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Persistent cognitive symptoms in mild COVID-19 infection: a retrospective cohort study

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Abstract

Background The COVID-19 pandemic represented a healthcare challenge of unparalleled magnitude worldwide. As patients recovered from the acute infection, a new challenge emerged, i.e., the development of post-acute symptoms. The main goal of this study was to evaluate the trajectory of cognitive symptoms since the acute phase of COVID-19 among patients followed through a telehealth program in Brazil.

Methods A retrospective cohort study was conducted with confirmed COVID-19 patients followed by a Brazilian telehealth program who presented cognitive symptoms in the acute phase of infection. The objective of the current analysis was to assess the persistence or remission of cognitive symptoms at 24 weeks after the onset of acute COVID-19 symptoms, as well as the factors associated with such manifestations. The study used chi-square tests and multivariate logistic regression models to assess the association between patients' parameters and the presence of cognitive symptoms. A backward stepwise method was applied to define significant characteristics, which were then evaluated using odds ratios and 95% confidence intervals.

Results Among 319 patients who had cognitive symptoms during acute COVID-19, 89 (27.9%) reported persistence of cognitive symptoms for more than 24 weeks from the acute onset of the infection. Female sex (OR 2.33 [95% CI 1.23–4.43]) and having been infected during the second wave of COVID-19 (OR 2.30 [95% CI 1.34–3.96]) were associated with the persistence of symptoms beyond 24 weeks.

Conclusions Approximately one-third of patients with COVID-19, mainly women and people infected during the second wave of infection, experienced persistent cognitive symptoms.

Keywords COVID-19, Post-acute COVID-19 syndrome, Long-COVID syndrome, Post-viral syndrome, Cognitive symptoms

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Background

The COVID-19 pandemic led to a healthcare overload worldwide and strained healthcare systems and resources [1, 2]. It is already known that COVID-19 is a complex inflammatory multi-organ disease that may generate a wide range of clinical manifestations that can last beyond its acute phase [1, 3].

A significant number of patients report long-lasting symptoms that may impair everyday activities [4]. The term "post-acute COVID-19 syndrome" refers to the persistence of symptoms beyond four weeks from the onset of the acute phase of the infection [1]. It has been proposed to divide this post-acute period into two different moments: (1) subacute COVID-19, which includes symptoms lasting from four to 12 weeks from the acute onset; and (2) chronic or long-COVID syndrome, which encompasses symptoms that persist for more than 12 weeks, and are not explained by an alternative diagnosis [1, 5, 6].

Cognitive symptoms, including mental fatigue, memory, and concentration impairments, have been well-recognized symptoms of post-acute COVID-19 syndrome [7]. In a systematic review and meta-analysis of 81 studies and 25,268 individuals, over a fifth of participants experienced cognitive impairment 12 or more weeks after being diagnosed with COVID-19. Only a small fraction of people showed signs of ongoing systemic inflammation, and post-acute COVID-19 syndrome was associated with significant functional impairment [8].

However, data regarding standardised symptom definitions and measurements, for extended follow-up periods, and domains in which cognitive functions are the most affected ones in post-acute COVID-19 syndrome are still lacking [4, 7].

Considering the substantial morbidity related to the post-acute COVID syndrome, it is critical to have a deeper understanding of the related health issues. The main goal of this study was to assess the trajectory of the cognitive symptoms over 24 weeks among patients diagnosed with COVID-19 and who were supported through a telehealth program available for the community of *Universidade Federal de Minas Gerais*, a large public university in Brazil.

Methods

This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [9], whose checklist is presented in Additional file 1.

Study design, setting, and participants

This study is a subanalysis of an extensive retrospective cohort investigation conducted at the *Universidade Federal de Minas Gerais (UFMG)*, a public institution in Belo Horizonte, southeastern Minas Gerais state, Brazil. Participants consisted of consecutive individuals diagnosed with COVID-19 who sought and received care through TeleCOVID-MG, an innovative telehealth service developed and implemented by the Telehealth Network of Minas Gerais (TNMG) [10, 11] between December 1, 2020, and March 31, 2022 [12]. Patients with cognitive symptoms during acute COVID-19 were selected for the current investigation. COVID-19 was confirmed by real-time reverse transcription–polymerase chain reaction assay (RT-PCR) or antigen testing, according to the World Health Organization (WHO) criteria [13]. Given that depression can evolve with cognitive symptoms, to control for this confounding factor, we excluded patients with clinically meaningful depressive symptoms, using the PHQ-2 instrument (Patient Health Questionnaire-2) [14]. Also, patients with missing data related to cognitive symptoms were excluded.

Data were collected from patients diagnosed during Brazil's second and third COVID-19 waves. The second wave, lasting from August 2020 to December 2021, was characterized by the predominance of the Delta and Gamma variants, while the Omicron variant was the most prevalent virus strain during the third wave, which occurred between December 2021 and May 2022 [15].

