



Ninety-day outcomes in patients diagnosed with COVID-19 in São Paulo, Brazil: a cohort study

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Submitted: 6 March 2023.

Accepted: 2 May 2023.

Study carried out at the Hospital Sírio-Libanês, São Paulo (SP) Brasil.

ABSTRACT

Objective: COVID-19 has been associated with a significant burden to those who survive the acute phase. We aimed to describe the quality of life and symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD) at 90 days after hospital discharge of COVID-19 patients. **Methods:** Patients with COVID-19 admitted to a private hospital in the city of São Paulo, Brazil, between April of 2020 and April of 2021 were interviewed by telephone at 30 and 90 days after discharge to assess the quality of life and symptoms of depression, anxiety, and PTSD. **Results:** A total of 2,138 patients were included. The mean age was 58.6 ± 15.8 years, and the median length of hospital stay was 9.0 (5.0–15.8) days. Between the two time points, depression increased from 3.1% to 7.2% ($p < 0.001$), anxiety increased from 3.2% to 6.2% ($p < 0.001$), and PTSD increased from 2.3% to 5.0% ($p < 0.001$). At least one physical symptom related to COVID-19 diagnosis persisted in 32% of patients at day 90. **Conclusions:** Persistence of physical symptoms was high even at 90 days after discharge. Although the prevalence of symptoms of anxiety, depression, and PTSD was low, these symptoms persisted for three months, with a significant increase between the time points. This finding indicates the need to identify at-risk patients so that they can be given an appropriate referral at discharge.

Keywords: COVID-19; Anxiety; Depression; Stress disorders, post-traumatic; Quality of life; Critical care outcomes.

INTRODUCTION

During the first two waves of the COVID-19 pandemic in Brazil, approximately half of patients hospitalized with the disease were admitted to an ICU. During these two waves, 44% to 55% of these critically ill patients experienced ARDS and required invasive mechanical ventilation, and mortality rates were higher than 75%.⁽¹⁾

Overall, survivors of COVID-19 now amount to more than 400 million worldwide.⁽²⁾ There is a high probability that at least some of these patients experience new or worsened physical, cognitive, and mental health symptoms that persist after hospital discharge, especially those who were admitted to the ICU (post-intensive care syndrome).^(3,4) Severely ill patients with COVID-19 are often discharged home with some degree of functional disability.⁽⁵⁾ These patients will most likely benefit from meticulous follow-up with rehabilitation programs aiming at physical and neuropsychological recovery.⁽⁶⁾

Pre-COVID-19 epidemiological studies have shown that up to 75% of patients undergoing mechanical ventilation in the ICU suffer from delirium during their stay.⁽⁷⁾ COVID-19

patients have been proven to be especially vulnerable to delirium, with more than 54% of those developing it during the first 21 days of ICU in a multicenter cohort.⁽⁸⁾ As a result, these patients may be at an increased risk of long-term cognitive impairment.⁽⁹⁾

There is now evidence of the psychiatric implications of COVID-19 both during the acute phase and after hospital discharge.^(4,10) A single-center study has shown that sequelae of COVID-19 were common (in 49% of patients), and symptoms, such as anxiety or depression, were present in 26% 1 year after the diagnosis of COVID-19. Moreover, even patients who have physically recovered from symptoms are at risk of suffering from long-term mental health problems such as posttraumatic stress disorder (PTSD), anxiety, and depression, which can negatively impact their quality of life (QoL).^(11,12) However, most studies have evaluated either the persistence of symptoms or the QoL after COVID-19. Therefore, we aimed to describe the QoL and symptoms of anxiety, depression, and PTSD at 90 days after hospital discharge in COVID-19 patients using validated instruments.

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Financial support: None.

