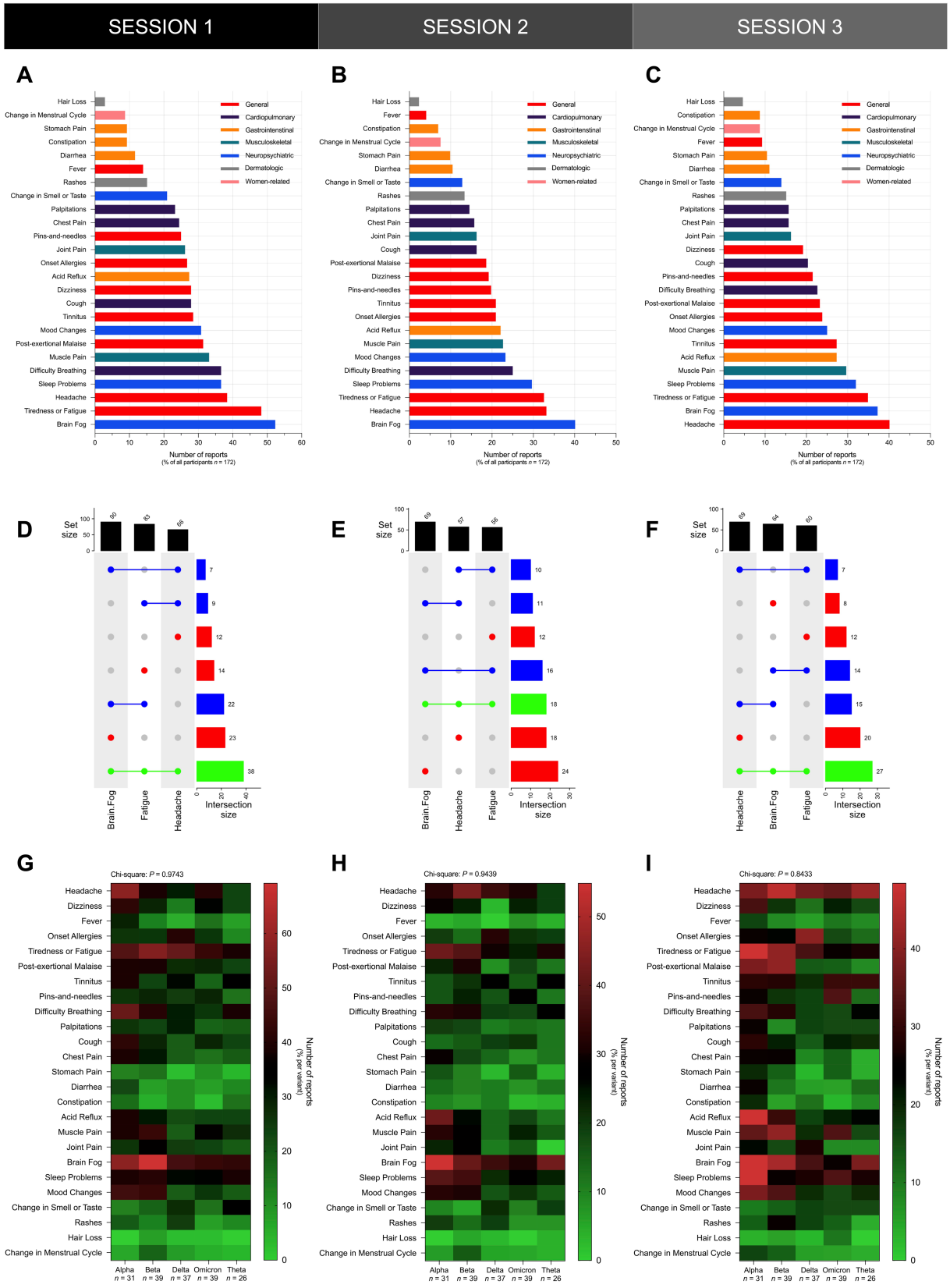

FIGURE 5
Brain fog, fatigue, and headache were the most frequently reported symptoms across all participants regardless of documented previous infecting SARS-CoV-2 variant. Shown is the overall frequency of specific Long COVID symptoms reported by participants in **(A)** S1, **(B)** S2, and **(C)** S3, and UpSet plots showing the co-occurrence of the top three Long COVID symptoms – namely brain fog, fatigue, and headache – reported by participants in **(D)** S1, **(E)** S2, and **(F)** S3. The distribution of the frequency of specific Long COVID symptoms did not vary significantly across different SARS-CoV-2

(Continued)

FIGURE 5 (Continued)
variants in **(G)** S1 (Chi-Square test; $P = 0.9743$), **(H)** S2 (Chi-Square test; $P = 0.9439$), and **(I)** S3 (Chi-Square test; $P = 0.8433$). Bars represent the set size, intersection size, or the percentage of all participants in the sample with statistically significant associations determined through the Chi-Square test (*$P < 0.05$, ns $P > 0.05$).

Alongside brain fog, headache was also the most frequently reported symptom in the Alpha (18 [58%]) cohort, and headache was the second most frequently reported symptom in the Omicron (16 [41%]) cohort (Figure 5G). Fatigue was the most frequently reported symptom in the Delta (19 [51%]) cohort, and alongside brain fog, fatigue was also the most frequently reported symptom in the Omicron (17 [44%]) cohort. Fatigue was the second most frequently reported symptom in the Beta (22 [56%]) and Theta (10 [38%]) cohorts (Figure 5G). In S2, brain fog was the most frequently reported symptom in the Alpha (17 [55%]), Delta (13 [35%]), Omicron (12 [31%]), and Theta (11 [42%]) cohorts, and the second most frequently reported symptom in the Beta (16 [41%]) cohort (Figure 5H). Headache was the most frequently reported symptom in the Beta (17 [44%]) cohort, and alongside brain fog, headache was also the most frequently reported symptom in the Delta (13 [35%]) and Omicron (12 [31%]) cohorts (Figure 5H). Next to brain fog, fatigue was the second most frequently reported symptom in the Alpha (13 [42%]) and Theta (8 [31%]) cohorts (Figure 5H). In S3, the most frequently reported symptoms were fatigue and brain fog in the Alpha (15 [48%]) cohort, and headache in the Beta (18 [46%]), Omicron (14 [36%]), and Theta (11 [42%]) cohorts (Figure 5I). The second most reported symptom was headache in the Alpha (12 [39%]) and Delta (14 [38%]) cohorts, and brain fog in the Beta (17 [44%]) and Theta (10 [38%]) cohorts (Figure 5I).

3.3 Long COVID symptoms have diverse manifestations and a predominant relapsing pattern

Apart from identifying the presence of Long COVID symptoms across the different cohorts, participants were also asked to characterize each symptom they encountered by providing detailed descriptions of each sequela (Table 4).

A separate assessment was made to characterize the intensity and frequency of Long COVID symptoms, wherein participants were asked to describe each symptom they encountered either as relapsing, meaning the symptom recurs after periods of improvement or remission; persistent, meaning the symptom remains consistently present over time; fluctuating, meaning the symptom varies in intensity and frequency over time; or increasing, meaning the symptom becomes more severe or frequent over time. Across all symptoms, most reported relapsing symptoms. Statistically significant differences were determined through one-way ANOVA followed by Tukey's multiple comparisons test to compare the mean number of reports from S1 to S3 for each symptom, highlighting the variations in the prevalence and nature of symptom reports over time (Table 5 and Supplementary Figures S1–S6).

3.4 The number of Long COVID symptoms varies with demographic and disease severity during acute infection

To determine if the prevalence of Long COVID varies with different variables, the average number of Long COVID symptoms from all three sessions was plotted by demographic, vaccination profile, and infection profile. In terms of age, the average number of reported symptoms exhibited a negative correlation with age, wherein those of older age reported less symptoms on average (Figure 6A). In terms of sex, females reported significantly more symptoms on average compared to males (Figure 6B). In terms of comorbidities, those with one, three, or more comorbidities reported significantly more symptoms on average compared to those with no comorbidities (Figure 6C). However, the average number of reported symptoms did not vary significantly with the presence of specific comorbidities (Figure 6D).

The average number of reported symptoms did not vary significantly with vaccination status (Figure 7A), vaccine combination (Figure 7B), and vaccine type/s taken at the time of the first session (Figure 7C). Additionally, the average number of reported symptoms did not show a significant correlation with the number of days between the last vaccination date and the first session of the participants (Figure 7D). Furthermore, we observed that the number of reported symptoms was not significantly correlated with the number of days between infection and vaccination dates (both pre- and post-infection) (Figures 7E,F).

Upon stratification of participants by variant, there was no significant difference in the average number of reported symptoms across all cohorts (Figure 8A). In contrast, the average number of reported symptoms varied significantly with disease severity during the time of infection. However, although one-way ANOVA indicated significant differences in the average number of reported symptoms by disease severity, the multiple comparisons test did not reveal any significant differences between specific groups (Figure 8B). In terms of number of infections, the average number of reported symptoms varied significantly with the number of tested infections before the first session and during the period of the three sessions (Figure 8C). Similarly, the average number of reported symptoms was also not significantly correlated with the number of days between date of last tested infection and S3 (Figure 8D).

4 Discussion

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC) is characterized by a complex and debilitating array of symptoms persisting beyond the acute phase of COVID-19. This chronic syndrome is characterized by a wide range of acquired sequela that affects many of the major organ systems in the body and can persist beyond 4 weeks from the onset of acute COVID-19 symptoms (6, 7, 25).

TABLE 4 Summary of Long COVID symptom descriptions provided by participants.

Long COVID symptom†	Descriptions
General symptoms	
Headache	Bilateral or unilateral; manifests as a migraine, tension headache, or cluster headache
Dizziness	Manifests as vertigo; feeling of swaying or experiencing earthquake-like sensations
Fever	Sensation of heat, chills, sweating; concurrent with flu-like symptoms
Onset allergies	Allergic rhinitis; allergies to seafood, pets, chicken, eggs
Tiredness or fatigue	More prone to tiredness; experienced after climbing a flight of stairs
Post-exertional malaise	Requires extended recovery time after physical exertion; pain in arms, back, legs, and feet after exercising
Tinnitus	Loud bilateral or unilateral ringing/humming which lasts for 5–10 s; occurs at different times of the day; sensation of deafness or loss of hearing
Pins-and-needles (peripheral neuropathy)	Numbness and difficulty moving hands and feet
Cardiopulmonary symptoms	
Difficulty breathing	Manifests as gasping or sharp sensations during breathing; breathing exhibits a whistling sound; experienced after physical exertion; occurs concurrent with continuous cough
Palpitations	Tachycardia experienced after drinking alcohol or carbonated drinks; can manifest as irregular heartbeats; experienced after physical exertion
Cough	More prone to cough; manifests as an irritated throat or through dry cough; concurrent with colds
Chest pain	Sensation of sharp pain or heaviness pressing on the chest; occurs concurrent with panic attacks; experienced after physical exertion or while resting
Gastrointestinal symptoms	
Stomach pain	Cramping or aching; experienced after drinking caffeine or carbonated drinks
Diarrhea	Bowel movement is usually fast and more frequent; stool is usually soft, and may not necessarily be watery
Constipation	Feeling of strain or pain when passing stools
Acid reflux	Manifests as Gastroesophageal Reflux Disease (GERD); experienced after drinking caffeine or carbonated drinks
Musculoskeletal symptoms	
Muscle pain	Pain in nape, arms, shoulders, upper back, lower back, or legs; experienced after physical exertion
Joint pain	Pain in shoulders, elbows, knees, ankles, and lower back; reported alongside high uric acid and/or cholesterol
Neuropsychiatric symptoms	
Brain fog	Struggle with maintaining focus over extended periods, recalling words, and remembering immediate tasks; memory lapses and periods of dissociation; disorientation resulting in altered motor function
Sleep problems	Difficulty falling asleep; sleep is interrupted and fragmented; concurrent with difficulty breathing and nightmares
Mood changes	More irritable, anxious, depressed, or emotional; less interested in activities
Changes in smell	Manifests as hyposmia, hyperosmia, parosmia, or phantosmia; detection of odors resembling metal, burning, or unpleasant scents
Changes in taste	Manifests as hypogeusia or dysgeusia; more/less sensitive to salty flavors; certain foods lack their expected taste; concurrent with loss of appetite
Dermatologic symptoms	
Rashes	Manifests as atopic dermatitis, urticaria, or Pityriasis rosea; skin is more sensitive and easily irritable; rashes in extremities, face, scalp, or back; concurrent with allergies
Hairfall	Concurrent with itchy scalp
Women-related symptoms	
Changes in menstrual cycle	Shorter or irregular menstrual cycles; decreased menstrual flow; blood appears clumped

†List of Long COVID symptoms was based on the clinical definitions of the WHO (23).

While the cause of Long COVID remains unclear, some believe that the condition develops because of putative viral reservoirs, sustained damage from the initial infection, elevated autoantibodies in response to the initial infection, dysregulated immune response, and adverse effects of medications used (8, 26). Because Long COVID shares many features with chronic disorders brought about by other infectious agents such as myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), this illness may involve common etiopathogenetic pathways (10, 11). Given

TABLE 5 Intensity and frequency of Long COVID symptoms as described by participants.

Long COVID symptom	Mean number of reports from S1 to S3 (% of all participants $n = 172$)				P-value[†]	
	Relapsing	Persistent	Fluctuating	Increasing		
General symptoms						
Headache	26.74^{a}	2.91^{bc}	6.98^{b}	0.58^{c}	**<0.0001**	****
Dizziness	18.41^{a}	1.16^{b}	2.52^{b}	0.00^{b}	**<0.0001**	****
Fever	8.33^{a}	0.39^{b}	0.39^{b}	0.00^{b}	**0.0042**	**
Onset allergies	10.47^{a}	6.59^{ab}	5.62^{b}	1.16^{c}	**0.0011**	**
Tiredness or fatigue	18.60^{a}	11.05^{b}	7.75^{bc}	1.16^{c}	**0.0003**	***
Post-exertional malaise	12.40^{a}	5.23^{b}	6.40^{ab}	0.39^{b}	**0.0016**	**
Tinnitus	16.86^{a}	3.29^{b}	3.88^{b}	1.55^{b}	**<0.0001**	****
Pins-and-needles (peripheral neuropathy)	15.12^{a}	3.49^{b}	2.91^{bc}	0.58^{c}	**<0.0001**	****
Cardiopulmonary symptoms						
Difficulty breathing	14.92^{a}	5.81^{b}	6.40^{b}	0.97^{b}	**0.0024**	**
Palpitations	12.98^{a}	2.13^{b}	2.71^{b}	0.00^{b}	**0.0002**	***
Cough	14.73^{a}	2.33^{b}	3.88^{b}	0.58^{b}	**<0.0001**	****
Chest pain	13.95^{a}	1.36^{b}	3.10^{b}	0.19^{b}	**<0.0001**	****
Gastrointestinal symptoms						
Stomach pain	5.62^{a}	1.16^{b}	1.94^{b}	1.16^{b}	**<0.0001**	****
Diarrhea	7.95^{a}	1.16^{b}	1.94^{b}	0.00^{b}	**0.0020**	**
Constipation	5.04^{a}	2.13^{b}	0.97^{bc}	0.19^{c}	**<0.0001**	****
Acid reflux	15.50^{a}	3.68^{b}	4.07^{b}	2.33^{b}	**<0.0001**	****
Musculoskeletal symptoms						
Muscle pain	14.92^{a}	6.59^{ab}	5.62^{b}	1.36^{b}	**0.0078**	**
Joint pain	12.79^{a}	3.49^{b}	2.52^{b}	0.78^{b}	**0.0004**	***
Neuropsychiatric symptoms						
Brain fog	23.06^{a}	9.11^{b}	8.14^{b}	2.91^{b}	**0.0034**	**
Sleep problems	11.82^{a}	8.91^{a}	7.95^{a}	4.07^{b}	**0.0133**	*
Mood changes	13.76^{a}	3.10^{b}	7.17^{c}	2.33^{b}	**<0.0001**	****
Changes in smell	7.17^{a}	6.01^{a}	1.74^{b}	0.97^{b}	**0.0020**	**
Dermatologic symptoms						
Rashes	7.56^{a}	3.49^{b}	3.10^{b}	0.39^{c}	**<0.0001**	****
Hairfall	2.13^{a}	0.78^{a}	0.00^{a}	0.39^{a}	0.0575	ns
Women-related symptoms						
Changes in menstrual cycle	3.10^{a}	2.71^{a}	2.13^{a}	0.39^{b}	**0.0026**	**

[†]Statistically significant differences were determined through one-way ANOVA followed by Tukey's multiple comparisons test to compare the mean number of reports from S1 to S3 for each symptom. Statistical significance is indicated by superscript letters above the means; means with the same letter are not significantly different from each other. After applying multiple corrections, the threshold for statistical significance was adjusted to $P < 0.05$ ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$, $^{ns}P > 0.05$). Bold values indicate statistically significant P values.

the heterogeneous nature of this illness, understanding the symptomatology and epidemiology of Long COVID is becoming increasingly crucial as it represents a significant public health concern and poses challenges for healthcare systems worldwide. Through this retrospective-prospective study using a Philippine cohort, longitudinal analysis hopes to provide insights into the presence, progression, and persistence of Long COVID symptoms across individuals infected with different SARS-CoV-2 variants over time.