TeleCOVID-MG

TeleCOVID-MG was a public teleconsultation and telemonitoring program developed by TNMG to assist individuals with respiratory symptoms during the COVID-19 pandemic. Initially implemented in two medium-sized cities in the state of Minas Gerais, it expanded to include students, faculty, and staff from UFMG in December 2020 [11, 12, 16, 17].

Variables

Information on the acute phase was obtained from the TeleCOVID-MG database, including demographics, symptoms, comorbidities, vaccination status, and laboratory testing details. Regarding race, "*pardo*" was used to describe individuals with mixed racial backgrounds, including combinations of African, European, and Indigenous ancestry, following the Brazilian Institute of Geography and Statistics definition. This broad category includes people of various racial ancestries, such as *mulatos* (people of mixed African and European ancestry), *cafuzos* (people of mixed Indigenous and African ancestry), *caboclos* (assimilated Amerindians), among others [18].

Regarding post-acute symptoms, they were assessed more than 24 weeks after diagnosis using a structured questionnaire developed for the study. The questionnaire covered a range of symptoms and self-reported

functional impacts, based on established clinical protocols and validated tools, as previously described [12, 19, 20].

In brief, it included questions from the Generalised Anxiety Disorder–7 (GAD-7), Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5), the Patient Health Questionnaire-9 (PHQ-9), the Chalder's Fatigue Scale, the New York Health Association's functional scale and a modified version of Charlson's comorbidity index [12, 21–26].

Patients with cognitive symptoms were identified through self-reporting during interviews conducted with all study participants more than 24 weeks after the onset of acute COVID-19 symptoms. This retrospective assessment captured symptoms that occurred during the acute phase. Cognitive symptoms were evaluated using four questions related to mental fatigue, obtained from the Chalder Fatigue Scale:

1. "Do you think as clearly as usual?"
2. "Do you find it more difficult to find the correct word?"
3. "Is your memory as good as ever?"
4. "Do you have difficulty concentrating?" [12, 23, 24].

The questionnaire assessed both the presence and duration of symptoms. Symptoms lasting up to four weeks were classified as acute, whereas those persisting beyond 24 weeks were defined as persistent.

The Chalder Fatigue Scale is a widely used and validated instrument for assessing fatigue, encompassing both physical and mental components. Its psychometric properties have been extensively evaluated, demonstrating good reliability and validity across different populations. Studies have shown that it effectively differentiates individuals with chronic fatigue syndrome from the general population, confirming that physical and mental fatigue are distinct constructs [27–30].

The questionnaire was applied via Google Forms® through phone calls by trained researchers supervised by a senior staff (LB) from December 2021 to November 2022. The research team followed a data collection protocol to standardise the collection [12]. Each participant received an initial phone call at least 24 weeks after the laboratory confirmation of COVID-19. There were four contact attempts per patient, including two phone calls at different times of the day, and two standardised text messages through an app (Whatsapp®), in which the individual was asked about the best time for the telephone call [12].

Cognitive symptoms were assessed by a positive response to at least one of four questions regarding memory issues, concentration difficulties, challenges in thinking clearly, and word retrieval problems, as performed in prior cognitive surveys in post-COVID conditions [31–33].

Definitions

The main goal of the current study was to assess the persistence or remission of cognitive symptoms 24 weeks after the onset of acute COVID-19 symptoms. **Persistence** was defined as the presence of cognitive symptoms for more than 24 weeks, while **remission** referred to the presence of cognitive symptoms during acute COVID-19, but symptoms remitting before 24 weeks of follow-up.

Statistical analysis

Descriptive statistical analyses were conducted to examine the duration of cognitive symptoms, relevant patient characteristics, and the impact of these symptoms on patients' daily lives. Categorical variables were represented as percentages, and the numerical variable (age) was expressed as median and interquartile range (IQR). The duration of the cognitive symptom persisting for the longest time was considered, both in its original scale (up to four weeks, up to 12 weeks, up to 24 weeks, more than 24 weeks) and in a dichotomous scale (up to 24 weeks, more than 24 weeks). Participants were categorised into age groups: 17–40, 41–60, and > 60 years [34].

The wave of infection was determined based on the patient's COVID-19 laboratory test date. Tests performed between November 8, 2020, and December 25, 2021, were classified as belonging to the second wave, while those from December 26, 2021, to March 31, 2022, were considered part of the third Brazilian COVID-19 pandemic wave [15]. Comorbidities were assessed using a modified Charlson comorbidity index, which included cardiac, respiratory (excluding asthma), chronic renal and hepatic diseases, dementia, chronic neurological conditions, connective tissue disease, diabetes mellitus, HIV, and malignancy [26]. Recognizing the impact of obesity on COVID-19 outcomes, we also added this variable to the index.

