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In-hospital mortality and severe outcomes after hospital discharge due to COVID-19: A prospective multicenter study from Brazil

Hugo Perazzo,[a]* Sandra W. Cardoso,[a] Maria Pia D. Ribeiro,[a] Rodrigo Moreira,[a] Lara E. Coelho,[a] Emilia M. Jalil,[a] André Miguel Japiassú,[a] Elias Pimentel Gouvêa,[a] Estevão Portela Nunes,[a] Hugo Boechat Andrade,[a] Luciano Barros Gouvêa,[a] Marcel Treptow Ferreira,[a] Pedro Mendes de Azambuja Rodrigues,[a] Ronaldo Moreira,[a] Kim Geraldo,[a] Lucilene Freitas,[a] Vinicius V. Pacheco,[a] Esau Custódio João,[b] Trevon Fuller,[b] Verônica Diniz Rocha,[c] Ceuci de Lima Xavier Nunes,[c] Tâmara Newman Lobato Souza,[d] Ana Luiza Castro Conde Toscano,[d] Alexandre Vargas Schwarzbold,[e] Helena Carolina Noal,[e] Gustavo de Araujo Pinto,[f] Paula Macedo de Oliveira Lemos,[f] Carla Santos,[g] Fernanda Carvalho de Queiroz Mello,[g] Valdilea G. Veloso,[a] Beatriz Grinsztejn,[a] and for the RECOVER-SUS Brasil Group [1]

[a]Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
[b]Hospital Federal dos Servidores do Estado, Rio de Janeiro, Brazil
[c]Instituto Couto Maia, Secretaria Estadual de Saúde da Bahia, Salvador, BA, Brazil
[d]Instituto de Infectologia Emilio Ribas, São Paulo, SP, Brazil
[e]Universidade Federal de Santa Maria, RS, Brazil
[f]Hospital Regional São José, SC, Brazil
[g]Complexo Hospital Universitário Clementino Fraga Filho — Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

Summary

Background We evaluated in-hospital mortality and outcomes incidence after hospital discharge due to COVID-19 in a Brazilian multicenter cohort.

Methods This prospective multicenter study (RECOVER-SUS, NCT04807699) included COVID-19 patients hospitalized in public tertiary hospitals in Brazil from June 2020 to March 2021. Clinical assessment and blood samples were performed at hospital admission, with post-hospital discharge remote visits. Hospitalized participants were followed-up until March 31, 2021. The outcomes were in-hospital mortality and incidence of rehospitalization or death after hospital discharge. Kaplan–Meier curves and Cox proportional-hazard models were performed.

Findings 1589 participants [54.5% male, age=62 (IQR 50-70) years; BMI=28.4 (IQR,24.9–32.9) Kg/m² and 51.9% with diabetes] were included. A total of 429 individuals [27.0% (95%CI,24.8–29.2)] died during hospitalization (median time 14 (IQR,9–24) days). Older age [vs<40 years; age=60–69 years-aHR=1.89 (95%CI,1.08–3.32); age=70–79 years-aHR=2.52 (95%CI,1.42–4.45); age≥80-aHR=2.90 (95%CI 1.54–5.47)]; noninvasive or mechanical ventilation at admission [vs facial-mask or none; aHR=1.69 (95%CI 1.30–2.19)]; SAPS-III score≥57 [vs<57; aHR=1.47 (95%CI 1.13–1.92)] and SOFA score≥10 [vs <10; aHR=1.51 (95%CI 1.08–2.10)] were independently associated with in-hospital mortality. A total of 65 individuals [6.7% (95%CI 5.3–8.4)] had a rehospitalization or death [rate=323 (95%CI 250–417) per 1000 person-years] in a median time of 52 (range 1–280) days post-hospital discharge. Age ≥ 60 years [vs <60, aHR=2.13 (95%CI 1.15–3.94)] and SAPS-III ≥57 at admission [vs <57, aHR=2.37 (95%CI 1.22–4.59)] were independently associated with rehospitalization or death after hospital discharge.

Interpretation High in-hospital mortality rates due to COVID-19 were observed and elderly people remained at high risk of rehospitalization and death after hospital discharge.

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Abbreviations: aHR, adjusted-hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase BMI, body mass index; CI, confidence interval; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; NIV, non-invasive ventilation; PD, person-days; PY, person-years; SAPS-III, simplified acute physiology score III; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, sequential organ failure assessment; REDCap, research electronic data capture; VIF, variance inflation factor; VOC, variant of concern; WHO, World Health Organization

*Corresponding author at: Laboratório de Pesquisa Clínica em DST e AIDS, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Av. Brasil, 4365, Rio de Janeiro CEP 21040-360, Brazil.
E-mail address: hugo.perazzo@ini.fiocruz.br (H. Perazzo).

[1] A full list of collaborators is provided at the end of the manuscript.

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Keywords: COVID-19; In-hospital mortality; Post-COVID-19

Research in context

Evidence before this study

Although risk factors of COVID-19 in-hospital mortality have been reported, most studies from Brazil have been based on retrospective cohorts and dataset analyses. More recently, long-term post-COVID-19 syndrome has been described as a potential complication. However, there is a paucity of data available regarding severe complications after hospital discharge in people hospitalized with COVID-19 in Latin America.

Added value of this study

In this study, we prospectively analyzed data from 1589 individuals hospitalized with COVID-19 and followed until hospital discharge, death, or a censured date (March 31, 2021) in seven centres in Brazil [RECOVER-SUS study; NCT04807699]. In addition, participants who were discharged from hospital were visited to follow-up on incidence, rehospitalization or death after hospital discharge. We identified factors associated with in-hospital mortality and incidence of severe outcomes post-hospital discharge due to COVID-19. In-hospital mortality rate was high; older age, substantial ventilation support and high severity scores (SAPS-III and SOFA scores) at hospital admission were significantly associated with in-hospital mortality. The incidence of severe outcomes after hospital discharge was also high. Even after hospital discharge, people aged $\geq$ 60 years and/or those with high SAPS-III score $\geq$ 57 at hospital admission had a 2-fold higher risk of death or rehospitalization during outpatient follow-up.

Implications of all evidence available

Our findings have important implications for optimizing patient management during hospitalization due to COVID-19 and after hospital discharge in low-to-middle income countries. These findings help to fill a knowledge gap regarding long-term impact of post-COVID-19 syndrome.

Introduction

Globally, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused the Coronavirus disease 2019 (COVID-19) pandemic has overwhelmed health systems due to high rates of hospitalization and intensive care unit (ICU) admissions.[1] Brazil, the largest country in Latin America, is characterized by deep social and economic inequalities.[2] As of March 2022, Brazil, an epicenter of the COVID-19 pandemic, ranks second in number of deaths (more than 650,000 since March 2020).[3] Relatively high intra-hospital mortality rates due to COVID-19 have been reported worldwide (from 17 to 38%).[4–7] Estimates of hospital admission and mortality rates in Brazil have been based on retrospective studies and dataset analyses.[7–9] However, prospective data evaluating risk factors associated with overall mortality in Brazil are still scarce. More recently, long-term post-COVID-19 syndrome has been described as a potential complication after COVID-19.[10] However, there is a paucity of available data regarding severe complications after hospital discharge in people hospitalized with COVID-19 worldwide. The RECOVER-SUS study was a collaboration among universities/research institutions and/or tertiary centers from the Brazilian Public Health System ("*Sistema Único de Saúde*") to tackle COVID-19 pandemic in Brazil. This analysis aimed to evaluate the incidence of in-hospital mortality and severe outcomes (rehospitalization or death) after hospital discharge due to COVID-19 in a multicenter prospective cohort from Brazil.

