Long-Term Symptoms among COVID-19 Survivors in Prospective Cohort Study, Brazil

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We conducted a prospective cohort study in a population with diverse ethnic backgrounds from Brazil to assess clinically meaningful symptoms after surviving coronavirus disease. For most of the 175 patients in the study, clinically meaningful symptoms, including fatigue, dyspnea, cough, headache, and muscle weakness, persisted for ≥120 days after disease onset.

Understanding is growing that coronavirus disease (COVID-19) can evolve and continue to cause prolonged symptoms, characterizing the post–COVID-19 condition (*1*–*3*). Potential implications go beyond effects on individual patients and might represent an additional burden on healthcare services and social security, which are both already affected by the pandemic. Therefore, learning more about the long-term repercussions of the disease among different populations is essential. This study aimed to describe the occurrence of long-term physical, psychological, and social consequences among patients who survived COVID-19 and received follow-up care at a post–COVID-19 outpatient clinic at a university hospital in Brazil.

The Study

This prospective cohort study (RECOVIDA) was performed among patients attending a post–COVID-19 outpatient clinic at Ribeirão Preto Medical School University Hospital, Ribeirão Preto, Brazil (*4*). The institutional review board approved the research protocol.

All adults with PCR-confirmed COVID-19 with symptom onset during February 1–December 31, 2020, who attended follow-up appointments at the study clinic were eligible. Most participants (85.7%) had been discharged after being hospitalized for COVID-19. The remaining participants (14.3%) were mostly healthcare workers from the study facility. No participants had been previously vaccinated against COVID-19. Patients were classified into 3 groups according to the World Health Organization (WHO) severity classification of COVID-19: mild/moderate, severe, and critical (*5*) (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/28/3/21-2020-App1.pdf).

This study was exploratory, and sample size was established through convenience. We aimed to include all patients who attended the clinic during the study period and agreed to participate.

Participants were recruited just before the scheduled medical consultation. After the informed consent form was signed, we performed a structured interview and a brief physical examination. We obtained secondary data from patients' electronic health records. Laboratory and imaging tests were performed at the attending physician's clinical discretion. We collected study data by using the Research Electronic Data Capture platform (*6*).

We collected information on economic and demographic social profile, medical history, date of symptom onset, hospitalization data, laboratory and imaging test results, persistent symptoms, and quality of life. We assessed quality of life by using the WHO Quality of Life questionnaire (*7*–*9*) (Appendix). The date of symptom onset was used as the reference for follow-up.

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We performed statistical procedures by using Minitab 19.2 (https://www.minitab.com) and Stata version 9 (https://www.stata.com). We used odds ratios, 95% CIs, and Fisher exact tests to verify the association between the persistence of symptoms and the severity of disease.

During the study period, 297 patients had a follow-up medical consultation scheduled at the outpatient clinic. We included 175 patients in this study (Table 1; Figure). In this sample, 20% of participants had illness that was considered mild/moderate, 45.7% were severe, and 34.3% were critical.

After COVID-19, 80% of the patients experienced persistent symptoms; the 5 most prevalent were fatigue, dyspnea, cough, headache, and loss of overall muscle strength. Compared with the mild/moderate group, patients from the critical group more frequently experienced headaches, change in skin sensitivity, hypogeusia, hyposmia, and loss of muscle strength (Table 2, https://wwwnc.cdc.gov/EID/article/28/3/21-2020-T2.htm).

Regarding quality of life after COVID-19, physical health was more severely affected than the other 3 domains evaluated by the WHO Quality of Life questionnaire (psychological, social relationships, and environmental). Moreover, the comparative evaluation before and after COVID-19 showed a decrease from 81.1% to 68.4% in the percentage of patients who believed that their quality of life was good or very good and an increase from 2.3% to 6.4% of those who believed that their quality of life was poor or very poor. Despite these changes, more than half of patients (56.7%) were satisfied with their current health status at the time of evaluation (Appendix).