The proportions of type of cognitive symptom (concentration problems, memory problems, difficulty finding words, and difficulty thinking clearly) in each phase (acute, remission, and persistence) were analyzed, as well as the remission/persistence rate by type of cognitive symptom. In addition, the proportion of cognitive symptoms stratified by psychiatric conditions (symptoms of post-traumatic disorder, depression, and anxiety) was assessed. This analysis used the chi-square test to measure the association between each characteristic and remission.

We employed a two-stage analytical approach to investigate the relationship between patient characteristics and duration of cognitive symptoms. Initially, chi-square tests were carried out to assess univariate associations

between various patient characteristics and duration of cognitive symptoms. Variables exhibiting a $p < 0.25$ were then considered for inclusion in multivariate models. Multivariate logistic regression models were then constructed, with the dichotomized duration of cognitive symptoms serving as the binary outcome and the original scale duration as an ordinal outcome. It is important to note that variables considered potential consequences of cognitive symptoms or other post-COVID-19 manifestations (e.g., impaired ability to perform daily tasks, prolonged absence from work, restrictions on return to work, and post-COVID functional status) were excluded from the multivariate models. A backward stepwise selection method was used to identify significant predictors, with a significance threshold of 5%. The strength of the association between clinical features and duration of cognitive symptoms was quantified using odds ratios and their corresponding 95% confidence intervals. The proportional odds assumption was assessed using the Brant test [35, 36] for ordinal regression models.

Ethical considerations

This study received approval from the Brazilian National Commission for Research Ethics [CAAE 30350820.5.1001.0008] and adhered to the Declaration of Helsinki. Informed consent was obtained from all participants before their inclusion in the study.

Results

Study population

Of the 630 patients who responded to the questionnaire, 344 (54.6%) reported cognitive symptoms during acute COVID-19, i.e., up to four weeks since the onset of symptoms. Forty-four patients with missing data related to cognitive symptoms, as well as 25 participants who tested positive for depression lasting more than 12 weeks, were excluded. Thus, the final sample, including patients who experienced cognitive symptoms in the acute phase of the disease, was 319 individuals (Fig. 1). Of those, 72.1% presented remission of these symptoms within 24 weeks, while 27.9% experienced cognitive symptoms persisting for more than 24 weeks after acute COVID-19 onset.

The main characteristics of the studied population stratified by the occurrence or not of cognitive symptoms more than 24 weeks after acute COVID-19 onset are described in Table 1 and Supplementary Table 1. The baseline features of the study cohort according to the presence of cognitive symptoms are listed in Table 2 and Supplementary Table 2.

Patients with persistent cognitive symptoms were more likely female and exhibited a higher median age compared to those with symptom remission within 24 weeks of acute COVID-19 onset (83.1% vs. 70.9%, $p = 0.024$; 36 years, interquartile range [IQR] 26–48 vs. 32 years, IQR 24–43, respectively). A higher proportion of patients in the remission group were infected during the third wave of COVID-19 compared to those with no cognitive symptom remission (76.5% vs. 61.8%, $p = 0.007$).

Furthermore, among patients with persistent cognitive symptoms for more than 24 weeks, there was a lower proportion of smokers (7.9% vs. 14.8%, $p = 0.098$) and a higher proportion of sedentary patients (51.7% vs. 41.3%, $p = 0.094$), as well as patients reporting loss of ability to carry out daily tasks (11.2% vs. 3.0%, $p = 0.003$). Regarding functional limitations, the group with no remission showed a greater proportion of patients with functional limitations post-COVID-19 compared to the remission group (66.3% vs. 20.9%, $p < 0.001$). However, there were no statistically significant differences between groups concerning age group, education level, occupation as a healthcare professional or intern, vaccination status, presence of fatigue, need for in-person care during the acute phase of the disease, initiation of treatment for psychiatric disorders, or prolonged absence from work beyond the usual isolation period (Table 1 and Supplementary Table 1).

The median age was higher in patient groups in which symptoms persisted longer (up to 12 weeks: 27 years, IQR 24–41; up to 24 weeks: 31 years, IQR 23–42; more than 24 weeks: 36 years, IQR 26–48). Likewise, the proportion of sedentary individuals was increased in the group with longer duration of post-COVID cognitive symptoms (up to 12 weeks: 32.4%; up to 24 weeks: 41.9%; more than 24 weeks: 51.7%; $p = 0.237$). A higher proportion of individuals with post-COVID limitations was also observed in groups of patients with prolonged cognitive symptoms compared to groups of patients whose symptoms remitted sooner (up to 12 weeks: 24.3%; up to 24 weeks: 51.2%; more than 24 weeks: 66.3%; $p < 0.001$). Regarding age group, being a healthcare professional or intern, vaccination *status*, comorbidities *index*, smoking, and absence from work longer than the usual period of isolation, there were no statistically significant differences among the groups (Table 2 and Supplementary Table 2).

