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Clinical characteristics and outcomes of patients hospitalized with COVID-19 in Brazil: Results from the Brazilian COVID-19 registry

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ABSTRACT

Objectives: To describe the clinical characteristics, laboratory results, imaging findings, and in-hospital outcomes of COVID-19 patients admitted to Brazilian hospitals.
Methods: A cohort study of laboratory-confirmed COVID-19 patients who were hospitalized from March 2020 to September 2020 in 25 hospitals. Data were collected from medical records using Research Electronic Data Capture (REDCap) tools. A multivariate Poisson regression model was used to assess the risk factors for in-hospital mortality.
Results: For a total of 2,054 patients (52.6% male; median age of 58 years), the in-hospital mortality was 22.0%; this rose to 47.6% for those treated in the intensive care unit (ICU). Hypertension (52.9%), diabetes (29.2%), and obesity (17.2%) were the most prevalent comorbidities. Overall, 32.5% required invasive mechanical ventilation, and 12.1% required kidney replacement therapy. Septic shock was observed in 15.0%, nosocomial infection in 13.1%, thromboembolism in 4.1%, and acute heart failure in 3.6%. Age >= 65 years, chronic kidney disease, hypertension, C-reactive protein $\geq$ 100 mg/dL, platelet count $< 100 \times 10^9$/L, oxygen saturation < 90%, the need for supplemental oxygen, and invasive mechanical ventilation at admission were independently associated with a higher risk of in-hospital mortality. The overall use of antimicrobials was 87.9%.
Conclusions: This study reveals the characteristics and in-hospital outcomes of hospitalized patients with confirmed COVID-19 in Brazil. Certain easily assessed parameters at hospital admission were independently associated with a higher risk of death. The high frequency of antibiotic use points to an over-use of antimicrobials in COVID-19 patients.

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Introduction

America has been the epicenter of the coronavirus disease 2019 (COVID-19) pandemic for the past few months, and Brazil ranks third worldwide in terms of the total number of COVID-19 cases and second in terms of the number of deaths. The impact of COVID-19 has been devastating for the country, with all regions and states being affected (Barberia and Gómez, 2020; Cimerman et al., 2020). As of February 3, 2020, there were over 9.2 million confirmed cases and 226,000 deaths, and these figures are probably an underestimate (Lancet, 2020).

The clinical characteristics of COVID-19 patients and the disease severity can vary across studies from different countries (Huang et al., 2020; Matsunaga et al., 2020; Munblit et al., 2020; Richardson et al., 2020). Recently, attention has been drawn to social and economic conditions as being important determinants of COVID-19 infection and mortality rates (Gutierrez and Bertozzi, 2020; Nayak et al., 2020). Public measures to mitigate the spread of the virus are much more difficult to implement in low- and middle-income countries. Socioeconomic disparities compromise access to adequate sanitation for a section of the population, and there is less opportunity to work from home and more crowded housing in these countries. There are also typically a greater number of coexisting non-communicable diseases (NCD), which are often more severe and experienced at a younger age than in high-income countries (Bambra et al., 2020; Lancet, 2020). Additionally, there tends to be delayed access to health care, lower intensive care unit (ICU) capacity, and lower availability of diagnostic testing for the virus.

Brazil is a middle-income country of continental dimensions, characterized by deep social and economic inequalities and a high prevalence of infectious diseases, such as dengue fever and Chagas disease (Lorenz et al., 2020; Martins-Melo et al., 2014; Teixeira et al., 2018). On January 28, 2020, the first National Contingency Plan (NCP) for COVID-19 was published, based on scientific evidence and guidance from the World Health Organization. All of the 26 Brazilian states were encouraged to adapt the NCP according to local infrastructure and regional characteristics, as well as to provide for actions to combat the disease within their territories. Brazil declared COVID-19 a public health emergency on February 3, 2020, and the Quarantine Law (Law Number 13,979) was approved on February 6, which aimed to protect the population by laying down measures concerning isolation, quarantine, compulsory notification, epidemiological investigation, and temporary restrictions on entering and leaving the country. The first case of coronavirus in Brazil was registered on February 26, 2020 in São Paulo (Croda et al., 2020). Non-essential businesses, industries, and services were closed all over the country from March 2020 to June 2020, and most teaching institutions have been closed since March 2020. Lockdowns were imposed in an attempt to contain the virus, but these were limited to a few cities (Aquino et al., 2020).