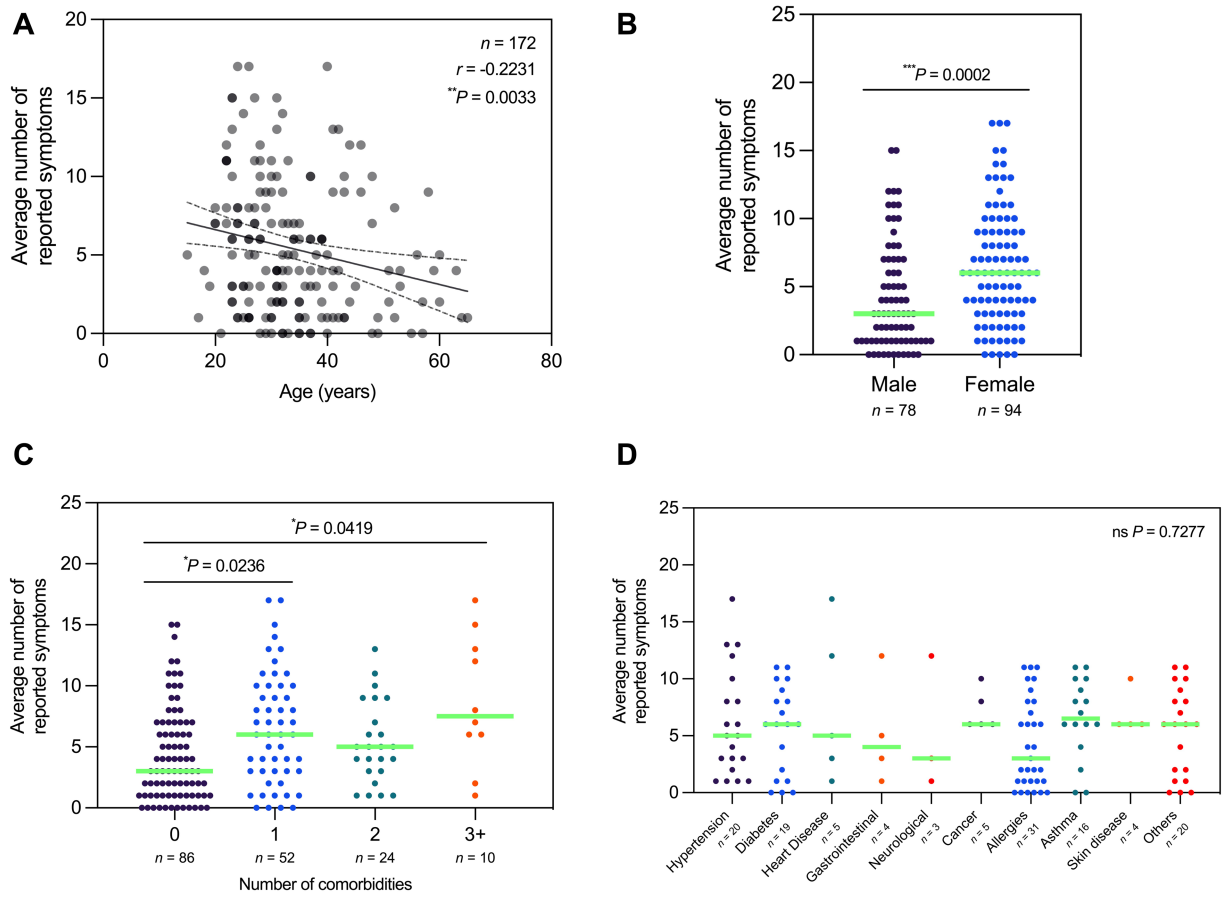

FIGURE 6
Average number of Long COVID symptoms reported varied by age, sex, and number of comorbidities. **(A)** Number of reported symptoms is negatively correlated with age (Spearman's rank-order correlation; $r = -0.2231$; $P = 0.0033$). **(B)** Number of reported symptoms is significantly higher in females relative to males (Mann–Whitney test; $P = 0.0002$). **(C)** Number of reported symptoms is significantly higher in participants with one or three or more comorbidities relative to those with none (Kruskal–Wallis test; $P = 0.0043$). **(D)** Number of reported symptoms does not vary significantly with the presence of specific comorbidities (Kruskal–Wallis test; $P = 0.7277$). Dots represent the number of reported symptoms, with the median indicated by a neon green line. Correlation studies are depicted with a line of best fit and 95% confidence bands. Statistically significant differences were assessed using Spearman's rank-order correlation, Mann–Whitney test, and Kruskal–Wallis test followed by Dunn's multiple comparisons test ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{ns}P > 0.05$).

4.1 Long COVID symptomatology in a Philippine cohort stratified with VoC infection

Globally, although exact numbers are uncertain, studies show that as much as 60% of those infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as Long COVID, consistent with a recent review that estimates that as much as 400 million individuals worldwide are affected by this condition (6, 27, 28). However, the prevalence of Long COVID and the number of reported cases varies globally, which could stem from underdiagnosing due to the lack of consensus on its definition or awareness of the condition, as well as underreporting since some symptoms might not have been severe enough to be noticed or reported (29). In our cohort, we found that the number of those symptomatic for Long COVID ranges between 68 and 88% of all participants, which is markedly higher than the 10–20% estimate seen in other studies (27). A pre-print meta-analysis reported as much as 80% of patients had prolonged post-infectious symptoms within a follow up period of up to 100 days post-recovery, but our study is the first in our region to evaluate symptoms after over a year post-infection (30).

The large proportion of Long COVID symptoms reported may be due in part to the nature of the follow-up method of patient interviews when recall bias could potentially influence the response of patients. The presence of a control group or a national registry for COVID-19 cases could help minimize this bias, but the identification of non-infected controls is challenging given the highly infectious nature of the virus. Although the cumulative case count of COVID-19 cases in the Philippines was roughly 4% of the population, limited availability of testing in the country underestimates the true number of cases, and as such many patients would have been exposed to the virus at the time of the study, whether through casual exposure or asymptomatic infection (31).

SARS-CoV-2 induces both direct and indirect pathology which results in dysfunction of almost all of the major organ systems in the human body (6, 32). Of the major organ systems affected by Long COVID, the nervous system and the respiratory system seem to be the

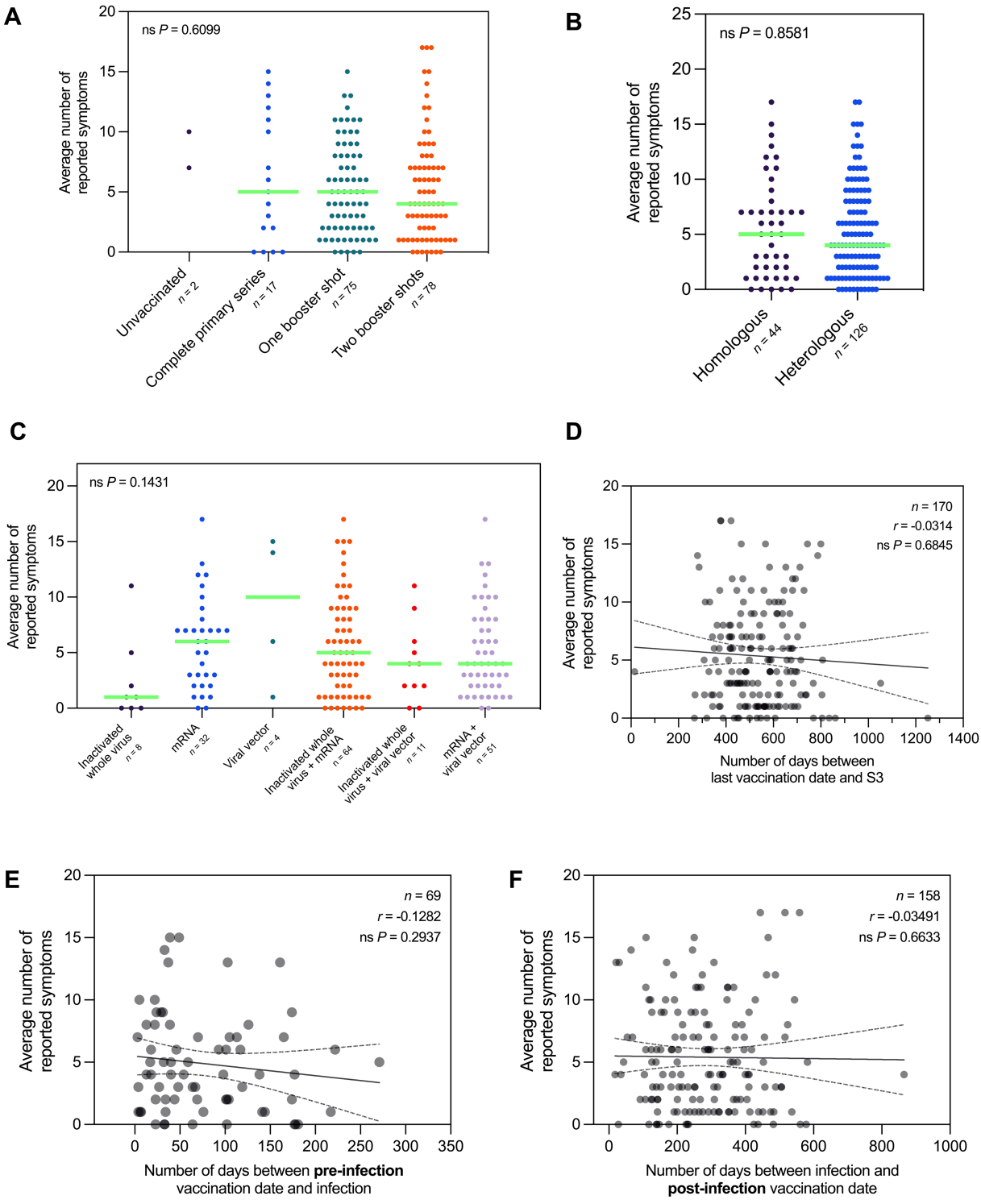

FIGURE 7
Average number of Long COVID symptoms did not vary by vaccination profile. **(A)** Number of reported symptoms does not vary significantly with vaccination status at the time of the first session (Kruskal–Wallis test; $P = 0.6099$). Likewise, the number of reported symptoms does not vary significantly with **(B)** vaccine combination taken (Mann–Whitney test; $P = 0.8581$) and **(C)** vaccine type/s taken (Kruskal–Wallis test; $P = 0.1431$). **(D)** Number of reported symptoms is not significantly correlated with the number of days between the last vaccination date and the third session (Spearman's rank-order correlation; $r = -0.0314$, $P = 0.6845$). Likewise, the number of reported symptoms is not significantly correlated with the number of days between pre-infection vaccination date and infection **(E)** (Spearman's rank-order correlation; $r = -0.1282$, $P = 0.2937$), and the number of days between infection and post-infection vaccination date **(F)** (Spearman's rank-order correlation; $r = -0.03491$, $P = 0.6633$). Dots represent the number of reported symptoms, with the median indicated by a neon green line for sample sizes of three (3) or more. Statistically significant differences were assessed using Mann–Whitney test and Kruskal–Wallis test followed by Dunn's multiple comparisons test ($^{*}P < 0.05$, $^{ns}P > 0.05$).

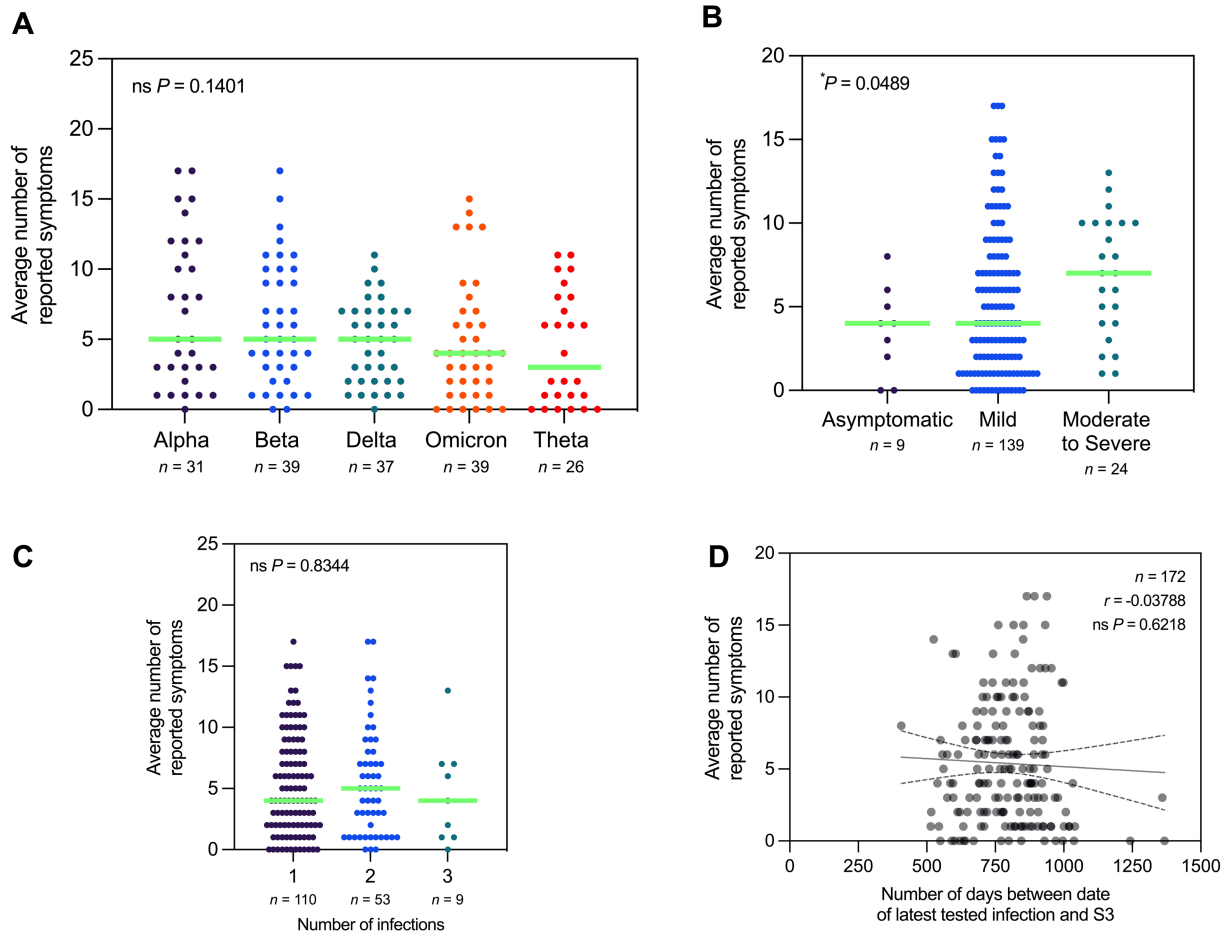

FIGURE 8
Average number of Long COVID symptoms varied by disease severity during acute infection. **(A)** Number of reported symptoms does not vary significantly with SARS-CoV-2 variant (Kruskal–Wallis test; $P = 0.1401$). **(B)** Number of reported symptoms varies significantly with disease severity during time of infection (Kruskal–Wallis test; $P = 0.0489$). **(C)** Number of reported symptoms does not vary significantly with the total number of tested infections (Kruskal–Wallis test; $P = 0.8344$). **(D)** Number of reported symptoms is not significantly correlated with the number of days between date of latest tested infection and third session (Spearman's rank-order correlation; $r = -0.03788$, $P = 0.6218$). Dots represent the number of reported symptoms, with the median indicated by a neon green line. Correlation studies are depicted with a line of best fit and 95% confidence bands. Statistically significant differences were assessed using Spearman's rank-order correlation and Kruskal–Wallis test followed by Dunn's multiple comparisons test (*$P < 0.05$, ns $P > 0.05$).

most well-studied as the majority of those with Long COVID report neuropsychiatric and pulmonary symptoms such as brain fog, sleep problems, dyspnea, and fatigue (33, 34). Consistent with these findings, neuropsychiatric Long COVID symptoms represented one of the top categories of the most frequently reported symptoms across all reports in our cohort.

Of the neuropsychiatric symptoms, the majority of the participants reported brain fog, which is an umbrella term encompassing a wide range of cognitive impairments such as memory loss, confusion, mental blocks, and difficulty thinking or concentrating (35). Consistent with the definition of brain fog, individuals in our cohort who experienced intermittent brain fog noted that they experienced disorientation, periods of dissociation, memory lapses, and that they struggle with maintaining focus over extended periods, recalling words, and remembering immediate tasks (35). The heterogeneous nature of brain fog poses significant challenges to professional performance and the overall quality of life for individuals, which thus underscores the importance of investigating its etiology and exploring its manifestations across diverse populations (36). Notably, the majority of the brain fog reports came from the Alpha and Beta cohorts, which suggests differences in neurotropism across variants and how these earlier variants could increase the risk of developing brain fog and other neurocognitive impairments. Some believe that this association may be attributed to the cumulative burden of adverse psychological and social factors linked to the prolonged duration of the pandemic (6, 10).