METHODS

Study design and participants

This is a single-center retrospective cohort study performed at the *Hospital Sírio-Libanês*, a private tertiary health care center in São Paulo, Brazil. We included all adult patients (≥ 18 years of age) with laboratory-confirmed COVID-19 by RT-PCR who were hospitalized and discharged alive between April of 2020 and April of 2021. All eligible patients received a telephone call at 30 and 90 days after hospital discharge and were invited to answer specific questions on their health status. This telephone follow-up interview was part of an institutional initiative to evaluate outcomes for COVID-19 patients and generate benchmarking and research data. The study protocol was approved by the local research ethics committee (*Hospital Sírio-Libanês*, approval number CAAE 51460021.6.0000.5461), which waived the need for informed consent.

Data collection during hospital-stay

The following demographic and clinical data were collected during hospital stay: age, sex, symptoms at admission, level of education, comorbidities, need for ICU admission, hospital/ICU length of stay (LOS), respiratory support (oxygen therapy, high flow nasal cannula, noninvasive mechanical ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation), hemodynamic support (vasopressors, intra-aortic balloon pump, and extracorporeal membrane oxygenation), nosocomial infections, treatments (antibiotics, corticosteroids, and others), need for tracheostomy, use of psychological support, need for physical rehabilitation, and vital status at hospital discharge.

30- and 90-day follow-up of COVID-19 survivors

A structured telephone interview questionnaire was administered twice (at 30 and 90 days after hospital discharge). The questionnaire contained questions on demographics, persistence of symptoms, need for oxygen therapy, need for dialysis, need for specific medical or rehabilitation care, return to work, among others.

Three specific validated questionnaires were also administered. To assess the quality of life, including usual activities of daily living, we used the EuroQol Group 5-Dimension 3-Level questionnaire (EQ-5D-3L),^(13,14) which has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are scored on a categorical scale ranging from 1 to 3, where 1 indicates no problem, 2 indicates some problems, and 3 indicates a severe problem. To screen for depression, we administered the Patient Health Questionnaire-2 (PHQ-2),^(15,16) a two-item questionnaire about the frequency of depressed mood and anhedonia in the past two weeks, ranging from 0 to 6 (scores ≥ 3 indicate a high likelihood of major depression). To screen for anxiety, we administered the Generalized

Anxiety Disorder-2 (GAD-2),⁽¹⁷⁾ a two-item questionnaire about the frequency of anxiety and worrying symptoms in the past two weeks, ranging from 0 to 6 (scores ≥ 3 indicate a high likelihood of generalized anxiety disorder). Finally, PTSD was defined according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria.⁽¹⁸⁾

Statistical analysis

Absolute and relative frequencies were used for qualitative variables and mean \pm standard deviation or median (IQR), as appropriate, was used to describe quantitative characteristics. The association with the outcomes of qualitative variables was assessed using the chi-square test or exact tests (Fisher's exact test or likelihood ratio), and that of quantitative variables was assessed with the Student's t-test. The analyses were performed with R (R version 4.0.2) and R Studio version 1.3.959 (The R Foundation for Statistical Computing, Vienna, Austria). Significance was set at $p < 0.05$.

RESULTS

A total of 3,086 patients with PCR-confirmed COVID-19 were admitted to the *Hospital Sírio-Libanês* during the study period. Of these, 2,952 (95.7%) were discharged alive. The mean age of survivors was lower than that of nonsurvivors (58.6 ± 15.8 years vs. 80.8 ± 10.5 years; $p < 0.001$). Additionally, survivors had shorter hospital lengths of stay as compared with nonsurvivors—median: 9.0 (5.0-15.8) days vs. 25.0 (13.0-48.0) days; $p < 0.001$). A total of 735 (23.8%) of patients were admitted to the ICU with a median ICU length of stay of 10 (5-17) days, 396 (53.9%) of whom required invasive mechanical ventilation for a median of 10 (6-21) days. The in-hospital mortality of patients admitted to the ICU was 14.6%.

