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Post-discharge follow-up of patients with COVID-19: A Brazilian experience

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Abstract

Objective: The objective of this study is to evaluate post-acute symptoms in patients with confirmed severe and critical coronavirus disease 2019 infections.

Methods: We evaluated patients with confirmed severe and critical coronavirus disease 2019 infections. Post-acute symptoms were defined as symptoms persisting 4 weeks after the onset of the symptoms and classified as pulmonary, muscular, hematologic, neuropsychiatric, renal, and dermatological.

Results: We recovered data from 565 patients (43.7% female) with a mean age of 61.1 years. In 18.2%, at least one hospital readmission was necessary and 11.1% died. In 62.6%, there was at least one persistent symptom, and 28.8% had more than one. Among associated factors, obesity, intensive care support, and mechanical ventilation were related to persistent symptoms.

Conclusion: The most prevalent symptoms were pulmonary and neuropsychiatric sequelae, as reported in previous studies. This finding underscores the severity of the coronavirus disease 2019 infection and the need for follow-up after recovery from the initial illness. Obese patients, those requiring mechanical ventilation, female patients, and increased hospital length are at greater chance of having persistent symptoms.

Keywords

COVID-19, post-COVID syndrome, SARS-CoV-2, coronavirus, post-COVID

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Introduction

In December 2019, the first cluster of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection cases was reported in Wuhan, China, and in March 2019, the World Health Organization declared the outbreak of coronavirus disease 2019 (COVID-19) infection. By March 2022, SARS-CoV-2 had already infected more than 438 million worldwide, with 5.9 million deaths and 370 million recovered patients.[1] Brazil is one of the most affected countries, with more than 28.8 million cases, 649,000 deaths, and 26.5 million recovered patients.

A Chinese report of 72,314 patients with COVID-19 infection found that 81% of the cases were mild, 14% were severe, and 5% were critical, with severe and critical cases requiring hospitalization and supplementary oxygen support.[2]

Post-COVID-19 syndrome is defined as persistent symptoms 12 weeks after the onset of the initial condition that may occur with any COVID-19 severity and cannot be explained by an alternative diagnosis. The proposed pathophysiology involves direct viral toxicity, microvascular and endothelial damage, immune system dysregulation, hypercoagulable state, and changes in the angiotensin-converting enzyme pathway in addition to immediate sequelae of hospitalization for COVID-19. The most common clinical manifestation of

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post-COVID-19 syndrome is pulmonary symptoms ranging from dyspnea to difficult ventilator weaning and fibrotic lung damage. Other common symptoms are headaches, cognitive impairment, memory loss, depression, anxiety, insomnia, hematologic events such as acute thromboembolism, renal replacement therapy, hair loss, skin rash[3,4], and a decrease in life quality.[5,6]

Studies from Italy,[7] the United Kingdom,[8,9] France,[10,11] the United States,[12] Spain,[13] and China[14] analyzed more than 3000 COVID-19 patients after hospital discharge, however, with different severity groups and follow-up duration after hospital discharge.

Identifying sequelae after acute infection by COVID-19 is essential to better understand the disease's pathophysiology, which is not limited to the initial presentation. Understanding the post-COVID syndrome is crucial for remodeling the health system for multidisciplinary treatment and rehabilitation.

This study aimed to report the repercussions and post-acute symptoms of severe and critical COVID-19 patients in a Brazilian hospital.

Methods

This retrospective cohort included patients admitted to the Municipal Hospital de Parelheiros Josanias Castanha Braga (HMP), in Sao Paulo, Brazil, a COVID-19-specialized hospital, from March 2020 to March 2021. The Institutional Review Board (IRB) approved this study, which accorded with the Helsinki Declaration. IRB of our institute approved verbal recorded consent. This was proposed due to social distancing measures, distance between patients and hospital site, and tele-interview evaluation. Patient information was summarized in a spreadsheet file accessible only to the research team with de-identified data.

The intra-hospital medical care followed international World Health Organization (WHO) guidelines regarding corticosteroids in severe cases, supplementary oxygen delivery, and Extracorporeal Membrane Oxygenation (ECMO) in selected cases.

We considered discharged patients from HMP who met the inclusion and exclusion criteria (see below). No sample size criteria were applied in the study design. We included data from patients more than 12 weeks post-discharge. Post-discharge contact was achieved through telephone calls by a trained medical team, where information about hospital readmissions, clinical events, persistent symptoms, and symptom duration were obtained.