Table 1. Baseline clinical and demographic characteristics among 175 patients surviving the acute phase of COVID-19, Ribeirão Preto, Brazil*

Characteristic	COVID-19 severity			
	Mild/moderate, n = 35 (20%)	Severe, n = 80 (45.7%)	Critical, n = 60 (34.3%)	Total, n = 175
Sex				
M	7 (20)	36 (45)	42 (70)	85 (48.6)
F	28 (80)	44 (55)	18 (30)	90 (51.4)
Mean age, y (SD)	44.9 (±10.3)	57.1 (±15.3)	54.2 (±13.2)	53.7 (±14.4)
Ethnic background†				
White (Caucasian or Latin)	19 (54.3)	36 (45)	25 (41.7)	80 (45.7)
Afro-American (Brown)	10 (28.6)	34 (42.5)	26 (43.3)	70 (40)
Afro-American (Black)	6 (17.1)	8 (10)	6 (10)	20 (11.4)
Asiatic	0	1 (1.3)	2 (3.3)	3 (1.7)
Brazilian Indigenous	0	1 (1.3)	1 (1.7)	2 (1.1)
Mean years of schooling (SD)	13.4 (±5.7)	8.1 (±5.5)	8.3 (±5.4)	9.2 (±5.9)
Mean income/person, USD (SD)‡	407.33 (±313.60)	273.01 (±295,85)	229.33 (±210.40)	285.57 (±279.56)
Median	364.01	200.21‡	182.01‡	216.77‡
Currently works as a health professional				
Yes	23 (65.7)	8 (10)	2 (3.3)	33 (18.9)
No	12 (34.3)	72 (90)	58 (96.7)	142 (81.1)
Mean BMI (SD)§	31.8 (±7.5)	32.1 (±7.3)§	31.1 (±7.5)	31.7 (±7.3)§
BMI ≥30§	17 (48.6)	44 (56.4)§	23 (38.3)	84 (48.6)§
Underlying conditions				
None	16 (45.7)	16 (20)	10 (16.7)	42 (24.0)
Hypertension	9 (25.7)	35 (43.8)	21 (35)	65 (37.1)
Diabetes	1 (2.9)	26 (32.5)	22 (36.7)	49 (28.0)
Dyslipidemia	2 (5.7)	12 (15)	12 (20)	26 (14.8)
Heart problems (other than hypertension)	1 (2.9)	10 (12.5)	8 (13.3)	19 (10.9)
Rhinitis or sinusitis	3 (8.6)	7 (8.8)	7 (11.7)	17 (9.7)
Cancer	1 (2.9)	9 (11.3)	1 (1.7)	11 (6.3)
Thyroid problems	0	4 (5)	6 (10)	10 (5.7)
Depression or anxiety	1 (2.9)	6 (7.5)	3 (5)	10 (5.7)
Smoking				
Current	0 (0)	2 (2.5)	0	2 (1.1)
Previous	2 (5.71)	18 (22.5)	19 (31.7)	39 (22.3)
Hospitalization				
Yes	10 (28.6)	80 (100)	60 (100)	150 (85.7)
No	25 (71.4)	0	0	25 (14.3)
Mean duration of hospitalization, d (SD)	5 (±4)	9.9 (±5.2)	24.1 (±11.1)	15.3 (±10.9)
Median	4	9	20.5	12

*Values are no. (%) except as indicated. BMI, body mass index; COVID-19, coronavirus disease.
†Ethnic background information was self-reported and consisted of Latin American, Caucasian, Afro-American, Asian, and Brazilian indigenous persons.
‡$1 US = R $5,49. Data on financial income by person were missing for 3 participants.
§BMI data were missing for 2 participants.

Conclusions

We describe the long-term repercussions of COVID-19 among a sample of patients in Brazil from diverse social and ethnic backgrounds who survived acute infection and attended a follow-up ambulatory clinic appointment. We identified that most patients experienced ≥1 symptom for ≥120 days after the onset of disease. This finding also applies to patients who had a mild or moderate form of COVID-19. These symptoms negatively affected the patients' quality of life; fatigue was the most common symptom, followed by dyspnea and cough.