Of the 2,952 patients discharged alive, 1,122 (38.0%) completed the interview on both occasions (at 30 and 90 days after discharge), 670 (22.6%) completed only the first interview (day 30), and 346 (11.7%) completed only the second interview (day 90). A total of 2,138 (72.3%) of patients completed the interview at least once after hospital discharge (Figure 1). The characteristics of the patients included at each time point are described in Table 1. There was no statistically significant difference between the groups of patients who completed the interview at 30 days (30-day group), at 90 days (90-day group), and on both occasions (30+90-day group), except for the use of corticosteroids during hospital stay, which was lower in the 90-day group.

On day 30, 41.2% of non-ICU patients reported persistence of at least one physical symptom related to COVID-19 diagnosis. Although a significant decrease was shown on day 90, 30.3% of the patients reported persistence of symptoms ($p < 0.001$). This decrease was also evident in the patients who had been admitted to the ICU—56.9% and 37.8% reported persistence

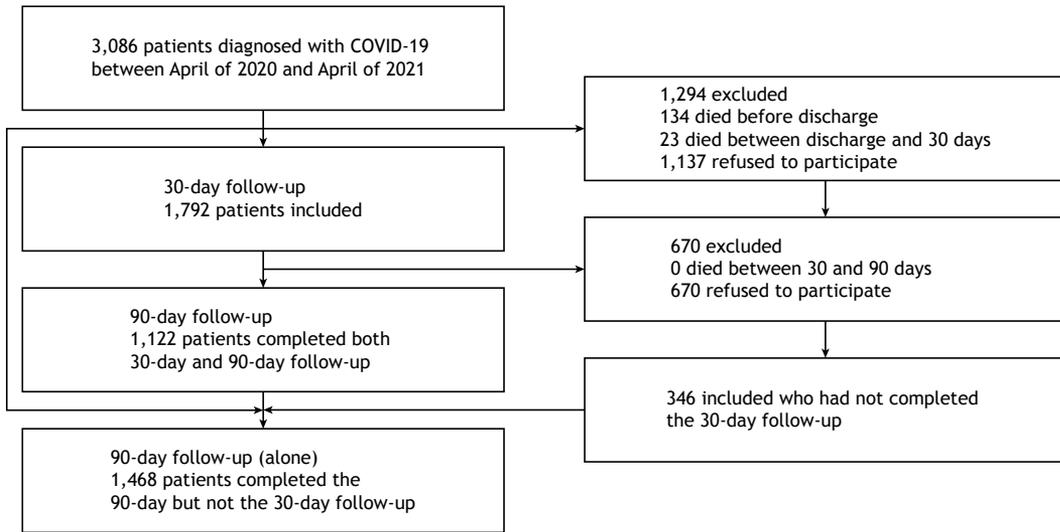


Figure 1. Flow chart of patient inclusion at 30- and 90-day follow-up interviews.

Table 1. Characteristics of the patients.^a

Characteristic	Group			p
	30-day (n = 1,792)	90-day (n = 1,468)	30 + 90 day (n = 1,122)	
Age, years	59.3 ± 15.8	59.6 ± 15.5	59.9 ± 15.6	0.59
Sex at birth, female	626 (34.9)	491 (33.4)	374 (33.3)	0.57
Ethnicity, White	1,571 (95.6)	1,306 (96.0)	990 (96.2)	0.52
Marital status, married	1,438 (81.1)	1,184 (81.5)	923 (83.2)	0.4
Higher education	1,509 (86.2)	1,257 (87.2)	963 (87.5)	0.38
Comorbidities	1,399 (78.1)	1,148 (78.2)	879 (78.3)	0.98
Arterial hypertension	702 (39.2)	587 (40.0)	456 (40.6)	0.72
Diabetes	381 (21.3)	324(22.1)	251 (22.4)	0.74
Cardiovascular disease	325 (18.1)	285 (19.4)	222 (19.8)	0.47
Cerebrovascular disease	48 (2.7)	39 (2.7)	30 (2.7)	0.99
Corticosteroids	1,385 (77.3)	1,015 (69.1)*,†	839 (74.8)	< 0.001
High-flow nasal cannula	323 (18.0)	227 (15.5)	188 (26.8)	0.15
NIV	446 (24.9)	327 (22.3)	278 (24.8)	0.17
Invasive MV	195 (10.0)	137 (9.3)	111 (9.9)	0.28
Vasopressor use	162 (9)	130 (8.9)	107 (9.5)	0.83
Psychological support during hospitalization	213 (11.9)	157 (10.7)	125 (11.2)	0.55
Rehabilitation support during hospitalization	1,414 (79.0)	1,127 (76.8)	875 (78.1)	0.34
Need of ICU admission	391 (21.8)	326 (22.2)	252 (22.4)	0.91
ICU LOS, days	15 [10-25]	15 [9-24]	16 [10-26]	0.15
Hospital LOS, days,	8 [5-14]	8 [5-13]	8 [5-14]	0.62