Methods

Study design and population

The RECOVER-SUS study [NCT04807699] is a prospective multicenter study that have been conducted in seven public tertiary hospitals from five cities in Brazil [*Instituto Nacional de Infectologia Evandro Chagas-Fundação Oswaldo Cruz* (INI/FIOCRUZ), *Hospital Federal Servidores do Estado do Rio de Janeiro* (HFSE/RJ) and *Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro* (HUCFF/UFRJ) in Rio de Janeiro (RJ); *Instituto de Infectologia Emilio Ribas* in São Paulo (SP), *Instituto Couto Maia* in Salvador (BA), *Hospital Regional São José* in Florianópolis (SC), and *Universidade Federal de Santa Maria* (UFSM) in Santa Maria (RS)]. Briefly, COVID-19 hospitalized patients are followed at multiple time-points. Additionally, a remote contact is performed for discharged RECOVER-SUS

participants to assess post-discharge complications after hospitalization with COVID-19. For the present study, we analyzed data from a convenience sample of all participants aged ≥18 years hospitalized with COVID-19 from June 2020 to March 2021 who were prospectively enrolled in the multicenter RECOVER-SUS study. Participants without suspected, probable or confirmed SARS-CoV-2 infection according to the World Health Organization (WHO) COVID-19 case definition were excluded.[11] The study protocol was approved by the Institutional Review Board (IRB) from INI/FIOCRUZ (IRB 32449420.4.1001.5262) and all co-participant institutions (IRB numbers 2449420.4.2004.5252, 32449420.4.2013.5257, 32449420.4.2001.0061, 32449420.4.2010.004, 32449420.4.2009.0113, 32449420.4.2006.5346). All participants or their legal representatives signed an informed consent prior to enrollment in the RECOVER-SUS study.

Data collection and in-hospital follow-up

Socio-demographic characteristics, comorbidities, co-medications, COVID-19 symptoms and vital signs and anthropometric measures (weight and height) were recorded at hospital admission (baseline). Clinical data and blood samples were collected by trained investigators at baseline and days 3 (D3), 7 (D7) and 14 (D14) of hospitalization. Additionally, clinical data were recorded at days 10 (D10), 21 (D21), 25 (D25), 30 (D30) and every 5 days thereafter if hospital stay was longer than 30 days. Laboratory tests included red and white blood-cells count, platelets count, international normalized ratio (INR), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, procalcitonin, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Severity of COVID-19 was defined according to the WHO severity classification.[12] Simplified Acute Physiology Score III (SAPS-III) and Sequential Organ Failure Assessment (SOFA) Score were calculated at baseline. Study data were collected and managed using REDCap electronic data capture tools hosted at INI-FIOCRUZ[13] All participants were followed from hospital admission until transfer to other institution, hospital discharge, death, or censured date on March 31, 2021, whichever occurred first. The primary outcome was in-hospital mortality.

Post discharge procedures

A remote visit (telephone call) at least 2 weeks after hospital discharge was performed by trained investigators for all discharged participants included in the RECOVER-SUS study. Participants (or authorized relatives/household members) were interviewed to assess participant's health status. The outcomes assessed during remote visits were any episode of rehospitalization (defined as minimum length of stay of 24 h in any hospital/institution) and post discharge death. If more than one hospitalization episode occurred during this post-discharge follow-up, the first one was considered for the analysis. Therefore, the secondary outcome of this study was rehospitalization or death.

Statistical analysis

Continuous variables were reported as median (interquartile range, IQR) and categorical variables were reported as absolute (n) and relative frequencies (%). Missing data were reported in Tables. Chi-squared and Mann-Whitney/Kruskal-Wallis tests were used for between groups comparisons. In-hospital follow-up started at the first day of hospitalization and ended at the earliest of death, hospital transfer or discharge, or March 31, 2021, whichever occurred first. The primary and secondary outcomes for this analysis were overall in-hospital mortality and rehospitalization or death after hospital discharge. Post-discharge follow-up started at day of discharge and ended at the earliest of death, rehospitalization or day of contact for those who were alive and did not have any rehospitalization. The incidence outcomes rates [per 1000 person-days (PD) for in-hospital mortality and per 1000 person-years (PY) for post-discharge outcomes] were calculated considering individuals who experienced and those who did not experience an outcome event. Kaplan–Meier curves were plotted, and the log-rank tests were calculated. We used the time to event Cox proportional-hazard model for uni- and multivariate analyses after checking that the main variables verified the proportional-hazard assumption using the Schoenfeld residuals. All continuous variables were categorized in Cox models to mitigate a potential influence of outliers on the estimate of risk for primary and secondary outcomes (hazard-ratios). All Cox models were adjusted for the variable "center" to minimize the risk of center-specific bias clustering effect due to an imbalance among centers of the RECOVER-SUS study. Variables associated with each outcome ($p \leq 0.05$) were entered into multivariate models adjusted for age and sex at birth. The severity of multicollinearity among variables entered in each multivariate Cox model was quantified by the variance inflation factor (VIF). Age was stratified into four group categories for analysis of in-hospital mortality: 18–39 years; 40–59 years; 60–69 years; 70–79 years and ≥80 years. Sensitivity analyses were performed considering hospital admission in different periods: from June to December 2020 and from January to March 2021. The analysis was performed using STATA-package, version 15, 2017 (StataCorp LP, College Station, TX, USA). Significance level was determined when $p \leq 0.05$ assuming two-tailed tests.

Ethics approval and consent to participate

The study was approved by the Ethical Committee from Instituto Nacional de Infectologia Evandro Chagas – Fundação Oswaldo Cruz (IRB n° 32449420.4.1001.5262); Hospital Federal Servidores do Estado do Rio de Janeiro (IRB n° 32449420.4.2004.5252); Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro (IRB n° 32449420.4.2013.5257); Instituto de Infectologia Emilio Ribas (IRB n° 32449420.4.2001.0061); Instituto Couto Maia (IRB n° 32449420.4.2010.0046); Hospital Regional São José (IRB n° 32449420.4.2009.0113); and Universidade Federal de Santa Maria (IRB n° 32449420.4.2006.5346)

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Results

A total of 1649 individuals hospitalized with COVID-19 symptoms from June 7, 2020, to March 31, 2021 were included in the RECOVER-SUS study. From those, 60 subjects not classified as suspected, probable, or confirmed case by the WHO definition were excluded from analysis. Thus, 1589 participants [54.5% male, median age=62 (IQR, 50–70), median body mass index (BMI) of 28.4 (IQR, 24.9–32.9) Kg/m^2; 51.9% with type-2 diabetes and 33.9% with systemic arterial hypertension] were included in the study (Figure 1). Table 1 summarizes clinical and demographic characteristics and laboratory results at hospital admission of participants included in the study. Symptoms were initiated in a median time of 8 (IQR, 5–11) days before hospitalization. The most common symptoms were shortness of breath [n = 1115 (70.2%)], cough [n = 1011 (63.6%)] and fever [n = 875 (55.1%)]. A total of 1321 (83.1%) participants had confirmed COVID-19, and most individuals (n = 1350; 87.4%) were classified as WHO severity score between 6 and 8. At hospital admission, 25.8% (n = 409) participants were receiving supplementary oxygen by facial mask, 1.4% (n = 22) by non-invasive ventilation (NIV) and 13.6% (n = 216) were under mechanical ventilation. Regarding laboratory results, the median (IQR) leucocytes and lymphocytes counts were 8.88 (6.24–12.41) x10^9/L and 0.98 (0.64–1.49) x10^9/L, respectively. Additionally, median (IQR) levels of procalcitonin, CRP and ESR were 0.16 (0.10–0.49) ng/ml, 14 (7–20) mg/dL and 75 (47–101) mm/h, respectively. Supplementary Table 1 shows baseline characteristics according to the study center. The cycle threshold values and SARS-CoV-2 variants of concern (VOC) were available for a sub-sample of 631 and 134 subjects hospitalized at INI/FIOCRUZ (Rio de Janeiro), respectively. Cycle threshold values were lower or equal to 25, representing high viral load, in 86% (n = 541) of those subjects. Regarding, SARS-Cov-2 VOCs, Pango lineages B.1.1.33 and B.1.1.28 were observed in 40% (n = 53) and 16% (n = 22); P.2 in 21% (n = 28) of cases and Gamma (P.1) in 22% (n = 29) of cases. B.1.1.33 and B.1.1.28 lineages were present mostly in people hospitalized in 2020 and Gamma was observed exclusively in those individuals hospitalized in 2021. There was no individual hospitalized up to March 31, 2021 presenting Delta SARS-CoV-2 VOC (Supplementary Table 2).