We used a questionnaire to obtain information regarding hospital readmission, vaccination status, pulmonary symptoms, supplementary oxygen need, thrombotic events, forgetfulness, tiredness, member pain, weakness, need for physiotherapy, hair loss, headache, anxiety, anosmia and dysgeusia, and other symptoms. We considered only new symptoms after COVID-19 disease or worsening of pre-disease conditions.

The inclusion criteria were as follows: (1) admission to HMP with a confirmed diagnosis of SAR-CoV-2 infection using real-time polymerase chain reaction testing or chest computed tomography suggestive of COVID-19 infection; (2) severe or critical COVID-19 infection, or cases in which medical support was needed, for example, cardiac events, acute renal failure, and pulmonary thromboembolism; and (3) follow-up 4 weeks from symptom onset. Severe infection was defined as dyspnea, respiratory frequency higher than 30/min, blood oxygen saturation lower than 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio lower than 300, more than 50% of lung infiltrates, and critical infection associated with respiratory failure, septic shock, or multiple organ dysfunction.[2] The exclusion criteria were as follows: (1) unfavorable outcome during hospitalization, (2) unconfirmed diagnosis of COVID-19, and (3) unavailability of telephone contact.

Persistent post-COVID-19 symptoms were defined as symptoms present four weeks after the onset of the initial symptoms following recent SARS-CoV-2 infection; these were classified as pulmonary (dyspnea, cough, need for domiciliary oxygen), muscular (muscular weakness, muscular pain), hematologic (thromboembolic events), neuropsychiatric (headache, anosmia, dysgeusia, cognitive impairment, memory loss, depression, anxiety, insomnia), renal (dialysis), and dermatological sequelae (skin rash, hair loss).[3]

A baseline descriptive analysis of demographics and comorbidities was performed to understand the sample characteristics. Hospital readmission, deaths, need for dialysis, need for domiciliary oxygen, receipt of COVID-19 vaccine, and thrombotic events were analyzed in the post-discharge period.

Statistical analysis

Continuous variables were tested for normality, and nonparametric tests were applied for data with skewed distribution. Statistical descriptive and logistic regression analyses were performed using JASP (JASP Team 2020, version 0.14.1). Persistent symptoms for more than 12 weeks were defined as a dependent variable. As independent factors were considered: patient sex, systemic arterial hypertension, diabetes mellitus, obesity, pulmonary obstructive disease, orotracheal ventilation need, and hospitalization length. The independent factors were defined according to previous studies on risk factors for post-acute COVID-19 symptoms.[3]

In each independent factor, a linear regression analysis was performed and, after a multicollinearity analysis with the stepwise method, considered every independent factor to determine the relationship of the variables. A two-tailed probability with a $p < .05$ was considered statistically significant.

Results

In the study period, 3031 patients were admitted to HMP, with 440 COVID negatives, 898 intra-hospital deaths, and