The Brazilian health system is composed of a complex network of service providers, which fall into three different subsectors: (i) public, which is free for all Brazilian citizens, with services financed and provided by governments at the federal, state, and municipal levels; (ii) private; and (iii) private health insurance, which includes a variety of plans. People may use the services in any of the three subsectors, depending on the ease of access and their ability to pay (Almeida-Filho, 2011; Uauy, 2011). The country is very heterogeneous in terms of the climate, economy, access to healthcare, and population demographics. Overall, Brazil's population is highly mixed, and there are various levels of African, European, Asian, and Indigenous genetic ancestries (Marson and Ortega, 2020). The pandemic has impacted the public health system and the population in an uneven way; there is no medical support for all which takes into consideration each particular state's characteristics (Lancet, 2020; Marson and Ortega, 2020; Neiva et al., 2020). Specific hospitals for treating COVID-19 patients were built in several state capitals and in the most populous cities. Sao Paulo, the biggest city in Brazil, has been the epicenter of the pandemic in the country.

Due to differences in the epidemiological profiles, socioeconomic conditions, and climate, it is not possible to predict whether the clinical characteristics of patients who are hospitalized due to COVID-19 and the determinants of disease severity in Brazil will be the same as those observed in China and Europe (Bambra et al., 2020). Determining the characteristics of hospitalized COVID-19 patients, the need for resources, and their clinical outcomes is of utmost importance to support clinical decision making and public health management. We therefore performed a multicenter study aimed at characterizing the clinical, laboratory, and imaging features of patients with COVID-19 admitted to Brazilian hospitals, as well as recording their outcomes. Additionally, we explored risk factors associated with in-hospital mortality.

Methods

The Brazilian COVID-19 Registry is an ongoing retrospective, multicenter, observational study. It is a partnership between 36 Brazilian hospitals. At the time of this study, 25 of the hospitals were actively participating. These hospitals are located in 11 different cities that cover three Brazilian states (Minas Gerais, Rio Grande do Sul, and São Paulo). Twelve are public hospitals, five are hospitals that provide exclusively private services, and eight are 'mixed' hospitals that provide both public and private services. The ongoing study is being conducted according to a predefined protocol.

Study cohort

All patients with laboratory-confirmed COVID-19 admitted to the participating hospitals were consecutively enrolled. Although hospitals started enrolling patients on different dates, the medical records were reviewed so that all patients were included who had been admitted from March 1, 2020. A COVID-19 diagnosis was confirmed through real-time reverse transcription polymerase chain reaction (RT-PCR) tests on nasopharyngeal or oropharyngeal swabs. Otherwise, serum or plasma serological assays were run to detect the presence of Immunoglobulin M (IgM) antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in accordance with guidance from the World Health Organization (World Health Organization, 2020a).

For the purposes of the present study, patients were included if they were no longer hospitalized and had been entered into the database by September 19, 2020. Patients who had been transferred to another hospital within the first 3 days following admission were only included if data was available from the second hospital; otherwise, they were excluded (Figure 1). A prespecified sample size was not calculated, as all patients who met the inclusion criteria were included.

