J Bras Pneumol. 2022;48(5):e20220083
https://dx.doi.org/10.36416/1806-3756/e20220083

Determinants of death in critically ill COVID-19 patients during the first wave of COVID-19: a multicenter study in Brazil

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Submitted: 7 March 2022.
Accepted: 7 June 2022.

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ABSTRACT

Objective: To evaluate clinical outcomes and factors associated with mortality, focusing on secondary infections, in critically ill patients with COVID-19 in three Brazilian hospitals during the first pandemic wave. **Methods:** This was a retrospective observational study involving adult patients with COVID-19 admitted to one of the participating ICUs between March and August of 2020. We analyzed clinical features, comorbidities, source of SARS-CoV-2 infection, laboratory data, microbiology data, complications, and causes of death. We assessed factors associated with in-hospital mortality using logistic regression models. **Results:** We included 645 patients with a mean age of 61.4 years. Of those, 387 (60.0%) were male, 12.9% (83/643) had undergone solid organ transplant, and almost 10% (59/641) had nosocomial COVID-19 infection. During ICU stay, 359/644 patients (55.7%) required invasive mechanical ventilation, 225 (34.9%) needed renal replacement therapy, 337 (52.2%) received vasopressors, and 216 (33.5%) had hospital-acquired infections (HAIs), mainly caused by multidrug-resistant gram-negative bacteria. HAIs were independently associated with a higher risk of death. The major causes of death were refractory shock and multiple organ dysfunction syndrome but not ARDS, as previously reported in the literature. **Conclusions:** In this study, most of our cohort required invasive mechanical ventilation and almost one third had HAIs, which were independently associated with a higher risk of death. Other factors related to death were Charlson Comorbidity Index, SOFA score at admission, and clinical complications during ICU stay. Nosocomial COVID-19 infection was not associated with death. The main immediate causes of death were refractory shock and multiple organ dysfunction syndrome.

Keywords: COVID-19/mortality; Sepsis; Multiple organ failure.

INTRODUCTION

The COVID-19 pandemic has continued to impact health care systems around the world since cases were first reported in China in December of 2019. A significant number of patients with COVID-19 develops critical illness and requires ICU management.[1] ICU mortality rates range from 8.1% to 97% in those requiring mechanical ventilation, depending on the country or the period of the pandemic.[2-5]

Older age and preexisting chronic health conditions are strongly associated with in-hospital mortality.[1,6,7] However, the mortality rates of critically ill COVID-19 patients are related not only to the severity of the disease but also to modifiable factors, such as the strain in the ICU, hospital acquired infections (HAIs), and organizational aspects.[8-11] Information on causality and mechanism of death is unclear and conflicting.[12,13] The impact of hospital-acquired COVID-19 is also inconsistent.[14] Although the most worrisome clinical feature of COVID-19 is ARDS requiring invasive mechanical ventilation (IMV) and respiratory failure is usually reported as the major cause of death,[15] the role of COVID-19-related HAIs, bacterial sepsis, and multiple organ dysfunction syndrome (MODS) needs to be further clarified, mainly in low- and middle-income countries (LMICs).[16]

The objective of the present study was to investigate the clinical features and factors associated with in-hospital mortality, focusing on secondary infections, in critically ill COVID-19 patients.

METHODS

This was a retrospective study involving adult COVID-19 patients admitted to the ICUs in three different hospitals in the city of São Paulo, Brazil. Hospital São Paulo is a public teaching hospital from the Federal University of São Paulo with 35 ICU beds dedicated to COVID-19 patients, whereas Hospital SEPACO and Hospital BP Mirante are private hospitals with 40 and 14 ICU beds dedicated to COVID-19 patients, respectively. The three ICUs were active before the pandemic and had appropriate staff,

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Financial support: None.

supplies, and well-established routines such as daily multidisciplinary rounds and clinical protocols. The three institutions developed specific guidelines for the management of COVID-19 patients, including the main aspects of care such as admission criteria, personal protection equipment use, noninvasive ventilation (NIV) support, IMV support, hemodynamic management, sedation, analgesia, nutrition, use of steroids, and rehabilitation. The Research Ethics Committee of the Hospital São Paulo approved the study (Protocol n. 38065220.9.1001.5505). Informed consent was waived because of the retrospective nature of the study.