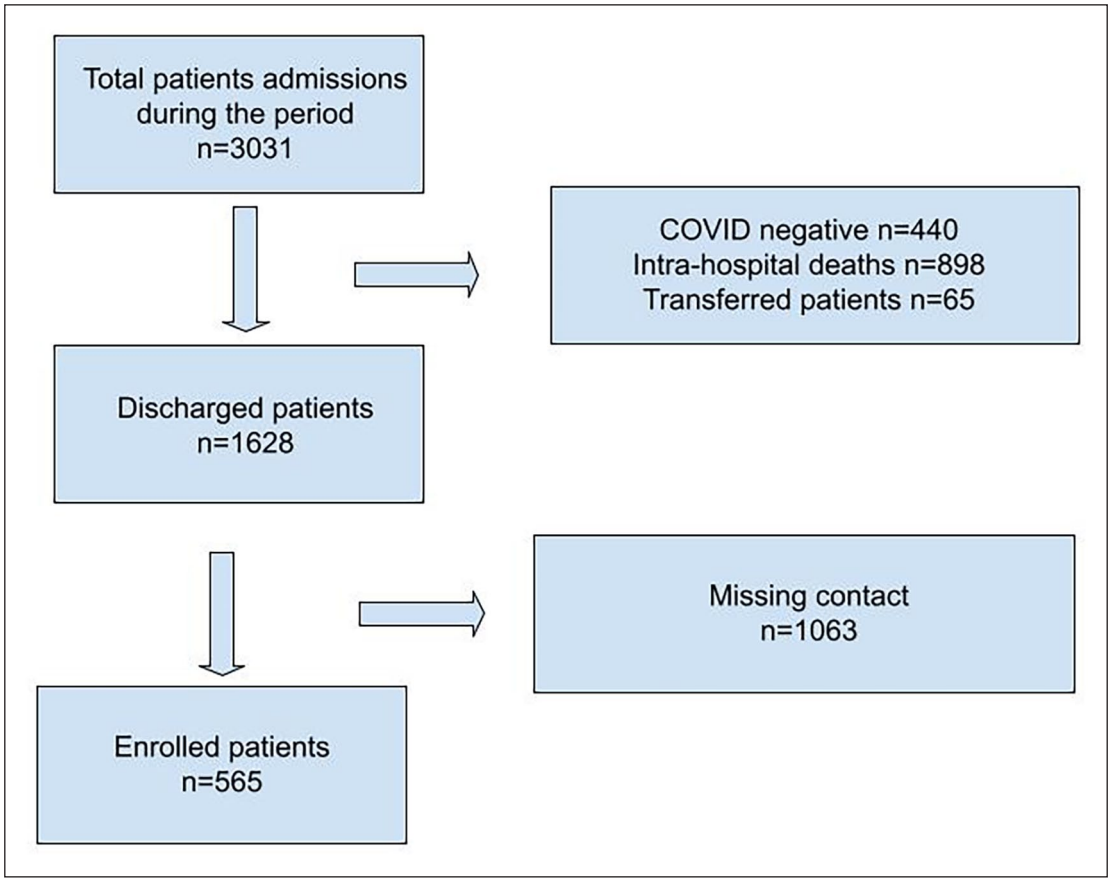

Figure 1. Flowchart of patients' selection: total patient admission, hospital discharge, deaths, missing contact, and enrolled patients.

65 transferred patients. From the discharged patients, data from 565 presumed/confirmed severe or critical COVID-19 diseases were analyzed (Figure 1). Of these, 247 (43.7%) were female and 318 (56.3%) were male ($p = .003$), with a mean age of 61.1 years (19–103); 72 (12.7%) patients had no comorbidities ($p < .001$). The mean overall length of hospital stay was 15.2 days (1–119 days). The mean length of hospitalization for intensive care unit (ICU)–admitted patients was 21.1 days (3–119 days), and non-ICU patients stayed an average of 9 days (1–46 days) (Table 1).

Regarding comorbidities, 18.23% were obese, 59.65% had systemic arterial hypertension, 36.63% had diabetes mellitus, 0% had chronic renal disease, 6% had chronic pulmonary disease, and 11.85% had cardiopathy. A total of 340 (60.2%) came to HMP requiring low-flow or no oxygen support, and 225 (39.8%) required high-flow oxygen support (invasive and non-invasive). During hospitalization, 291 (51.5%) needed ICU care, and 150 (26.5%) required mechanical invasive ventilation support.

Telephone contact was made within a median of 318 days (standard deviation = 54.3 days) after hospital discharge. We found that 18.2% (103) of the patients had at least one hospital readmission after initial discharge, and 11.1% (63) died during the follow-up period (Table 2).

At the time of telephone contact, 295 (52.2%) patients received at least one dose of the SARS-CoV-2 vaccine. Distinct phases of the vaccination calendar should be considered when analyzing vaccination coverage in these patients.

After hospital discharge, 36 (6.4%) of the patients suffered a thrombotic event involving the lower limbs, lungs, central neural system, or myocardium. Among the 48 patients (8.5%) who needed physiotherapy after discharge, 54.2% (26) needed motor therapy, 25% (12) required respiratory therapy, and 20.8% (10) required both motor and respiratory therapies that had been required before hospitalization. Of our total sample, 276 (48.8%) had at least one post-acute symptom, and in 137 (24.2%), there was more than one persistent symptom. In 179 (31.7%) of the patients, at least one symptom persisted until the time of telephone contact.

The most prevalent persistent symptoms were pulmonary sequelae (27.1%). Neuropsychiatric, muscular, hematologic, dermatological, and renal symptoms were reported at 18.2%, 18.2%, 1.5%, 4.2%, and 0.005%, respectively (Table 3).