Data collection

Medical records were reviewed to collect data concerning the patients' characteristics, including age, sex, and occupation (whether the patient was a healthcare professional); pre-existing comorbid medical conditions and medications taken at home; COVID-19-associated symptoms at hospital presentation; clinical assessment on the first, third, and fifth admission days; laboratory, imaging, electrocardiogram, and echocardiogram results; inpatient medication, treatment, and outcomes. The data collection instrument was designed with reference to COVID-19 guidelines

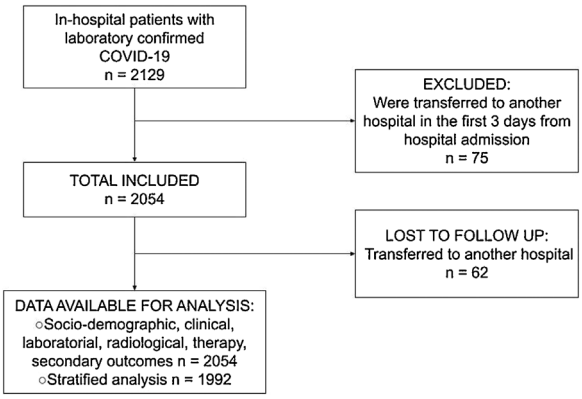

Figure 1. Flowchart of COVID-19 patients included in the study.

from the World Health Organization and the Brazilian Ministry of Health. The definitions used in the study are shown in the supplementary material.

The data was collected from the medical records by trained hospital staff or interns using Research Electronic Data Capture (REDCap) tools (Harris et al., 2019;Harris et al., 2009), hosted at the *Universidade Federal de Minas Gerais*. In order to ensure reliable data collection, all those involved underwent online training, and they were provided with a coding manual, developed for this research, guiding data collection for each variable (Supplementary Material 1). There was also ongoing communication with research staff (Gregory and Radovinsky, 2012). If there were any doubts about the accuracy and reliability of the data, the investigators contacted the relevant center and asked them to check the information.

The primary outcome was in-hospital mortality. Secondary outcomes included ICU mortality, clinical complications (acute kidney injury, acute hepatic injury, cardiovascular complications, bleeding, thromboembolic events, septic shock, disseminated intravascular coagulation, nosocomial infection, failed extubation), and resource utilization (admission to the ICU, ICU length of stay, use of invasive/non-invasive mechanical ventilation, number of days on invasive mechanical ventilation, need for renal replacement therapy, prone positioning, need for vasopressors, extracorporeal membrane oxygenation [ECMO], hospital length of stay). Acute kidney injury during hospitalization was defined according to the clinical practice guidelines of the Kidney Disease Improving Global Outcomes (KDIGO; Kellum et al., 2012). Acute hepatic injury was defined as an elevation in aspartate aminotransferase or alanine aminotransferase levels exceeding 15 times the upper limit of normal (Richardson et al., 2020).

The study was approved by the National Commission for Research Ethics (CAAE 30350820.5.1001.0008). Individual informed consent was waived owing to the pandemic situation and the use of deidentified data, based on medical chart review only.

This manuscript adheres to the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology; von Elm et al., 2007).

Statistical analyses

Descriptive analyses were run to summarize all of the variables, stratified by in-hospital survival status. The Shapiro-Wilk normality test was performed to determine whether the continuous variables were normally distributed. As all of the variables were found to have a non-normal distribution, they were summarized using medians and interquartile ranges (IQR). Categorical variables were summarized by calculating the counts and percentages. The study population was divided into ten age groups: 0–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, 80–89 years, and $\geq$ 90 years.

Fisher's exact test was used to compare proportions, and the Mann-Whitney U test was used to compare the medians of those patients who had died with those who survived. A p value lower than 0.05 was considered to be statistically significant.

A Poisson regression model with robust variance estimation (relative risk [RR], 95% confidence intervals [95% CI]) was used to determine whether the variables at hospital admission were potential risk factors for in-hospital mortality. This model was chosen as it estimates the relative risk, which is the parameter of primary interest, given the expectation of a high event rate (Zou, 2004). This analysis excluded patients who were assessed to need palliative care (n = 128).