All consecutive adult patients admitted to the participating ICUs between the 10th of March and the 31st of August, 2020, were included in the study. All patients had a confirmed diagnosis of COVID-19 or a high clinical suspicion. Confirmed cases were those with positive RT-PCR results of samples obtained from nasopharyngeal swabs, BAL fluid, or nasopharyngeal/tracheal aspirates. Suspected cases were defined based on the presence of clinical symptoms, compatible clinical history, and CT results highly suggestive of COVID-19. There were no exclusion criteria.

Our primary outcome was in-hospital mortality. We also collected secondary outcomes such as source of SARS-CoV-2 infection (community-acquired or hospital-acquired), clinical complications, solid organ transplant mortality, major cause of death, prevalence of secondary infections, and microbiological profile.

We collected data using a web-based platform (REDCap—Research Electronic Data Capture) that was accessed on a site-by-site basis. We used data from electronic medical records and from an electronic administrative database (Epimed Solutions, Rio de Janeiro, Brazil). We collected data regarding demographic and clinical characteristics (age, gender, comorbidities, source of ICU admission, diagnosis, and presence of bacterial/fungal coinfection), source of COVID-19 infection (community-acquired or hospital-acquired), severity of illness as determined by the Simplified Acute Physiology Score 3 (SAPS 3) and the SOFA score at ICU admission for patients with community-acquired and hospital-acquired COVID-19, main medications administered during the first 48 h from ICU admission (oseltamivir, antiviral therapy, antibiotics, antifungal agents, and corticosteroids), laboratory data, and presence of frailty as defined by a Clinical Frailty Scale score > 4.[17] we recorded the use of resources such as oxygen therapy, NIV, high-flow nasal catheter, IMV, vasopressors, renal replacement therapy (RRT), prone positioning therapy, extracorporeal membrane oxygenation, and nitric oxide during the ICU stay. We also recorded the main complications during the ICU stay, focusing on HAIs and isolated bacteria and fungi in cultures. We defined HAIs according to medical records and positive cultures. Reported or suspected HAIs were confirmed or ruled out by the authors of this study. The attending physicians and the ICU team, together with family members or legal representatives of the patients and in accordance with the Brazilian ethical rules, decided on palliative care. Patients were followed until hospital discharge. Data on length of ICU and hospital stay and the main immediate cause of death in the ICU reported by the attending physician were collected. The main immediate cause of death (Chart S1) was also confirmed or disproved by one of our research team members using a structured form adapted from previous studies.[12,18] We reported our results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[19]

Statistical analysis

No sample size calculations were performed for this exploratory, descriptive study. We used absolute and relative frequencies to describe categorical variables and medians and interquartile ranges or means and standard deviations to describe continuous variables. For comparisons between survivors and nonsurvivors, we used the Student's t test and the Mann-Whitney test for continuous variables with normal distribution and non-normal distribution, respectively. Categorical variables were compared with the Pearson's chi-square test.

Associations with in-hospital mortality were estimated using a logistic regression model. We included in the model all variables with a p value < 0.05 in the univariate analysis, including those at baseline and during evolution, as well as medications used during the ICU stay. In order to limit the number of variables to avoid overfitting, we assessed both biological plausibility and collinearity. We assessed collinearity first by examining the scatter plot matrix and Pearson's correlation coefficient for continuous variables or cross-tabulation for categorical variables. In the presence of collinearity (e.g., frailty score and age; type of infection and source of admission; and neutrophils and lymphocytes), the most clinically relevant variable was maintained in the model. Results were expressed an odds ratios and their respective 95% confidence intervals.

In all tests, significance was set at $p < 0.05$. Statistical analyses were carried out with the statistical software R 4.0 (R Core Team, 2018).