In univariate analysis, mechanical ventilation was associated with a 2.72-fold greater risk of presenting persistent symptoms (95% confidence interval (CI) = 0.68–1.39, $p < .001$). Obesity was associated with a 2.45-fold greater risk (95% CI = 0.44–1.34, $p > .001$), female sex was

Table 1. Baseline and admission data.

Demographics	
Age (mean), years	61.1 (19–103)
Males (%)	56.3 (318)
ICU need	291 (51.5%)
Comorbidities	
Hypertension	335 (59.3%)
Diabetes	204 (36.1%)
Obesity	102 (18.0%)
Cardiovascular disease	67 (11.8%)
Chronic respiratory disease	34 (6%)
Admission data	
OTI need	150 (26.5%)
Length of hospital stay, mean	15.24 days
ICU patients	21.1 days
Non-ICU patients	9 days

ICU: intensive care unit; OTI: orotracheal intubation.

Table 2. Death causes in discharged patients.

Post-discharge death causes	
Respiratory	25.4% (16)
Cardiac	22.2% (14)
Sepsis	15.9% (10)
Unknown	9.5% (6)
Cancer complications	9.5% (6)
Renal	6.3% (4)
Cerebral vascular accident	6.3% (4)
Thrombosis	3.2% (2)
Hepatic complications	1.6% (1)

Note: The values in parantheses indicate the absolute number.

Table 3. Post-discharge persistent symptoms.

Post-discharge symptoms	
One persistent symptom	191 (33.8%)
More than one persistent symptom	163 (28.8%)
Pulmonary sequelae	229 (40.5%)
Neuropsychiatric sequelae	129 (22.8%)
Muscular sequelae	138 (24.4%)
Hematologic sequelae	36 (6.4%)
Dermatological sequelae	32 (5.7%)
Renal symptoms	17 (3%)

associated with 1.67-fold greater risk of presenting persistent symptoms (95% CI = 0.181–0.851, $p = .003$), hospital length was associated with 0.97-fold greater risk (95% CI = –0.042 to 0.015, $p < .001$), and intensive care need was associated with 1.86-fold greater risk (95% CI = 0.29–0.95, $p < .001$) (Table 4).

In multivariate analysis, mechanical ventilation, obesity, sex, and hospitalization length remained statistically significant (Table 4).

Systemic hypertension ($p = .56$), diabetes mellitus ($p = .39$), chronic pulmonary disease ($p = .62$), and patient age ($p = .034$) were not associated with persistent symptoms.

In the long-term post-discharge mortality univariate analysis, systemic hypertension was associated with a 1.8-fold greater risk ($p = 0.04$), and diabetes mellitus ($p = 0.08$), chronic pulmonary disease ($p = 0.22$), and patient gender ($p = 0.69$) were not associated with post-discharge mortality. In multivariate analysis, no parameter showed statistical significance in post-discharge mortality.

Discussion

As of March 2022, more than 438 million persons worldwide had been infected with SARS-CoV-2, and 370 million had recovered. In Brazil, there were more than 26.5 million patients who recovered from COVID-19.

Persistent symptoms four weeks after the onset of acute respiratory symptoms characterize the post-COVID-19 syndrome. The proposed pathophysiology involves direct viral toxicity, microvascular and endothelial damage, immune system dysregulation, hypercoagulable state, and changes in the angiotensin-converting enzyme pathway, in addition to direct consequences of hospitalization for the treatment of COVID-19.[3] SARS-CoV-2 infection overloads the health care system during waves of disease, and follow-up after hospital discharge is critical in these patients.

Our study is the first Brazilian report of patients hospitalized with severe and critical COVID-19 infection with the longest follow-up time after hospital discharge.

Our intra-hospital mortality of 29.62% is similar to previous reports of 15% to 20% in overall hospital mortality and up to 40% in ICU admission.[15] The group of Chopra et al. reported a prevalence of 32.6% of persistent symptoms, and the group of Carvalho-Schneider et al. reported a prevalence of 66% of persistent symptoms, with 2 months follow-up, also with a telephone survey.[10,12] Our study reports a prevalence of 48.8% in at least one persistent symptom, a difference that could be explained due to distinct patients' COVID severity and greater follow-up time.

The most prevalent symptoms were pulmonary and neuropsychiatric sequelae, similar to previous reports.[14,16] Moreno-Pérez et al.[13] also reported that muscular sequelae represented the third most prevalent sequela in 19.6% of patients, a similar value to our study prevalence (18.2%). After the multivariate analysis, we found an increased risk of presenting persistent post-discharge symptoms in obese patients, and, like previous studies, we found an increased risk of the need for mechanical ventilation support, female patients, and increased hospital length.[3] Distinctly from Nalbandian et al.,[3] in our study, intensive care need was related to persistent symptoms only in univariate analysis, but in the multivariate stepwise analysis, it did not show statistical significance.