Apart from brain fog, headache is another neurological symptom commonly reported among those who develop Long COVID. Long COVID headache can present in the form of a worsening of a pre-existing headache or in the form of an intermittent or fluctuating headache after acute infection; the latter being consistent with findings from our study (37, 38). Notably, the majority of the headache reports came from either the Alpha or Beta cohort, and headache was consistently a top reported symptom in the Omicron cohort in all three sessions, which suggests an association between specific variants and Long COVID headaches.

Alongside brain fog and headache, fatigue was one of the most frequently reported symptoms among all participants in all three sessions, similar to findings from Italy and UK cohorts wherein the majority also reported experiencing chronic fatigue post-infection (6, 10). Because COVID-19 is primarily a respiratory infection, it makes sense that long-term pulmonary abnormalities constitute a central aspect of Long COVID syndrome (10). Among the fatigue reports, the majority came from either the Alpha or Beta cohorts, similar to our findings on brain fog and fatigue, while a minority came from either the Omicron or Theta cohorts. These contrasting results, again, highlight the differences in the risk of developing Long COVID between earlier circulating variants and later circulating variants (10).

In general, we observed that most of the brain fog, headache, and fatigue reports came from either the Alpha or Beta cohorts in our study, which points to the possibility that those infected by earlier variants are at higher risk of developing these symptoms. While the reason behind the co-occurrence of brain fog, headache, and fatigue in a number of recovered cases remains unclear, these symptoms share common underlying pathophysiological mechanisms, including inflammation, dysregulated immune responses, neurotransmitter imbalances, and alterations in cerebral blood flow, which could explain why these symptoms were consistently among the top reported symptoms in all three sessions (10, 35, 39). In addition, central sensitization has also been linked to Long COVID and may explain the prevalence of these three symptoms (40). This phenomenon is characterized by CNS hypersensitivity to sensory stimuli that leads to the amplification of neurocognitive symptoms such as headache and brain fog, as well as increased fatigue due to heightened neural responses (40).

Brain fog, headache, fatigue, and the other symptoms assessed in this study were all consistently reported as relapsing or intermittent among the participants, consistent with a meta-analysis showing a decreased prevalence of symptoms 30 days after onset, a posterior increase 60 days after but with another decrease > 90 days after (41). The relapsing nature of these symptoms may explain the observed decline in the number of symptomatic cases throughout the three sessions; however, it is possible that during subsequent sessions, the symptoms simply had not recurred yet in some individuals, which thus highlights the dynamic and temporal nature of Long COVID and need for longitudinal monitoring throughout weeks, months or years after the infection (42). Alternatively, the observed decline in the number of symptomatic cases on subsequent sessions could represent improvements or resolution of symptoms during the study period; however, this assumption should be taken with caution as potential recall bias among the participants could have masked the true prevalence symptoms in the study population.

4.2 Variability of Long COVID manifestation, duration, and its episodic nature

Previous studies have identified age as a risk factor for the severity of acute infection and the development of Long COVID, with older individuals at higher risk of developing sequelae post-infection (43, 44). Older individuals, in particular, are more likely to have pre-existing conditions and comorbidities, which makes them more susceptible to severe disease and sequelae post-infection (6). Contrasting results were observed in our cohort, wherein age was negatively correlated with the number of reported symptoms, but such findings could be attributed to the limited sample size for older age groups. The disparity in these findings underscores the need for additional research to clarify underlying mechanisms and discern patterns of Long COVID across various age groups.

Although women seem to experience less severe complications during the acute phase of COVID-19, they seem to suffer worse long-term complications post-infection (45). In our cohort, females exhibited a higher prevalence of Long COVID symptoms compared to males on average, consistent with previous findings which illustrate how females are at higher risk of Long COVID compared to men (7, 46). Although the precise mechanism driving these distinctions remains unclear, existing data suggests that sex-related variations in hormones and immune responses may contribute to a heightened inflammatory state during the acute phase, persisting even after recovery in females (46). While in other studies, no gender association was observed, these contrasting results may be due to differences in ethnicity and socio-economic status (46).

Pre-existing conditions and comorbidities correlate with the severity at the acute stage and are also risk factors for developing Long COVID (6). A previous study found that patients with three or more comorbidities are at a two-fold risk of not returning to the basal health status (47). We observe similar findings in our study wherein the prevalence of Long COVID is higher in those with comorbidities than those without, particularly in those with one, three, or more comorbidities. While we were only able to assess the number of reported symptoms based on the presence and number of comorbidities, it is worth noting that certain comorbidities (e.g., Type 2 diabetes, obesity, mental illness) may make an individual more predisposed to Long COVID than others (6, 47, 48).

It is well-established that vaccines reduce the severity of acute SARS-CoV-2 infection. However, whether or not this confers protection against the development of Long COVID has yet to be established. While some studies report a reduction in Long COVID symptoms and symptom severity after one or two doses of vaccine, others report no change or even worsening of symptoms after vaccination. Various studies suggest that vaccination generally tends to lessen the severity and frequency of these symptoms, highlighting the potential protective effect of vaccines against the development or persistence of Long COVID (49–52). Although the findings of the present study show that there is no significant difference in the number of reported symptoms between the different vaccination groups, it should be emphasized that no statistical analysis could be reliably applied to the unvaccinated group due to the limited number of participants in the cohort ($n = 2$). Majority of patients have already received at least one type of vaccine at the time of recruitment. An observable trend toward less symptoms with increasing number of vaccine doses can be inferred from the data suggesting the potential effect of antigen diversity in heterologous dosing strategies and inactivated whole virus preparations. This is consistent with recent systematic reviews supporting the idea of a protective effect of vaccines on Long COVID, thus underscoring the importance of comparative studies to help clarify this effect (49, 53).

Another curious observation would be the timing of vaccination to proliferation of variants. As vaccines had yet to be distributed during the peak periods of Alpha and Beta variant proliferation, greater vaccine exposure and uptake during the Omicron surge may explain differences noted in symptoms reported by patients albeit not statistically significant. Theta, which proliferated during the Delta surge, was noted to have less reported symptoms despite being in the same vaccination time frame as Delta. This may suggest that despite displaying spike protein mutations

consistent with Beta, which could confer for it heightened immune evasion capabilities, it could be surmised that Theta exhibited a milder clinical phenotype that translates to a similarly lower incidence of Long COVID symptoms (54). However, a small Theta population precludes any definitive assessment regarding the severity of the variant, but still provides some insight to the role of vaccination status on COVID-19 severity and Long COVID sequelae.

In terms of vaccine type, the risk of developing Long COVID does not vary across different vaccine types and mechanisms, consistent with the results from our study (55, 56). However, it is worth noting that the assumptions made are limited to the vaccine brands examined in this study and the small sample size of those who took a homologous vaccine combination. Although vaccination status, vaccine combination, and vaccine types seem to have no appreciable outcome on Long COVID development in our Philippine cohort, vaccination may emerge as a potential therapeutic for those with Long COVID by resetting a dysregulated immune response after acute infection or by eradicating residual viral reservoir (49). We also examined the timing of vaccination relative to onset of infection to understand how this might affect the risk of developing Long COVID. The lack of significant correlation between the number of days between infection and vaccination date, either pre- or post-infection, indicates that the timing of vaccination, whether before or after infection, did not significantly influence the development of symptoms in our cohort. Taken together, our results suggest that vaccination status at the time of infection did not influence the manifestation of Long COVID symptoms. It remains to be seen, however, whether vaccination status will have any effect on Long COVID symptom severity.

Many studies have described the sequelae of acute SARS-CoV-2 infection, however, the association between changes in the SARS-CoV-2 genetic code and the development of Long COVID has been poorly understood (57). Because of fitness-enhancing mutations in the viral genome, different variants have varying degrees of transmissibility and virulence, which affects both acute infection and Long COVID (6). In general, patients infected with an earlier variant (e.g., Alpha, Beta, and Theta) tend to be at higher risk of developing Long COVID than those infected with a subsequent variant (e.g., Omicron or Delta); however, this assumption should be considered under the potential effect of reinfections and vaccines (42). For instance, one study found that cases attributed to the Omicron variant had lower odds of developing long-term cardiopulmonary symptoms compared to those attributed to the Delta variant (57). In another study, they found that those infected with Delta and Omicron reported less severe olfactory dysfunction than those infected with the wild-type strain (10). In this study, however, symptom prevalence did not vary significantly upon stratification of participants by variant and the number of reported symptoms did not vary significantly across those previously infected with different SARS-CoV-2 variants, contrary to findings that suggest that certain phenotypic presentations of Long COVID may be associated with previous exposure to specific SARS-CoV-2 variants (58, 59). Future studies with larger sample sizes and longitudinal designs should further investigate the variability of Long COVID symptoms in relation to different SARS-CoV-2 variants that circulated in the Philippines. This is of particular importance given the distinct demographic profile of the Philippines, characterized by a unique population of mobile workers, including over 100,000 Overseas Filipino Workers (OFWs) who returned home during the pandemic, heightening the potential for exposure to diverse viral strains and other health risks (60).

While differences in virulence and transmissibility of SARS-CoV-2 variants may account for the development of Long COVID, reports show that disease severity during acute infection and subsequent reinfections may also be associated with the development and severity of Long COVID. A previous study shows that those with severe disease during acute infection reported a higher number of Long COVID symptoms, consistent with our findings that those with moderate to severe disease reported a higher number of symptoms compared to those with mild disease (61). Moderate to severe cases of COVID-19 are often associated with higher viral loads and greater tissue damage throughout the body, both of which are known to contribute to the development of Long COVID (48). In addition, prolonged hospital stays, physical deconditioning, and complications associated with critical illness can further exacerbate the risk of long-term physical, cognitive, and psychological impairments. Although the number of studies examining the relationship between Long COVID and multiple reinfections is limited, the consensus at present is that reinfection further increases the risk of Long COVID sequelae in the acute and post-acute phase, contrary to what we observed in our cohort (55, 62). While both symptomatic and asymptomatic SARS-CoV-2 reinfections may result in Long COVID, the risk of developing Long COVID was found to be significantly lower in asymptomatic individuals (63).

Another important aspect to consider is the variability in Long COVID severity, which can range from mild complaints to life-changing debilitation (64). In this study, we assessed Long COVID severity by counting the number of reported symptoms. However, this approach does not fully capture the impact of Long COVID on the quality of life. A follow-up study involving quality of life surveys and patient-administered disability rating scales can help quantify the long-term sequelae and impact of Long COVID on this cohort. This is particularly important in the context of the Philippines where the impression of medical practitioners on the severity of Long COVID symptoms has yet to be studied despite a general assumption that most reported cases of Long COVID are mild and not as debilitating as reported elsewhere (65). Such non-chalance may also be due to a lack of awareness, highlighting the need for a multifaceted approach in assessing Long COVID that captures both quantitative and qualitative symptoms.

5 Summary

Long COVID presents as a long-term complication of COVID characterized by a highly heterogeneous set of debilitating symptoms. In this retrospective-prospective study using a Philippine cohort, we were able to identify the presence, intensity, and number of Long COVID symptoms across the dominant SARS-CoV-2 variants circulating in the country. We found that a large proportion of participants who were infected from 2021 to 2022 reported intermittent fatigue, headache, and brain fog even after more than a year post-infection consistent with other studies. The findings of our study provide a valuable foundation for developing interventions and treatment strategies to help address the challenge of rehabilitating patients facing a disease with a myriad of clinical presentations. Furthermore, it highlights the need for long-term monitoring of Long COVID and its impact on human health and the need for our health systems to adopt policy response strategies. To our

knowledge, this study is the first to provide insights into post-COVID sequelae in a Philippine cohort and the possible risk factors that contribute to the prevalence of this chronic syndrome.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Single Joint Research Ethics Board of the Department of Health (DOH-SJREB), University of the Philippines Manila Research Ethics Board (UPMREB/NCR), Vicente Sotto Memorial Medical Center Research Ethics Committee (VSMMC-REC/Region VII), Teresita L. Jalandoni Provincial Hospital Ethics Review Committee (TLJPH-ERC/Region VI), and West Visayas State University Ethics Review Committee (WVSU-ERC/Region VI) institutional review boards. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CS: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. MEA: Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. PT: Formal analysis, Investigation, Visualization, Writing – original draft. MRA: Investigation, Methodology, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was funded by the Department of Science and Technology – Philippine Council for Health Research and Development (DOST-PCHRD).

Acknowledgments

The authors would like to acknowledge the contributions of those who worked under the Immunogenomics Surveillance Program of the Philippine Genome Center – Maricris Macasinag, Pauline Shean Garcia, Juverlyn Joy Panagdato, Jasmin Lee, Jhassiy Layacan, Elaiza Camille Pigao, Katrina Tagasa, Danica Velasco, and Jenny Manuel – for their generosity and assistance. The authors would also like to thank the participants of the study for their generosity and willingness to participate. Lastly, the authors would like to acknowledge the Core Facility for Bioinformatics of the Philippine Genome Center for providing the epidemiological data used in the study.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1455729/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 04 October 2024
DOI 10.3389/fmed.2024.1459583

OPEN ACCESS

EDITED BY
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RECEIVED 04 July 2024
ACCEPTED 25 September 2024
PUBLISHED 04 October 2024

CITATION
Aldhawyan AF, BuSaad MA, Almaghlouth NE, Alnasser AH, Alnasser JA, Almansour AH and AlHarkan KS (2024) Understanding long COVID: prevalence, characteristics, and risk factors in the Eastern Province of Saudi Arabia.
Front. Med. 11:1459583.
doi: 10.3389/fmed.2024.1459583

Understanding long COVID: prevalence, characteristics, and risk factors in the Eastern Province of Saudi Arabia

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Background: The COVID-19 pandemic has significantly raised public health concerns and efforts to limit its spread, impacting societies and health systems worldwide. As challenges persist, the emergence of Long COVID (LC) marks a turning point in understanding the pandemic's long-term effects.

Aim: This study aimed to determine the prevalence of LC in the Eastern Province of the Kingdom of Saudi Arabia (KSA) and explore factors contributing to its persistence.

Methods: This descriptive, cross-sectional, questionnaire-based study was carried out between December 1, 2023, and March 1, 2024, involving 1,355 patients who recovered from COVID-19. Participants were conveniently chosen and information was gathered through in-person interviews in public settings after obtaining consent.

Results: A majority of the patients ($N = 1{,}355$; 47.5% female; 93.8% Saudis; mean Age $\pm$ SD 33.13 ± 12.60 years) had received three COVID-19 vaccine doses (89.5%). Women experienced 17.4% more LC symptoms than men ($p < 0.001$). The risk of having a higher symptom count increased by 42.5% 12 months after acute COVID-19 infection compared with baseline (<3 months, $p < 0.001$). A higher body mass index (BMI) was associated with more symptoms (1.1% increase per unit, $p = 0.004$). More acute-phase symptoms correlated with more LC symptoms ($p < 0.001$). Higher educational attainment reduced LC risk by 33% ($p < 0.001$). Finally, age and vaccination status had no effect on LC symptoms count ($p > 0.05$).

Conclusion: Sociodemographic and clinical factors contribute differently to the chances of having LC and the count of symptoms. Awareness of such factors could provide insight into improving management, leading to better health outcomes.

KEYWORDS

long COVID, post-COVID-19 syndrome, post-COVID condition, ongoing symptomatic COVID-19, COVID-19

Introduction

Amidst the global upheaval triggered by the coronavirus disease (COVID-19), an extremely contagious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus identified first in Wuhan, China in December 2019, the virus rapidly spread worldwide, prompting the World Health Organization (WHO) declared it a worldwide pandemic on March 11, 2020 (1). The toll has been staggering, with over 704 million cases and 7 million deaths recorded worldwide (2). In the Kingdom of Saudi Arabia (KSA) alone, over 841 thousand confirmed cases and 9,640 deaths were attributed to the virus (2). This rapid escalation raised public health concerns and sparked efforts to limit its spread. The COVID-19 pandemic has profoundly affected societies worldwide, exposing and exacerbating social issues such as income inequality, health disparities, and the strain on public health systems. It has also severely disrupted mental health, education, and social interactions. Moreover, the pandemic highlighted significant inequities in access to healthcare, reshaping perceptions of health, resilience, and societal vulnerabilities (3, 4). In investigating COVID-19, researchers have identified varying degrees of illness severity. The majority of individuals experience mild to moderate illness and recover without the need for hospitalization. For instance, a 2022 cohort study involving 162 COVID-19 patients reported that 22.9% were asymptomatic, 74.6% experienced mild to moderate symptoms that did not require hospitalization, and only 2.5% of patients required hospital care (5). The WHO has outlined COVID-19 symptoms, ranging from common signs such as fever, cough, and loss of taste/smell to less frequent symptoms such as sore throat, headache, and skin rash, and serious symptoms such as chest pain and difficulty in breathing (6).