RESULTS

Between the 10th of March and the 31st of August, 2020, 645 adult patients diagnosed with COVID-19 and admitted to one of the participating ICUs were included in the study. The mean age was 61.4 ± 16.6 years. Most were men (387 [60.0%]) and White (434 [67.2%]). Demographic characteristics and comorbidities are described in Table 1. Hypertension and diabetes were the most common comorbidities (Charlson Comorbidity Index = 3.7 ± 2.6). Frailty was present in 20.4% of our patients, and 83 (12.9%) had a history of solid organ transplantation, mainly kidney transplant. The main source of admission was the emergency department (398 patients [62.1%]),

and 582 (90.8%) had community-acquired COVID-19. Table S1 shows laboratory data at admission.

Data regarding severity of disease and organ support during ICU stay are available in Table 2. The mean SAPS 3 was 53.8 ± 15.3, and the median SOFA score at ICU admission was 4.0 (2.0-7.0). Almost 21% (134/641) of our patients received vasopressors, and almost 30% (181/641) required IMV at ICU admission. The length of ICU stay was 13.9 ± 29.7 days, 55.7% (359/644) of our cohort received IMV, almost 30% (189/638) required prone positioning, and 35.1% (225/641) needed RRT. Table 3 describes the most common clinical complications during ICU stay. Overall, the ICU mortality rate was 39% (252/645). More than one third of our patients developed HAIs. Positive cultures were most commonly obtained from blood and tracheal aspirates, with *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* being the predominant gram-negative agents (Table 4). Data regarding drug resistance are presented in the supplementary material (Tables S2 to S6) and shows a high proportion of carbapenem resistance for both *Klebsiella pneumoniae* (> 90%) and *Pseudomonas aeruginosa* (50%).

In the multivariate analysis, the occurrence of HAIs was independently associated with a higher risk of death (OR = 3.57; 95% CI: 2.29-5.59; p < 0.001) even after adjustment for age and SOFA score. Patients with

Table 1. Demographic variables and comorbidities.[a]