Remission/persistence by type of cognitive symptom

In general, the prevalence of cognitive symptoms decreased over time: during the acute phase (up to four weeks after the onset of COVID-19 symptoms) 319 patients presented at least one cognitive symptom, in the remission phase (up to 24 weeks) 230 patients and in the persistence phase (more than 24 weeks) only 89 patients. Among the cognitive symptoms reported in the acute phase, concentration problems (79.0%) were followed by memory problems (67.7%), difficulty finding words (63.3%), and, difficulty thinking clearly (52.0%). In the remission phase of cognitive symptoms, there was a more significant proportion of concentration problems

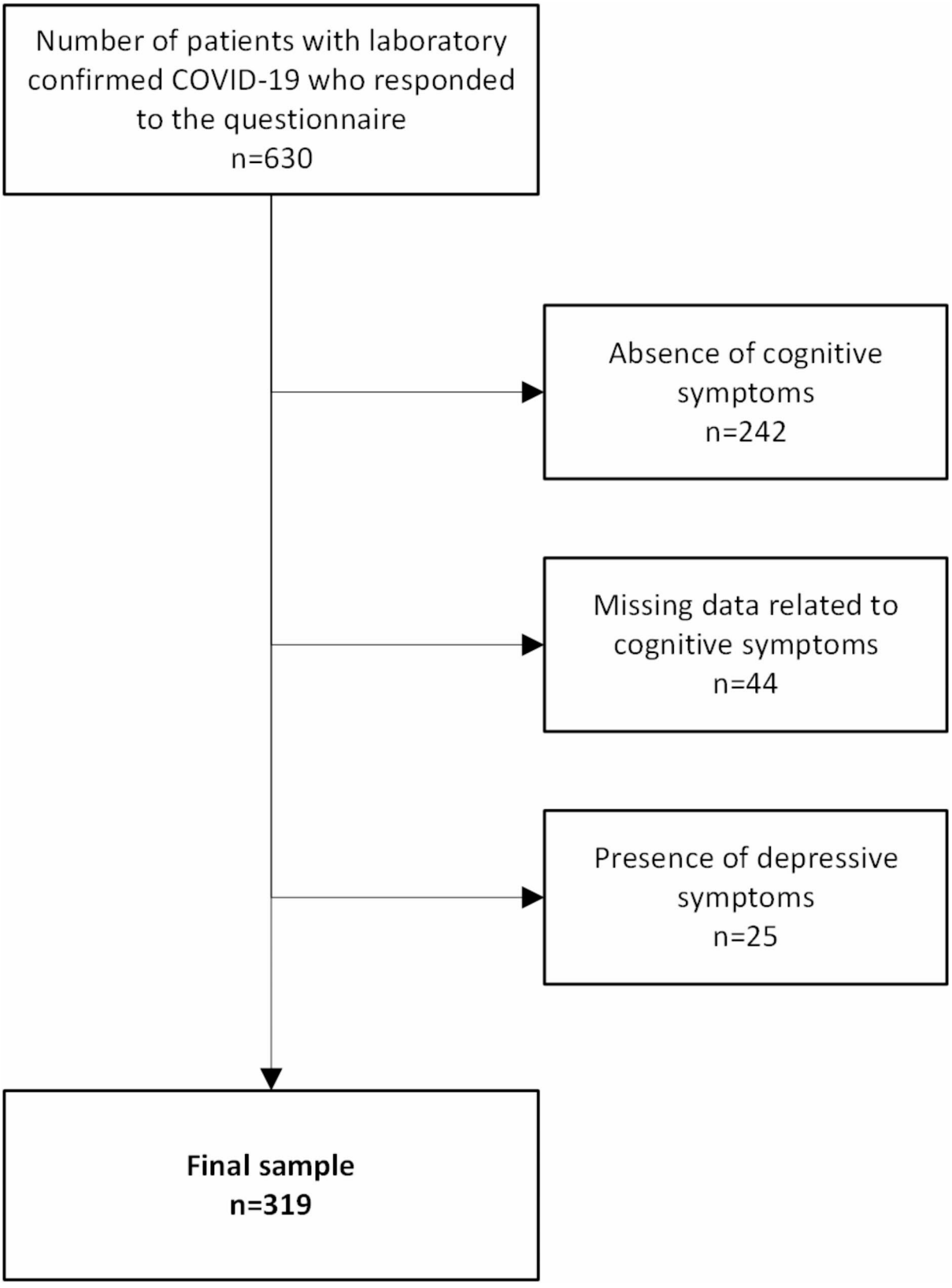

Fig. 1 Flowchart of patients included in the study

Table 1 Baseline characteristics of the study cohort at 24 weeks after acute COVID-19 onset