As the world struggles with the ongoing challenges posed by the virus, the advent of Long COVID (LC) marks a significant chapter in our understanding of the enduring impact of this pandemic. The Centers for Disease Control and Prevention (CDC) and the National Institute for Health and Care Excellence (NICE) have undertaken a dynamic process of refining guidelines, defining LC/post-COVID-19 syndrome (PCS) as signs and symptoms develop during or after COVID-19 infection, persist for 12 weeks or more, and cannot be explained by an alternate diagnosis, while ongoing symptomatic COVID-19 as signs and symptoms persist for less than 12 weeks after the initial infection (7, 8). Despite rigorous investigations of the factors contributing to the persistent development of post-COVID-19 complications in some patients, the precise pathophysiological mechanisms underlying LC remain unclear (9, 10). Some leading hypotheses include autoimmunity, immune dysregulation, microembolization, and endothelial activation or dysfunction (9, 10).

Although LC presentations vary, common symptoms include fatigue, respiratory symptoms, hair loss, muscle and joint pain, attention deficits, and headache (11, 12). However, more serious symptoms include renal failure, pulmonary fibrosis, myocarditis, arrhythmia, and more (12). A detailed list of the most common LC symptoms by affected body system can be found in Supplementary Table S1. This broad spectrum of symptoms contributes to variations in the reported prevalence across global populations. A UK study published in February 2023 estimated that approximately 2 million individuals reported experiencing LC symptoms (13). Continuous analyses by the CDC in the US found that during March–April 2024, approximately 18% of adults had persistent COVID-19 symptoms beyond acute presentation (14). A large observational meta-analysis of 1.2 million people reported that 6.2% of patients with symptomatic COVID-19 had LC, which included ongoing respiratory problems (3.7%), persistent fatigue with bodily pain or mood swings (3.2%), and cognitive issues (2.2%) (15). Additionally, among 21,797 patients surveyed in China, 8.89% self-reported experiencing LC symptoms, with 2.92% reporting two or more symptoms. The most commonly reported symptom was Fatigue (3.38%), followed by sleep difficulties (2.20%), hair loss (2.06%), cough (1.74%), and sore throat (1.27%) (11).

Moreover, a meta-analysis and comprehensive review with a sample size of 1,680,003 patients published in November 2022 found that the pooled worldwide prevalence of LC was 0.43. Estimates were 0.54 for hospitalized patients and 0.34 for non-hospitalized individuals (16). The United States of America (0.31%), Europe (0.44%), and Asia (0.51%) were the other regions with high prevalence (16). Additionally, in January 2023, cross-sectional research including 520 Arabic patients residing in the KSA was published; 25% of them had LC and the most common recorded symptoms were cough, anosmia, fatigue, headache, muscle pain, arthritis, and shortness of breath (32, 32, 28, 19, 19, 18, and 17% of LC patients, respectively) (17). However, data from 504 patients at King Abdulaziz University Hospital in Jeddah revealed a 45% frequency of LC (18).

In light of this, LC presents a significant challenge to patients' wellbeing, inducing long-lasting physical discomfort, cognitive decline, and emotional stress, ultimately reshaping their quality of life, increasing healthcare utilization, and increasing chronic sickness-related unemployment (19, 20). Several risk variables have also been found to increase the probability of developing LC. These factors include demographic risks, comorbidities, age, and severity of the acute COVID-19 infection, and other factors (11, 21).

Throughout this article, we endeavor to shed light on the LC prevalence in the Eastern Provinces of the KSA and explore the factors contributing to its persistence, including demographic variables, comorbidities, and the severity of the initial infection.

Materials and methods

Study design

This was a descriptive, cross-sectional, questionnaire-based study conducted from December 1, 2023, to March 1, 2024 among 1,350 COVID-19 recovered patients who are currently residing in the Eastern Province of the KSA, who were conveniently selected and whose information was obtained through face-to-face interviews in public community settings.

Study sample

This study included all COVID-19 diagnosed patients who were at least 18 years old. Patients who refused to provide consent to participate or all requested information were excluded. The Epi Info software (version 7.0) was used to calculate the sample size for a target population of 162,176 patients who recovered from COVID-19, and an expected frequency of 50% for LC. Given a 5% margin of error and

a 95% confidence level, 251 participants were the minimum calculated sample size.

Data collection

Participants' responses were collected by trained volunteers who administered the surveys using tablet devices. The 25-question survey was structured using questionnaires from previously published literature (16, 22–24). Family physicians reviewed the wording of the survey to ensure accuracy. Moreover, the questionnaire included questions regarding sociodemographic data such as age, sex, and occupation; medical history related to COVID-19 infection, including a history of medical illness, hospital, or intensive care unit admission; history of smoking; and lastly, questions about COVID-19 lingering manifestations and questions about the LC. The survey model is provided in Supplementary Document S1 for reference.

Acute COVID-19 was defined as the signs and symptoms of COVID-19 that lasted for up to 4 weeks after the acute infection. The LC/PCS is defined as signs and symptoms that develop during or after a COVID-19 infection, persist for at least 12 weeks, and cannot be explained by an alternative diagnosis, while ongoing symptomatic COVID-19 is defined as signs and symptoms that persist for less than 12 weeks after the initial infection (7, 8).

Statistical analysis

The mean and standard deviation were used to describe continuous variables. The Kolmogorov–Smirnov test of statistical normality was used to assess the statistical normality assumption for the metric variables. The metric variables with statistical Normality assumption violations such as skewness were described using median and interquartile range (IQR) scores. Moreover, the categorically measured variables were described with frequencies and percentages, and multiple response dichotomies analysis was used to describe the variables measured with more than one option, such as COVID-19 symptoms. Generalized estimating equation gamma regression analysis was applied to the reported number (i.e., count) of LC symptoms across time. The data had to be restructured into longitudinal data to account for the effects of time on the GEE analysis. The association between the independent predictor variables in the multivariate analysis and the analyzed outcome variables was expressed as exponentiated beta coefficients (Risk Rates) with their associated 95% confidence intervals. The commercially available SPSS IBM statistical analysis program (version 21) was used for statistical data analysis. The statistical significance level was set at $p < 0.05$.

Ethical considerations

All participants were informed of their enrolment in the study and participant's informed written consent was obtained before participation. The Declaration of Helsinki's ethical standards were followed during data collection, handling, and storage, and all precautions were taken to ensure participant confidentiality. The Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University in the Eastern Province of Saudi Arabia gave their approval to the study protocol (IRB Number: IRB-2023-01-320).

Results

Sociodemographic characteristics

One thousand three hundred and fifty-five people residing in the KSA were participated, and interview-based questionnaires were completed by those who consented to participate in the study.

Most of the participants (93.8%) were Saudi citizens, and 6.2% were expatriates living and working within the Kingdom; 47.5% were women and the remainder (52.5%) were men. The mean ± SD age for the sample was 33.13 ± 12.60 years. The mean body mass index (BMI) score was measured at 26.34 ± 5.19%. Participants were also asked to indicate their smoking habit status; the findings showed that 7.9% were ex-smokers and 32.5% were current smokers, while most of the sample (59.6%) were never smokers. Finally, 48.3% of the participants reported having two or more comorbidities (Table 1).

Prevalence of comorbidities

Figure 1 shows the prevalence of comorbidities among patients with COVID-19. A notable proportion of the patients exhibited coexisting medical conditions. The most prevalent comorbidities exceeding the 10% threshold were diabetes (17.6%), obesity (15.3%), G6PD deficiency (15.3%), hypertension (15.0%), and asthma (13.7%). These conditions were followed by migraine, which was reported in 12.4% of patients, and dyslipidemia, which affected 11.6% of the study cohort.

Acute COVID-19 manifestations and clinical characteristics

The patients were asked to state the number of PCR-confirmed COVID-19 infections they had experienced, and the findings showed that 75.9% of them had at least one PCR-confirmed infection. Moreover, the results revealed that the majority (89.5%) had received three COVID-19 vaccine doses. Upon presentation to the hospital, 11.4% of patients had positive evidence of pneumonia. Regarding the need for healthcare, 19% of the patients had no need for any healthcare services, whereas 60.8% needed some form of healthcare that could be managed at home. On the other hand, about 15% of our patients required Emergency Room/Outpatient services, and the remainder, 5.2% of the patients, needed hospital admission (Table 2).

Prevalence of COVID-19 symptoms across acute, ongoing, and LC/PCS phases

Table 3 displays a head-to-head description of the most prevalent COVID-19 symptoms during the acute phase (<1 month) versus the ongoing symptomatic COVID-19 phase (1–3 months) and the LC/PCS phase (≥3 months). Comparing the prevalence of symptoms across the different phases, fever dropped significantly

TABLE 1 Baseline sociodemographic characteristics of study participants ($n = 1,355$).

Characteristic	Mean (SD) or n(%)
Sex	
Female	643 (47.5)
Male	712 (52.5)
Age (years), mean (SD)	33.13 (12.60)
Age group	
20–30 years	752 (55.5)
31–40 years	279 (20.6)
41–50 years	165 (12.2)
51–60 years	101 (7.5)
≥61 years	58 (4.3)
Body mass index (BMI) level	
Body mass index (BMI), mean (SD)	26.34 (5.19)
Underweight	118 (8.7)
Normal	457 (33.7)
Overweight	513 (37.9)
Obese class I	187 (13.8)
Obese class II	57 (4.2)
Obese class III	23 (1.7)
Marital state	
Never married	645 (47.6)
Ever married	710 (52.4)
Level of education	
High school or less education	475 (35.1)
Diploma degree	99 (7.3)
University degree	729 (53.8)
Higher studies	52 (3.8)
Socioeconomic state level	
Very low	10 (0.7)
Low	88 (6.5)
Medium	795 (58.7)
High	238 (17.6)
Very high	224 (16.5)
Smoking	
Never smoker	807 (59.6)
Former smoker	107 (7.9)
Current smoker	441 (32.5)
Comorbidity (2 or more)	
No	700 (51.7)
Yes	655 (48.3)

SD, standard deviation.

from 74.2% in the acute phase to 2.07% in the LC/PCS phase. Similarly, dyspnea, anosmia, and headache significantly decreased but remained among the most reported symptoms in the LC/PCS phase. Cough, which was reported by 74.2% of patients in the acute phase, witnessed a significant drop in the ongoing symptomatic COVID-19 phase (7%), while still being the most reported symptom. However, in the LC/PCS phase, cough increased in prevalence and was the second most reported symptom (14.24%). Finally, fatigue, which was not the most prevalent symptom in the acute phase, was among the top reported symptoms in the ongoing symptomatic COVID-19 phase (4.1%), and then spiked to rank first in the LC/PCS phase (17.49%).

Longitudinal trends in prevalence of top reported long COVID symptoms

Analysis of the top-reported symptoms among COVID-19 patients over different time periods (1–3 months, 3–6 months, 6–12 months, and > 12 months) revealed distinct trends (Figure 2). Symptoms such as hair loss, memory loss/impairment problems, concentration problems, low mood, joint pain, insomnia, and low performance increased over time, peaking at more than 12 months post-infection. Conversely, the prevalence of smell loss decreased after its initial peaks at 1–3 months. Several symptoms, including headache, shortness of breath, palpitations, vertigo, and muscle pain, exhibited a U-shaped trend, with initial peaks in the early months (1–3 months), a decrease at 3–6 and 6–12 months, and a subsequent increase at >12 months. Fatigue showed a relatively consistently high prevalence over time with a slight increase during the 3–6-month period but no significant long-term increase or decrease. Other symptoms, such as exertional dyspnea, orthostatic hypotension, back pain, and sleep disturbances, declined steadily after their initial peaks of 1–3 months, before re-emerging in prevalence after 12 months. These findings suggest a diverse range of symptom trajectories, some indicating long-term persistence, others resolving over time, and others showing fluctuating patterns.

GEE multivariable gamma regression analysis results of risk factors for long COVID symptom count

Notably, women had a significantly higher mean LC symptom rate (17.4% more) compared to men ($p < 0.001$). However, the patients' age did not converge significantly on their symptom rate across time ($p = 0.228$). Moreover, the patients' measured count of symptoms was significantly higher (42.5% more) after 12 months on average compared to their baseline (<3 months) ($p < 0.001$), but the patients' mean measured symptom rate at 6–12 months and during 3–6 months may not differ significantly compared to the 1–3 months ongoing symptomatic COVID-19 time ($p > 0.050$) (Table 4).

Interestingly, the patients' mean BMI score was positively associated with the mean number of LC symptoms. For each additional unit in the patients' BMI, the mean predicted symptom rate tended to increase by a factor of 1.1% on average ($p = 0.004$), and heavier people reported a greater number of symptoms in general. The patients' COVID-19 vaccination status had no significant influence on the mean number of reported persistent COVID-19 symptoms, ($p = 0.568$). In significant ways, the number of acute COVID-19 symptoms was positively associated with the mean number of LC symptoms ($p < 0.001$). For each additional symptom in the acute

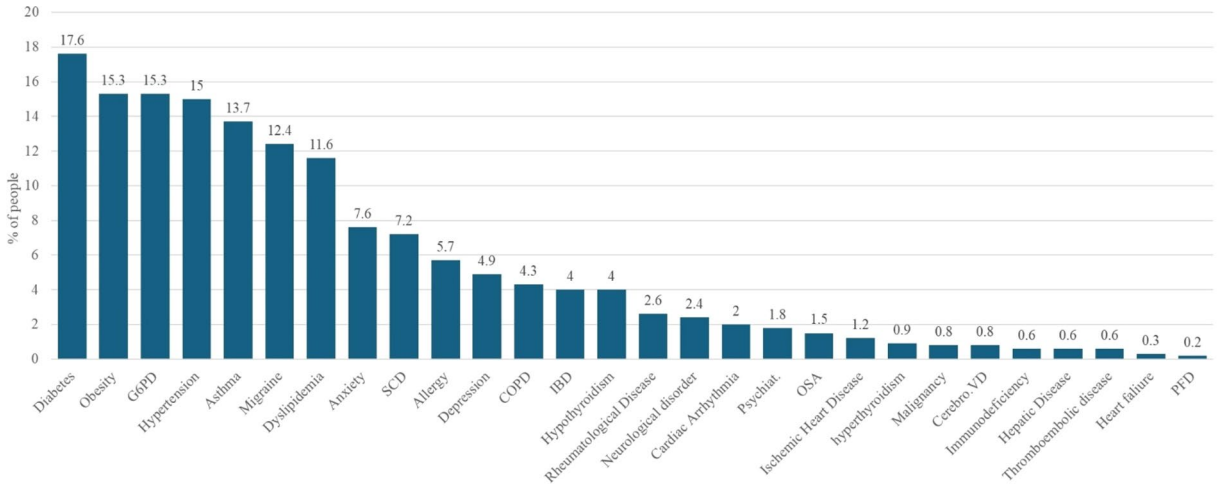

FIGURE 1
Baseline prevalence of comorbidities among study participants ($n = 1,355$).

phase, the mean number of LC symptoms increased by an average of 4% (Table 4). Lastly, patients with higher education had a 33% lower risk of developing LC symptoms than those with a high school degree or lower ($p < 0.001$).

Discussion

When looking at the results of our analysis of the responses of the 1,355 participants, it is evident that women had considerable odds of having a higher count of persistent symptomatology from their acute COVID-19 infection. Every unit increase in BMI in our study increased the risk of having higher symptoms count by 1%. Regarding economic capacity and education, there were elevated chances of persistent symptoms, only with an increase in the former (5.4%). Moreover, after looking at a timeline trend, it appeared that the number of LC symptoms was on average higher 12 months than before, and the number of acute COVID-19 symptoms was directly correlated with the number of lingering symptoms.

Research has demonstrated a 26% higher relative risk for individuals with COVID-19 to develop at least one of the LC symptoms. Several factors have been identified as contributing to this increased risk, including female gender, low socio-economic status, smoking, high BMI, and comorbidities (25). Among individuals with a proven history of COVID-19 infection, many risk factors were linked to the reporting of symptoms ≥12 weeks post-infection. Previous studies have consistently shown that women are more susceptible to experiencing long-lasting symptoms (26). In our analysis, the multivariate regression model revealed that women had a 17% chance (RR = 1.174) of having a higher count of persistent symptoms. This phenomenon is consistent with the findings of previous studies. While the literature offers many hypotheses on the underlying mechanisms that explain why women are at a higher risk of LC, among the most cited are immunological variations, such as reduced pro-inflammatory interleukin-6 (IL-6) production following viral infection in women, which would explain their more lasting symptoms (27). Additional variables, such as heightened psychological stress, isolation effects, and inactivity, may have also contributed to their higher risk (28).

Regarding BMI, larger target population studies found that a higher BMI is associated with more persisting symptoms, especially >30 kg/m^2 as there is around a 10% relative increase in comparison to those with a BMI between 18.5–25 kg/m^2 (28). Another study labeled BMI as the third strongest predictor of LC after increasing age and female sex (29). Notably, there was a positive correlation between the patients' mean BMI score and the average number of LC symptoms. Every one-unit increase in BMI tended to increase LC symptoms by a factor of 1.1% on average. This relationship was statistically significant ($p = 0.004$). Age was not found to be a significant predictor in our study. However, the majority of other studies, including a 2023 meta-analysis of over 40 studies, suggested that older age was a significant contributing factor to LC (30). According to another study, this issue is primarily a liability for people who are already frail when infected (31).