The variables at hospital admission included the demographic characteristics; medical history data; outpatient medication; tobacco, alcohol, and illicit drug use; symptoms and clinical characteristics at admission; laboratory test results; X-ray, CT scan, electrocardiogram, and echocardiogram findings; and the type of hospital (Supplementary Material 1). As the Poisson regression model omits patients with missing values from the analysis (complete case analysis), we opted to run univariate analyses for those variables missing less than 25% of the values. These univariate analyses were adjusted for age and sex. For the multivariate model, age and sex were included, as well as variables with $p <$ 0.10 in the univariate analyses. For the continuous variables, cutoffs were literature-driven and prespecified, as recommended by the Prediction model Risk Of Bias ASsessment Tool (PROBAST; Wolff et al., 2019).

Mortality over time was calculated as the proportion of hospitalized patients with confirmed COVID-19 who died each day. A seven-day moving average was used to present these values, along with the numbers of hospital admissions, hospitalized patients, and in-hospital deaths due to COVID-19.

Statistical analyses were conducted using R version 4.0.2 (R foundation for Statistical Computing, Vienna, Austria), and IBM SPSS Statistics (IBM SPSS Statistics for Macintosh, Version 26.0 Armonk, NY: IBM Corp.).

Results

Of the 2,129 patients in the database, 75 were transferred to another hospital within the first 3 days following admission, and the outcomes were unknown (whether the patients had died or survived). Therefore, 2,054 patients were included in the present analysis. Of those, COVID-19 was confirmed by RT-PCR in 94.0%. Men represented 52.6% of the sample, with a median age of 58 years (IQR = 46–69), and women had a median age of 60 years (IQR = 48–73; p = 0.003). Baseline demographics, comorbidities, and medication are summarized in Table 1 and in the supplementary Table 1.

The in-hospital mortality rate was 22.0% (95% confidence interval [CI] = 20.2–23.9%), and the median time between admission and death was 12 days (IQR = 6–18). Figure 2 shows the number of admissions and the mortality over time. The apparently higher mortality in September is due to a reduction in the number of hospitalized patients at that time, corresponding to lower numbers in the database.

The in-hospital mortality and the hospital lenght of stay are presented in supplementary Table 2, with results shown for different age groups (age intervals of 10 years) and sex. Overall, there was no difference between men and women in terms of the in-hospital mortality (22.9% vs. 21.1%, p = 0.322), although it was higher for men at every 10-year age interval up to 69 years.

Table 1
Demographic characteristics and medical history data of the study population at baseline, stratified by vital status at discharge[a].

Variable	Total N (%) (n = 2054)	Died N (%) (n = 439)	Discharged alive N (%) (n = 1553)	*p* value
Age	59 (47-71)	70 (59 - 81)	56 (44 - 68)	< 0.001
Age ≥ 65 years	758 (36.9)	272 (62.5)	464 (30.1)	< 0.001
Male	1080 (52.6)	239 (54.4)	804 (51.8)	0.330
Healthcare professional	84 (4.1)	8 (1.8)	76 (4.9)	0.003
Comorbidities				
Cardiovascular diseases				
Hypertension	1087 (52.9)	310 (70.6)	746 (48.0)	< 0.001
Coronary artery disease	129 (6.3)	37 (8.4)	86 (5.5)	0.032
Heart failure	135 (6.6)	54 (12.3)	74 (4.8)	< 0.001
Atrial fibrillation/flutter	61 (3.0)	23 (5.2)	32 (2.1)	< 0.001
Stroke	60 (2.9)	28 (6.4)	31 (2.0)	< 0.001
Chagas heart disease	10 (0.5)	3 (0.7)	5 (0.3)	0.385
Rheumatic valve disease	4 (0.2)	0 (0.0)	4 (0.3)	0.582
None	888 (43.2)	112 (25.5)	751 (48.4)	< 0.001
Respiratory diseases				
Asthma	121 (5.9)	22 (5.0)	95 (6.1)	0.423
COPD	144 (7.0)	52 (11.8)	84 (5.4)	< 0.001
Pulmonary fibrosis	9 (0.4)	3 (0.7)	6 (0.4)	0.423
Metabolic diseases				
Diabetes mellitus	599 (29.2)	173 (39.4)	406 (26.1)	< 0.001
Obesity	353 (17.2)	67 (15.3)	278 (17.9)	0.225
Other health conditions				
Cirrhosis	20 (1.0)	9 (2.1)	9 (0.6)	0.008
Psychiatric illness	167 (8.1)	32 (7.3)	126 (8.1)	0.618
Chronic kidney disease	104 (5.1)	47 (10.7)	55 (3.5)	< 0.001
Rheumatological disease	38 (1.9)	6 (1.4)	30 (1.9)	0.545
HIV infection	28 (1.4)	8 (1.8)	19 (1.2)	0.350
Cancer	92 (4.5)	39 (8.9)	49 (3.2)	< 0.001
Previous transplantation	19 (0.9)	4 (0.9)	15 (1.0)	1.000
Surgical procedure < 90 days	108 (5.3)	40 (9.1)	61 (3.9)	< 0.001
Lifestyle habits				
Illicit drugs	24 (1.2)	3 (0.7)	20 (1.3)	0.447
Alcoholism	116 (5.6)	23 (5.2)	84 (5.4)	1.000
Current smoker	82 (4.0)	22 (5.0)	56 (3.6)	0.209
Previous smoker	311 (15.1)	83 (18.9)	219 (14.1)	0.016