In-hospital mortality

From participants included (n = 1589), 1108 [69.7% (95% confidence interval – 95%CI 67.4–71.9) were discharged, 21 [1.3% (95%CI 0.9–2.0)] were transferred to another hospital, 31 [2.0% (95%CI 1.4–2.8)] were censored on March 31, 2021 and 429 individuals [27.0% (95%CI 24.8–29.2)] died. Median length of stay was 10 (IQR, 6–19) days; shorter among participants that were discharged 9 (IQR, 5–17) than in participants that died during hospitalization 14 (IQR, 9–24) [p < 0.001]. A total of 98 [22.8% (95%CI 19.1–27.1)] and 156 [36.4% (95%CI 31.9–41.0)] deaths occurred from days 6–10 and 11–20 of hospitalization, respectively. The overall mortality rate was 16.2 (95%CI 14.8–17.8) deaths per 1000 PD. Supplementary Table 3 describes mortality rates according to socio-demographic characteristics or comorbidities/clinical conditions. The 14-day in-hospital survival was significantly higher in people aged lower than 60 years [86.8% (95%CI 82.8–89.9)] at hospital admission compared to those aged 60 years or older [71.7% (95%CI 67.8–75.2)] (log-rank p < 0.001) (Figure 2A). Additionally, 14-day in-hospital overall survival was higher in people hospitalized from January to March 2021 compared to those hospitalized from June to December 2020 [86.0% (95%CI 81.1–89.7) vs 74.2% (95%CI 70.7–77.4); p < 0.001] (Figure 2B). However, people hospitalized in 2021 were significantly younger and had significantly less severe COVID-19 compared to those hospitalized from June to December 2020 (Supplementary Table 4). Factors independently associated with intra-hospital mortality were [adjusted-Hazard Ratio (aHR) (95%CI)] age=60–69 years [vs age < 40 years; aHR=1.89 (1.08–3.32), p = 0.027]; age=70–79 years [vs age < 40 years; aHR=2.52 (1.42–4.45),

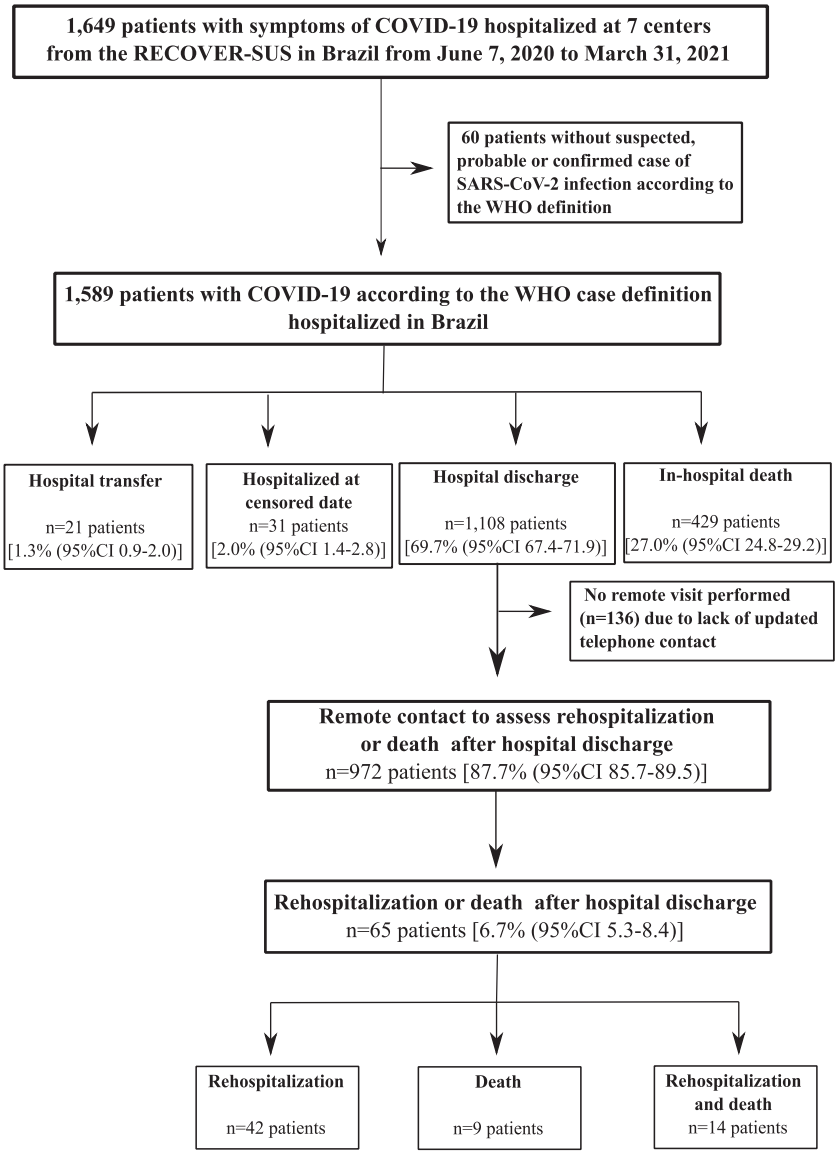

Figure 1. Flow-chart of RECOVER-SUS participants included for in-hospital mortality and post-discharge analyses.

$p = 0.002$]; age ≥ 80 [vs age < 40 years; aHR=2.90 (1.54−5.47), $p = 0.001$]; NIV or mechanical ventilation at admission [vs facial mask or none; aHR=1.69 (1.30−2.19), $p < 0.001$], SAPS-III score ≥ 57 [vs SAPS-III score < 57; aHR=1.47 (1.13−1.92), $p = 0.004$] and SOFA score ≥ 10 [vs SOFA score < 10; aHR=1.51 (1.08−2.10), $p = 0.016$] (Table 2).

Post-hospital discharge outcomes

From 1108 participants who were discharged, 972 subjects [87.7% (95%CI 85.7−89.5)] were remotely contacted in a median time of 58 (IQR, 48−74) days after hospital discharge. Overall, 53.3% of post-discharge participants were male, had a median age of 59 (IQR, 48−68) years and median BMI of 28.8 (IQR, 25.0−33.1) Kg/m$^{2.}$ (Table 3). Type-2 diabetes and systemic arterial hypertension were reported in 50.0% and 35.3% of participants, respectively. Most individuals had confirmed COVID-19 (83.3%) and had been admitted with non-significant respiratory support (none or nasal cannula=70%). The median length of hospital stay of those individuals was 9 (range, 1−116) days. A total of 65 individuals [6.7% (95%CI 5.3−8.4)] had a rehospitalization or death in a median time of 52 (range, 1−280) days post-hospital discharge. Of those 65 participants with a severe outcome, 9 died without hospitalization, 42 were rehospitalized but remained alive, and 14 died during rehospitalization. Among those who died ($n = 23$), 57% were female, had a median age of 73 (IQR 70−82) years