Most research examining health disparities has utilized singular outlooks, focusing on individual factors such as sex, race, or deprivation, without adequately exploring the combined impact of intersecting inequalities on population health (32). For example, a study conducted in Brazil highlighted how the cumulative effects of poor health coverage, community disengagement, and low-income households are determinants that may play a significant role in the burden of COVID-19 disease and its complications (33). Their increased vulnerability to the virus may be linked to weakened immune systems owing to relatively higher stress levels (34). To complement this, a recent study inferred that individuals belonging to the most socioeconomically disadvantaged populations face the greatest susceptibility to LC, with an 11% higher risk than thriving individuals, and this disparity persists regardless of variations in the risk of initial infection (34). Our results however, showed that the scales minutely tip in favor of higher socioeconomic status correlated with persistent symptoms. However, this could be explained by the nature of our study population, as more than 90% had medium to high socioeconomic status. In the aforementioned study conducted in Brazil, researchers examined regions with comparatively

TABLE 2 Acute COVID-19 manifestations and clinical characteristics of study participants ($n = 1,355$).

Characteristic	Median (IQR) or n(%)
How many times did you get PCR confirmed COVID-19 infection?	
Once	1,029 (75.9)
Twice	264 (19.5)
Three times	53 (3.9)
Four times	4 (0.3)
Five times	5 (0.4)
How many COVID-19 vaccine shots did you receive?	
None	9 (0.7)
One dose	10 (0.7)
Two doses	104 (7.7)
Three doses	1,213 (89.5)
Four doses	19 (1.4)
Did you present to the hospital with pneumonia?	
No	1,201 (88.6)
Yes	154 (11.4)
Need for healthcare	
Not needed	258 (19)
Home management	823 (60.7)
ER/Out-patient services	203 (15)
Required hospital admission	71 (5.2)
Type of hospital admission	
Hospital floor admission	50 (3.7)
ICU admission	21 (1.5)
Number of acute COVID-19 symptoms	
Number of acute COVID-19 symptoms, median (IQR)	6 (8)
None/very mild	105 (7.7)
1–3 symptoms	239 (17.6)
4–6 symptoms	350 (25.8)
7–9 symptoms	249 (18.4)
10–15 symptoms	270 (19.9)
≥16 symptoms	142 (10.5)

IQR, interquartile range; PCR, polymerase chain reaction.

TABLE 3 Prevalence of COVID-19 symptoms across acute, ongoing, and LC/PCS phases among study participants ($n = 1,355$).

	Acute phase (<1 month)	Ongoing phase (1–3 months)	LC/PCS phase (≥3 months)
Symptom	n (%)	n (%)	n (%)
Cough	928 (74.2)	95 (7)	193 (14.24)
Expectoration	223 (17.8)	11 (0.8)	22 (1.62)
SOB	496 (39.7)	33 (2.4)	78 (5.76)
Dyspnea	331 (47.2)	25 (1.8)	89 (6.57)
Chest pain	324 (25.9)	15 (1.1)	41 (3.03)
Nasal congestion	389 (31.1)	13 (1)	29 (2.14)
Sinusitis	200 (16)	12 (0.9)	44 (3.25)
Fever	953 (76.2)	12 (0.9)	28 (2.07)
Back pain	309 (27.7)	17 (1.3)	63 (4.65)
Joint pain	337 (27)	14 (1)	69 (5.09)
Hypoxia	99 (7.9)	6 (0.4)	14 (1.03)
Ageusia	382 (30.6)	0	58 (4.3)
Dysgeusia	159 (12.7)	0	53 (3.91)
Anosmia	512 (41)	0	131 (9.67)
Hearing problems	28 (2.2)	6 (0.4)	19 (1.4)
Visual problems	21 (1.7)	0	8 (0.59)
Headache	562 (45)	45 (3.3)	102 (7.53)
sleep disturbance	214 (17.1)	14 (1)	56 (4.13)
Excessive sleepiness	144 (11.5)	3 (0.2)	27 (1.99)
Dizziness	199 (15.9)	7 (0.5)	31 (2.29)
Muscle pain	343 (27.4)	20 (1.5)	48 (3.54)
Palpitation	106 (8.5)	21 (1.5)	68 (5.02)
Fatigue	684 (54.7)	56 (4.1)	237 (17.49)

LC, long COVID; PCS, post COVID-19 syndrome.

broad healthcare coverage and observed an increase in the likelihood of identifying new cases only because their symptoms were more reportable and had better accessibility to healthcare facilities, which is also known as a detection bias (33). This was also the main takeaway message from a 2022 Swiss study that found that public health surveillance that determines epidemic severity depending on the number of positive testing cases alone was rather precarious, as it was highly limited to the availability of testing methods at certain locations (35). A higher education level was found to be a protective factor against LC in our data. This was consistent with a Spanish study that found that individuals with tertiary education were not only less likely to be affected by LC but also recovered faster if affected (36).

The regression table illustrates that the measured number of symptoms was significantly higher (42.5%) for >12 months than for the baseline phase (< 3 months). Correspondingly, this study shows how French patients' COVID-related health conditions started to intensify 6 months after onset (37). Another study from South America showed that approximately 64% patients had at least one symptom reported 12 months after infection. The main risk factor is the mean number of symptoms observed during the acute phase (38). In our data, it was found that every symptom increases in acute presentation raised the risk of more persistent symptoms by approximately 4%. This is not surprising, as we know that the number of acute-phase symptoms correlates with disease severity, which tends to significantly increase the occurrence odds of LC, according to another UK study (39). Figure 2 shows that among the 18 top reported symptoms, 14 were reported at >12 months more than in the acute/ongoing phase.

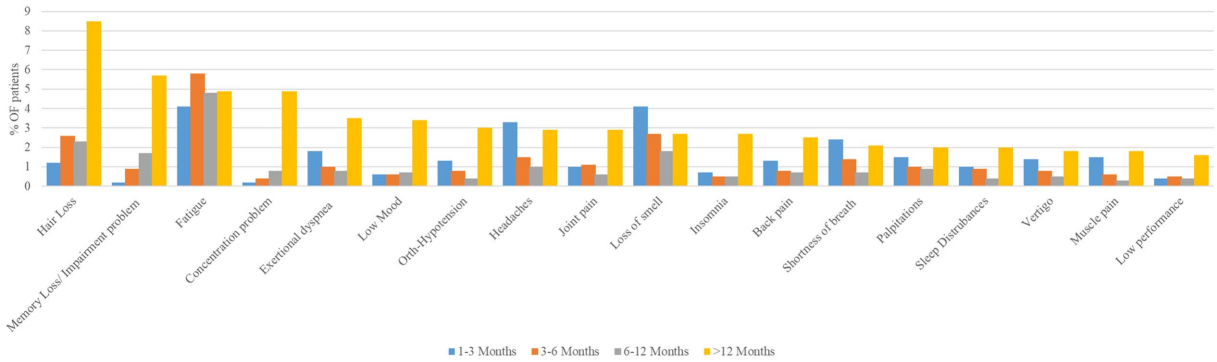

FIGURE 2
Longitudinal trends in prevalence of top reported long COVID symptoms among study participants across different time periods ($n = 1,355$).

TABLE 4 GEE multivariable gamma regression analysis results of risk factors for long COVID symptom count among study participants ($n = 1,355$).

Variable	Adjusted risk rate (RR)	95% CI	*p*-value
Age (years)	1.00	(1, 1)	0.23
Gender			
Male	Reference		
Female	1.17	(1.1, 1.25)	<0.001*
Socioeconomic status			
Low–very low	Reference		
Medium–high	1.05	(1.01, 1.1)	0.022*
Education			
High school or less	Reference		
Diploma	1.01	(0.86, 1.18)	0.95
University degree	1.03	(0.94, 1.13)	0.51
Higher studies	0.67	(0.57, 0.8)	<0.001*
Body mass index (BMI)	1.01	(1, 1.02)	0.004*
COVID-19 vaccination status	0.96	(0.85, 1.09)	0.57
Number of acute COVID-19 symptoms	1.04	(1.03, 1.05)	<0.001*
Time			
Baseline <3 month	Reference		
3–6 months	0.96	(0.86, 1.07)	0.43
6–12 months	0.94	(0.83, 1.07)	0.37
>12 months	1.43	(1.28, 1.59)	<0.001*
(Intercept)	1.07	(0.62, 1.83)	0.82

*$p < 0.05$ considered statistically significant; CI, confidence interval.

Strengths and limitations

As for the strengths, the questionnaire used was conducted via face-to-face interviews rather than online, prompting more genuine responses and immediate clarification by volunteers if any question was slightly confusing for the participants. Second, the study assessed syndrome prevalence 2 years post-COVID, a research area that is understudied. Moreover, this patient pool was evident because of its large sample size. It is also notable that a significant subgroup of the patients only needed at-home management, which is interesting as much of the literature regarding the topic always tends to target hospitalized patients or outpatient visitors.

This study has its limitations. First, it was conducted approximately 18 months after the peak of COVID-19 infections in the KSA (according to the WHO), so its retrospective nature may have led to a recall bias of acute and lingering symptoms. Second, the raw data were dependent on face-to-face interviews using questionnaires in public places, potentially leading to selection bias where individuals with LC symptoms may have been more motivated to participate; however, individuals with more severe symptoms may not have been equally represented due to difficulty in participating. Furthermore, the use of convenience sampling may limit the generalizability of the results to the broader population. The symptom ratings in the questionnaire could introduce a degree of subjectivity, and the lack of a control group consisting of non-COVID individuals complicates comparison. However, given the nature of a pandemic, it is challenging, if not impossible, to find individuals who have not been infected to act as a control group, which presents a methodological challenge. Additionally, the absence of objective clinical measures or biomarkers reduces the accuracy and precision of symptom assessment.

Due to these limitations, this study might not accurately reflect the experiences of the entire LC population. Our sample exhibited a significantly higher level of immunity and vaccination compared to other locations, where the majority of individuals may have received only one or two doses, or even none. This factor could possibly explain the distinct findings in our sample and may further limit the generalizability of the results to less vaccinated populations.

We recommend that the data presented be interpreted within the parameters of this study, and caution should be taken when generalizing the findings to all individuals with the condition.

Conclusion

Potential factors linked to a higher number of LC manifestations included female sex, lower socioeconomic status, higher BMI, timing

>12 months since COVID-19 infection, and a higher number of acute COVID-19 symptoms. Conversely, higher education offers a greater likelihood of protection against lingering symptoms. Thus, prospective health policy recommendations should integrate several elements of inequality, including sex, occupation, education, and socioeconomic disadvantages, when addressing the approach to and management of LC.

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 Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University in the Eastern Province of Saudi Arabia gave their approval to the study protocol (IRB Number: IRB-2023-01-320). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AFA: Writing – review & editing, Writing – original draft, Visualization, Resources, Conceptualization. MB: Writing – review & editing, Software, Methodology, Formal analysis, Data curation. NA: Writing – original draft, Investigation. AAln: Writing – original draft, Methodology. JA: Writing – original draft, Project administration. AAlm: Writing – review & editing, Supervision. KA: Writing – review & editing, Validation.

Funding

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

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1459583/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 05 December 2024
DOI 10.3389/fmed.2024.1499239

OPEN ACCESS

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RECEIVED 20 September 2024
ACCEPTED 04 November 2024
PUBLISHED 05 December 2024

CITATION
Fernández-Pedruelo D, Juárez-Vela R, Ruiz de Viñaspre-Hernández R, Alonso-Alonso J, Criado-Gutiérrez JM and Sancho-Sánchez C (2024) Influence of smoking and obesity on post-COVID-19 sequelae and risk of hospitalization. *Front. Med.* 11:1499239. doi: 10.3389/fmed.2024.1499239

Influence of smoking and obesity on post-COVID-19 sequelae and risk of hospitalization

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Introduction: The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has significantly impacted the global healthcare system, with particularly harmful effects on the human respiratory system. Beyond the acute symptoms, there is growing concern about persistent symptoms that last for weeks or months after the initial infection, known as long COVID syndrome. This study focuses on investigating the relationship between smoking, obesity, and the presence of post-COVID-19 sequelae, as well as their influence on the risk of hospitalization.

Materials and methods: An observational and retrospective study was conducted using medical records of patients diagnosed with COVID-19 in Castilla y León, Spain, between November 1 and 30, 2020. The patients were divided into three groups: smoking (current and former), obesity/overweight, and control group. Various variables were analyzed, including age, sex, and the presence of post-COVID-19 sequelae, chronic pathologies, cardiovascular diseases, psychological conditions, and hospitalization. Descriptive statistics and Odds Ratio analysis were used for comparisons.

Results: The results revealed that obesity was significantly associated with a higher risk of post-COVID-19 sequelae, particularly memory disorders and neurological, mental, or psychological symptoms. In contrast, smoking was correlated with an increase in memory problems but did not show a direct influence on post-COVID-19 sequelae or hospitalization. Additionally, women were found to have a higher prevalence of obesity in the studied population.

Conclusion: This study provides evidence that obesity increases the risk of post-COVID-19 sequelae, especially in terms of memory disorders and neuropsychological symptoms. On the other hand, smoking is related to memory problems. Regarding cardiovascular pathologies, there was not enough statistical evidence for analysis, while for hospitalization, it was determined that smoking and obesity do not have a direct influence on these post-COVID consequences.

KEYWORDS

COVID-19, smoking, obesity, sequelae, hospitalization

1 Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has had an unprecedented impact on global health and has posed numerous challenges for the medical and scientific community worldwide. While the acute symptoms of the disease, such as fever, cough, and difficulty breathing, have been widely documented, it has become increasingly evident that the virus's impact is not limited to the acute period of infection. COVID-19, caused by the SARS-CoV-2 virus, primarily affects the human respiratory system, with symptoms manifesting within one to 2 weeks (1). However, studies show a growing trend of patients experiencing post-COVID symptoms ranging from 30 days to 12 weeks after diagnosis, known as long COVID syndrome (2–4).

The scientific literature has documented the presence of persistent symptoms that last for weeks or even months after the initial infection, giving rise to what is known as long COVID syndrome or "Long COVID." Long COVID symptoms vary widely and include extreme fatigue, memory loss, difficulty concentrating, headaches, and problems with smell and taste, among others (5). Also, Long COVID symptoms may persist for more than 2 years (6).

There are mechanisms that are being studied as potential factors behind the development of long COVID including the persistence of SARS-CoV-2 RNA in reservoir cells (7, 8) and the potential role of autoantibodies (9). However, researchers are studying preventive measures that can reduce the risk of long COVID development (10–12)

On the other hand, obesity is another health condition identified as a risk factor for COVID-19 (13). Obese patients may experience a greater need for mechanical ventilation, increasing their risk of hospitalization. Additionally, obesity has been linked to a higher prevalence of chronic conditions such as diabetes and hypertension, which can also increase the severity of COVID-19 (14).

However, despite the growing concern about the impact of smoking and obesity on COVID-19 patients, evidence on these associations is still inconclusive. Some studies have found significant links, while others have reported contradictory results (15, 16).

1.1 Objective

The primary objective of this study is to investigate the influence of smoking and obesity on the occurrence of post-COVID-19 sequelae and the risk of hospitalization. To achieve this, we conducted a detailed analysis of a group of patients diagnosed with COVID-19 during a specific period, evaluating multiple variables and using descriptive statistics and Odds Ratios to gain a clearer understanding of these associations.

1.2 Hypothesis

Therefore, as research on Long COVID progresses, understanding the risk factors that may contribute to the occurrence and severity of these sequelae has become essential. We hypothesize that previous health factors, such as smoking and obesity, increase the probability of suffering persistent symptoms after the acute phase of COVID-19. Smoking is a known risk factor for respiratory diseases and has been a concern in relation to COVID-19 infection due to its detrimental effects on lung function and the respiratory system (17). Given the virus's primary impact on the lungs, there is a hypothesis that smoking could increase the risk of severe complications in COVID-19 patients (18). Obesity appears as a risk factor, since prolonged metabolic and inflammatory dysfunction could delay recovery and exacerbate prolonged symptoms, such as fatigue, muscle pain and respiratory distress, thus increasing vulnerability to long-lasting sequelae (19).

> *H1*: Smoking increases the risk of having Long COVID sequalae symptoms.
>
> *H2*: Obesity increases the risk of having Long COVID sequalae symptoms.

2 Materials and methods

2.1 Investigation design

An observational and retrospective study was conducted to investigate the influence of smoking and obesity on post-COVID-19 sequelae and the risk of hospitalization. This research design allowed for the analysis of previously collected data and the generation of comparative results between different groups of patients.

2.2 Study population

The study population consisted of patients diagnosed with COVID-19 through polymerase chain reaction (PCR) tests conducted by professionals from the public health system of Castilla y León between November 1, 2020, and November 30, 2020, and recorded in the "MEDORA" electronic health record system of the public health system "SACYL," who follows WHO guidelines to identify symptoms. These dates were selected to ensure that the data were representative of a specific period of the pandemic. They were 56.32% of women in the smoking group (401 male, 517 female), 59.92% in the obesity group (515 male, 770 female), and 54.30% in the control group (6,497 male, 7,719 female). For detailed data about the study population, check Table 1.

TABLE 1 Distribution of patients according to characteristics and post COVID-19 sequelae.