Characteristics	Total sample *N* = 319	Remission *N* = 230	Persistence *N* = 89	*p*-value
Median (IQR) age, years	32 (25–44)	32 (24–43)	36 (26–48)	0.223
Women	237 (74.3)	163 (70.9)	74 (83.1)	0.024
Pregnancy	3 (1.3)	2 (1.2)	1 (1.1)	
Race				0.224
White	166 (52.0)	116 (50.4)	50 (56.2)	
Pardo	109 (34.2)	81 (35.2)	28 (31.5)	
Black	35 (11.0)	35 (15.2)	11 (12.4)	
Undeclared or yellow	9 (2.8)	9 (3.9)	0 (0)	
Wave				0.007
Third wave	231 (72.4)	176 (76.5)	55 (61.8)	
Second wave	34 (10.7)	53 (23.0)	34 (38.2)	
Missing data	1 (0.3)	1 (0.4)	0 (0)	
Modified Charlson Index				0.131
0 comorbidity	268 (84.0)	189 (82.2)	79 (88.8)	
1 comorbidity	47 (14.7)	39 (17.0)	8 (9.0)	
2 comorbidities	4 (1.3)	2 (0.9)	2 (2.2)	
Smoking	41 (12.9)	34 (14.8)	7 (7.9)	0.098
Sedentary lifestyle	141 (44.2)	95 (41.3)	46 (51.7)	0.094
Restrictions on returning to work	7 (2.2)	3 (1.3)	4 (4.5)	0.081
Loss of ability to carry out daily tasks	17 (5.3)	7 (3.0)	10 (11.2)	0.003
Post-COVID functional status				< 0.001
No limitation	212 (66.5)	182 (79.1)	30 (33.7)	
Insignificant limitation	81 (25.4)	39 (17.0)	42 (47.2)	
Slight limitation	25 (7.8)	8 (3.5)	17 (19.1)	
Moderate limitation	1 (0.3)	1 (0.4)	0 (0)	

Remission: presence of cognitive symptoms up to 24 weeks after the onset of acute SARS-CoV-2 infection

Persistence: presence of symptoms for more than 24 weeks

Numbers are presented as n (%) or median; IQR: interquartile range

(85.7%). In contrast, in the persistence period, the proportion of memory problems and difficulty finding words was higher, 69.7% and 68.5%, respectively (Supplementary Table 3). The highest remission rates occurred for the symptoms 'difficulty thinking clearly' (80.1%) and concentration problems (78.2%), while the highest percentages of persistence were related to difficulty finding words and memory problems, 30.2% and 28.7%, respectively (Supplementary Table 4).

When analyzing the prevalence of cognitive symptoms stratified by psychiatric conditions (symptoms related to post-traumatic stress disorder, depression, and anxiety), the proportion of patients exhibiting cognitive symptoms did not significantly change For example, in the group of patients with post-traumatic stress disorder-related symptoms in the acute phase, 46.7% of individuals reported cognitive symptoms, 47.8% had remission and 43.8% persisted ($p = 0.512$). This pattern was evidenced for all psychiatric conditions, except "insomnia" symptoms ($p = 0.015$) (Supplementary Table 5).

Predictive factors for prolonged cognitive symptoms

In both binary and ordinal multivariate analyses, there were statistically significant associations between persistence and duration of cognitive symptoms and female sex (OR 2.33 [95% CI 1.23–4.43] for persistence and OR 1.84 [95% CI 1.13–2.99] for duration) and having been infected during the second wave of COVID-19 (OR 2.30 [95% CI 1.34–3.96] for persistence and OR 1.97 [95% CI 1.24–3.13] for duration). In our study, women and individuals infected in the second wave of COVID-19 were more likely to experience prolonged cognitive symptoms after acute SARS-CoV-2 infection. The goodness of fit tests indicated well-adjusted logistic regression models: Pearson's chi-squared p-value is 0.443 for binary logistic regression and 0.334 for ordinal logistic regression.

Discussion

This study represents, to our knowledge, the first investigation in the Latin American context to specifically examine cognitive symptoms persisting beyond 24 weeks following COVID-19 infection. Cognitive symptoms persisting for more than 24 weeks are a prominent feature of post-acute COVID-19 syndrome, with a prevalence of 27.9% among non-depressed patients who experienced cognitive symptoms during the acute phase of COVID-19. Female sex (OR 2.33 [95% CI 1.23–4.43]) and having been infected during the second wave of COVID-19 (OR 2.30 [95% CI 1.34–3.96]) were associated with cognitive symptoms persisting for more than 24 weeks. This study advances the literature on long COVID by looking at the trajectory of cognitive symptoms over a longer period.