	All (*n* = 1589)	Discharged from hospital (*n* = 1160)	In-hospital death (*n* = 429)	P value
Socio-demographic characteristics				
Male sex [a]	866 (54.5)	614 (52.9)	252 (58.7)	0.039
Age [b]	62 (50−70)	59 (47−68)	68 (59−75)	<0.001
Race/skin-color [a]				0.041
White	442 (27.8)	330 (28.4)	112 (26.1)	
Black	139 (8.7)	114 (9.8)	25 (5.8)	
Mixed ("Pardo")	859 (54.1)	617 (53.2)	242 (56.4)	
Other	13 (0.9)	12 (1.1)	1 (0.2)	
Unknown/not reported	136 (8.5)	87 (7.5)	49 (11.4)	
Annual family income (USD) [a]				0.019
Up to 2268	284 (17.9)	220 (19.0)	64 (14.9)	
2269 to 6804	694 (43.7)	490 (42.2)	204 (47.6)	
6805 to 13596	329 (20.7)	241 (20.8)	88 (20.5)	
More than 13597	97 (6.1)	81 (7.0)	16 (3.7)	
Unknown/not reported	184 (11.6)	128 (11.0)	56 (13.3)	
Years of schooling [a]				0.023
Less than 8 years	360 (22.7)	252 (21.7)	108 (25.2)	
8 to 10 years	407 (25.6)	288 (24.8)	119 (27.7)	
11 to 14 years	530 (33.4)	401 (34.6)	129 (30.1)	
More than 14 years	200 (12.6)	162 (14.0)	38 (8.9)	
Unknown/not reported	92 (5.7)	57 (4.9)	35 (8.2)	
Comorbidities				
Former or current smoker [a]	164 (10.3)			
BMI, Kg/m2 [a, b]	28.4 (24.9−32.9)	28.7 (25.0−33.1)	28.0 (24.5−31.6)	0.011
BMI < 25 Kg/m^2	394 (24.8)	271 (23.4)	123 (28.7)	
BMI=25−29.99 Kg/m^2	518 (32.6)	366 (31.6)	152 (35.4)	
BMI=30−34.99 Kg/m^2	349 (22.0)	269 (23.2)	80 (18.6)	
BMI=35−39.99 Kg/m^2	144 (9.1)	104 (9.0)	40 (9.3)	
BMI ≥ 40 Kg/m^2	101 (6.4)	79 (6.8)	22 (5.1)	
Unknown/not reported	83 (5.1)	71 (6.1)	22 (5.1)	
Type-2 diabetes [a]	824 (51.9)	587 (50.6)	237 (55.2)	0.100
Arterial Systemic Hypertension [a]	538 (33.9)	407 (35.1)	131 (30.5)	0.089
COPD [a]	88 (5.5)	48 (4.1)	40 (9.3)	< 0.001
Heart disease	142 (8.9)	93 (8.0)	49 (11.4)	0.035
Chronic kidney disease [a]	49 (3.1)	32 (2.8)	17 (4.0)	0.220
Symptoms				
Time from onset of symptoms to hospital admission, days[b]	8 (5−11)	8 (5−11)	7 (4−10)	0.002
Fever[a]	875 (55.1)	675 (58.2)	200 (46.6)	< 0.001
Cough[a]	1011 (63.6)	767 (66.1)	244 (56.9)	< 0.001
Nasal congestion[a]	143 (9.0)	113 (9.7)	30 (7.0)	0.089
Headache[a]	251 (15.8)	211 (18.2)	40 (9.3)	< 0.001
Myalgia[a]	398 (25.0)	317 (27.3)	81 (18.9)	< 0.001
Shortness of breath or difficulty breathing[a]	1115 (70.2)	317 (27.3)	81 (18.9)	0.084
Anosmia[a]	203 (12.8)	170 (14.7)	33 (7.7)	< 0.001
Ageusia[a]	153 (9.6)	128 (11.0)	25 (5.8)	0.002
Digestive symptoms[a]	271 (17.1)	212 (18.3)	59 (13.8)	0.033
WHO definition case[a]				0.36
Confirmed COVID-19 case	1321 (83.1)	967 (83.4)	354 (82.5)	
Probable COVID-19 case	164 (10.3)	123 (10.6)	41 (9.6)	
Suspected COVID-19 case	104 (6.6)	70 (6.0)	34 (7.9)	
WHO classification of severity at admission[a]				< 0.001
WHO score = 4−5	103 (6.5)	54 (4.7)	49 (11.4)	

Table 1 *(Continued)*

	All (*n* = 1589)	Discharged from hospital (*n* = 1160)	In-hospital death (*n* = 429)	P value
WHO score = 6–8	1350 (85.0)	1042 (89.8)	308 (71.8)	
WHO score = 9–10	91 (5.7)	35 (3.0)	56 (13.1)	
Unknown/not reported	45 (2.8)	29 (2.5)	16 (3.7)	
Respiratory support at admission [a]				< 0.001
None	242 (15.2)	224 (19.3)	18 (4.2)	
Supplementary oxygen at nasal cannula	675 (42.5)	562 (48.4)	113 (26.3)	
Supplementary oxygen at facial mask or NIV	409 (25.8)	285 (24.6)	124 (28.9)	
Mechanical ventilation	216 (13.6)	58 (5.0)	158 (36.8)	
Unknown/not reported	47 (2.9)	31 (2.7)	16 (3.7)	
Vital signs at hospital admission [b]				
Pulse, bpm	87 (78–98)	86 (77–97)	90 (80–105)	<0.001
Respiratory rate, rpm [b]	22 (19–26)	21 (19–25)	22 (20–27)	<0.001
Systolic blood pressure, mmHg [b]	137 (120–150)	137 (123–150)	136 (118–150)	0.084
Diastolic blood pressure, mmHg [b]	80 (71–90)	80 (72–90)	80 (68–90)	<0.001
Laboratory results [b]				
Leucocytes, x10^9/L	8.88 (6.24–12.41)	8.33 (5.78–11.34)	11.5 (7.49–16.08)	<0.001
Lymphocytes, x10^9/L	0.98 (0.64–1.49)	0.99 (0.65–1.47)	0.96 (0.62–1.55)	0.67
Platelet count, x10^9/L	241 (145–317)	246(179–321)	231 (169–304)	0.032
INR	1.05 (1.00–1.19)	1.03 (0.99–1.16)	1.10 (1.01–1.26)	<0.001
Creatinine, mg/dL	1.0 (0.8–1.3)	1.0 (0.8–1.2)	1.2 (0.9–2.0)	<0.001
AST, U/L	40 (28–61)	41 (25–72)	36 (23–56)	0.002
ALT, U/L	40 (25–68)	40 (27–60)	44 (31–68)	<0.001
Total bilirubin, mg/dL	0.5 (0.3–0.7)	0.4 (0.3–0.6)	0.5 (0.3–0.8)	<0.001
Procalcitonin, ng/ml	0.16 (0.10–0.49)	0.1 (0.1–0.3)	0.4 (0.2–1.6)	<0.001
C-reactive protein, mg/L	14 (7–20)	13 (7–20)	16 (10–21)	<0.001
Erythrocyte sedimentation rate (ESR), mm/hr	75 (47–101)	73 (45–100)	80 (50–110)	0.002

***Table 1*: Baseline characteristics of individuals hospitalized at 7 centers in RECOVER-SUS, Brazil, from June 7, 2020 to March 31, 2021.**
Data expressed as n (%)[a] or median (IQR)[b]. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus disease 2019; INR, international normalized ratio; USD: US dollars; WHO, World Health Organization. COVID-19 was defined according to the WHO COVID-19: Case Definitions (Updated in Public health surveillance for COVID-19, published 16 December 2020) available at https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2. Severity of COVID-19 was defined according to the WHO classification of severity[12] . Missing (n): time form onset of symptoms (*n* = 77); pulse (*n* = 74); respiratory rate (*n* = 98), systolic and diastolic blood pressure (*n* = 75), leucocytes levels (*n* = 28); lymphocytes levels (*n* = 35), platelet count (*n* = 29); INR (*n* = 213); creatinine levels (*n* = 38), ALT (*n* = 134), AST (*n* = 131), procalcitonin levels (*n* = 372), c-reactive protein (*n* = 73), ESR (*n* = 374).

and 17% were admitted to mechanical ventilation at initial hospitalization. Among those who were rehospitalized but remained alive (*n* = 42) 50% were female, had a median age of 63 (IQR, 46–72) years, 29% were admitted receiving oxygen support by facial mask at initial hospitalization, and none were in mechanical ventilation.