NIV: noninvasive ventilation; MV: mechanical ventilation, and LOS: length of stay. ^aValues expressed as n (%), mean ± SD, or median [IQR]. ^bOnly for patients admitted to the ICU. To correct for multiple comparison between two groups of study participants, we used a Bonferroni corrected p-value of 0.0167 for statistical significance. *p < 0.001 (90-day vs. 30-day). †p = 0.002 (90-day vs. 30+90-day).

of symptoms on day 30 and on day 90, respectively (p < 0.001; Table 2).

The temporal trends in the EQ-5D-3L domains, GAD-2 score, PHQ-2 score, and other symptoms in non-ICU and ICU patients are shown in Table 2. Between 30 and 90 days after hospital discharge, the proportion of ICU patients with mobility problems decreased (from 31.6% to 21.0%, p = 0.003), as did the proportion of ICU patients with problems in performing usual activities

(from 21.3% to 14.5%; p = 0.047), whereas there was no difference in the self-care and pain/discomfort domains of the EQ-5D-3L. Non-ICU patients had similar mobility, self-care, and usual activities domain results, but there was a decrease in the proportion of non-ICU patients without pain or discomfort (from 92.3% to 84.1%; p < 0.001) between 30 and 90 days after hospital discharge. In both the ICU and non-ICU groups, there was a decrease in the number of patients

Table 2. Outcomes at 30 days and at 90 days after discharge.

Outcome	Total sample (n = 2,138)		Group			
	30-day	90-day	p	Non-ICU	ICU	p
EQ-5D-3L						
Mobility			0.1	< 0.001	< 0.001	< 0.001
I have no problems in walking about	1,458/1,783 (81.8%)	1,237/1,462 (84.6%)		1,192/1,394 (85.5%)	266/389 (68.4%)	981/1,138 (86.2%)
I have some problems in walking about	292/1,783 (16.4%)	202/1,462 (13.8%)		184/1,394 (13.2%)	108/389 (27.8%)	146/1,138 (12.8%)
I am confined to bed	33/1,783 (1.8%)	23/1,462 (1.6%)		18/1,394 (1.3%)	15/389 (3.9%)	11/1,138 (1%)
Self-care						
I have no problems with self-care	1,640/1,783 (92%)	1,347/1,463 (92.1%)	0.87	1,306/1,394 (93.7%)	334/389 (85.9%)	1,062/1,138 (93.3%)
I have some problems washing or dressing myself	104/1,783 (5.8%)	81/1,463 (5.5%)		66/1,394 (4.7%)	38/389 (9.8%)	58/1,138 (5.1%)
I am unable to wash or dress myself	39/1,783 (2.2%)	35/1,463 (2.4%)		22/1,394 (1.6%)	17/389 (4.4%)	18/1,138 (1.6%)
Usual activities						
I have no problems with performing my usual activities	1,565/1,781 (87.9%)	1,289/1,461 (88.2%)	0.95	1,258/1,391 (90.4%)	307/389 (78.7%)	1,012/1,137 (89%)
I have some problems with performing my usual activities	178/1,781 (10%)	142/1,461 (9.7%)		111/1,391 (8%)	67/389 (17.2%)	107/1,137 (9.4%)
I am unable to perform my usual activities	38/1,781 (2.1%)	30/1,461 (2.1%)		22/1,391 (1.6%)	16/389 (4.1%)	18/1,137 (1.6%)
Pain/Discomfort						
I have no pain or discomfort	1,623/1,772 (91.69%)	1,223/1,455 (84.1%)	<0.001	1,279/1,386 (92.3%)	344/386 (88.4%)	953/1,133 (84.1%)
I have moderate pain or discomfort	134/1,772 (7.6%)	198/1,455 (13.6%)		99/1,386 (7.1%)	35/386 (9%)	153/1,133 (13.5%)
I have extreme pain or discomfort	15/1,772 (0.8%)	34/1,455 (2.3%)		8/1,386 (0.6%)	7/386 (1.8%)	27/1,133 (2.4%)
Anxiety/Depression						
I am not anxious or depressed	1,529/1,765 (85.7%)	1,151/1,451 (79.4%)	< 0.001	1,198/1,379 (86.9%)	331/386 (85.1%)	902/1,130 (79.8%)
I am moderately anxious or depressed	195/1,765 (11%)	256/1,451 (17.6%)		149/1,379 (10.8%)	46/386 (11.8%)	192/1,130 (17%)
I am extremely anxious or depressed	41/1,765 (2.3%)	44/1,451 (3%)		32/1,379 (2.3%)	9/386 (2.3%)	36/1,130 (3.2%)