The clinical picture we describe here, in a population with a mixed ethnic background consisting of Latin American, Caucasian, Afro-American, Asian, and Brazilian indigenous persons, is similar to those encountered in other parts of the world, mainly in Caucasian or Asian populations (*1*,*10*–*12*). Some persistent symptoms found in our study, such as altered skin sensitivity and muscle weakness, primarily affected the patients whose illness was critical, and this finding could be more related to their stay in the intensive care unit than to the COVID-19 itself (*13*).

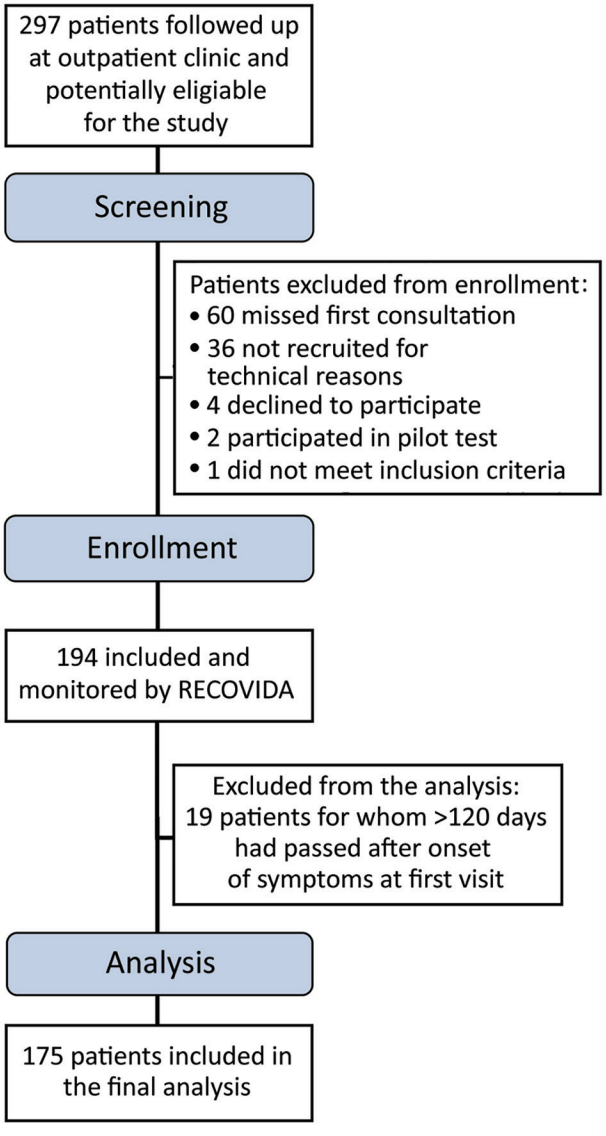

Figure. Flowchart of screening and inclusion of coronavirus disease survivors with long-term symptoms in prospective cohort study, Ribeirão Preto, Brazil.

Several possible pathophysiological explanations for the persistence of symptoms after COVID-19 have been proposed. The most commonly elicited in the literature are direct viral toxicity, endothelial damage, dysregulated immune response, hyperinflammation, hypercoagulability, and poor adaptation of the angiotensin-converting enzyme 2. So far, the actual mechanisms behind this scenario are not entirely understood and deserve further evaluation (*1*,*10*–*13*). Our sample identified that respiratory and heart rates were significantly higher in the patients whose illness was critical, possibly indicating impairment of autonomic function in these patients (*14*,*15*).

We highlight the need to study the persistent symptoms of patients with COVID-19, given the implications for the healthcare system and social security, both of which are already profoundly affected by the pandemic itself. From this perspective, most persons with COVID-19 requiring medical consultation would not be expected to recover fully or resume working immediately after the end of the disease's acute phase. Instead, they will require a prolonged interdisciplinary healthcare approach focused on physical, mental, and social rehabilitation (*1*,*10*–*15*).