The incidence rates of outcomes post-hospital discharge were 123 (95%CI 82–185) deaths per 1000 PY, 272 (95%CI 206–359) rehospitalization per 1000 PY and 323 (95%CI 250–417) death or rehospitalization per 1000 PY. The 60-day-post-discharge survival without severe outcomes (death or rehospitalization) was significantly lower in people aged ≥ 60 years [90.7% (95%CI 87.4–93.1)] compared to those aged lower than 60 years [97.2% (95%CI 95.1–98.5)] ($p < 0.001$) (Figure 3). There was no significant difference in survival without outcomes after hospital discharge according to year of hospital admission between those admitted in hospital from June to December 2020 [93.4% (95% 91.6–95.5)] compared to those hospitalized in 2021 [94.9 (95%CI 91.2–97.1)] ($p = 0.577$). In the multivariate Cox model considering the parameters at hospital admission (baseline), age ≥ 60 years [vs <60 years; aHR=2.13 (1.15–3.94), $p = 0.017$] and SAPS-III score > 57 [vs ≤57; aHR=2.37 (1.22–4.59), $p = 0.010$] were associated with rehospitalization or death after hospital discharge post-COVID-19 (Table 4). Presence of diabetes showed a trend to be associated with this outcome adjusted for confounding factors [aHR=1.67 (95%CI 0.95–2.94), $p = 0.077$].

Discussion

This prospective study, the first to our knowledge describing incidence and risk factors associated with severe COVID-19 outcomes after hospital discharge in

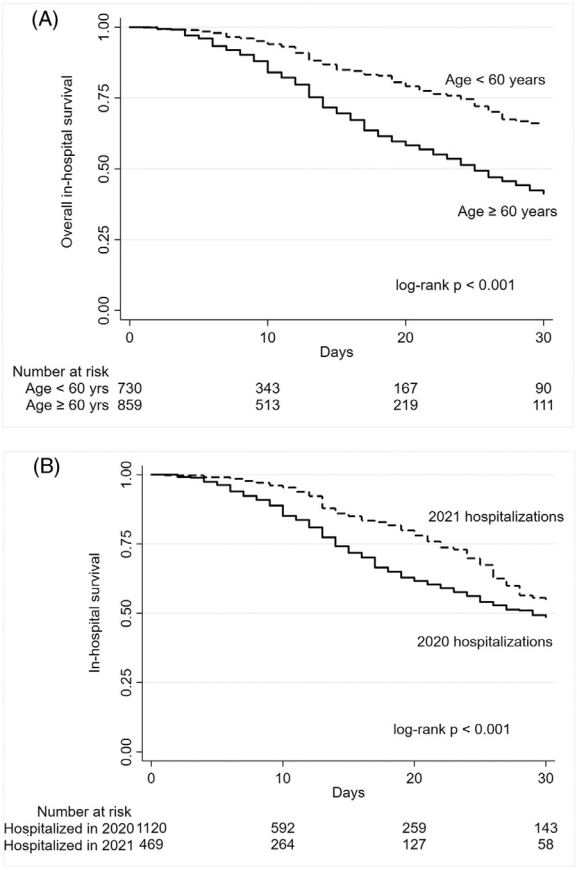

Figure 2. In-hospital survival. Overall RECOVER-SUS study survival is shown according to age (A) or year of admission (B) starting on admission day until March 31, 2021in participants hospitalized due to COVID-19.

Brazil, revealed factors associated with in-hospital mortality and incidence of severe outcomes, including rehospitalization or death, in a large multicentric cohort. The main strengths of the study were the prospective study design, the structured data collection in electronic forms by trained abstractors and the follow-up after hospital discharge of a large real-life cohort in Brazil. Most studies reporting in-hospital mortality due to COVID-19 to date in Brazil have been retrospective analyses. Our findings have important implications for optimizing the management during hospitalization due to COVID-19 and after hospital discharge in low-to-middle income countries. We observed high mortality rates during hospitalization; older age, substantial ventilation support and high severity scores at hospital admission were significantly associated with in-hospital mortality. Even after hospital discharge, people aged more than 60 years and with high SAPS-III scores at hospital admission remained at relatively high risk of complications during outpatient follow-up.

Several studies have reported risk factors associated with in-hospital mortality due to COVID-19. Our findings were aligned with a previous multicenter study performed in Greece that analyzed in-hospital mortality in a cohort enrolling 3062 individuals with similar demographic and clinical characteristics.[4] On the other hand, a U.S. multicentric, retrospective study, which analyzed data from 2491 patients with similar median age (62 years) and higher proportion of individuals under mechanical ventilation at admission (19%) compared to our sample, reported lower in-hospital mortality rate (17%).[5] Additionally, a retrospective study that analyzed data from 10,021 patients from 920 hospitals in Germany reported that 22.3% of individuals died during hospitalization due to COVID-19.[6] Our study identified that older people needing substantial ventilation support are at higher risk of in-hospital mortality, as previously described. The effect of age on mortality of patients hospitalized with COVID-19 with or without association with comorbidities or medical conditions remain unclear.[14] Zeiser et al. reported that in-hospital mortality subsequently increased in sub-groups of patients aged ≥60 years in a retrospective analysis of a nationwide Brazilian database.[15] Our prospective study confirmed this finding, as we observed an increased

		Univariate analysis		Multivariate analysis	
		HR [95% CI]	p value	HR [95% CI]	p value
Male gender (vs female)		0.84 [0.69−1.02]	0.077	0.80 [0.64−1.01]	0.058
Age group	40−59 years (vs < 40 years)	1.46 [0.87−2.44]	0.153	1.20 [0.68−2.12]	0.535
	60−69 years (vs < 40 years)	2.27 [1.37−3.76]	0.001	1.89 [1.08−3.32]	0.027
	70−79 years (vs < 40 years)	3.05 [1.83−5.08]	< 0.001	2.52 [1.42−4.45]	0.002
	≥ 80 years (vs < 40 years)	3.96 [2.30−6.83]	< 0.001	2.90 [1.54−5.47]	0.001
Non-white skin color (vs white)		0.84 [0.67−1.05]	0.136		
Family income < $4536 per year (vs ≥ $4536)		0.95 [0.78−1.17]	0.631		
Schooling < 8 years (vs ≥ 8 years)		1.29 [1.05−1.57]	0.013	1.08 [0.86−1.35]	0.508
BMI ≥ 30 Kg/m2 (vs < 30 Kg/m^2)		0.75 [0.62−0.92]	0.007	0.97 [0.77−1.23]	0.816
Type-2 Diabetes (yes vs no)		1.02 [0.84−1.23]	0.846		
Arterial Systemic Hypertension (yes vs no)		0.91 [0.74−1.12]	0.363		
COPD (yes vs no)		1.22 [0.88−1.69]	0.238		
NIV or mechanical ventilation (vs nasal cannula or none)		2.20 [1.81−2.69]	< 0.001	1.69 [1.30−2.19]	< 0.001
Leukocytosis (vs leucocytes < 10 × 10^9/L)		1.49 [1.22−1.81]	< 0.001	1.00 [0.79−1.26]	0.964
Lymphopenia (vs lymphocytes > 1.00 × 10^9/L)		1.09 [0.90−1.32]	0.371		
Low platelet count (vs > 150 × 10^9/L)		1.28 [1.00−1.64]	0.054		
Creatinine levels ≥ 1.5 mg/dL (vs < 1.5 mg/dL)		1.71 [1.39−2.09]	< 0.001	1.11 [0.88−1.41]	0.401
ALT levels ≥ 80 UI/L (vs < 80 UI/L)		0.82 [0.62−1.09]	0.168		
AST levels ≥ 80 UI/L (vs < 80 UI/L)		1.14 [0.88−1.47]	0.322		
Protein-C reactive levels ≥ 20 mg/L (vs < 20 mg/L)		1.30 [1.05−1.61]	0.016	1.12 [0.88−1.41]	0.365
SAPS III score ≥ 57 (vs SAPS score < 57)		2.40 [1.96−2.94]	< 0.001	1.47 [1.13−1.92]	0.004
SOFA score ≥ 10 (vs SOFA score < 10)		2.68 [2.04−3.53]	< 0.001	1.51 [1.08−2.10]	0.016