Variable	In-hospital outcome		Total	OR	95% CI		p*
	Discharge (n = 371)	Death (n = 274)			2.5%	97.5%	
Age, years	58.1 ± 17.7	65.9 ± 13.9	61.4 ± 16.6	1,03	1.02	1.04	< 0.01
Skin color							
White	258/371 (69.5)	176/274 (64.2)	434/645 (67.3)	1 (ref)	-	-	-
Black	30/371 (8.1)	21/274 (7.7)	51/645 (7.9)	1,03	0.57	1.85	0.93
Brown	75/371 (20.2)	73/274 (26.6)	148/645 (22.9)	1,43	0.98	2.08	0.06
Yellow	8/371 (2.2)	4/274 (1.5)	12/645 (1.9)	0,73	0.22	2.47	0.62
Sex							
Men	220/371 (59.3)	167/274 (60.9)	387/645 (60.0)	1 (ref)	-	-	-
Women	151/371 (40.7)	107/274 (39.1)	258/645 (40.0)	0.93	0.68	1.28	0.67
Source of admission							
Emergency department	238/368 (64.7)	160/273 (58.6)	398/641 (62.1)	1 (ref)	-	-	-
Ward	93/368 (25.3)	73/273 (26.7)	166/641 (25.9)	1.17	0.81	1.68	0.1
Another ICU	10/368 (2.7)	29/273 (10.6)	39/641 (6.1)	4.31	2.05	9.10	< 0.01
Another hospital	27/368 (7.3)	11/273 (4.0)	38/641 (5.9)	0.61	0.29	1.26	0.18
COVID-19							
Community-acquired	348/368 (94.6)	234/273 (85.7)	582/641 (90.8)	1 (ref)	-	-	-
Hospital-acquired	20/368 (5.4)	39/273 (14.3)	59/641 (9.2)	2.90	1.65	5.10	< 0.01
Comorbidities							
Charlson Comorbidity Index	2.9 ± 2.5	4.7 ± 2.4	3.7 ± 2.6	1.33	1.24	1.42	< 0.01
Diabetes (not complicated)	75/371 (20.2)	53/274 (19.3)	128/645 (19.8)	0.95	0.639	1.401	0.78
Diabetes (complicated)	57/371 (15.4)	77/274 (28.1)	134/645 (20.8)	2.15	1.464	3.168	< 0.01
Chronic heart disease	46/370 (12.4)	74/272 (27.2)	120/642 (18.7)	2,63	1.75	3.96	< 0.01
Hypertension	221/371 (59.6)	201/272 (73.9)	422/643 (65.6)	1.92	1.37	2.70	< 0.01
Chronic kidney disease	58/371 (15.6)	76/271 (28.0)	134/642 (20.9)	2.10	1.43	3.09	< 0.01
Chronic neurologic disease	27/371 (7.3)	14/271 (5.2)	41/642 (6.4)	0.69	0.36	1.35	0.28
Dementia	21/371 (5.7)	10/271 (3.7)	31/642 (4.8)	0.64	0.30	1.38	0.25
Chronic hematologic disease	7/371 (1.9)	13/271 (4.8)	20/642 (3.1)	2.62	1.03	6.66	0.04
Smoking							
Current	16/274 (5.8)	22/236 (9.3)	38/510 (7.5)	1.84	0.94	3.63	0.08
Former	53/274 (19.3)	61/236 (25.8)	114/510 (22.4)	1.54	1.01	2.36	0.04
Obesity	90/371 (24.3)	41/273 (15.0)	131/644 (20.3)	0.55	0.37	0.83	< 0.01
BMI, kg/m²	27.6 ± 6.0	26.3 ± 6.3	27.0 ± 6.1	0.96	0.94	0.99	< 0.01
Solid organ transplant	28/371 (7.5)	55/272 (20.2)	83/643 (12.9)	3.10	1.91	5.05	< 0.01
Immunosuppressive therapy	38/371 (10.2)	71/270 (26.3)	109/641 (17.0)	3.13	2.03	4.81	< 0.01
Frailty (CFS > 4)				1.75	1.19	2.56	< 0.01
No	307/369 (83.2)	200/268 (74.6)	507/637 (79.6)				
Yes	62/369 (16.8)	68/268(25.4)	130/637 (20.4)				

ref: reference; and CFS: Clinical Frailty Scale. [a]Values expressed as n/N (%) or mean ± SD. *Fisher's exact test.

Table 2. Severity scores and treatment during ICU stay [a]

