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

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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 1.42–4.43); 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 ≥2.19 (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.

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
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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. Brazil, the largest country in Latin America, is characterized by deep social and economic inequalities. 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). Relatively high intra-hospital mortality rates due to COVID-19 have been reported worldwide (from 17 to 38%). Estimates of hospital admission and mortality rates in Brazil have been based on retrospective studies and dataset analyses. 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. However, there is a paucity of available data regarding severe complications after hospital discharge in people hospitalized with COVID-19 in Latin America.

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 (Universidade Federal do Rio de Janeiro (UFRJ); Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro (HUCFF/UFRJ) in Rio de Janeiro (RJ); Instituto de Infectologia Evandro Chagas (INPA); Hospital Federal Servidores do Estado do Rio de Janeiro (HFSE/RJ) and Hospital Universitário Clementino Fraga Filho/Universidade Federal de Santa Maria (UFSC) 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. 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 32449420.4.2004.5252, 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. The 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. 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 ≤ 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 ≤ 0.05 assuming two-tailed tests.
Articles

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° 32449420.4.2004.5232); Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro (IRB n° 32449420.4.2013.5257); Instituto de Infectologia Emílio Ribas (IRB n° 32449420.4.2001.0061); Instituto Couto Maia (IRB n° 32449420.4.2010.0046); Hospital Regional São José (IRB n° 32449420.4.2009.013); 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 the 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/m²; 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) x10⁹/L and 0.98 (0.64–1.49) x10⁹/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 70.7–77.7): 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).
1,649 patients with symptoms of COVID-19 hospitalized at 7 centers from the RECOVER-SUS in Brazil from June 7, 2020 to March 31, 2021

1,589 patients with COVID-19 according to the WHO case definition hospitalized in Brazil

Hospital transfer
n=21 patients [1.3% (95%CI 0.9-2.0)]

Hospitalized at
censored date
n=31 patients [2.0% (95%CI 1.4-2.8)]

Hospital discharge
n=1,108 patients [69.7% (95%CI 67.4-71.9)]

In-hospital death
n=429 patients [27.0% (95%CI 24.8-29.2)]

No remote visit performed (n=136) due to lack of updated telephone contact

Remote contact to assess rehospitalization or death after hospital discharge
n=972 patients [87.7% (95%CI 85.7-89.5)]

Rehospitalization or death after hospital discharge
n=65 patients [6.7% (95%CI 5.3-8.4)]

Rehospitalization
n=42 patients

Death
n=9 patients

Rehospitalization and death
n=14 patients

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

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/m² (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...
### Table 1 (Continued)

|                          | All (n = 1589) | Discharged from hospital (n = 1160) | In-hospital death (n = 429) | P value   |
|--------------------------|----------------|------------------------------------|-----------------------------|-----------|
| **Socio-demographic characteristics** |                |                                    |                             |           |
| Male sex *               | 866 (54.5)     | 614 (52.9)                         | 252 (58.7)                  | 0.039     |
| Age *                    | 62 (50–70)     | 59 (47–68)                         | 68 (59–75)                  | <0.001    |
| Race/skin-color *        |                |                                    |                             | 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) *** |                |                                    |                             | 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 * ** |                |                                    |                             | 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 * | 164 (10.3)     |                                    |                             |           |
| BMI, Kg/m² *             |                |                                    |                             |           |
| BMI < 25 Kg/m²           | 394 (24.8)     | 271 (23.4)                         | 123 (28.7)                  |           |
| BMI=25–29.99 Kg/m²       | 518 (32.6)     | 366 (31.6)                         | 152 (35.4)                  |           |
| BMI=30–34.99 Kg/m²       | 349 (22.0)     | 269 (23.2)                         | 80 (18.6)                   |           |
| BMI=35–39.99 Kg/m²       | 144 (9.1)      | 104 (9.0)                          | 40 (9.3)                    |           |
| BMI ≥ 40 Kg/m²           | 101 (6.4)      | 79 (6.8)                           | 22 (5.1)                    |           |
| Unknown/not reported     | 83 (5.1)       | 71 (6.1)                           | 22 (5.1)                    |           |
| **Type-2 diabetes * **   |                |                                    |                             | 0.100     |
| Arterial Systemic Hypertension * |                |                                    |                             | 0.089     |
| COPD *                   | 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 * | 49 (3.1)       | 32 (2.8)                           | 17 (4.0)                    | 0.220     |
| **Symptoms**             |                |                                    |                             |           |
| Time from onset of symptoms to hospital admission, days * | 8 (5–11) | 8 (5–11) | 7 (4–10) | 0.002 |
| Fever *                  | 875 (55.1)     | 675 (58.2)                         | 200 (46.6)                  | <0.001    |
| Cough *                  | 1011 (63.6)    | 767 (66.1)                         | 244 (56.9)                  | <0.001    |
| Nasal congestion *       | 143 (9.0)      | 113 (9.7)                          | 30 (7.0)                    | 0.089     |
| Headache *               | 251 (15.8)     | 211 (18.2)                         | 40 (9.3)                    | <0.001    |
| Myalgia *                | 398 (25.0)     | 317 (27.3)                         | 81 (18.9)                   | 0.084     |
| Shortness of breath or difficulty breathing * | 1115 (70.2) | 317 (27.3) | 81 (18.9) | <0.001 |
| Anosmia *                | 203 (12.8)     | 170 (14.7)                         | 38 (7.7)                    | <0.001    |
| Ageusia *                | 153 (9.6)      | 128 (11.0)                         | 25 (5.8)                    | 0.002     |
| Digestive symptoms *     | 271 (17.1)     | 212 (18.3)                         | 59 (13.8)                   | 0.033     |
| WHO definition case *    |                |                                    |                             | 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 * |                |                                    |                             | <0.001    |
| WHO score = 4–5          | 103 (6.5)      | 54 (4.7)                           | 49 (11.4)                   |           |
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 95.1–98.3]] (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% CI 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...
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. 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%). 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. 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. 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. Our prospective study confirmed this finding, as we observed an increased