***Table 2*: Cox proportional-hazard model for uni- and multivariate analyses.to identify factors associated with intra-hospital mortality in 1589 individuals hospitalized at 7 centers in RECOVER-SUS, Brazil, from June 7, 2020, to March 31, 2021.**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, NIV, non-invasive ventilation; Simplified Acute Physiology Score (SAPS) III; Sequential Organ Failure Assessment (SOFA). Variables found be associated ($p \leq 0.05$) with the analyzed outcome were entered into multivariate models adjusted for age and sex at birth. Procalcitonin level was not entered in the Cox analysis since this variable was not available in all centers. Variables from uni- and multivariate analysis were controlled by center in all Cox analyses. The severity of multicollinearity among variables entered in the multivariate model was quantified by the variance inflation factor (VIF). All variables entered in the multivariate model had VIF values < 2.00 [model mean VIF=1.23].

age-related risk of in-hospital mortality in patients hospitalized with COVID-19 adjusted for confounding factors. Our findings highlight the importance of stratifying patients with COVID-19 with SAPS-III and SOFA scores at hospital admission to predict in-hospital mortality.[16] Interestingly, metabolic features or co-morbidities were not associated with in-hospital mortality. This finding might be explained by collinearity with severity scores (SAPS-III and/or SOFA) that include parameters related with multiple organs/systems dysfunctions. A retrospective study from the Brazilian COVID-19 Registry (data from 25 hospitals) reported that in-hospital mortality was 22%, but this can be up to 48% for patients treated in ICU.[8] Another retrospective analysis of a nationwide Brazilian database with more than 250,000 hospitalizations reported a high proportion of deaths (38%) that dramatically increased when people were admitted under mechanical ventilation (up to 80%). These contradictory findings might be explained because Brazil is the fifth largest country in the world, with different climates and ethnically and culturally diverse, which might comprise different epidemiological stages of COVID-19 pandemic in different regions at the same time. A recent study retrospective analysis of a dataset that characterizes the COVID-19 pandemic in Brazil (n = 11,321) reported different mortality rates according to geographic distribution and ethnical characteristics.[17]

We observed that in-hospital survival increased throughout the pandemic, as the mortality rate was significantly higher in individuals hospitalized in 2020 compared to those admitted since January 2021. This finding was also reported in a systematic review and meta-analysis that identified a significant reduction in

	All (*n* = 972)	No post-discharge outcomes (*n* = 907)	Post-discharge outcomes (*n* = 65)	P value
Socio-demographic characteristics				
Male sex [a]	518 (53.3)	487 (53.7)	31 (47.7)	0.350
Age [b]	59 (48−68)	58 (47−68)	68 (54−78)	< 0.001
Race/skin-color [a]				0.860
White	255 (26.2)	240 (26.5)	15 (23.1)	
Black	97 (10.0)	89 (9.8)	8 (12.3)	
Mixed ("Pardo")	548 (56.4)	510 (56.2)	38 (58.5)	
Other	9 (0.9)	9 (1.0)	0 (0.0)	
Unknown/ not reported	63 (6.5)	59 (6.5)	4 (6.2)	
Family income (USD) [a]				
Up to 2268	185 (19.0)	170 (18.7)	15 (23.1)	0.790
2269 to 6804	424 (43.6)	397 (43.8)	27 (41.5)	
6805 to 13596	215 (22.1)	203 (22.4)	12 (18.5)	
More than 13597	75 (7.7)	70 (7.7)	5 (7.7)	
Unknown/not reported	73 (7.6)	67 (7.3)	6 (9.2)	
Years of schooling [a]				0.088
Less than 8 years	205 (21.1)	190 (20.9%)	15 (23.1%)	
8 to 10 years	241 (24.8)	223 (24.6%)	18 (27.7%)	
11 to 14 years	344 (35.4)	323 (35.6%)	21 (32.3%)	
More than 14 years	144 (14.8)	137 (15.1%)	7 (10.8%)	
Unknown/ not reported	38 (4)	34 (3.7)	7 (6.2)	
Comorbidities				
Former or current smoker [a]	104 (10.7)	94 (10.4)	10 (15.4)	0.870
BMI, Kg/m2 [a, b]	28.8 (25.0−33.1)	29.0 (25.3−33.1)	26.7 (23.0−31.3)	0.009
BMI < 25 Kg/m^2	227 (23.3)	203 (22.4)	24 (36.9)	
BMI=25−29.99 Kg/m^2	314 (32.3)	296 (32.6)	18 (27.7)	
BMI=30−34.99 Kg/m^2	227 (23.3)	215 (23.7)	12 (18.5)	
BMI=35−39.99 Kg/m^2	93 (9.6)	89 (9.8)	4 (6.2)	
BMI ≥ 40 Kg/m^2	60 (6.2)	57 (6.3)	3 (4.6)	
Unknown/ not reported	51 (5.3)	47 (5.2)	4 (6.1)	
Type-2 diabetes [a]	486 (50.0)	443 (48.8)	43 (66.2)	0.007
Arterial Systemic Hypertension [a]	343 (35.3)	317 (35.0)	26 (40.0)	0.411
COPD [a]	40 (4.1)	36 (4.0)	4 (6.2)	0.390
Heart disease [a]	78 (8.0)	66 (7.3)	12 (18.5)	0.001
Chronic kidney disease [a]	19 (2.0)	12 (1.3)	7 (10.8)	< 0.001
Symptoms				
Fever [a]	584 (60.1)	552 (60.9)	32 (49.2)	0.064
Cough [a]	650 (66.9)	608 (67.0)	42 (64.6)	0.690
Nasal congestion [a]	94 (9.7)	89 (9.8)	5 (7.7)	0.580
Headache [a]	173 (17.8)	170 (18.7)	3 (4.6)	0.004
Myalgia [a]	263 (27.1)	247 (27.2)	16 (24.6)	0.650
Shortness of breath or difficulty breathing [a]	680 (70.0)	635 (70.0)	45 (69.2)	0.890
Anosmia [a]	141 (14.5)	137 (15.1)	4 (6.2)	0.048
Ageusia [a]	105 (10.8)	103 (11.4)	2 (3.1)	0.038
Digestive symptoms [a]	176 (18.1)	167 (18.4)	9 (13.8)	0.360
WHO definition case [a]				< 0.001
Confirmed COVID-19 case	810 (83.3)	768 (84.7)	42 (64.6)	
Probable COVID-19 case	102 (10.5)	87 (9.6)	15 (23.1)	
Suspected COVID-19 case	60 (6.2)	52 (5.7)	8 (12.3)	
WHO classification of severity at admission [a]				0.230
WHO score = 4−5	38 (4.0)	33 (3.6)	5 (7.7)	
WHO score = 6−8	887 (93.1)	828 (91.3)	59 (90.8)	

Table 3 *(Continued)*

	All (*n* = 972)	No post-discharge outcomes (*n* = 907)	Post-discharge outcomes (*n* = 65)	P value
WHO score = 9–10	28 (2.9)	27 (3.0)	1 (1.5)	
Respiratory support at admission [a]				0.410
None	193 (19.9)	175 (19.3)	18 (27.7)	
Supplementary oxygen at nasal cannula	487 (50.1)	457 (50.4)	30 (46.1)	
Supplementary oxygen at facial mask or NIV	231 (23.7)	218 (24.0)	13 (20.0)	
Mechanical ventilation	40 (4.1)	36 (4.0)	4 (6.2)	
Unknown/ not reported	21 (2.2)	21 (2.3)	0 (0.0)	
Vital signs at hospital admission [b]				
Pulse, bpm	86 (77–97)	86 (77–97.)	88 (75–96)	0.560
Respiratory rate, rpm	21 (19–25)	22 (19–25)	21 (19–24)	0.520
Systolic blood pressure, mmHg	137 (123–150)	137 (123–150)	138 (120–150)	0.970
Diastolic blood pressure, mmHg	80 (72–90)	80 (72–90)	80 (72–90)	0.380
Laboratory results [b]				
Leucocytes, x10^9/L	8.32 (5.80–11.27)	8.25(5.79–11.15)	9.13 (6.31–11.72)	0.130
Lymphocytes, x10^9/L	1.00 (0.65–1.47)	1.00 (0.66–1.46)	0.97 (0.65–1.68)	0.470
Platelet count, x10^9/L	248 (183–325)	247 (184–323)	249 (178–342)	0.780
INR	1.03 (0.98–1.14)	1.03 (0.98–1.14)	1.08 (1.00–1.20)	0.017
Creatinine, mg/dL	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.1 (0.8–1.5)	0.077
AST, U/L	41 (25–71)	41 (26–71)	34 (20–60)	0.060
ALT, U/L	40 (27–60)	40 (27–60)	35 (26–57)	0.190
Total bilirubin, mg/dL	0.4 (0.3–0.6)	0.4 (0.3–0.6)	0.5 (0.3–0.7)	0.180
Procalcitonin, ng/dL	0.1 (0.1–0.3)	0.1 (0.1–0.3)	0.2 (0.1–0.9)	0.002
C-reactive protein, mg/L	13 (7–20)	13 (7–20.)	9 (6–17)	0.110
Erythrocyte sedimentation rate (ESR), mm/hr	72 (45–100)	72 (45–100)	70 (35–105)	0.850