Variable	In-hospital outcome		Total	OR	95% CI		p*
	Discharge (n = 371)	Death (n = 274)			2.5%	97.5%	
First 24 h							
SAPS 3	47.5 ± 12.0	62.5 ± 15.2	53.8 ± 15.3	1.09	1.07	1.10	< 0.01
SOFA	2.0 [1.0-5.0]	6.0 [4.0-9.0]	4.0 [2.0-7.0][b]	1.39	1.31	1.48	< 0.01
Vasopressors	39/368 (10.6)	95/273 (34.8)	134/641 (20.9)	4.50	2.97	6.82	< 0.01
Renal replacement therapy	18/368 (4.9)	23/273 (8.4)	41/641 (6.4)	1.79	0.95	3.39	0.07
Oxygen therapy							
None	55/370 (14.9)	14/274 (5.1)	69/644 (10.7)	1 (ref)	-	-	-
Nasal catheter	213/370 (57.6)	117/274 (42.7)	330/644 (51.2)	2.16	1.15	4.05	0.02
High-flow nasal catheter	31/370 (8.4)	16/274 (5.8)	47/644 (7.3)	2.03	0.87	4.70	0.01
NIV	10/370 (2.7)	7/274 (2.6)	17/644 (2.6)	2.75	0.89	8.51	0.08
IMV	61/370 (16.5)	120/274 (43.8)	181/644 (28.1)	7.73	3.98	14.99	< 0.01
Medications within 48 h							
Oseltamivir	101/370 (27.3)	97/274 (35.4)	198/644 (30.7)	1.46	1.04	2.05	0.03
Ribavirin/lopinavir/ritonavir	100/371 (27.0)	97/274 (35.4)	197/645 (30.5)	1.49	1.06	2.08	0.02
Hydroxychloroquine	65/370 (17.6)	66/274 (24.1)	131/644 (20.3)	1.49	1.01	2.19	0.04
Azithromycin	168/371 (45.3)	120/274 (43.8)	288/645 (44.7)	0.94	0.69	1.29	0.71
Antibiotics	346/371 (93.3)	273/274 (99.6)	619/645 (96.0)	19.73	2.66	146.39	0.003
Antifungal therapy	2/371 (0.5)	9/274 (3.3)	11/645 (1.7)	6.27	1.34	29.24	0.02
Corticosteroids	154/371 (41.5)	148/274 (54.0)	302/645 (46.8)	1.66	1.21	2.27	0.002
Whole ICU stay							
Vasopressors	106/371 (31.5)	231/274 (68.5)	337/645 (52.2)	19.52	12.4	30.61	< 0.01
Renal replacement therapy	61/368 (16.6)	164/273 (60.1)	225/641 (35.1)	7.59	5.26	10.95	< 0.01
Ventilatory support							
High-flow nasal catheter	68/368 (18.5)	43/272 (15.8)	111/640 (17.3)	0.83	0.54	1.26	0.4
NIV	70/365 (19.2)	63/268 (23.5)	133/633 (21.0)	1.28	0.87	1.88	0.24
IMV	108/370 (29.2)	251/274 (91.6)	359/644 (55.7)	50.10	26.3	95.20	< 0.01
Duration of IMV, days	13.8 ± 13.6	13.6 ± 14.4	13.7 ± 14.1	-	-	-	0.9
Prone positioning	82/367 (22.3)	107/271 (39.5)	189/638 (29.6)	2.27	1.61	3.21	< 0.01
Nitric oxide	2/371 (0.5)	1/274 (0.4)	3/645 (0.5)	3.12	0.28	34.6	0.56
ECMO	0/367 (0.0)	2/273 (0.7)	2/640 (0.3)	-	-	-	0.18
Length of ICU stay, days	11.7 ± 29.2	16.8 ± 30.3	13.9 ± 29.7	-	-	-	0.03
Palliative care	3/370 (0.08)	44/272 (16.1)	47/642 (7.3)	12.67	0.98	162.25	0.07

SAPS 3: Simplified Acute Physiological Score; ref: reference; NIV: noninvasive ventilation; and IMV: invasive mechanical ventilation; and ECMO: extracorporeal membrane oxygenation. [a]Values expressed as n/N (%), mean ± SD, or median [IQR]. [b]N = 643. *Pearson's chi-square test, Student's t test, or Mann-Whitney test.

higher Charlson Comorbidity Index (OR = 1.15; 95% CI: 1.02-1.28; p = 0.02) and clinical complications, such as liver failure, cardiac arrhythmia, hand/foot ischemia, and hemorrhage, also had higher mortality rates (Table 5). The most common causes of death were refractory shock and MODS but not hypoxemia (Table 6).

DISCUSSION

In this retrospective study, we analyzed clinical and laboratorial characteristics, ICU support, clinical complications, and immediate cause of death in the ICU in a sample of 645 adult patients with COVID-19 admitted to the ICU. We found that most of our cohort required IMV and that almost one third needed RRT and had HAIs as a complication during their ICU stay. The main causes of death were refractory shock and MODS. Nosocomial infections as a complication at ICU admission were associated with higher mortality even after adjusting for baseline characteristics such as age, Charlson Comorbidity Index, solid organ transplant, and SOFA score.