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, 2021 in participants hospitalized due to COVID-19.
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. Interestingly, metabolic features or co-morbidities were not associated with in-hospital mortality. 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 ethnic characteristics.

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

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.

| Variable                                      | 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 (vs 40–59 years)                    | 1.46 [1.67—2.44] | 0.153   | 1.20 [1.06—1.21] | 0.535   |
| BMI ≥ 30 kg/m² (vs < 30 kg/m²)                | 2.27 [1.37—3.76] | <0.001  | 1.89 [1.08—3.32] | 0.027   |
| SAPS-III score ≥ 5 (vs < 5)                   | 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   |              |         |
| BMI ≥ 30 kg/m² (vs < 30 kg/m²)                | 1.29 [1.05—1.57] | 0.013   | 1.08 [0.86—1.35] | 0.508   |
| Type-2 Diabetes (yes vs no)                   | 0.75 [0.62—0.92] | 0.007   | 0.97 [0.77—1.23] | 0.816   |
| Arterial Systemic Hypertension (yes vs no)    | 1.02 [0.84—1.23] | 0.846   |              |         |
| COPD (yes vs no)                              | 0.91 [0.74—1.12] | 0.363   |              |         |
| 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 leukocytes < 10 × 10⁹/L)     | 1.49 [1.22—1.81] | <0.001  | 1.00 [0.79—1.26] | 0.964   |
| Lymphopenia (vs lymphocytes > 1.00 × 10⁹/L)  | 1.09 [0.90—1.32] | 0.371   |              |         |
| Low platelet count (vs < 150 × 10⁹/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 U/L (vs < 80 U/L)             | 0.82 [0.62—1.09] | 0.168   |              |         |
| AST levels ≥ 80 U/L (vs < 80 U/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   |

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 to be associated (p ≤ 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].
Table 3 (Continued)

| Socio-demographic characteristics | All (n = 972) | No post-discharge outcomes (n = 907) | Post-discharge outcomes (n = 65) | P value |
|----------------------------------|--------------|-------------------------------------|---------------------------------|---------|
| Male sex * | 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 * | 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) * | 790 | | | |
| Up to 2268 | 185 (19.0) | 170 (18.7) | 15 (23.1) | |
| 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 * | 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 * | 870 | | | |
| BMI, Kg/m² * | 28.8 (25.0–33.1) | 29.0 (25.3–33.1) | 26.7 (23.0–31.3) | 0.009 |
| BMI = 25 Kg/m² | 227 (23.3) | 203 (22.4) | 24 (36.9) | |
| BMI = 25–29.99 Kg/m² | 314 (32.3) | 296 (32.6) | 18 (27.7) | |
| BMI = 30–34.99 Kg/m² | 227 (23.3) | 215 (23.7) | 12 (18.5) | |
| BMI = 35–39.99 Kg/m² | 93 (9.6) | 89 (9.8) | 4 (6.2) | |
| BMI ≥ 40 Kg/m² | 60 (6.2) | 57 (6.3) | 3 (4.6) | |
| Unknown/not reported | 51 (5.3) | 47 (5.2) | 4 (6.1) | |
| Type-2 diabetes * | 43 (4.4) | 43 (4.4) | 4 (6.2) | |
| Arterial Systemic Hypertension * | 343 (35.3) | 317 (35.0) | 26 (40.0) | 0.411 |
| COPD * | 40 (4.1) | 36 (4.0) | 4 (6.2) | 0.390 |
| Heart disease * | 78 (8.0) | 66 (7.3) | 12 (18.5) | 0.001 |
| Chronic kidney disease * | 19 (2.0) | 12 (1.3) | 7 (10.8) | < 0.001 |
| Symptoms | | | | |
| Fever * | 584 (60.1) | 552 (60.9) | 32 (49.2) | 0.064 |
| Cough * | 650 (66.9) | 608 (67.0) | 42 (64.6) | 0.690 |
| Nasal congestion * | 94 (9.7) | 89 (9.8) | 5 (7.7) | 0.580 |
| Headache * | 173 (17.8) | 170 (18.7) | 3 (4.6) | 0.004 |
| Myalgia * | 263 (27.1) | 247 (27.2) | 16 (24.6) | 0.650 |
| Shortness of breath or difficulty breathing * | 680 (70.0) | 635 (70.0) | 45 (69.2) | 0.890 |
| Anosmia * | 141 (14.5) | 137 (15.1) | 4 (6.2) | 0.048 |
| Ageusia * | 105 (10.8) | 103 (11.4) | 2 (3.1) | 0.038 |
| Digestive symptoms * | 176 (18.1) | 167 (18.4) | 9 (13.8) | 0.360 |
| WHO definition case * | | | | |
| 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 * | 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: 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 from 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 = 75), procalcitonin levels (n = 221), c-reactive protein (n = 239), ESR (n = 220).