Table 4. Univariate and multivariate analysis in persistent symptoms.

Persistent symptoms			
Univariate			
	Odds ratio	Confidence interval	*p*
Sex (female)	1.67	0.181 to 0.851	.003
Systemic arterial hypertension	1.10	–0.434 to 0.237	.566
Diabetes mellitus	1.16	–0.149 to 0.49	.395
Obesity	2.45	0.44 to 1.34	<.001
Pulmonary obstructive disease	1.19	–0.52 to 0.869	.622
Orotracheal ventilation need	2.72	0.608 to 1.39	<.001
Hospitalization length	0.97	–0.042 to 0.015	<.001
Intensive care need	1.86	0.29 to 0.95	<.001
Multivariate stepwise			
Orotracheal ventilation need	1.93	0.197 to 1.121	.05
Obesity (No)	0.49	0.197 to 1.121	.05
Sex (male)	1.59	0.112 to 0.813	.04
Hospitalization length	0.98	–0.033 to –0.001	.003

Zangrillo et al.[17] group applied a validated EuroQol Group EQ-5D-3L questionnaire in a follow-up of a small sample of patients (56) but found a smaller prevalence of post-COVID-19 symptoms in the 1-year follow-up, not distinguishing the symptoms time length.

The lack of statistical significance regarding long-term mortality in discharged patients considering the variables could be explained due to the small sample size.

The incidence of persistent symptoms for more than 4 weeks after hospital discharge in almost half of the severe or critically ill patients highlights the need to remodel the health system and represents a decrease in quality of life in a significant portion of the population. Monitoring health programs such as the British Thoracic Society algorithm recommend clinical assessment and chest X-ray at 12 weeks, and echocardiogram and pulmonary function testing in selected patients.[18]

After discharge, the rate of readmissions and deaths underscores the potential severity of COVID-19 and the need for follow-up after recovery from the initial respiratory condition.[19] Thrombotic events, cardiopulmonary, and infectious complications are relevant causes of death and hospital readmission in post-discharge COVID-19 patients.

Our post-discharge mortality is higher than reported in other studies but with a distinct cohort (severe and critical COVID) and greater follow-up time.[12,14]

Acute respiratory distress syndrome (ARDS) is reported in post-COVID-19 patients and occurs due to diffuse inflammatory damage into alveolar-capillary barrier consequences. Long-term, computed tomography images and other pulmonary sequelae were not evaluated in this study and will be the next steps.[16,17,20,21]

This study has some limitations. Our study presented a single-hospital analysis that did not include objective post-COVID-19 symptom parameters such as pulmonary function and without a sample size calculation. Our findings depended on self-reported symptoms and readmissions, introducing the risks of systematic error and study generalizability. Furthermore, this study was limited to severely ill patients who needed hospitalization. Finally, a telephone non-previously validated questionnaire does not substitute for an in-person interview and may create overestimation bias related to reporting symptoms. This study's next steps will be a 2-year follow-up of those post-COVID patients, with objective measurements and quality-of-life evaluation.[22] This study focused on post-discharge symptoms prevalence and outcomes; no intra-hospital management data were included.

The discrepancies between our post-COVID-19 symptom prevalence and those of previous studies may be explained by racial and ethnic considerations, disparate COVID-19 severities, and the telephone interview modality.[3]

Conclusion

The post-COVID-19 syndrome is a common condition reported in almost half of the discharged patients in a Brazilian hospital. Obese patients, those requiring mechanical ventilation, female patients, and increased hospital length are at greater chance of having persistent symptoms.

Authors' note

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Author contributions

L.F.N. and M.G.U. contributed to project leading, data acquisition, analysis, and data interpretation. All authors contributed to article conception, draft, and final version approval.

Declaration of conflicting interests

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Ethics committee approval SMSSP 45429121.0.

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Informed consent

The Institutional Review Board (IRB) of our institute approved verbal recorded consent. This was proposed due to social distancing measures, distance between patients and hospital site, and tele-interview evaluation.

Trial registration

Not applicable—this study is not a clinical trial.

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Supplemental material

Supplemental material for this article is available online.

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