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Table 3. Patients who completed the questionnaires at 30 and 90 days after discharge (n = 1,122).^a

	Total			Group					
	(n = 1,122)			30-day			90-day		
	30 days	90 days	p	Non-ICU	ICU	p	Non-ICU	ICU	p
EQ-5D-3L									
Mobility	0.112			< 0.001			< 0.001		
I have no problems in walking about	918 (82.2)	944 (84.5)		746 (85.9)	174 (69.3)		746 (85.9)	201 (79.8)	
I have some problems in walking about	175 (15.7)	152 (13.6)		111 (12.8)	64 (25.5)		113 (13.0)	39 (15.5)	
I am confined to bed	24 (2.1)	21 (1.9)		11 (1.3)	13 (5.2)		9 (1.0)	12 (4.8)	
Self-Care	0.584			< 0.001			< 0.001		
I have no problems with self-care	1,030 (92.2)	1,025 (91.8)		817 (94.2)	215 (85.3)		807 (93.0)	221 (87.7)	
I have some problems washing or dressing myself	61 (5.5)	60 (5.4)		37 (4.3)	24 (9.5)		46 (5.3)	14 (5.6)	
I am unable to wash or dress myself	26 (2.3)	32 (2.9)		13 (1.5)	13 (5.2)		15 (1.7)	17 (6.7)	
Usual activities	0.803			< 0.001			0.011		
I have no problems with performing my usual activities	975 (87.4)	985 (88.3)		784 (90.4)	194 (77.0)		774 (89.3)	214 (84.9)	
I have some problems with performing my usual activities	117 (10.5)	105 (9.4)		70 (8.1)	47 (18.7)		79 (9.1)	26 (10.3)	
I am unable to perform my usual activities	24 (2.2)	26 (2.3)		13 (1.5)	11 (4.4)		14 (1.6)	12 (4.8)	
Pain/Discomfort	< 0.001			0.057			0.800		
I have no pain or discomfort	1,020 (92.3)	927 (83.9)		804 (93.2)	222 (89.2)		722 (83.4)	212 (85.1)	
I have moderate pain or discomfort	75 (6.8)	150 (13.6)		54 (6.3)	22 (8.8)		121 (14.0)	31 (12.4)	
I have extreme pain or discomfort	10 (0.9)	28 (2.5)		5 (0.6)	5 (2.0)		23 (2.7)	6 (2.4)	
Anxiety/Depression	< 0.001			0.700			0.452		
I am not anxious or depressed	971 (88.2)	869 (78.9)		760 (88.4)	218 (87.2)		688 (79.8)	190 (76.3)	
I am moderately anxious or depressed	114 (10.4)	201 (18.3)		89 (10.3)	27 (10.8)		150 (17.4)	52 (20.9)	
I am extremely anxious or depressed	16 (1.5)	31 (2.8)		11 (1.3)	5 (2.0)		24 (2.8)	7 (2.8)	
GAD-2 ≥ 3	17 (1.9)	50 (5.6)	< 0.001	15 (2.0)	4 (2.2)	0.777	42 (5.6)	9 (4.7)	0.623
PHQ-2 ≥ 3	25 (2.8)	66 (7.4)	< 0.001	19 (2.5)	6 (3.2)	0.610	48 (6.4)	18 (9.4)	0.144
Persistence of any physical symptoms related to the COVID-19 diagnosis	509 (45.9)	364 (32.9)	< 0.001	367 (42.5)	143 (56.7)	< 0.001	264 (30.6)	102 (40.5)	0.003
Post-traumatic stress disorder									
Repetitive and disturbing thoughts, memories or images	19 (2.1)	52 (5.8)	< 0.001	13 (1.7)	8 (4.3)	0.049	33 (4.4)	22 (11.4)	< 0.001
Physical symptoms related to the hospitalization	26 (2.9)	22 (2.5)	0.608	20 (2.7)	6 (3.2)	0.663	13 (1.7)	12 (6.3)	0.001