We did not perform genetic sequencing of the severe acute respiratory syndrome coronavirus 2 detected in our patients. Therefore, we cannot evaluate whether different virus variants might affect the occurrence of long-term symptoms among survivors differently.

One of the strengths of our study was our systematic follow-up on participants with prespecified instruments, which ensured high-quality and consistent data. A novelty of the study was that we were able to recruit patients who had mild or moderate COVID-19, which is less common in other studies.

A limitation of our study was the small sample size; the results therefore cannot be generalized to the wider population. Another limitation is the lack of a control group for comparison and selection bias. Most likely, many patients who did not attend a medical consultation after being discharged from the hospital experienced only mild or no prolonged

symptoms at all. The same can be said for healthcare workers who were affected by COVID-19 but did not seek medical consultation. The actual prevalence of long-term symptoms among the reference population is unknown, and our data probably overestimate that prevalence.

In summary, it is likely that a substantial proportion of patients surviving COVID-19 will experience long-term symptoms requiring prolonged care, even after mild to moderate disease. These symptoms might negatively affect patients' quality of life and represent an additional burden for healthcare services and social security.

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References

1. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27:601–15. https://doi.org/10.1038/s41591-021-01283-z
2. World Health Organization. Emergency use ICD codes for COVID-19 disease outbreak [cited 2021 May 3]. https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak
3. Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, et al. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. JAMA. 2021;325:2015–6. https://doi.org/10.1001/jama.2021.5612
4. Instituto Brasileiro de Geografia e Estatística. Geographic and statistical overview of Ribeirão Preto [in Portuguese] [cited 2021 Mar 29]. https://cidades.ibge.gov.br/brasil/sp/ribeirao-preto/panorama
5. World Health Organization. Global COVID-19 clinical platform case report form (CRF) for post COVID condition (Post COVID-19 CRF) [cited 2020 Oct 20]. https://cdn.who.int/media/docs/default-source/3rd-edl-submissions/who_crf_postcovid_feb9_2021.pdf
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–81. https://doi.org/10.1016/j.jbi.2008.08.010
7. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med. 1998;28:551–8. https://doi.org/10.1017/S0033291798006667
8. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Application of the Portuguese version of the abbreviated instrument of quality of life WHOQOL-bref [in Portuguese]. Rev Saude Publica. 2000;34:178–83. https://doi.org/10.1590/S0034-89102000000200012
9. Pedroso B, Pilatti LA, Gutierrez GL, Picinin CT. Calculating WHOQOL-BREF scores and descriptive statistics through Microsoft Excel [in Portuguese]. Revista Brasileira de Qualidade de Vida. 2010;2:31–6. https://doi.org/10.3895/S2175-08582010000100004
10. Centers for Disease Control and Prevention. COVID-19: Long-term effects [cited 2021 May 3]. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html
11. Nature. Long COVID: let patients help define long-lasting COVID symptoms [editorial]. Nature. 2020;586:170. https://doi.org/10.1038/d41586-020-02796-2
12. Nehme M, Braillard O, Chappuis F, Courvoisier DS, Guessous I; CoviCare Study Team. Prevalence of symptoms more than seven months after diagnosis of symptomatic COVID-19 in an outpatient setting. Ann Intern Med. 2021;174:1252–60. https://doi.org/10.7326/M21-0878
13. Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, et al. Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study. Clin Infect Dis. 2021 Jul 5 [Epub ahead of print].
14. Antwi-Amoabeng D, Beutler BD, Singh S, Taha M, Ghuman J, Hanfy A, et al. Association between electrocardiographic features and mortality in COVID-19 patients. Ann Noninvasive Electrocardiol. 2021;26:e12833. https://doi.org/10.1111/anec.12833
15. Dixit NM, Churchill A, Nsair A, Hsu JJ. Post-acute COVID-19 Syndrome and the cardiovascular system: what is known? Am Heart J Plus. 2021;5:100025.