The in-hospital mortality rate was 42.4% in our cohort. Several studies reported similar results, and patients who needed IMV and RRT had higher mortality rates (69.9% and 72.8% respectively).[2,3,5] In studies in Brazil, the reported mortality rates were usually high. Ranzani et al.[20] reported a high mortality rate (55%) in ICU patients in Brazil and an even higher rate for those on IMV (80%). However, severity of illness, as assessed by the use of organ support, is also high mainly in public hospitals. Ferreira et al.[5] reported the use of IMV, vasopressors, and RTT, respectively, in 79%, 73%, and 35% of the patients in a public referral hospital. Socolovithc et al.[4] reported data from

Table 3. Clinical complications during ICU stay.[a]

Variable	In-hospital outcome		Total	p*
	Discharge (n = 371)	Death (n = 274)	(N = 645)	
Acute coronary syndrome	0 (0.0)	2 (0.7)	2 (0.3)	0.15
Arrhythmias	23 (6.2)	79 (28.8)	102 (15.8)	< 0.01
Myocarditis/pericarditis	2 (0.5)	0 (0.0)	2 (0.3)	0.52
Deep vein thrombosis	11 (3.0)	11 (4.0)	22 (3.4)	0.64
Hand/feet ischemia	2 (0.5)	21 (7.7)	23 (3.6)	< 0.01
Hemorrhage	6 (1.6)	22 (8.0)	28 (4.3)	< 0.01
ICU readmission	16 (4.3)	17 (6.2)	33 (5.1)	< 0.01
Liver dysfunction	4 (1.1)	36 (13.1)	40 (6.2)	< 0.01
Hospital-acquired infection	70 (18.9)	146 (53.3)	216 (33.5)	< 0.01
Pleural effusion	4 (1.1)	7 (2.6)	11 (1.7)	0.12
Pneumothorax	8 (2.2)	16 (5.8)	24 (3.7)	0.06
Pulmonary embolism	9 (2.4)	12 (4.4)	21 (3.3)	0.37
Stroke	2 (0.5)	7 (2.6)	9 (1.4)	0.03
Seizures	8 (2.2)	12 (4.4)	20 (3.1)	0.06

[a]Values expressed as n (%). *Fisher's exact test or Pearson's chi-square test.

Table 4. Microbiological profile according to the source of infection.[a]

Agent	Sample					Total[b]
	Blood	Tracheal aspirate	Urine	Catheter tip	Blood from catheter	
Gram-negative bacteria						
Acinetobacter baumannii	2 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)
Acinetobacter sp.	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Escherichia coli	5 (0.8)	2 (0.3)	7 (1.1)	1 (0.2)	0 (0.0)	14 (2.2)
Klebsiella pneumoniae	21 (3.3)	45 (7.0)	12 (1.9)	7 (1.1)	1 (0.2)	69 (10.7)
Pseudomonas aeruginosa	2 (0.3)	17 (2.6)	1 (0.2)	2 (0.3)	0 (0.0)	19 (2.9)
Other gram-negative bacillus	5 (0.8)	8 (1.2)	3 (0.5)	8 (1.2)	0 (0.0)	21 (3.3)
Gram-positive bacteria						
Enterococcus faecalis	3 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	6 (0.9)
Staphylococcus aureus	5 (0.8)	11 (1.7)	0 (0.0)	2 (0.3)	2 (0.3)	17 (2.6)
Other *Enterococcus* sp.	1 (0.2)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	4 (0.6)
Other *Staphylococcus* sp.	50 (7.8)	1 (0.2)	0 (0.0)	6 (0.9)	7 (1.1)	56 (8.7)
Other *Streptococcus* sp.	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Fungi						
Aspergillus spp.	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Candida albicans	1 (0.2)	16 (2.5)	10 (1.6)	1 (0.2)	0 (0.0)	25 (3.9)
Candida glabrata	1 (0.2)	1 (0.2)	4 (0.6)	0 (0.0)	0 (0.0)	6 (0.9)
Candida sp.	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	3 (0.5)
Other yeasts	1 (0.2)	1 (0.2)	4 (0.6)	1 (0.2)	0 (0.0)	7 (1.1)
Other pathogens	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

[a]Values expressed as n (%). Relative frequencies were calculated as number of positive samples divided by the total number of patients (N = 645) × 100. [b]A microorganism may have appeared in more than one culture.