EQ-5D-3L: EuroQol Group 5-Dimension 3-Level questionnaire; GAD-2: Generalized Anxiety Disorder-2; and PHQ-2: Patient Health Questionnaire-2. ^aValues expressed as n (%).

prevalence of depression and anxiety of 45-47% after COVID-19 infection.⁽²²⁾ Several reasons could underlie this difference. First, many studies used the

EuroQol-5D to determine the prevalence of anxiety and depression, while we used the GAD-2 and PHQ-2 questionnaires. When measured by the EuroQol-5D

(20.5%), the prevalence of anxiety and depression was similar to that in the study by Huang et al.,⁽⁴⁾ but still considerably lower than that described by Deng et al.⁽²²⁾ Second, we studied patients from a hospital that serves a population of high socioeconomic status, with full access to health care both before and after hospitalization. The differences in prevalence may result from differences in accessibility to health care.

Our study has several limitations. First, it was a single-center, retrospective study in a hospital which is not representative of most of Brazilian health care institutions. Thus, the generalizability of our findings is limited, at least to most people living in low- and middle-income countries. Second, we used an administrative database not originally designed for research purposes to assess 30- and 90-day outcomes. However, this database is systematically fed by dedicated personnel with previous training on administering different questionnaires over the phone. Third, we could only obtain 90-day follow-up interviews of two-thirds of the patients who participated in the telephone interview at 30 days. However, in a sensitivity analysis in which we restricted all comparisons to patients who completed the interviews on both occasions, the results were not appreciably altered. Finally, we used simplified versions of questionnaires for anxiety (GAD-2) and depression (PHQ-2), which are mainly used as screening, not diagnostic tools.

In conclusion, we found that hospital admission due to COVID-19 seems to be associated with a relatively

low prevalence of anxiety and depression 90 days after hospital discharge. However, of concern is the fact that there was an increase over time in the prevalence of anxiety and depression 90 days after discharge, which points to the necessity to identify patients at risk of developing anxiety/depression so that they can be given an appropriate referral at discharge.

ACKNOWLEDGMENTS

We would like to thank the entire team of the Hospital Outcomes Department for their effort and engagement, which made this study possible.

AUTHOR CONTRIBUTIONS

RRLF, ELVC, and BMT: formal analysis; methodology; writing of the original draft; and review and editing of the manuscript. LVC and MMS: data curation; project administration; and review and editing of the manuscript. CBL, TCN, LFC, LPJ, and JMVJ: conceptualization; formal analysis; methodology; project administration; and review and editing of the manuscript. CVM, LCPA, MSO, and LUT: reviewing/editing the manuscript.

All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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