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Appendix

Variables of Interest

• Demographic, social, and economic data (age, sex, ethnicity, years of schooling, financial income/person)

• Body mass index (kg/m^2)

• Underlying conditions including chronic heart disease (not hypertension); hypertension; diabetes; chronic lung disease; asthma; tuberculosis; chronic kidney disease; chronic liver disease; chronic neurologic disorder; asplenia; cancer; depression/anxiety; HIV; gastrointestinal disease/gastritis; dyslipidemia; thyroid disease; hearing problem or deficit; vision problem or deficit; stroke; prostatic hyperplasia; transplant; previous surgery; obesity (body mass index >30)

• Smoking history

• Hospitalization data

• Laboratory tests, including hemoglobin, hematocrit, lymphocytes, leukocyte count, platelet count, C-reactive protein, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase), D-dimer, urea, and creatinine.

• Imaging exam: computed tomography

The chest computed tomography findings regarding the degree of severity and impairment of the lungs, such as those identifying viral pneumonia, were evaluated through consensus of 2 radiologists. Severity was evaluated according to the recommendations of the French Society of Thoracic Imaging.

Abbreviated Version of the WHO Quality of Life Questionnaire (WHOQOL-Bref)

The WHOQOL Group created the WHO Quality of Life Questionnaire (WHOQOL-Bref) to develop a tool with satisfactory psychometric characteristics to assess quality of life in a shorter time (*1*–*3*).

This instrument is composed of 26 questions; the first 2 questions comprise a self-assessment of quality of life, while the remaining questions represent the facets of each of the domains evaluated: physical, psychological, social, and environmental relationships. The scores of the domains are calculated by summing the mean scores of "n" questions that make up each domain. The result is multiplied by 4, being represented on a scale from 4 to 20, where a score closer to 20 represents a better and more satisfactory overall quality of life and that of each domain evaluated (*1*–*3*).

References

1. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med. 1998;28:551–8. PubMed https://doi.org/10.1017/S0033291798006667

2. Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Application of the Portuguese version of the abbreviated instrument of quality of life WHOQOL-bref [in Portuguese]. Rev Saude Publica. 2000;34:178–83. PubMed https://doi.org/10.1590/S0034-89102000000200012

3. Pedroso B, Pilatti LA, Gutierrez GL, Picinin CT. Calculating WHOQOL-BREF scores and descriptive statistics through Microsoft Excel [in Portuguese]. Revista Brasileira de Qualidade de Vida. 2010;2:31–6. https://doi.org/10.3895/S2175-08582010000100004

Appendix Table 1. World Health Organization classification of severity of the presentation of COVID-19*

WHO Clinical Classification	On the basis of available clinical records	On the basis of self-report, if clinical records are not available
Mild	No hypoxia or pneumonia	Did not receive oxygen
Moderate	Clinical signs of nonsevere pneumonia AND SpO_2>90% on room air	Did not receive oxygen
Severe	Adults/adolescents: Clinical signs of severe pneumonia AND SpO_2 ≥30 breaths/min; Children: Clinical signs of severe pneumonia AND ≥1 of the following: central cyanosis; OR SpO_2<90%; OR severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing); OR general danger sign(s) (inability to breastfeed or drink, lethargy or unconsciousness, convulsions)	Received oxygen (or said they needed it, but it was not available)
Critical	ARDS; OR sepsis/septic shock; OR pulmonary embolism, acute coronary syndrome, acute stroke; OR multi-inflammatory syndrome in children and adolescents temporally related to COVID-19	Received invasive ventilation (or max available respiratory support)

*Taken from World Health Organization Global COVID-19 Clinical Platform Case Report Form for Post COVID condition (Post COVID-19 CRF), https://cdn.who.int/media/docs/default-source/3rd-edl-submissions/who_crf_postcovid_feb9_2021.pdf?sfvrsn = 76afd14_1&download = true. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease; SpO2, oxygen saturation; WHO, World Health Organization.