Most patients included in this cohort had mild COVID-19 infection and were followed by a telehealth service. Specifically, only 13.8% of patients required in-person medical care, and a much lower proportion (0.6%) needed hospitalization, suggesting that the TeleCOVID-MG service primarily served individuals with mild COVID-19 cases. Despite the overall mild presentation and relatively young age of the patients, approximately one-third reported cognitive symptoms persisting beyond 24 weeks. This number supports prior research in which cognitive symptoms were common among COVID-19 patients [8, 37–39]. It is noteworthy that patients who presented depressive symptoms were excluded from the sample, which is also a strong point of the current analysis, given the major confounding effect of this factor.

According to a systematic review of 57 studies involving over 250,000 COVID-19 survivors, the most common neurocognitive symptoms that persisted for more than 24

Table 2 Baseline characteristics of the study cohort stratified by duration of symptoms (*N* = 319)

Characteristics	Up to 4 weeks *N* = 150	Up to 12 weeks *N* = 37	Up to 24 weeks *N* = 43	> 24 weeks *N* = 89	*p*-value
Median (IQR) age, years	33 (15–44)	27 (24–41)	31 (23–42)	36 (26–48)	0.228
Women	105 (70.0)	27 (73.0)	31 (72.1)	74 (83.1)	0.155
Pregnancy	2 (1.9)	0 (0)	0 (0)	1 (1.4)	
Race					0.221
White	81 (54.0)	16 (43.2)	19 (44.2)	50 (56.2)	
Pardo	45 (30.0)	18 (48.6)	18 (41.9)	28 (31.5)	
Black	17 (11.3)	3 (8.1)	4 (9.3)	11 (12.4)	
Undeclared or yellow	7 (4.7)	0 (0)	2 (4.7)	0 (0)	
Education					0.201
Post-graduation	57 (38.0)	9 (24.3)	19 (44.2)	33 (37.1)	
Graduation	88 (58.7)	23 (62.2)	22 (51.2)	51 (57.3)	
High or middle school	5 (3.3)	5 (13.5)	2 (4.7)	5 (5.6)	
Wave					0.026
Third wave	117 (78.0)	25 (67.6)	34 (79.1)	55 (61.8)	
Second wave	32 (21.3)	12 (32.4)	9 (20.9)	34 (38.2)	
Sedentary lifestyle	65 (43.3)	12 (32.4)	18 (41.9)	46 (51.7)	0.237
Physical fatigue	135 (90.0)	29 (78.4)	40 (93.0)	81 (91.0)	0.132
Needed to seek in-person care	14 (9.3)	7 (18.9)	8 (18.6)	15 (16.9)	0.182
Started treatment for psychiatric diseases	25 (16.7)	3 (8.1)	12 (27.9)	14 (15.7)	0.120
Loss of ability to carry out daily tasks	1 (0.7)	1 (2.7)	5 (11.6)	10 (11.2)	0.001
Restrictions on returning to work	0 (0)	2 (5.4)	1 (2.3)	4 (4.5)	0.040
Post-COVID functional status					< 0.001
No limitation	133 (88.7)	28 (75.7)	21 (48.8)	30 (33.7)	
Insignificant limitation	12 (8.0)	9 (24.3)	18 (41.9)	42 (47.2)	
Slight limitation	4 (2.7)	0 (0)	4 (9.3)	17 (19.1)	
Moderate limitation	1 (0.7)	0 (0)	0 (0)	0 (0)	

Numbers are presented as n (%)

weeks after the onset of acute COVID-19 were difficulty concentrating (median 23.8%; IQR 20.4–25.9%), memory deficits (18.6%; 17.3–22.9%), and global cognitive impairment (17.1%; 14.1–30.5%). In terms of overall symptom duration, the median (IQR) proportion of COVID-19 survivors who had at least one post-acute overall sequelae of COVID-19 was 54.0% (45.0–69.0%) in four weeks [short term], 55.0% (34.8–65.5%) in 8 to 20 weeks [intermediate], and 54.0% (31.0–67.0%) in 24 weeks or more [long term] [40]. Similarly, a recent systematic review covering data from 1,374 patients [median age ranged from 36.2 years (SD = 11.7) to 67.23 years (SD = 12.89)] found that, after 12 weeks of COVID-19 infection, cognitive impairment varied from 21 to 65%, with executive functioning, attention, and episodic memory being the most affected domains [41]. These numbers are generally consistent with the results of the present analysis.

Our findings indicate that women were 2.33 times more likely to experience persistent cognitive symptoms than men (95% CI 1.23–4.43). This aligns with results from large cohort studies in Iran and Norway, which also identified female sex as a significant risk factor for post-COVID "brain fog," with reported odds ratios of 1.4 (95% CI 1.06–1.90) and relative risks of 2.0 (95% CI 1.3–3.2), respectively [42, 43]. In a Polish study 12 weeks after acute COVID-19, women also reported higher rates of problems with writing, reading, counting (17.0 vs. 5.1%), and communicating thoughts to others (34.3 vs. 20.7%) compared to men [44].