a private hospital during the first wave of COVID-19 and observed lower rates of organ support with the use of IMV, vasopressors, and RTT, respectively, in 49.5%, 50.9% and 13.2% of the patients. We analyzed patients from both private and public hospitals and also demonstrated a high use of support for organ dysfunction. In our study, 55.7% of patients underwent IMV, approximately 20% used NIV or high-flow nasal catheter during ICU stay, and 35% needed RTT. Mortality rates are influenced by the severity of illness, and IMV and RRT are the interventions most commonly associated with death, being proxies for severity. We did not assess mortality according to the main source of income of hospitals, because previous studies in Brazil already demonstrated that convenience samples from public and private hospitals can bias the results.[21] In a previous random sample of patients admitted to Brazilian ICUs, mortality rates of septic patients showed no differences between public and private institutions.[21]

Table 5. Multivariate analysis of factors associated with in-hospital mortality.

Variable	OR (95% CI)	p
Oseltamivir use within 48 h after ICU admission	1.88 (1.19-2.94)	0.006
Liver failure	13.60 (4.12-44.51)	< 0.001
Cardiac arrhythmias	3.16 (1.76-5.67)	< 0.001
Hand/foot ischemia	12.55 (2.41-65.57)	0.003
Hospital-acquired infection	3.60 (2.33-5.56)	< 0.001
Hemorrhage	3.97 (1.36-11.71)	0.012
Age	1.02 (1.00-1.03)	0.065
SOFA score at admission	1.30 (1.21-1.38)	< 0.001
Charlson Comorbidity Index	1.21 (1.09-1.35)	< 0.001

We included in the model all variables with a p value < 0.05 on Tables 1 to 3 in the univariate model, in the presence of collinearity, we selected the most clinically relevant variable (in bold): type of infection and admission type; frailty and age; SAPS 3, use of vasopressors, renal replacement therapy, ventilatory support, platelets, creatinine, bilirubin at admission and SOFA score at admission; diabetes, chronic heart disease, hypertension, chronic kidney disease, chronic hematologic disease, history of smoking and Charlson Comorbidity Index; obesity and BMI; immunosuppressive therapy and solid organ transplant. We excluded laboratory variables with missing data.

Table 6. Causes of death (n = 269 patients).

Cause	n (%)
Refractory shock	175 (65.1)
Multiple organ dysfunction	37 (13.8)
Hypoxemia	16 (5.9)
Central nervous system failure	9 (3.3)
Acute myocardial infarction	7 (2.6)
Hemorrhagic shock	3 (1.1)
Pulmonary embolism	2 (0.7)
Other	20 (7.5)

Requião-Moura et al.[22] reported a mortality rate of 58.2% in kidney transplant patients with COVID-19 admitted to the ICU and a mortality rate of 75.7% in such patients if they had undergone IMV. Moreover, patients that required RRT had a mortality rate of 69.8%. Alberca et al.[23] analyzed the mortality among solid organ transplant patients and found that kidney and heart recipients presented with a higher risk of death when compared with liver recipients. Almost 35% of the patients in our cohort needed RRT, which is much higher than that reported in a previous study.[3] This finding could be explained by the number of patients with chronic kidney disease and kidney transplant recipients in our cohort. A multicenter study in Brazil included data from 35 kidney transplant centers, involving 1,680 hospitalizations and 577 COVID-19-related admissions to the ICU, and reported that 23.4% of the patients required RRT.[22] In part, our higher mortality rates in patients on IMV and RRT could be explained by the severity of the disease at ICU admission and the high proportion of transplant patients. Patients with a history of transplantation are immunosuppressed and at risk for more severe disease and HAIs.[24]