	Smoking (current and former)	Obesity and overweight	Control group
Male sex	401	515	6.497
Female sex	517	770	7.719
Age	42.65 (22–64)	34.33 (19–52)	36.37 (16–68)
Chronic conditions	0	3	11
Cardiovascular diseases	0	0	1
Long COVID sequelae	12	44	256
Memory disorders and loss	9	14	59
Hospitalization	0	3	36

2.3 Inclusion criteria

1 Hospitalization: The risk of hospitalization within twelve months following a positive PCR diagnosis of COVID-19 was recorded (Continuous variable).
2 Belong to one of the three defined study groups: patients with a history of smoking (current or former), patients with obesity or overweight (with a body mass index [BMI] over 25), and a third control group composed of individuals who have never smoked and are not overweight or obese.
3 For the control group, individuals who did not meet the characteristics of the study groups and did not have chronic conditions such as hypertension (HTN), diabetes, or dyslipidemia were included to ensure the homogeneity of the results.

2.4 Exclusion criteria

Patients with a history of chronic conditions such as hypertension (HTN), diabetes, and dyslipidemia before contracting COVID-19 were excluded. For the control group, individuals with current or past issues of smoking or obesity were also excluded.

2.5 Sample size

Initially, the database contained information on 27,184 patients. However, following the previously mentioned inclusion and exclusion criteria, the study sample was reduced to a total of 16,434 patients. The 10,750 excluded patients did not meet the defined characteristics and are detailed in the Flowchart of Results (Figure 1) presented.

Table 1 shows the characteristics of the study groups according to age, sex, and the number of patients who presented any type of post-COVID-19 sequelae, classified by each group and the control group. Memory disorders and memory loss have been analyzed independently of other post-COVID sequelae because only physical sequelae were considered within the group, while these are neurological, mental, or psychological in nature, and therefore have been analyzed separately.

2.6 Sample characterization

To characterize the sample, the following exact variables were analyzed:

- *Age:* The average age (Discrete variable) of the patients in each group was calculated, as well as the age range (minimum and maximum). The mean age in the sample was 48,8 years, with a standard deviation of 24,6 years.
- *Sex:* The gender proportion in each group was determined (Binary variable, 0 = male, 1 = female). They were 56.32% of women in the smoking group, 59.92% in the obesity group, and 54.30% in the control group.
- *Chronic conditions:* The presence or absence of chronic conditions, including HTN, dyslipidemia, and diabetes, was recorded (Binary variable, 0 = Absence, 1 = Presence).
- *Cardiovascular diseases:* The presence or absence of cardiovascular diseases, such as heart attack and heart failure, was recorded (Binary variable, 0 = Absence, 1 = Presence).
- *Long COVID sequelae:* The presence of sequelae such as headaches, expectoration, myalgias, fatigue, and taste and smell alterations was analyzed (Binary variable, 0 = Absence, 1 = Presence).
- *Memory disorders and memory loss:* The incidence of memory disorders and memory loss was evaluated (Binary variable, 0 = Absence, 1 = Presence).

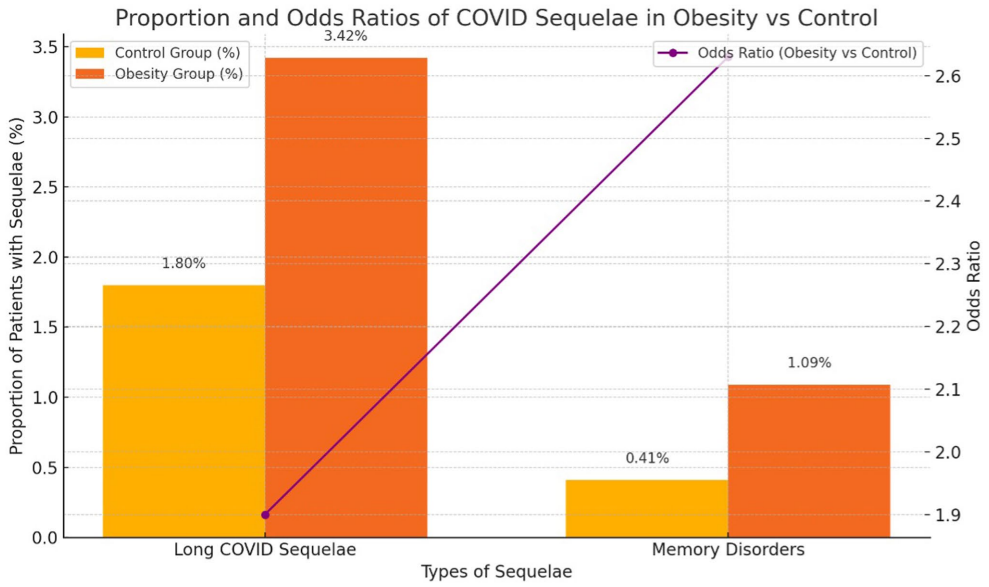

FIGURE 1
Proportion and Odds Ratios of COVID Sequelae in Obesity vs Control.

- *Hospitalization*: The hospitalization risk of patients was recorded (Continuous variable).

2.7 Statistical analysis

Descriptive statistics were used to characterize the sample, and Odds Ratios (OR) were calculated to analyze the relationships between the independent variables (smoking and obesity) and the dependent variables (post-COVID-19 sequelae, chronic conditions, cardiovascular diseases, and hospitalization risk). A 95% confidence level was considered for these analyses, corresponding to a 5% significance level *($p = 0.05$)*. The statistical software SPSS V25.0 (New York, United States) was used for the analyses.

2.7.1 Ethical considerations

This study was approved by the Bioethical Committee of the University of Salamanca (registration number 734). The study was conducted in accordance with the principles of the Declaration of Helsinki and the recommendations of good clinical practice. For reporting, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.

3 Results

In this section, detailed results of our study are presented, focused on investigating the intricate relationships between obesity, smoking, and post-COVID-19 sequelae in recovered patients. These findings offer a profound understanding of how these variables influence population health following COVID-19 infection.

3.1 Patient characterization

Initially, we characterized the participants selected for the study. The analysis revealed significant differences in the average ages of the groups: the smoking group had a mean age of 42.65 years, the obesity group showed a mean age of 34.33 years, and the control group had a mean age of 36.37 years. Additionally, we observed a predominance of females in all groups, with 56.32% of women in the smoking group, 59.92% in the obesity group, and 54.30% in the control group.

3.2 Sequelae and pathologies post-COVID-19

Next, we examined the sequelae and pathologies following COVID-19 infection. The most common sequelae were "Long COVID" symptoms such as headache, cough, myalgia, fatigue, and changes in taste and smell. These manifested in 3.42% of patients with obesity, 1.8% of the control group, and 1.34% of smokers, indicating a higher incidence among patients with obesity.

Memory disorders occurred in 1.1% of patients with obesity, 0.98% of smokers, and 0.42% of the control group, showing a higher incidence in the obesity and smoking groups.

For chronic conditions and hospitalization risk, the smoking group showed no cases, while patients with obesity had a 0.23% incidence in both categories. The control group had a 0.08% incidence in chronic conditions and 0.25% in hospitalization risk. Lastly, a single cardiovascular case was noted in the control group, with no cases in the experimental groups.

3.3 Simple and relative risk factors

Tables 2, 3 illustrate the simple risk and the odds ratio of the study groups to experience any of the analyzed sequelae.

3.4 CHI-SQUARE test results

Below are the results obtained using the CHI-SQUARE methodology, which allows for evaluating the dependency relationship between the risk of experiencing sequelae or hospitalization risk during the post-COVID period and the obesity and smoking pathologies of the patients (Table 4). A specific confidence level was used to define the significance of the relationship *($p = 0.05$)*.

TABLE 2 Simple risk results.

Variable	Chronic conditions (hypertension, dyslipidemia, diabetes)	Long Covid sequelae (headache, cough, myalgia, fatigue, taste and smell alterations)	Memory disorders and loss	Hospitalization
Healthy	0.08%	1.80%	0.41%	0.25%
Smoking (current and former)	–	1.31%	0.98%	–
Obesity and overweight	0.23%	3.42%	1.09%	0.23%
Between experimental groups	–	2.54%	1.04%	–

TABLE 3 Odds ratio results.

Variable	Chronic conditions (hypertension, dyslipidemia, diabetes)	Long Covid Sequelae (headache, cough, myalgia, fatigue, taste and smell alterations)	Memory disorders and loss	Hospitalization
Obesity and overweight / healthy	3.01	1.90	2.63	0.92
Smoking / healthy	–	0.73	2.36	–
Obesity and overweight / smoking	–	2.62	1.11	–
RRR: odds ratio				

TABLE 4 Results of χ^2 analysis for the level of risk of previous chronic conditions.

Variable	Chronic conditions (hypertension, dyslipidemia, diabetes)			Long Covid sequelae (headache, cough, myalgia, fatigue, taste and smell alterations)			Memory disorders and loss			Hospitalization		
	Est. test	χ^2	*p*-value	Est. test	χ^2	*p*-value	Est. test	χ^2	*p*-value	Est. test	χ^2	*p*-value
Smoking (current and former)	–	3.8	–	1.2	3.8	0.27	6.18	3.8	0.01	–	3.8	–
Obesity and Overweight	3.17	3.8	0.07	16.42	3.8	0.00	11.46	3.8	0.00	0.02	3.8	0.89
Between experimental groups	–	3.8	–	9.69	3.8	0.00	0.06	3.8	0.80	–	3.8	–

3.5 Relationships between variables of interest and their implications in post-COVID-19 health

3.5.1 Chronic conditions and their association with obesity

In the first analysis (Table 5), we investigated the potential association between the presence of chronic conditions (Hypertension, Dyslipidemia, and Diabetes) and obesity status in a representative sample of the post-COVID-19 population. The results of the CHI-SQUARE test (X^2) indicated a lack of significant association between these two variables (Test = 3.17 < X^2 = 3.84, $p < 0.05$), suggesting that obesity may not be directly related to the presence of these chronic conditions in COVID-19 recovered patients.

TABLE 5 Chronic conditions in relation to obesity.

	With chronic conditions	Without chronic conditions	Total
Obesity and overweight	3	1,285	1,288
None	11	14,220	14,231
Total	14	15,505	15,519

TABLE 6 Long Covid sequelae in relation to obesity and smoking

	With long Covid sequelae	No long Covid sequelae	Total
Smoking	12	906	918
Obesity and overweight	44	1,241	1,285
None	256	13,975	14,231
Total	268	14,881	16,434

3.5.2 Post-COVID-19 sequelae and their relationship with smoking

Next (Table 6), we explored the relationship between the presence of post-COVID-19 sequelae (Headache, Cough, Myalgias, Fatigue, Taste and smell alterations) and smoking history (either current or former). The results revealed that there is no significant association between these two variables (Test = 1.20 < X^2 = 3.84, $p < 0.05$). This indicates that smoking may not directly be related to the occurrence of post-COVID-19 sequelae in the studied patients.

3.5.3 Post-COVID-19 sequelae and their relationship with obesity

Later (Table 6), we focused on the association between obesity and the presence of post-COVID-19 sequelae. The results showed a

significant relationship between these two variables (Test = 16.42 > X^2 = 3.84, $p < 0.05$), suggesting that patients with obesity may be more likely to experience post-COVID-19 sequelae compared to those without obesity.

3.5.4 Interaction between obesity and smoking in post-COVID-19 sequelae

Afterwards (Table 6), we evaluated the potential interaction between obesity and smoking in the occurrence of post-COVID-19 sequelae. The results revealed a significant association between these variables (Test = 9.69 > X^2 = 3.84, $p < 0.05$), indicating that patients with obesity and a history of smoking may have a significantly higher risk of developing post-COVID-19 sequelae compared to other groups.

3.5.5 Memory disorder and loss in post-COVID-19 patients in relation to smoking

In the fifth analysis (Table 7), we examined the presence of memory disorders in COVID-19 recovered patients in relation to their smoking history. The results demonstrated a significant relationship between these variables (Test = 6.18 > X^2 = 3.84, $p < 0.05$), suggesting that patients with a history of smoking may have a higher risk of experiencing memory disorders after COVID-19 infection.

3.5.6 Memory disorder and loss in post-COVID-19 patients in relation to obesity

In the next analysis (Table 7), we explored the association between obesity and memory disorders in post-COVID-19 patients. The results indicated a significant relationship between these variables (Test = 11.46 > X^2 = 3.84, $p < 0.05$), suggesting that obesity may be associated with a higher risk of memory disorders in COVID-19 recovered patients.

3.5.7 Interaction between obesity, smoking, and memory disorders

To follow (Table 7), we investigated the potential interaction between obesity, smoking, and memory disorders in post-COVID-19 patients. The results did not show a significant association between these variables (Test = 0.06 < X^2 = 3.84, $p < 0.05$), indicating that these variables may be independent of each other in the studied population.

3.5.8 Interaction between obesity and hospitalization risk

Finally (Table 8), we investigated the potential interaction between obesity and hospitalization risk in post-COVID-19 patients. The results did not show a significant association between these variables (Test = 0.02 < X^2 = 3.84, $p < 0.05$), indicating that these variables may be independent of each other in the studied population.

3.5.9 Comparative analysis of obesity and smoking with Long COVID sequelae

On the other hand, based on the test statistic to determine the relationship between obesity and smoking with Long COVID sequelae, it was established that smoking does not represent a risk factor that increases the likelihood of experiencing this type of sequelae, while obesity does have a direct relationship with the increased likelihood of incidence of these consequences in patients affected by it. When conducting a comparative analysis between patients with smoking and obesity, it was determined that overweight individuals have a higher percentage of risk than tobacco consumers to suffer from Long COVID sequelae.

TABLE 7 Memory disorder and loss in relation to obesity and smoking.

	With memory disorder and loss	Without memory disorder and loss	Total
Smoking	9	909	918
Obesity and overweight	14	1,271	1,285
None	59	14,172	14,231

TABLE 8 Hospitalization based on obesity.

	With hospitalization	Without hospitalization	Total
Obesity and overweight	3	1,282	1,285
None	36	14,195	14,231
Total	39	15,477	15,516

Regarding memory disorders and loss, the test statistics were higher than the X^2, both for patients with smoking and those with obesity. Therefore, it can be defined that the risk of these sequelae occurring increases in people who smoke and/or have overweight or obesity issues. Finally, regarding hospitalization risk, it was determined that it was not influenced by any of these chronic conditions.

Overall, our findings underscore the importance of understanding the complex interactions between obesity, smoking, and post-COVID-19 sequelae in the health of recovered patients. These results may have significant implications for healthcare and the planning of prevention and treatment strategies in the post-COVID-19 pandemic era.

To confirm the results obtained in the X^2 test, odds ratios were determined to establish the probability risk relationship of experiencing some of the analyzed post-COVID sequelae among each established population group. Each disease was evaluated separately.

From these results, the following findings can be established:

- Patients with obesity are 3.01 times more likely to suffer from chronic conditions (Hypertension, Dyslipidemia, Diabetes) post-COVID than those without such issues prior to the coronavirus diagnosis.
- Similarly, with Long COVID sequelae (headache, cough, myalgias, fatigue, taste and smell alterations), it was determined that individuals with obesity have a 1.92 times higher probability of experiencing these conditions in the post-COVID period.
- Regarding memory loss and disorders, it was determined that patients with obesity and smoking have a higher risk index than those without these pre-existing conditions, resulting in odds ratios of 2.38 and 2.65, respectively.

On the other hand, it was determined that patients with obesity have a 1.11 times higher probability of experiencing memory disorders and loss compared to those with a history of smoking, a difference that can be considered relatively insignificant.

4 Discussion

This study has focused on analyzing the possible relationship between the risk of developing chronic, cardiovascular, and psychological sequelae, as well as the risk of hospitalization in the post-COVID period, with smoking and obesity. The results cover a one-year period and include patients of all ages. Adding interest to this research is the fact that it is the first analysis of its kind conducted in the Castilla y León region. According to the results obtained, the following analyses are presented.

Based on the results obtained, it was determined that the three groups consist mostly of women, with 59.92% of the female population being obese patients, 56.32% being smokers, and 54.30% being categorized as healthy. Of the total selected patients, it was determined that 1.90% presented cardiovascular sequelae, which is similar to the findings presented by studies by other authors, who established that the incidence rate of this type of sequelae ranges from 1.82 to 2.42%, translating to 179 to 236 cases annually per 100,000 inhabitants (20–23).

On the other hand, the results show that the incidence rate of Long COVID sequelae (headache, cough, myalgias, fatigue, taste and smell alterations) was 1.31%, which differs from the results presented by Jiménez et al. (17), who established an incidence rate of 7.63% of this type of post-COVID disease in smokers. Additionally, this study determined that smokers do not have a higher risk of presenting Long COVID sequelae than those who do not smoke, which also contradicts the results of another study, where it was determined that the smoking population had a 25.6% higher probability of suffering from any of these post-COVID diseases.

> *H1*: Smoking increases the risk of having Long COVID sequalae symptoms.

The hypothesis is rejected.