Patients infected during the second wave of COVID-19, corresponding to the dominant delta variant in Brazil, were 2.30 (95% CI 1.34–3.96) times more likely to present persistent cognitive symptoms compared to the infection that occurred during the third wave (omicron variant). This result is also consistent with previous evidence demonstrating the association between the occurrence of post-COVID-19 cognitive symptoms and the SARS-CoV-2 wave/variant. In a large community study involving more than 112,000 adults, COVID-19 was found to be associated with objectively measurable long-term global cognitive deficits, as well as an attenuation of these symptoms as the pandemic progressed, indicating the occurrence of milder cognitive symptoms in the most recent variants of SARS-CoV-2 [7]. Similarly, a case-control study that examined prevalence and risk factors for post-COVID-19 condition (PCC) among children and adolescents in Japan (8167 individuals, 3141 (1800 cases, mean age: 10.4 years, 46.1% females; 1341 controls, mean

age 10.5 years, 47.1% females) found that patients with earlier variants (alpha and delta) had higher PCC than those with omicron (13.7 vs. 5.8%), necessitating preventive strategies, notably vaccination [45]. According to meta-analyses of published studies on the omicron and delta variants of COVID-19, the combined percentage of asymptomatic cases of SARS-CoV-2 omicron infection is 25.5% (95% CI 17.0%– 38.2%), and the combined percentage of non-severe cases is 97.9% (95% CI 97.1%– 98.7%), which is significantly higher than that of the delta variant, which it was 8.4% (95% CI 4.4%– 16.2%) and 91.4% (95% CI 87.0%– 96.0%). Getting a COVID-19 booster dose also played a significant role in increasing the proportion of asymptomatic cases and reducing the severity of the disease [46].

Contrary to this finding, the results of our study have not demonstrated an association between the persistence of post-COVID-19 cognitive symptoms and the vaccination status of research participants. Perhaps the explanation for this non-association lies in the nature of the sample, made up of mild patients and the majority vaccinated. A more recent systematic review and meta-analysis that evaluated 17 studies covering 257,817 patients confirmed that at least one dose of a SARS-CoV-2 vaccine was associated with a protective effect against the development of long COVID, relative to individuals who have not received the SARS-CoV-2 vaccine before infection, or those who received fewer doses (OR 0.539, 95% CI 0.295–0.987, $p = 0.045$, I2 = 96.46) [47]. For long COVID symptoms, vaccination reduced the risk of cognitive dysfunctions/symptoms, among others [48].

Within our TeleCOVID-MG cohort, we did not find any statistically significant association between pre-existing comorbidities and the development of persistent cognitive problems following COVID-19 infection. This could be attributed to the composition of the sample, which included patients with mild COVID-19, and not very sick, i.e., not with many comorbidities [12]. A comprehensive review and meta-analysis of 677,045 COVID-19 survivors found that underlying comorbidities could be a risk factor for developing long-term COVID-19 symptoms [49]. However, investigations that specifically evaluate comorbidities as a risk factor for post-COVID-19 cognitive symptoms are missing.

With regards to the start of any treatment for psychiatric disorders after COVID-19 infection, there were no statistically significant differences between "remission" and "persistence" groups (Supplementary Table 1). It is worth highlighting that the sample used in this analysis excluded patients with depressive symptoms, in an attempt to control this important confounding factor.

From a pathophysiological perspective, it is known that SARS-CoV-2 infection can cause brain changes, leading to behavioral and cognitive changes. In addition to vascular and inflammatory mechanisms of neuronal injury, SARS-CoV-2 selective neuronal mitochondrial targeting could contribute to neural dysfunction and subsequent symptoms [50]. The persistence of cognitive symptoms may be related to neuroanatomical changes, neurodegeneration, cerebral microvascular injury, and metabolic alterations following the acute infection. Endothelial dysfunction, hyperinflammation, autoimmunity, multiorgan pathology, and autonomic nervous system dysfunction, may interact with these factors [8].

However, cognitive symptoms, such as difficulties with memory, multitasking, processing speed, and attention, can manifest even in mild COVID-19 cases, independent of severe neurological complications. Systemic inflammation and immune responses triggered by the virus, even in the absence of direct central nervous system invasion, can disrupt the blood-brain barrier, initiate neuroinflammatory processes, and induce endothelial dysfunction, ultimately affecting brain function [51]. Notably, cognitive impairment and orthostatic intolerance, which are exacerbated by upright posture, are common in both post-acute COVID-19 syndrome and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Similar structural, metabolic, and inflammatory abnormalities in the brain, peripheral neurovascular dysregulation, and immune dysfunction have been observed in ME/CFS, suggesting shared pathophysiological mechanisms. Characterized as a multi-systemic metabolic-inflammatory disorder with altered bioenergetics, ME/CFS provides a potential framework for understanding the lingering cognitive effects of COVID-19. Therefore, research into post-acute COVID-19 syndrome may also offer insights into ME/CFS [52].