Values in numbers (percentage) or median (interquartile range).
COPD: chronic obstructive pulmonary disease.
[a] Of the 2,054 patients included in the analysis, 62 patients were transferred to another hospital. As the final survival status was unknown, they were not included in the stratified analysis.

For the 84 healthcare workers the rate of who were COVID-19 patients, in-hospital mortality was 9.5%. The median age was 46 years [IQR = 37–55], the median number of comorbidities was 1 (IQR = 0–2), and the median time from symptom onset to presentation was 7 days (IQR = 5–10). When the results were adjusted for age and sex, being a healthcare worker was not significantly associated with a reduced risk of mortality (RR = 0.60; 95% CI = 0.30–1.10).

Overall, 79.8% of the patients had at least one comorbidity. The mortality of those who had at least one comorbidity was higher than those who had none (25.5% vs 8.6%, $p < 0.001$). In addition, the median number of comorbidities was higher among those who died compared to those who survived (2 comorbidities [IQR = 1–3] vs. 1 comorbidity [IQR = 1–2], $p < 0.001$). Hypertension (52.9%), diabetes mellitus (DM; 29.2%), and obesity (17.2%) were the most frequent comorbidities. Patients who died were more likely to have cardiovascular diseases, DM, chronic obstructive pulmonary disease, chronic kidney disease, and cancer (Table 1 and Supplementary Table 1).

Of the 2,054 patients, 52.8% were from public hospitals, 21.4% from private and 25.8% from mixed ones. Mortality was higher in the mixed (26.2%) and public (24.7%) hospitals compared to the private ones (10.8%, $p < 0.001$). Patients in the private hospitals were younger (median age = 55 years [IQR = 43–67]) and had a lower number of comorbidities (median number of comorbidities = 1 [IQR = 0–2]) than the patients in the public hospitals (median age = 59 years [IQR = 47–71]; median number of comorbidities = 2 [IQR = 1–3]) and the mixed hospitals (median age = 62 years [IQR = 49–74], $p < 0.001$; median number of comorbidities = 2[IQR = 1–3], $p < 0.001$).

Cough (65.1%), dyspnea (61.6%), and fever (59.0%) were the most common symptoms at hospital presentation. Dyspnea and neurological impairment at the time of hospital admission were more common among the patients who died (Table 2).

Seventy-three (3.6%) patients who were admitted to hospital for other reasons later developed COVID-19 during their stay. Excluding these patients, the median time from symptom onset to presentation was 6 days (IQR = 3–9). The median duration of symptoms prior to hospitalization was shorter for the patients who died compared to those who survived (median duration = 5 days [IQR = 2–8] vs. median duration = 7 days [IQR = 4–10], respectively; $p < 0.001$).