***Table 3*: Characteristics at hospital admission of individuals who were hospitalized due to COVID-19 from June 7, 2020 to March 31, 2021 and were remotely contacted to assessment of outcomes post-hospital discharge, RECOVER-SUS, Brazil.**
Data expressed as n (%)[a] or median (IQR)[b]. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus disease 2019; NIV, non-invasive ventilation; INR, international normalized ratio; USD: US dollars; WHO, World Health Organization. COVID-19 was defined according to the WHO COVID-19: Case Definitions (Updated in Public health surveillance for COVID-19, published 16 December 2020) available at https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2. Severity of COVID-19 was defined according to the WHO classification of severity[12]. Missing (n): BMI (*n* = 51), time form onset of symptoms (*n* = 38); respiratory support at admission (*n* = 21); pulse (*n* = 42); respiratory rate (*n* = 51), systolic and diastolic blood pressure (*n* = 40), leucocytes levels (*n* = 18); lymphocytes levels (*n* = 19), platelet count (*n* = 18); INR (*n* = 130); creatinine levels (*n* = 20), ALT (*n* = 74), AST (*n* = 75), procalcitonin levels (*n* = 221), c-reactive protein (*n* = 25), ESR (*n* = 220).

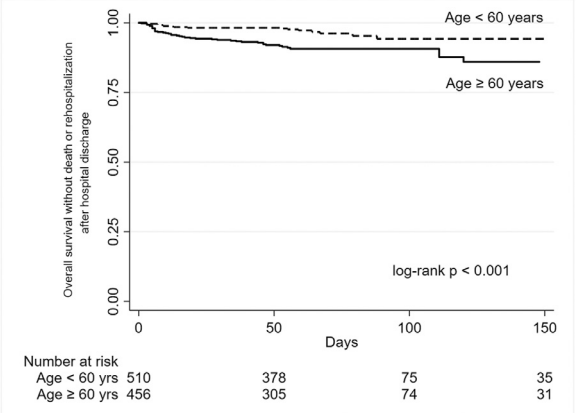

Figure 3. Survival without severe outcomes after hospital discharge. Survival for COVID-19 patients without rehospitalization or death outcomes in the RECOVER-SUS study is shown for age groups ≤60 and ≥60 years from day of discharge until 9 months after hospital discharge.

	Univariate analysis		Multivariate analysis	
	HR [95% CI]	p value	HR [95% CI]	p value
Male gender (vs female)	1.09 [0.66−1.82]	0.733	0.91 [0.53−1.56]	0.726
Age ≥ 60 years (vs < 60 years)	2.87 [1.63−5.04]	< 0.001	2.13 [1.15−3.94]	0.017
Non-white skin color (vs white)	1.17 [0.62−2.18]	0.628		
Family income < $4536 per year (vs ≥ $4536)	1.48 [0.86−2.56]	0.160		
Schooling < 8 years (vs ≥ 8 years)	1.21 [0.71−2.06]	0.483		
BMI ≥ 30 Kg/m2 (vs < 30 Kg/m2)	0.62 [0.35−1.11]	0.106		
Diabetes (yes vs no)	2.13 [1.24−3.67]	0.006	1.67 [0.95−2.94]	0.077
Hypertension (yes vs no)	1.21 [0.72−2.04]	0.478		
COPD (yes vs no)	1.25 [0.39−4.00]	0.705		
NIV or mechanical ventilation (vs facial mask or none)	0.89 [0.28−2.87]	0.850		
Duration of hospitalization ≥ 28 days (vs < 28 days)	1.25 [0.56−2.75]	0.586		
Leukocytosis (vs leucocytes < 10 × 109/L)	1.48 [0.88−2.48]	0.135		
Lymphopenia (vs lymphocytes > 1.00 × 109/L)	1.31 [0.79−2.20]	0.298		
Low platelet count (vs > 150 × 109/L)	1.59 [0.83−3.02]	0.160		
Creatinine levels ≥ 1.5 mg/dL (vs < 1.5 mg/dL)	3.00 [1.71−5.27]	< 0.001	1.60 [0.82−3.14]	0.169
ALT levels ≥ 80 UI/L (vs < 80 UI/L)	0.77 [0.38−1.57]	0.472		
AST levels ≥ 80 UI/L (vs < 80 UI/L)	1.17 [0.57−2.38]	0.670		
Protein-C reactive levels ≥ 20 mg/L (vs < 20 mg/L)	0.60 [0.30−1.19]	0.141		
SAPS III score ≥ 57 (vs SAPS score < 57)	3.67 [2.06−6.52]	< 0.001	2.37 [1.22−4.59]	0.010
SOFA score ≥ 10 (vs SOFA score < 10)	1.02 [0.14−7.42]	0.981		

***Table 4*: Cox proportional-hazard model for uni- and multivariate analyses.to identify factors associated with severe outcomes (rehospitalization or death) in 972 individuals discharged from hospital admission due to COVID-19 at 7 centers in RECOVER-SUS, Brazil, from June 7, 2020, to March 31, 2021.**

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, NIV, non-invasive ventilation; Simplified Acute Physiology Score (SAPS) III. Variables found be associated ($p \leq 0.05$) with the analyzed outcome were entered into multivariate models adjusted for age and sex at birth. Procalcitonin level was not entered in the Cox analysis since this variable was not available in all centers. Variables from uni- and multivariate analysis were controlled by center in all Cox analyses. The severity of multicollinearity among variables entered in the multivariate model was quantified by the variance inflation factor (VIF). All variables entered in the multivariate model had VIF values < 2.00 [model mean VIF=1.09].

mortality rates during the pandemic in patients admitted into ICUs after adjusted for geographic location.[18] This might be explained by a better knowledge of the disease and its clinical management through the COVID-19 pandemic and/or changes in patients' profile due to the emergence of new variants with different severity. We observed that people admitted in 2021 were younger and seemed to have less severe disease at hospital admission compared to those hospitalized in 2020 (**Supplementary Table 4**). However, other factors might be related to the difference of in-hospital mortality observed between both periods, such as different virus lineages and a seasonal effect due to potential co-infections with other respiratory viruses in winter. In addition, a better survival might be associated with a lower level of occupation of hospital beds in the second period. Protection from vaccination was probably minimal if any, as a very low proportion (2.0%) of people in Brazil were fully vaccinated by this study's censure date (March 31, 2021).[19]

Importantly, we described relatively high incidence of severe outcomes (rehospitalization or death) after hospital discharge. To the best of our knowledge, this was one of the first studies conducted in Brazil, epicenter of the COVID-19 pandemic in South America, that described incidence of post-discharge outcomes. After hospitalization, 6.7% of the study participants initially discharged were readmitted for any cause or died after hospital discharge. This finding was aligned with previous multicentric studies that reported readmission rates from 4.5 to 7%.[20–22] Our study highlighted that older individuals and those admitted with severe COVID-19 disease remain at risk of complications after discharge. The higher mortality and rehospitalization rates in the elderly could be due to a lower avidity in mounting a humoral response in those individuals.[23] These results can help policymakers to reduce the burden of COVID-19 rehospitalizations in a short-term follow-up. However, it should be noted that hospital readmission is only one of multiple impacts of critical illness due to COVID-19. In the long term, patients recovering from severe COVID-19 may require lengthy rehabilitation before resuming work and other daily activities.[24] Therefore, the healthcare system will need to develop best practices and clinical recommendations for the management of COVID-19 patients after initial hospital discharge.