It is crucial to acknowledge that a significant proportion of patients with post-acute COVID-19 syndrome exhibit symptoms consistent with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a debilitating condition characterized by persistent post-exertional malaise, non-restorative sleep, cognitive impairments, and a variety of other neurological and systemic symptoms. Recent studies have shown that between 13.0% and 58.7% of post-COVID patients meet the diagnostic criteria for ME/CFS, highlighting the substantial burden of this condition in the long-term recovery phase [53].

Longitudinal analysis of brain imaging data from the UK Biobank revealed that, compared to controls, individuals who had COVID-19 exhibited reduced gray matter thickness in the orbitofrontal cortex and parahippocampal gyrus– regions linked to the olfactory system– as well as a decrease in the overall brain volume and accelerated cognitive decline, even among those not requiring hospitalization [51]. On the other hand, a study carried out in Israel, which evaluated cognitive impairment in post-COVID-19 patients between December 2020 and June

2021, revealed impairments in executive function, attention and phonemic fluency, but normal laboratory and imaging results [54].

The main limitation of this study is its dependence on the report of cognitive symptoms and the lack of concomitant neuropsychological assessment. Self-report assessments can be influenced by a variety of factors, including mood. It is also important to acknowledge the immense socioeconomic impact of the pandemic, which could have contributed to lingering subclinical stress and related cognitive symptoms. The study's potential weaknesses include "temporal reports" and recall biases, given that the application of the questionnaire to investigate post-COVID cognitive symptoms occurred more than 24 weeks after the onset of acute COVID-19 symptoms. Other investigators have already noted variations in the concepts of cognitive impairment, brain fog, memory problems, and attention deficit [37].

Regarding psychiatric treatment/medication initiated after the onset of the acute phase of COVID-19, we do not have information about its interruption or duration. This represents a limitation of the study, as it prevents us from assessing the potential impact of medication use or psychiatric treatment initiation on the results. Furthermore, the lack of comparison with control groups makes it impossible to distinguish between the direct and indirect effects of COVID-19 on the occurrence of cognitive symptoms. In contrast, the homogeneity of the investigated population is a strength of this study, as well as the exclusion of patients with depressive symptoms from the sample, considering the confounding effect of this factor.

Future research should use quantitative neuropsychological tests to map specific cognitive deficiencies (for example, attention, memory, and executive function). Furthermore, more research is needed to better understand the underlying mechanisms of post-COVID cognitive symptoms to enable early identification of these symptoms, as well as the development of effective therapeutic options to improve quality of life and reduce disease burden.

Conclusions

In a retrospective cohort of generally mild COVID-19 patients, we found that cognitive symptoms were a common component of post-acute COVID-19 syndrome. Among patients who present cognitive symptoms in the acute phase of COVID-19, 27.9% persist with these symptoms beyond 24 weeks since the onset of the disease. Female sex and having been infected during the second wave of COVID-19 were associated with cognitive symptoms persisting for more than 24 weeks when compared to male sex and those who were infected in the third wave.

Abbreviations

CI	Confidence interval
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
GAD-7	Generalized anxiety disorder – 7
HIV	Human immunodeficiency virus
IQR	Interquartile range
ME/CFS	Myalgia encephalomyelitis/chronic fatigue syndrome
NICE	National institute for health and care excellence
OR	Odds ratio
PCC	Post-COVID condition
PCL-5	Posttraumatic stress disorder checklist for DSM-5
PHQ-2	Patient health questionnaire-2
PHQ-9	Patient health questionnaire-9
RT-PCR	Reverse transcription-polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCD-Q	Subjective cognitive decline questionnaire
TNMG	Telehealth Network of Minas Gerais
UFMG	Universidade Federal de Minas Gerais

Supplementary Information

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Supplementary Material 1

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Author contributions

LB: Conceptualization, project administration, data curation, writing of the original draft, and review/editing of the manuscript. CO: Conceptualization, writing of the original draft, and review/editing of the manuscript. TC: Data curation, writing of the original draft, and review/editing of the manuscript. LK: Data curation, writing of the original draft, and review/editing of the manuscript. AT: Conceptualization, writing of the original draft, and review/editing of the manuscript. MM: Conceptualization, project administration, data curation, writing of the original draft, and review/editing of the manuscript.

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Data availability

Additional material for this article can be found throughout the body of the text, as recommended.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Brazilian National Commission for Research Ethics (Comissão Nacional de Ética em Pesquisa– CONEP; CAAE: 30350820.5.1001.0008). All participants provided informed consent prior to their inclusion in the study.

Consent for publication
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Competing interests
The authors declare no competing interests.

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