| Characteristics | 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)                          | 0.410   |
| **Respiratory support at admission** |              |                                     |                                  |         |
| 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** |              |                                     |                                  |         |
| 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** |              |                                     |                                  |         |
| 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   |

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.
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Brazil were fully vaccinated by this study’s censure date and if any, as a very low proportion (2.0%) of people in the second period. Protection from vaccination was probably minimal if any, as a very low proportion (2.0%) of people in Brazil were younger and seemed to have less severe disease at hospital admission compared to those hospitalized in 2020 (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 by association ($p \leq 0.05$) 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. Variability 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].

| Variable | HR [95% CI] | p value | Variable | 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 $\geq$ 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 $< 5435$ per year (vs $\geq 5435$) | 1.48 [0.86–2.56] | 0.160 | | | |
| Schooling $< 8$ years (vs $\geq 8$ years) | 1.21 [0.71–2.06] | 0.483 | | | |
| BMI $\geq 30$ 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 $\geq 28$ days (vs $< 28$ days) | 1.25 [0.56–2.75] | 0.586 | | | |
| Leukocytosis (vs leucocytes $< 10 \times 10^9$/L) | 1.48 [0.88–2.48] | 0.135 | | | |
| Lymphopenia (vs lymphocytes $> 1.0 \times 10^9$/L) | 1.31 [0.79–2.20] | 0.298 | | | |
| Low platelet count (vs $> 150 \times 10^9$/L) | 1.59 [0.83–3.02] | 0.160 | | | |
| Creatinine levels $\geq 1.5$ 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 $\geq 80$ UI/L (vs $< 80$ UI/L) | 0.77 [0.38–1.57] | 0.472 | | | |
| AST levels $\geq 80$ UI/L (vs $< 80$ UI/L) | 1.17 [0.57–2.38] | 0.670 | | | |
| Protein-C reactive levels $\geq 20$ mg/L (vs $< 20$ mg/L) | 0.60 [0.30–1.19] | 0.141 | | | |
| SAPS III score $\geq 57$ (vs SAPS score $< 57$) | 3.67 [2.06–6.52] | < 0.001 | | 2.37 [1.22–4.59] | 0.010 |
| SOFA score $\geq 10$ (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.

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%.55–58 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.51 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.64 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 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

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recruited participants for the RECOVER-SUS study (Supplementary Table 4), 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). 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 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; MTD, RM, LC, EJ, AMJ, EPG, EPN, HBA, LBG, MTP, PMAR, TF, VDR, ALCCCT, 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
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Supplementary materials

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

References

1 Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(11):1708–1720.
2 Teixeira MC, Costa M, Pascho ESD, Carmo EH, Barreto FR, Penna GO. The achievements of the SUS in tackling the communicable diseases. Cienc Saude Colet. 2018;23(6):1819–1828.
3 Coronavirus Pandemic (COVID-19) – the data URL: https://ourworldindata.org/coronavirus-data. Accessed 8 March 2022.
4 Bertsimas D, Luikin G, Mingardi L, et al. COVID-19 mortality risk assessment: an international multi-center study. PLoS One. 2020;15(2):e0243162.
5 Kim I, Garg S, O’Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)- associated hospitalization surveillance network (COVID-NET). Clin Infect Dis. 2021;72(6):e2126–e2134.
6 Karagiannidis C, Mostert C, Hentschker C, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med. 2020;8(9):853–862.
7 Ranzani OT, Bastos LSI, Gelli JGM, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. Lancet Respir Med. 2021;9(4):478–481.

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