Laboratory and imaging findings are presented in Table 3 and in the supplementary Table 3. Patients who died from COVID-19 infection had higher mean white blood cell counts, higher absolute neutrophil counts, lower lymphocyte counts, higher creatinine levels, and a heightened inflammatory response with significantly elevated C-reactive protein (CRP) levels.

Chest X-rays were obtained for 1,219 patients (59.3%) at admission, and were found to be abnormal in 98.7%, the most common patterns being reticular interstitial thickening (53.0%) and ground-glass opacity (22.7%). Of the 913 patients (44.4%) who

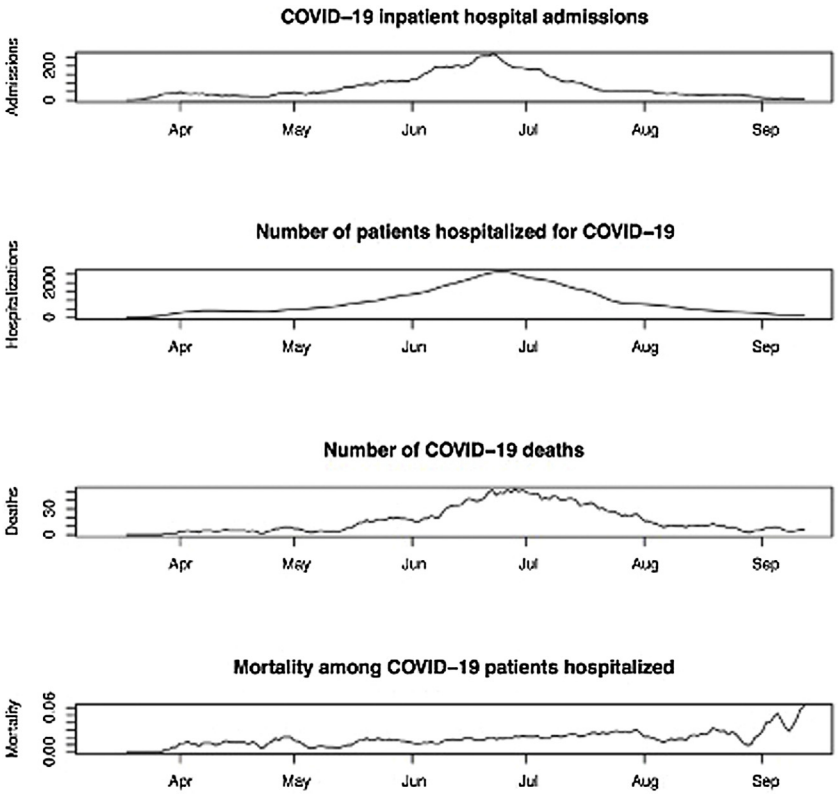

Figure 2. Seven-day moving average of (A) COVID-19 inpatient hospital admissions; (B) number of patients hospitalized for COVID-19; (C) number of COVID-19 deaths; (D) mortality among hospitalized COVID-19 patients (number of deaths/number of patients hospitalized).

had a chest CT scan at admission, most had abnormal findings (94.2%). Ground-glass opacities were the most frequent finding (89.2%). Of the 101 patients who had a normal chest X-ray and also underwent a chest CT scan, 89.1% had abnormalities: 79.2% had ground-glass opacities, 20.8% had consolidation, and 9.9% had pleural effusion.

Only 23.0% of the patients had an electrocardiogram recorded on admission and registered in the medical records. Patients who died had a higher frequency of atrial fibrillation/flutter, first degree atrioventricular block, complete atrioventricular block, and left anterior fascicular block.

Table 4 summarizes hospital medications and secondary outcomes. During hospitalization, 41.4% were treated in the ICU, 32.5% required invasive mechanical ventilation, 12.1% were treated with kidney replacement therapy, and 0.3% were placed on extracorporeal membrane oxygenation (ECMO). Mortality for those who required invasive mechanical ventilation was 59.5%.