Appendix Table 2. Data regarding previous hospital admission among 150 patients surviving the acute phase of COVID-19, Ribeirão Preto, Brazil, 2021

Hospitalization Data	Total, n = 150
Ventilatory support/oxygen therapy	
Yes	139 (92.7)
No	11 (7.3)
Admitted to the ICU	76 (50.6)
Mechanical ventilation	
Yes	57 (38.0)
No	93 (62.0)
Mean duration of intubation, d (SD)	13.5 (±9)
Median	10
Need for vasoactive drugs/vasopressors	42 (28.0)
Need for hemodialysis	12 (8.0)
Any complication during hospitalization	82 (54.6)
Most common complications during hospitalization	
Acute kidney injury	23 (15.3)
Bacterial pneumonia	20 (13.3)
Thromboembolic phenomena	14 (9.3)
Shock	12 (8.0)
Cardiac arrhythmia	7 (4.6)
Anemia	6 (4.0)
Convulsion	3 (2.0)
Pericarditis/myocarditis	2 (1.3)
CT exam during hospitalization	Total, n = 61
Viral pneumonia on CT	
Consistent	56 (91.8)
Nonsuggestive	2 (3.3)
Indeterminate	3 (4.9)
Severity on CT (SIT)	Total, n = 59†
Absent or minimal (<10%)	3 (5.1)
Moderate (10%–25%)	9 (15.2)
Extensive (25%–50%)	26 (44.1)
Severe (50%–75%)	21 (35.6)
Critical (>75%)	0

*Values are no. (%) except as indicated. CT, computed tomography; ICU, intensive care unit; SIT, French Society of Thoracic Imaging.
†In the 2 cases where CT results were considered nonsuggestive of viral pneumonia, the severity was not evaluated.

Appendix Table 3. Long-term clinical and laboratory parameters of COVID-19 survivors, Ribeirão Preto, Brazil, 2021*