In our cohort there was a high incidence of HAIs (33.5%), *K. pneumoniae* and *P. aeruginosa* being the gram-negative bacteria most commonly isolated in cultures. Several studies have reported a high incidence of and mortality from secondary HAIs in patients with COVID-19.[9,25] Data from Italy on 774 adult patients with severe COVID-19 in 8 Italian hub hospitals showed that 359 patients (46%) developed 759 HAIs.[9] The authors reported a high prevalence of multidrug-resistant bacteria (35% of all isolated agents). As expected, ventilator-associated pneumonia, bloodstream infections, and catheter-associated bloodstream infections were the most common HAIs.[9] HAIs prolonged IMV and hospitalization, and HAIs complicated by septic shock almost doubled mortality. There is no robust data from LMICs regarding HAIs in COVID-19 patients. A systematic review reported 44% of nosocomial infection in patients with COVID-19 in China, suggesting that the impact might be greater in LMICs than in developed countries.[26] Our data showed that HAIs, which potentially can lead to sepsis, were associated with mortality even after adjusting for baseline characteristics, suggesting that preventive measures are key to reduce COVID-19-associated mortality in LMICs.

In the present study, 56 patients (9.2%) had hospital-acquired COVID-19. Read et al.[27] estimated that almost 11.3% of COVID-19 cases occurred after hospital admission in the United Kingdom. Earlier in the beginning of the COVID-19 pandemic, Wake et al.[28] described similar results. Recently, a meta-analysis reported that hospital-acquired COVID-19 is associated with a higher risk of mortality when compared with community-acquired COVID-19, especially in immunosuppressed patients.[14] In our study, we did not observe the same results. One of the potential reasons might have been the high mortality rates even for community-acquired COVID-19 in our population, which might have biased the results.

The most common causes of death in our cohort were refractory shock and MODS, differently from other studies in which respiratory failure was the main cause of death, with a smaller proportion of patients dying from shock and multiorgan failure.[13,15,29,30] Ketcham et al.[15] reported that the most common organ dysfunction prior to death was pulmonary failure (81.7%), septic shock being the primary cause of death in only 26.8% of the cases. Gupta et al.[30] analyzed the cause of death in 787 patients and found that 92.7% of those

died from respiratory failure; however, almost 40% also had septic shock. Data from LMICs are scarce, but Aggarwal et al.[11] recently reported sepsis and MODS as the major causes of death in COVID-19 patients in India, followed by ARDS and cardiogenic shock. One possible explanation for the inconsistency in mortality rates and main causes of death might be related to hospitals' financial resources, as previously reported for sepsis.[21,31] Main causes of death are influenced by the rates of bacterial and fungal sepsis as a consequence of HAIs, which probably lead to a higher frequency of refractory septic shock and MODS. Previous data already suggested that the rates for HAIs are higher in resource-poor settings.[32] In addition, overcrowding in ICUs, temporary ICU beds, lack of trained and experienced health care workers, low nurse-to-patient staffing ratios, burnout syndrome in staff, insufficient medical equipment and supplies, antibiotic stewardship, personnel workload, and infection prevention may contribute to increased rates of HAIs, antibiotic overuse, and increased multidrug resistance.[10]

Our study has some strengths. This was a multicenter study, with detailed data collection focused on the relevance of secondary infections in the outcome of COVID-19 patients, including data on microbiology and multidrug resistance. However, it also has some limitations. First, this was a retrospective study that collected data from electronic m-health reports concerning the first wave of the COVID-19 pandemic in Brazil. Second, we estimated HAIs according to medical records and positive culture results, but we did not use a specific criterion to confirm the infection.

In conclusion, the COVID-19-related mortality rate in our cohort was similar to that in international reports, being very high in patients on IMV and RRT. Mortality was associated with the presence of HAIs even after adjustment for known risk factors such as comorbidities, solid organ transplant, disease severity, and age. Reflecting the relevance of sepsis, the main cause of death was refractory shock. Measures to HAI prevention should be emphasized to improve outcomes.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

FJSR: guarantor of the article from inception to publication. FJSR, FCA, MAS, EMF, DYVT, ESP, FSCS, MJ, NFN, FSVA, TMLA, FRM, and FGRF: study design. FJSR, FCA, MAS, EMF, FRM, and FGRF: data collection. FJSR, FCA, MAS, EMF, DYVT, ESP, FSCS, MJ, NFN, FSVA, TMLA, FRM, and FGRF: data analysis and interpretation, as well as drafting and review of the manuscript. All authors: final approval of the manuscript.

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