Regarding Long COVID sequelae in patients with obesity, an incidence rate of 3.42% was determined, which is below the probability risk range defined in other research, where incidence rates between 10.5 and 33.3% were defined, resulting in a risk level three to ten times lower than that defined by other research (24, 25). When comparing the risk percentage of obese patients to those without this condition, this study determined an incidence 1.92% higher, which is similar to the results shown by other studies that establish odds ratios in a range between 1.58 and 2.0 (26, 27).

> *H2*: Obesity increases the risk of having Long COVID sequalae symptoms.

The hypothesis is accepted.

For the case of sequelae related to memory disorders and loss, a risk percentage of 0.50% of the total study population was determined. These results are lower than those presented by the study of Soraas (28), which established an incidence rate of 4%, with memory loss being the most common sequelae among the psychological sequelae of Long COVID. Unfortunately, there are no previous studies evaluating the influence of obesity and smoking on the risk of memory disorders post-COVID-19, which would allow for a comparison with the results obtained in the present study.

Finally, during the present study, it was determined that obesity does not increase the risk level of hospitalization in COVID-19 patients. In fact, an odds ratio of 0.92% was determined compared to the population without obesity, which can be considered a 1:1 relationship. This contradicts the results presented by Rodríguez et al. (29), where it was determined that obese individuals had a 33% higher likelihood of hospitalization compared to those without overweight issues. However, it is important to note that our study specifically examines the risk of hospitalization within 12 months following a COVID-19 diagnosis, a timeframe not addressed in Rodríguez et al.'s analysis. To our knowledge, no previous research has determined the increased risk of hospitalization in the 12 months post-diagnosis for COVID-19 patients, highlighting the unique contribution of our findings.

In this scientific article, a thorough analysis of the relationship between smoking, obesity, and post-COVID-19 sequelae has been conducted in the Castilla y León region. This study represents a valuable contribution to understanding the long-term effects of the disease, considering significant risk factors such as tobacco consumption and elevated body mass index. Through the evaluation of a large group of patients over a one-year period, results have been obtained that provide essential information for medical care and future research. A significant prevalence of cardiovascular sequelae and Long COVID symptoms has been observed in the studied population. These findings align with previous research, although notable differences in the incidence of some sequelae in relation to smoking and obesity have been recorded.

Regarding the relationship between smoking and Long COVID sequelae, this study contradicts previous findings suggesting a higher risk in smokers. The results show that smoking does not seem to significantly increase the likelihood of developing these sequelae in post-COVID-19 patients. However, this finding raises additional questions about potential interactions between smoking and other risk factors. On the other hand, it has been confirmed that obesity is associated with a higher risk of experiencing Long COVID sequelae, although at a lower risk level than defined in previous research. This highlights the importance of considering body mass index as a relevant risk factor in planning long-term care strategies for COVID-19 patients.

Regarding sequelae of memory disorders and loss, a lower incidence has been identified compared to other studies, although the influence of obesity and smoking on these sequelae still requires further exploration.

Finally, concerning hospitalization, it has been demonstrated that obesity does not significantly increase the risk of hospitalization within 12 months following COVID-19 diagnosis in COVID-19 recovered patients.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Comité de Ética de la Investigación. 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 this study used de-identified, publicly available data from medical records or databases, which do not contain any personally identifiable information. As per ethical guidelines, written informed consent was not required since the analysis was performed on anonymous data and did not involve direct contact with participants.

Author contributions

DF-P: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. RJ-V: Supervision, Validation, Visualization, Writing – review & editing. RV-H: Data curation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JA-A: Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JC-G: Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CS-S: Conceptualization, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

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

Acknowledgments

Data was facilitated by SACYL (Sanidad de Castilla y León).

Conflict of interest

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

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frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 02 May 2025
DOI 10.3389/fmed.2025.1521472

OPEN ACCESS

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RECEIVED 01 November 2024
ACCEPTED 15 April 2025
PUBLISHED 02 May 2025

CITATION
Ranque B and Cogan E (2025) Internal medicine at the crossroads of long COVID diagnosis and management.
Front. Med. 12:1521472.
doi: 10.3389/fmed.2025.1521472

Internal medicine at the crossroads of long COVID diagnosis and management

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The lack of specificity in its definition is a major obstacle to both explanatory and therapeutic research in long COVID. It brings together, on the one hand, patients with severe COVID-19 who suffer the classic complications of prolonged hospitalization and decompensation of comorbidities and, on the other hand, patients with non-severe acute COVID-19 who report multiple symptoms that cannot be fully explained by a biomechanical model. Indeed, despite numerous studies, it remains unclear how persistent viral infection, immunological or coagulation disturbances may contribute mechanistically to long COVID. Nevertheless, internal medicine should be in good place to manage these patients. Indeed, the diversity of symptoms may evoke a broad spectrum of differential diagnoses that are familiar to internists. Their experience in the exploration of unexplained symptoms is also valuable. It can reduce the need for multiple consultations with specialists and unnecessary laboratory or imaging tests. However, long COVID diagnosis cannot be limited to the exclusion of all other conditions one by one. An open and non-dualistic approach is required to identify other mechanisms that may explain the symptoms. Based on their clinical experience, most French internists who responded to an opinion survey consider that long COVID corresponds most closely to a functional somatic disorder (FSD) and seek the help of specialists in mental health care to assist in the management of the patients in a multi-disciplinary approach. However, as with other FSDs, patients with long COVID are usually reluctant to be managed by mental health care specialists, given the very physical nature of their presentation. Unfortunately, most physicians are in turn reluctant to take care of them, due to poor knowledge about FSD, leading to management failure. Alternatively, a comprehensive multidisciplinary care orchestrated by an experienced internist is generally well-accepted. It includes providing rational cognitive explanations for the symptoms and support for behavioral changes tailored to the patient. While waiting for hypothetical randomized controlled trials assessing drugs with positive results, such a holistic approach has been successfully applied in many individuals with severe long COVID. However, its generalization would require a much broader training for FSD of all health care providers.

KEYWORDS

long COVID-19, functional somatic disorder (FSD), post-acute COVID-19 syndrome, internal medicine, holistic care

Introduction

Long COVID is considered a public health problem, since its incidence was estimated as high as 10% among patients infected by SARS-CoV-2 (1). More recent data suggest a gradual reduction in the risk over time. The cumulative incidence of long Covid during the first year after infection was estimated to be 10 events per 100 persons in the pre delta period, 7.8 events per 100 persons in the omicron period, and about 3.5 events per 100 persons during the omicron era in vaccinated individuals (2). Noteworthy, this incidence decrease was actually independent of SARS-CoV-2 genetic variant since it was also observed between the first and second epidemic waves that involved the same variant in 2020 (3). However, prevalence estimations may vary greatly depending on the definition used (4). Indeed, although the main symptoms of long COVID reported by patients and the literature are fatigue, respiratory disturbances and cognitive issues (such as "brain fog"), a multitude of unspecific symptoms has been reported (5). According to the WHO definition established by Delphi method, there is neither a maximum timeframe for its onset after COVID infection—although it is stated that symptoms "usually occur 3 months from the onset of COVID-19" —nor a necessity for proof of SARS-CoV-2 infection to retain the diagnosis (6). Therefore, any unexplained symptom that occurred after March 2020 and lasted more than 2 months potentially meets the definition of long COVID.

A critical approach to literature

A wealth of medical literature has developed since the summer of 2020 regarding the potential causes of long COVID, which is particularly difficult to synthesize due to significant heterogeneity. This might partly be due to publication bias and frequent methodological flaws.

First, as mentioned above, the lack of specificity of the long COVID definition allows very dissimilar populations to be included in studies. The early studies primarily included patients who had been hospitalized for severe COVID (7). These patients often had objective pulmonary sequelae and non-specific physical sequelae due to prolonged hospitalization (malnutrition, muscle atrophy, post-traumatic stress…). Then, studies tended to mix this population and patients who were not hospitalized for COVID-19, some of whom did not even have confirmed SARS-CoV-2 infection due to the lack of availability of testing in the community during the early months of the epidemic (5). It is this second population that poses a real problem due to the absence of an obvious cause for symptoms that can nevertheless be severe and very disabling. Unlike the post-hospitalization population, the majority are women, with an average age between 30 and 50 years (compared to over 60 years for hospitalized patients) and few comorbidities. Unfortunately, most translational studies on long COVID do not describe how patients were recruited, nor their clinical characteristics, and do not adjust their statistical analyses for the presence of comorbidities, even though these could explain part of the results (8–10). The early immunological studies also did not include an appropriate control group: they compared healthy subjects who had never been infected with COVID to patients with long COVID and found higher level of inflammation in patients (11), while it is now well established that sub-clinical inflammation markers decrease after infection but can persist in the human body for several months, independently of the persistence of symptoms (10, 12, 13). Therefore, the appropriate control group is patients who were infected by Sars-Cov-2, but did not have persistent symptoms with the same follow-up time since infection than patients with long COVID. Furthermore, immunological studies involve numerous cytokine assays, cellular phenotyping, transcriptome studies, etc., using modern multiplex methods, but very few consider the alpha risk inflation (false positive results) due to the multiplication of statistical tests. Additionally, most of them only highlight positive results and fail to discuss negative findings that contradict other publications (8–12). Finally, even in the case of statistically significant differences, the distributions of biological marker concentrations largely overlap between cases and controls, preventing their use as prognostic or diagnostic markers. Thus, although many immunological markers have been shown to be marginally but differentially distributed between cases and controls, none have been consistently replicated to date (10–12, 14). Consequently, no consensus can be reached regarding the potential specific immunological mechanisms at play in the genesis of long COVID (15).

Similarly, early studies exploring viral persistence were conducted without controls or with inappropriate controls (patients who had never been infected) or at an early stage (less than 3 months symptoms duration). Some of them suggested that viral persistence could explain long COVID based on the presence of SARS-CoV-2 RNA in olfactive bulbs, digestive biopsies or feces (16). However, subsequent studies including patients with or without persistent symptoms after COVID-19 did not find evidence of longer viral persistence in those with persistent symptoms (12, 17). One recent study investigated the persistence of viral RNA in various tissue samples of patients who had mild COVID-19. A significant association has been identified between the detection of viral RNA in at least one tissue and the presence of long COVID symptoms. This association strongly decreased between 1 and 2 months after infection and was no more significant 4 months after infection (18).

Regarding the specific aspect of central nervous system (CNS) involvement, it is important to note that persistence of SARS-CoV-2 in the CNS has never been directly described in long COVID. Studies suggesting the presence of SARS-Cov-2 in the brain have been conducted using autopsies of patients who died of severe acute COVID-19. They found CNS symptoms such as hemorrhagic infarction, microglial activation and neuronal phagocytosis, but detectable levels of virus in the brain were very low and not associated with histopathological changes (19). Furthermore, while *in vitro* studies have suggested several theoretical pathways by which this virus may enter the CNS, clinical studies suggest that direct invasion of the CNS by SARS-CoV-2 is rare and extremely limited. Nevertheless, it is possible that the SARS-CoV-2 spike (S) protein has direct inflammatory and procoagulant effects. The addition of cytokine release syndrome (CRS) with loss of blood–brain barrier integrity may contribute to the expression of pro-inflammatory mediators by neural cells that may affect brain function (20). However, as the presence of Sars-Cov-2 RNA in other tissues, markers of CNS damage do not correlate with long-term clinical symptoms. For example, a study comparing the CNS effects of the virus during the acute phase of COVID-19 and six months later found that plasma concentrations of neurofilament light chain (sNfl) and glial fibrillary acidic protein (GFAp) normalized, while a large number of patients continued to have neurological and cognitive

symptoms (21). A notable exception may be noted for persistent anosmia/ageusia, which correlates with evidence of viral material and inflammation in olfactive bulbs/tongue biopsies (22, 23). It should also be noted that prolonged viral persistence has been well (and easily) documented in patients who are severely immunocompromised (notably organ transplant recipients), who also have a very different clinical presentation and evident paraclinical anomalies (18, 24). In contrast to studies using ultra-sensitive biological techniques not commonly used in current practice (mostly dosage of plasma cytokines by multiplex essay or leukocyte immunophenotyping by flow cytometry), studies published by clinicians consistently failed to demonstrate biological difference between patients infected by COVID-19, with and without persistent symptoms (17, 25–30).

Last, 4 years after the clinical characterization of long COVID, no efficient pharmacological treatment has been reported (31, 32). In particular, unlike in acute COVID-19, neither antiviral drugs, anti-SARS-CoV-2 monoclonal antibodies, nor immunosuppressive drugs such as steroids or interleukine-6 inhibitor have proved efficient in long COVID (33, 34).

By contrast, certain non-biological risk factors have been regularly identified in patients with long COVID and mild initial COVID-19, such as female sex and the number of initial symptoms (29, 35), the history of anxiety or depressive disorders (28, 36–39), or negative feelings regarding COVID-19, such as the COVID-related anxiety (40), the burden associated with symptoms of acute COVID (41), and the fear that acute symptoms will persist (42). It is unfortunate that this non-somatic dimension is completely ignored, even in the most recent high-quality reviews of the causes of long COVID (1, 43).

Arguments for a functional disorder

For patients who search for information on the internet, or for doctors who are not expert clinicians, the combination of long COVID symptoms may evoke several rare pathologies: systemic immunological diseases (lupus, vasculitis, connective tissue diseases, autoinflammatory diseases, etc.), hematological conditions (mast cell activation syndrome…), infectious or genetic diseases (cryopyrinopathies, interferonopathies…). However, unlike patients suffering from these biologically explained diseases, patients with long COVID do not present objective clinical signs that would allow their diagnosis. Most symptoms are either subjective or compatible with a dysfunction of the autonomic nervous system (hyperventilation, postural orthostatic tachycardia syndrome…), but without criteria of severe dysautonomia (38, 44). Furthermore, in patients without history of severe acute COVID-19, there is no abnormal biological or imaging findings or they cannot entirely explain the symptoms (13, 17, 26–30). As mentioned above, one exception is anosmia and dysgeusia, that are associated with pathological findings at MRI and nose or tongue biopsies (23, 45) and probably arise from direct neurological viral toxicity. For other symptoms than anosmia and dysgeusia, the only abnormal results that are frequently observed are hypometabolisms of right medial temporal lobes (hippocampus and amygdala), right thalamus brainstem and cerebellum at brain PET scans (46), whose interpretation is controversial. Indeed, there is no established correlation with the type and intensity of symptoms (47) and the cause of the observed anomalies could be organic or functional (48).

The clinical picture of long COVID, on the other hand, has strong semiological similarities with other biomedically unexplained conditions that have different presumed causes (like chronic Lyme disease, hypersensitivity to electromagnetic waves or chemicals, etc.) or are defined by a main symptom (fatigue for myalgic encephalomyelitis/chronic fatigue syndrome, pain for fibromyalgia, etc.). It is commonly, though not unanimously accepted, that these entities are part of the broader group of "functional somatic disorders" (FSD) (49). FSD are usually defined as patterns of persistent bodily complaints for which adequate examination does not reveal sufficiently explanatory structural abnormality or other specified pathology, with severe impact on functioning and quality of life (49–51). FSD vary in names based on the predominant symptoms and the medical specialty involved (e.g., irritable bowel syndrome in gastroenterology, hyperventilation syndrome in pneumology, fibromyalgia in rheumatology, chronic fatigue syndrome in internal medicine….). They represent the medical side of the psychiatric nosologic category "somatic symptom disorder" in DSM V (50). Importantly, FSD is often triggered by a somatic illness (in particular an infectious disease) but also involves brain conditioning along with socio-psychological predisposing factors (perfectionism, alexithymia, childhood traumatic experience…). Most importantly the long term persistence of symptoms is favored by cognitive (involuntary attentional focusing on symptoms, catastrophism, illness-related anxiety, feeling of rejection…) and behavioral factors, including avoidance of physical effort that leads to physical deconditioning as well as avoidance of uncertainty that leads to never-ending request for medical tests and consultations (51, 52). These conditions can be associated to varying degrees in the same person, suggesting shared transdiagnostic mechanisms (49, 51), Thus, the term "bodily distress syndrome" (International Classification of Diseases 11), has been suggested as a more neutral term to cover them all (53). Strikingly, bodily distress syndrome shares all its symptoms with those that are most common in long COVID (see Table 1).

A significant number of symptoms observed in patients with long COVID are also similar to those found in people suffering from

TABLE 1 Diagnostic criteria for bodily distress symptoms.

1. ≥ 3 symptoms from at least one of the following groups:
   - *Cardiopulmonary/autonomic arousal:*
     Palpitations /heart pounding, precordial discomfort, breathlessness without exertion, hyperventilation, hot or cold sweats, dry mouth
   - *Gastrointestinal arousal:*
     Abdominal pains, frequent loose bowel movements, feeling bloated/full of gas/distended, regurgitations, diarrhea, nausea, burning sensation in chest or epigastrium
   - *Musculoskeletal tension:*
     Pains in arms or legs, muscular aches or pains, pains in the joints, feelings of paresis or localized weakness, back ache, pain moving from one place to another, unpleasant numbness or tingling sensations
   - *General symptoms:*
     Concentration difficulties, impairment of memory, excessive fatigue, headache, dizziness.
2. The patient has been disabled by the symptoms (i.e., daily living is affected)
3. Relevant differential diagnoses have been ruled out

post-traumatic stress disorder (PTSD). In particular, experiencing neurocognitive symptoms, such as difficulties with memory and thinking, after mild COVID-19 infection was strongly associated with the presence of persistent PTSD-like symptoms (54). The occurrence of PTSD is common in the context of infectious epidemics (55) Noteworthy, in contrast to patients with FSD, patients with PTSD experience flashbacks—reliving the traumatic COVID episode, or have recurring memories or dreams related to this acute COVID episode. Therefore, this condition is essentially observed in patients who have dealt with severe COVID-19 (56).