	COVID-19 Severity				
Clinical Parameter	Mild/Moderate, n = 35	Severe, n = 80	Critical, n = 60	p value†	Total, n = 175
Respiratory frequency (n = 174)‡					
Mean	17.3‡	19.2	20		19.1
Min–Max	12–34	10–32	12–32		10–34
Median (IQR)	16.5 (14–18.5)	18 (16–22)	20 (16–23.75)	0.012§	18 (16–22)
Oxygen saturation in ambient air, n = 174‡					
<92%	0/35	1/79‡	0/60		1/174
92%–94%	0/35	5/79	2/60		7/174
≥95%	35/35	73/79	58/60		166/174
Median (IQR)	98 (97–99)	98 (96–99)	98 (97–99)	0.088	98 (97–99)
Heart rate, n = 173‡					
Mean	77.8‡	78.2‡	87.7		81.4
Min-max	50–103	50–112	53–117		50–117
Median (IQR)	78.5 (69.5–84.5)	78 (71–85)	87.5 (77.25–98.75)	>0.001§	81 (72–88)
Blood pressure, n = 172‡					
SBP≥140 mm Hg	7/33‡	20/79‡	15/60		42/172
DBP≥90 mm Hg	9/33	28/79	21/60		58/172
SBP≤100 mm H	5/33	13/79	10/60		28/172
DBP≤70 mm Hg	9/33	31/79	23/60		63/172
Median SBP (IQR)	120 (110–130)	120 (110–140)	120 (110–137.5)	0.623	120 (110–130)
Median DBP (IQR)	80 (70–90)	80 (70–90)	80 (70–90)	0.943	80 (70–90)
Laboratory tests	Mild/Moderate, n = 19	Severe, n = 56	Critical, n = 37	p value†	Total, n = 112
Hemoglobin (ref: 13.9–17.7 g/dL)					
Median (IQR)	13.7 (12.4–14.3)	13 (12.2–14.2)	12.9 (10.8–13.9)	0.396	13 (12.1–14.1)
Hematocrit (ref: 39.6%–51.8%)					
Median (IQR)	42 (37–43)	40 (37–42)	40 (34–43)	0.668	40 (36–42)
Leukocytes (ref: 3.79–10.33 × 10^3/µL)					
Median (IQR)	6.7 (5–7.8)	6.4 (5.2–8.3)	7.7 (6.3–9.7)	0.065	6.8 (5.5–8.6)
Lymphocytes (ref: 1.07–3.12 × 10^3/µL)					
Median (IQR)	1.8 (1.6–2.6)	1.7 (1.3–2)	2.2 (1.7–2.8)	0.001§	1.8 (1.4–2.4)
Platelets (ref: 166–389 × 10^3/µL)					
Median (IQR)	293 (219–337)	239 (191–332)	291 (233–374)	0.113	268 (202–341)
C-reactive protein (ref: <1.0 mg/dL)					
Median (IQR)	0.4 (0.4–1.6)	0.9 (0.4–2.3)	1.4 (0.4–2.9)	0.128	0.9 (0.4–2.3)
LDH (ref: 120–246 U/L)					
Median (IQR)	185.8 (178–237.8)	231.35 (204.2–270)	252.55 (202.25–310.05)	0.024§	236.8 (195.3–289.9)
AST (ref: <38.0 U/L)					
Median (IQR)	22 (16–32)	24.95 (20–34)	23.8 (18.2–29.9)	0.219	24 (18.5–33)
ALT (ref: 10–49 U/L)					
Median (IQR)	22 (12.5–44.5)	40.2 (25–62)	27.5 (17.95–48)	0.023§	35.7 (21–50.1)
D-dimer (ref: ≤0.5 UG/ml)					
Median (IQR)	0.37 (0.31–0.8)	0.73 (0.52–0.99)	0.92 (0.44–2.54)	0.021§	0.735 (0.41–1.27)
Urea (ref: 19–49 mg/dL)					
Median (IQR)	30.17 (24.4–37.24)	31.88 (25.47–40)	32.96 (24.8–40.87)	0.696	31.78 (25.02–40.76)
Creatinine (ref: 0.70–1.30 mg/dL)					
Median (IQR)	0.78 (0.73–0.96)	0.87 (0.75–0.97)	0.88 (0.74–0.95)	0.766	0.865 (0.735–0.96)

*ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease; DBP, diastolic blood pressure; IQR, interquartile range; LDH, lactate dehydrogenase; SBP, systolic blood pressure.
†P values calculated by using the Kruskal–Wallis test.
††Missing value.
§p<0.05.

Appendix Table 4. Results of the WHOQOL questionnaire domains (4–20 pts) in inclusion data of COVID-19 survivors, Ribeirão Preto, Brazil, 2021*

Domains	Mean	SD	Minimum value	Maximum value
Physical domain	12.63	1.86	7.43	17.71
Psychological domain	13.89	1.94	7.33	18.00
Social relationships domain	15.72	2.78	4.00	20.00
Environment domain	14.42	2.17	8.50	19.50
Self-assessment of quality of life	14.49	2.89	4.00	20.00
Total	13.97	1.65	8.62	18.15

*COVID-19, coronavirus disease; WHOQOL, World Health Organization Quality of Life.

Appendix Table 5. Results of WHOQOL questionnaire self-evaluation inclusion data of COVID-19 survivors, Ribeirão Preto, Brazil, 2021

Quality of Life Assessment	Before COVID-19, n = 175	After COVID-19, n = 171
Very poor	1 (0.6)	5 (2.9)
Poor	3 (1.7)	6 (3.5)
Neither poor nor good	29 (16.6)	43 (25.2)
Good	113 (64.5)	96 (56.1)
Very good	29 (16.6)	21 (12.3)
Satisfaction with your health (in the past 15 d)		
Very dissatisfied		4 (2.3)
Dissatisfied		20 (11.7)
Neither satisfied nor dissatisfied		50 (29.3)
Satisfied		78 (45.6)
Very satisfied		19 (11.1)

*Values are no. (%). COVID-19, coronavirus disease; WHOQOL, World Health Organization Quality of Life.