This study has some limitations. First, there was a considerable imbalance among the seven centers that

recruited participants for the RECOVER-SUS study (**Supplementary Table 1**), since 87% of participants were from Rio de Janeiro, mainly at INI-FIOCRUZ (n = 1325). However, we minimized a potential within-center clustering effect by adjusting all analyses by the variable "center". The variable age could be stratified in five sub-groups to evaluate the effect of different age strata on in-hospital mortality. However, this was unfeasible for analysis of incidence of outcomes post-hospital discharge due to a relatively low number of events (n = 65). Second, the COVID-19 vaccination status of participants at hospital admission was lacking. However, participants included in 2020 were not vaccinated, and COVID-19 vaccination officially started in 2021 (end of January) exclusively for elderly people (> 80 years) and healthcare workers. Moreover, only 2.0% of the Brazilian population were fully vaccinated on the date of censure for this analysis (March 31, 2021).[19] Third, the SARS-CoV-2 genetic lineages were available for a limited sub-sample of participants. Finally, despite repeated contact attempts, 12% of the participants discharged were not evaluated at and hence not included in the post discharge outcomes analysis. However, most clinical and laboratorial characteristics were similar between those participants included and excluded in this analysis (**Supplementary Table 5**). In addition, causes of death for those who died after discharge were unknown, which is a limitation of the present study.

In conclusion, this prospective study reported high in-hospital mortality rates in a multicentric, well characterized cohort of individuals hospitalized in Brazil. Older age, need of substantial ventilation support, especially mechanical ventilation, and high severity scores were independently associated with in-hospital mortality. Additionally, individuals aged ≥ 60 years and those with high SAPS-III score at hospital admission remained at high risk of rehospitalization and death after hospital discharge. This study underscores the need to monitor critically ill patients with COVID-19 after hospital discharge. Further studies are needed to understand the long-term impact of post-COVID-19 syndrome.

Contributors

HP: conceptualisation, investigation, formal analysis, writing – original draft, writing – review & editing; SWC: project administration, investigation, writing – review & editing; MPD, RM, LC, EJ, AMJ, EPG, EPN, HBA, LBG, MTF, PMAR, TF, VDR, ALCCT, HCN, PMOL, CS: data curation, investigation, writing – review & editing; RM, VP: software, investigation, formal analysis, writing – review & editing; KG, LF: Project administration; ECJ, CLXN, TNLS, AVS, GAP, FCQM: supervision, investigation, writing – review & editing; VGV, BG: conceptualization, supervision, project administration, funding acquisition, investigation, writing – review & editing

Data sharing statement

All data from the current study are reported in the manuscript, tables and supplementary material. In addition, data are available upon a reasonable request to Hugo Perazzo, the corresponding author, from The Evandro Chagas National Institute of Infectious Disease, Oswaldo Cruz Foundation, Rio de Janeiro (RJ), Brazil

Declaration of interests

Estevão Portela Nunes has received payment for lectures by Gilead; Alexandre Vargas Schwarzbold has received grants from AZ, MSD and Clover Biopharm; Fernanda Carvalho de Queiroz Mello has been acting as the President of the Society of Pneumonology and Tisiology fo the State of Rio de Janeiro (no payment) and Beatriz Grinsztejn has been participating in Advisory Board of Merck; GSK/ViiV and Janssen; The other authors declare no conflicts of interest.

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† The RECOVER-SUS Brasil Group is comprised of the following contributors

Instituto Nacional de Infectologia Evandro Chagas/Fundação Oswaldo Cruz, Rio de Janeiro (RJ), Brazil: Beatriz Grinsztejn, Valdilea G Veloso, Sandra W Cardoso, Hugo Perazzo, Maria Pia Diniz, Emilia Jalil, Lara Coelho, Rodrigo Moreira, Ronaldo Moreira, Kim Geraldo, Lucilene Freitas, Vinicius Pacheco, Hugo Boechat Andrade, Pablo Quesado, Estevão Portela Nunes, Pedro Azambuja Rodrigues, Andre Japiassu, Marcel Treptow Ferreira, Luciano Gouvea, Elias Gouvea, Juan Carlos Carrion Arias, Livia Cristina Fonseca Ferreira, Mayara Secco Torres da Silva, Mariana Machay Pinto Nogueira, Paula Simplicio da Silva, Lívia Dumont Facchinetti, Mônica Rodrigues da Cruz, Ionara Ferreira da Silva, Tania de Souza Brum, Monique do Vale da Silveira, Nathalia Rachid de Lacerda, Daniel Munoz McMahon Waite, Marina Harter Pamplona, Ana Claudia Barbosa da Silva, Ana Carolina Machado de Abreu Coelho, Cristiane

Gomes Cabral, Michelle Ramos da Silva, Luciana Alves Cruz de Castro, Driele Silva Cerqueira, Alexandra Saraça da Cruz, Rodrigo Pernas Cunha, Rita de Cássia Ottoline Cockrane, Tamiris Vilela Baião, Jessica Bezerra Felix, Tamiris Paixão da Silva, Flavia Cristina Serrão Lessa, Luiz Ricardo Siqueira Camacho, Kátia Sena Mendonça Derrico, Mauro Derrico, Natalia Ibiapino Proença, Sandro Coutinho Nazer da Costa, Wladmyr Davila da Silva, Lorena Marques dos Santos, Erika Verissimo Monteiro, Ulysses Padrão de Sousa

Hospital Federal Servidores do Estado do Rio de Janeiro, Rio de Janeiro (RJ), Brazil: Trevon Fuller, Ana Luisa de Oliveira, Clarisse Bressan, Leo Claude Sidi, Esaú Custódio João.

Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brazil: Carla Conceição dos Santos, Aline Lopes, Keila Suéllen de Moura Nunes Vide, Luana de Souza Andrade, João Paulo Bortot Soares, Fernanda Oliveira Baptista da Silva, Cláudio Ballesteros de Aguiar, Fernanda Mello.

Instituto de Infectologia Emilio Ribas, São Paulo (SP), Brazil: Karina Takeda, Gustavo Leal Dittmar, Bernardo Porto Maia, Nely Fantini, Ana Luiza Castro Conde Toscano, Tâmara Newman Lobato Souza.

Instituto Couto Maia, Salvador (BA), Brazil: Rafael Rodamilans de Macêdo, Kamila Verena de Jesus Vitória, Euclimeire da Silva Neves, Marijan Bárbara Teixeira Neves de Almeida, Betânia Mara de Freitas Nogueira, Verônica de França Diniz Rocha, Ceuci de Lima Xavier Nunes.

Hospital Regional São José, Florianópolis (SC), Brazil: Gustavo Araújo Pinto, Paula Macedo de Oliveira Lemos.

Universidade Federal de Santa Maria, Santa Maria (RS), Brazil: Alexandre Vargas Schwarzbold, Helena Carolina Noal, Gabriela de Britto Barcellos, Roberta Senger.

Hospital Municipal Ronaldo Gazolla; Secretaria Municipal de Saúde do Rio de Janeiro, Rio de Janeiro (RJ), Brazil: Roberto Rangel Alves Silva, Danielle Furtado de Oliveira, Bruno Cesar Sabino de Figueiredo, Rivelino Trindade de Azevedo, Douglas Souto da Silva Oliveira, Bruno de Almeida Campos Tessitore, Allyevison Ulisses Alves Cavalcanti, Sormame Dias, Francisco Charles Sousa Carvalho, Daniela da Silva Araújo Basilio, Luiza Chimeli Ormonde.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100244.

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