In our clinical center dedicated to long COVID in Paris, after standardized multidisciplinary evaluation, 76% of patients who had mild acute COVID-19 and exhibited prolonged symptoms (median duration 429 days) meet the criteria for FSD (57). This observation has been shared by other clinicians worldwide (58–60). In our experience, 21% patients were also diagnosed with (i) anxiety (including panic disorders, whose manifestations are primarily physical) or (ii) depressive disorders that account for their symptoms, (iii) with or without associated FSD. This is consistent with a recent meta-analysis reporting a global prevalence of depression and anxiety in 23% of patients with long COVID (61). In our cohort, only a minority of patients (10%) did not fit into one or more of these three diagnoses, most of them having another condition explaining the symptoms, unlinked to COVID-19 (57).

A final argument in favor of the FSD hypothesis is that to date, only cognitive behavioral therapy and gradual physical activity have proven effective in treating long COVID (34). It is noteworthy that, whereas nirmarelvir/ritonavir was reported as inefficient as a curative for long COVID (33), it has been successfully tested as a preventive treatment (62). This finding is not surprising even in the hypothesis of FSD, as nirmarelvir/ritonavir decreases the intensity and the number of symptoms of the acute episode of SARS-CoV-2, which are risk factors for long COVID.

Current management of patients with long COVID symptoms

In Belgium, the management of long-COVID is primarily predicated on a personalized care pathway, which is funded by the Ministry of Health. As also recommended in French national guidelines (63), this care is coordinated by the general practitioner, who refers patients to various health professionals, including physiotherapists, ergotherapists, neuropsychologists, and dieticians.

Unfortunately, many physicians are reluctant to handle these patients, who often require considerable time and attention, leading to diagnostic and therapeutic failures. Many tend to rid themselves of the problem either by dismissing the legitimacy of the complaint ("you do not have anything!" or "it will pass on its own!"), or, on the contrary, by conducting numerous tests and requesting many specialized opinions to reduce their own uncertainty, out of fear of missing a serious illness (64). This second attitude is understandable to the novelty of COVID-19 infection, its pleiomorphism and sometimes alarming scientific literature. However, this diagnostic quest quickly becomes detrimental for the patients. Both attitudes aggravate the situation, with the first intensifying feelings of rejection and the second exacerbating catastrophizing, both worsening the attentional focus on symptoms, which perpetuates or even exacerbates symptoms. In the doctors' defense, an exhaustive search—though impossible—is often advocated by the patients themselves.

Indeed, patients with FSD spontaneously consult doctors because of the physical nature of their symptoms and are generally reluctant to be referred to mental health specialists. Even when patients do accept a psychiatric assessment, the psychiatrist most often focuses on the identification and treatment of classical psychiatric disorders (anxiety, depression, etc.), which affect only a minority of patients. Few psychiatrists are trained to actively seek out FSD and fear misattributing physical symptoms to a psychological cause. A "return to sender" is therefore common, further reinforcing the patient's belief in an exclusively somatic cause (51, 64). This path marked by non-recognition and medical nomadism is that of patients with long COVID and is an integral part of their problem. In fact, in most countries, the notion of FSD is very poorly understood and is often equated with a psychiatric illness, or attributed exclusively to the patient, or at worst, seen as malingering. This leads to significant hetero and self-stigmatization, as well as a feeling of non-recognition or even humiliation, which perpetuates the need to prove the reality of the symptoms and to search for an external, or at least physical, cause.

There is indeed a major training deficit for FSD in somatic physicians, psychiatrists, psychologists, physiotherapists, and the general population. One of the problems is the poor reputation of psychiatric illnesses and the belief in a body/mind duality, which often leads to the rejection of any "psychologizing" explanation. Recently, a German team proposed a very integrative vision of persistent physical symptoms (PPS)—that is, symptoms lasting several months, regardless of their cause (52)—which seems to particularly apply to long COVID. These symptoms affect up to 9% of the general population. The more they persist, the more their link to a pathophysiological cause weakens. Examples include persistent digestive symptoms after the remission of chronic intestinal disease, hyperventilation syndrome distinct from co-existing asthma, or chronic fatigue syndrome following a viral infection. The factors of chronicity are biological (e.g., low-grade inflammation, alterations in microbiome…), cognitive-perceptual and emotional (e.g., symptom focus, catastrophism, alexithymia, health-centered anxiety), behavioral (e.g., physical deconditioning due to inactivity and avoidance behaviors), and related to interaction with the health system (e.g., drug side effects and conflicting relationships with health care professionals). There is a continuum between physical and psychological causes, but even diseases with a well-accepted pathophysiological explanation, such as systemic lupus erythematous, multiple sclerosis or spondyloarthropathy, are strongly modulated by cognitive-behavioral factors. When there is a discrepancy between a high symptom burden and normal clinical and paraclinical exams, these PPS meet the criteria for FSD.

We believe that this vision is capable of reconciling patients and doctors, based on a shared and accepted diagnosis. It allows them to focus on the essential, which is the personalized search for effective therapeutic solutions. In our experience and that of many colleagues, acceptance of the diagnosis is very good if it is explained in a positive and scientific way, with empathy and without judgment (65). This includes providing rational cognitive explanations for the symptoms and support for behavioral changes, such as stopping medical explorations and resuming exercise very gradually.

What place for the general internist in the management of patients with long-COVID?

Because of the multiplicity of possible causes, internists have several assets that should in theory allow them to take good care of patients with long COVID who do not improve after a first line treatment by their general practitioner. First, they have large semiology skills and good knowledge of the potential differential diagnoses (including immunological, metabolic and multi-system infectious diseases) that should allow them to avoid unnecessary and deleterious examinations if the clinical presentation is incompatible.

In France, the post graduate teaching of internal medicine is coupled with that of clinical immunology for 5 years. Unfortunately, French internists are also often guilty of excessive diagnostic work-up, which is sometimes poorly related to symptoms. However, they are used to coordinating care with other specialists, thus avoiding or at least reducing medical nomadism. They also usually have a genuine willingness to achieve holistic care. Finally, they have a long-standing experience with patients with unexplained symptoms, including many patients with FSD who consult them in the hope for a new diagnostic.

However, internists' views on long COVID are far from unanimous. Recently, we performed an online survey of French senior internists, that showed that beliefs are disparate. Among 240 responders (females 42%), representing all French regions, age groups and type of medical practice (Supplementary Figures 1, 2), 214 (89%) considered that long COVID may be an FSD. They also think other causes may be associated, such as physical deconditioning (77%), post-traumatic stress (41%), anxio-depressive disorder (43%), dysimmune disease (23%), SARS-CoV-2 persistence (8%) or other miscellaneous hypotheses (Figure 1). When they were asked to choose a primary cause, 63% chose FSD, 19% physical deconditioning, and only 9% biological cause (Figure 2).

One striking fact is that 229/240 (95%) of French internists do not want to manage patients with long COVID on their own, contrary to most multi-systemic immune mediated inflammatory disorders. Many internists (111/240, 46%) do not want to take care of them anymore once the etiological assessment is carried out and does not highlight any objective anomaly. Even more, 69 (29%) wish they would not see any patient with long COVID in consultation. This is a good example of the rejection experienced by patients with FSD, which makes their fear of being labeled with this diagnosis quite understandable. This is partly due to a lack of doctors' training for FSD diagnostic and treatment. Indeed, most internists, although they often quickly have the intuition that the patient has a FSD, are not aware of their specific positive criteria. Therefore, they usually retain this diagnosis by default, after a very broad biomedical work-up and often without telling the patient explicitly. Furthermore, even with a good knowledge of FSD, consultations are often difficult and sometimes frankly tedious for the doctor. Notably, the time of anamnesis is particularly long (easily an hour if one tries to be exhaustive) and difficult to synthesize afterwards. The mobilization of empathy must be maximum and requires a lot of energy. Last, the management of uncertainty is anxiogenic ("Doctor, how can you be sure that you have looked for everything?"). Thus, these consultations are very energy and time consuming, and most physicians fear them (66).

Therefore, almost all French internists endorse a multidisciplinary management of patients with long COVID, as they do for patients with FSD. Noteworthy, existing national management guidelines for long COVID (63, 67) also praise for such a holistic approach, modeled on existing recommendations for FSD (65, 68), even if FSD is not mentioned explicitly or even excluded (69). Indeed, such an approach is recommended for several other complex conditions without any detectable organic lesion, such as fibromyalgia (70) or chronic fatigue syndrome (71). Both graduated physical activity (72) and cognitive behavioral therapy (73, 74) proved efficient in individuals with long COVID. Physical rehabilitation is usually well tolerated if well explained and realized correctly (75). However, if the exercise intensity is initially too high, the occurrence of post exertional malaises can reinforce the fear of exercising. Although no trial has assessed the superiority of a multidisciplinary approach combining graduated physical activity and cognitive behavioral therapy, trials are ongoing (e.g., ECHAP COVID, https://clinicaltrials.gov/study/NCT05532904) and integrated programs have already provided high satisfaction rates among patients with severe long COVID (57). Such programs include the delivery of rational cognitive explanations for the symptoms and support for behavioral changes tailored to the patient. Many patients with very disabling long COVID, who benefited from this type of psycho-corporal treatment, have also reported their recovery story on the Norwegian site recoverynorway.org.

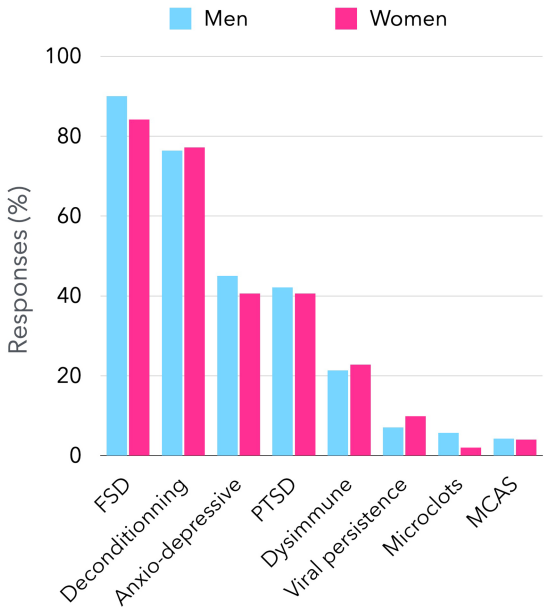

FIGURE 1
Possible causes for long COVID considered by senior internists in France. The figure presents the findings of a survey conducted among senior internists who are members of the French Society of Internal Medicine regarding the causes of long-term symptoms associated with long COVID. By the close of March 2025, a total of 240 responses had been documented through a Google Form platform, accessible via an access link. Participants were invited to identify one or more possible causes of long COVID, which are shown on the x-axis. The figure illustrates the proportion of respondents (both male and female) who consider each of the eight propositions. There was no significant difference between men's and women's responses. FSD: functional somatic disorder. PTSD: post-traumatic stress disorder. MCAS: mast cell activation syndrome.

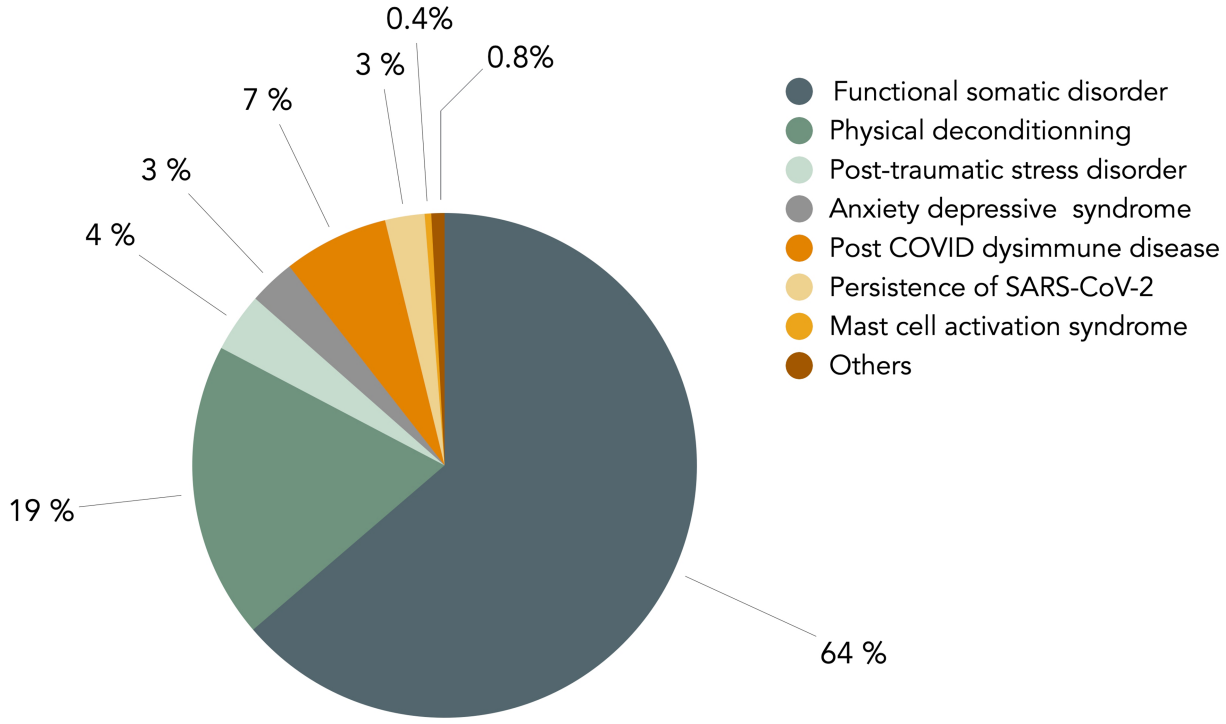

FIGURE 2
Main cause for long COVID considered by senior internists in France. In the survey delineated in the legend of Figure 1, a second question was asked of senior French internists about the main cause of long COVID. The figure presents a graphical representation of the responses to this question. The question posed to participants was: "Among the hypotheses you selected in the initial question, which do you consider to be the primary cause?" The non-somatic causes, depicted in grey-green, account for a substantial proportion of the responses, amounting to 90%.

Conclusion

Along with Saunders et al. (76) we think that "it is time to break taboos based on a dualistic understanding of physical versus mental illness and bring in existing knowledge about functional somatic symptoms to provide improved explanations and treatments."

Except for those patients who have an identified cause of prolonged symptoms, such as depression or PTSD or post intensive care physical sequelae, we argue to treat long COVID as a FSD, rather than waiting for hypothetical pharmacological treatments that biological studies might bring us in the future. It is therefore necessary to federate motivated and competent health care professionals to distribute the mainstays of treatment in a coordinated and synergistic way (77). In addition to the physicians, several other health care professionals are key actors of the patient's recovery, such as psychiatrists, psychologists, physiotherapists, speech-language pathologists and teachers of adapted physical activity.

The position of the physician must probably remain central due to the physical nature of long COVID symptoms, with regular reassessment to not omit another associated disease. This is crucial to reassure the patient, so that he/she can concentrate on his/her personal physical and mental work. Along with general practitioners, internists certainly have a key role to play in the management of patients with the most severe conditions. Nevertheless, all health care professionals certainly need to be trained to better know the various mechanisms in play in the persistence of symptoms, avoid inappropriate behaviors and communication mistakes (78) and tailor patient-centered appropriate management, especially regarding the modalities of resuming physical activity. To be widely accepted, this proposal requires a radical change in the way mind–body interaction is viewed in the medical community and the general population. Less alarmist and more balanced media coverage should help the public to recognize the reality of FSD, understand its mechanisms and the potential for complete recovery.

Author contributions

BR: Writing – original draft, Writing – review & editing. EC: Writing – original draft, Writing – review & editing.

Funding

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

Acknowledgments

The authors thank Benoit Vokaer (HUB, Hôpital Erasme, ULB, Brussels, Belgium) and Jacques Pouchot (Hôpital Européen Georges Pompidou, Paris, France) for helpful discussion and careful reading of our manuscript.

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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1521472/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Demographics and practice patterns. The results of the demographic data and professional practice of 240 French internists who responded to our survey on long COVID are presented. This sample reflects the practice of internal medicine in France, with a higher proportion of men **(A)**, an age distribution with most internists aged between 40 and 49 **(B)**, and most of the practice in university or general hospital structures **(C)**. The distribution of the number of long COVID patients treated by the respondents is shown in **(D)**. A very small proportion of respondents do not treat any patients and more than one in three treat more than 50 patients. ESPIC, Private Health Establishment of Collective Interest.

SUPPLEMENTARY FIGURE 2
Geographical distribution of survey respondents. The figure shows the geographical location of internists who responded to the long COVID survey. This distribution is consistent with the distribution of internists by region in France.

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