Of the 860 patients who were admitted to the ICU, mortality was 47.6%. Among the 70.4% who required invasive mechanical ventilation, the median duration of mechanical ventilation was 10 days (IQR = 6–16; range = 0–63).

Although the univariate analysis showed public and mixed hospitals to be associated with a higher mortality risk compared with private hospitals (RR = 2.21; 95% CI = 1.62–3.02), this association was not found to be significant in the multivariate analysis (RR = 1.34; 95% CI = 0.89–2.04). In the multivariate Poisson regression model (Table 5) various factors were independently associated with a higher risk of death: age $\geq$ 65 years, male sex, chronic kidney disease (CKD), hypertension, high CRP levels, low blood platelet count, the need for supplemental oxygen, invasive mechanical ventilation at admission, and oxygen saturation $<$ 90% despite supplemental oxygen.

Discussion

This study reports clinical characteristics, laboratory and imaging findings, and in-hospital outcomes of 2,054 hospitalized COVID-19 patients in 25 Brazilian hospitals. In line with other studies, the most frequent symptoms were a cough, shortness of breath, and fever (Borobia et al., 2020; Giacomelli et al., 2020; Goyal et al., 2020). Ageusia, anosmia, headaches, rhinorrhea, a dry cough, a sore throat, fever, myalgia, nausea, vomiting, and diarrhea were more common among patients who were discharged alive, while dyspnea and neurological abnormalities at admission were more common among the patients who died, although none of these were independent risk factors for mortality.

The overall mortality was 22.0%, which is similar to that found in studies in Spain and Italy (Borobia et al., 2020; Giacomelli et al., 2020), but higher than in studies in the US, Asia, France, Iran, Japan, Russia, Turkey, and the Democratic Republic of the Congo (Chen et al., 2020; Goyal et al., 2020; Jourdes et al., 2020; Matsunaga et al., 2020; Munblit et al., 2020; Myers et al., 2020; Nachega et al., 2020; Nikpouraghdam et al., 2020; Quisi et al., 2020; Richardson et al., 2020; Yu et al., 2020).

The mortality rate for patients requiring invasive mechanical ventilation during the hospital stay was 59.5%, which is higher than that observed in a recent metanalysis which included 5,7420 adult patients in 69 studies across 23 countries (45% [95% CI = 38–52%]; Lim et al., 2020). The majority of the studies included in the metanalysis were from developed countries. We hypothesize that the higher mortality rate may relate to differences in access to healthcare, which tends to be delayed in developing countries such as Brazil, with lower availability of intensive care unit (ICU) beds, a lower healthcare provider to patient ratio, and poorer quality ventilators. Owing to the need for a rapid increase in ICU capacity,

Table 2
Clinical data at presentation of the study population[a].

Variable Symptoms	Total N (%) (n = 2052)	Died N (%) (n = 439)	Discharged alive N (%) (n = 1551)	*p* value
Adynamia	471 (23.0)	92 (21.0)	364 (23.5)	0.275
Ageusia	132 (6.4)	9 (2.1)	117 (7.5)	< **0.001**
Anosmia	201 (9.8)	27 (6.2)	171 (11.0)	**0.002**
Arthralgia	24 (1.2)	3 (0.7)	21 (1.4)	0.328
Headache	406 (19.8)	43 (9.8)	354 (22.8)	< **0.001**
Rhinorrhea	278 (13.5)	35 (8.0)	237 (15.3)	< **0.001**
Diarrhea	288 (14.0)	39 (8.9)	239 (15.4)	< **0.001**
Dyspnea	1265 (61.6)	303 (69.0)	924 (59.6)	< **0.001**
Sore throat	217 (10.6)	31 (7.1)	180 (11.6)	**0.006**
Fever	1212 (59.1)	221 (50.3)	959 (61.8)	< **0.001**
Hemoptysis	14 (0.7)	2 (0.5)	11 (0.7)	0.745
Hyporexia	229 (11.2)	47 (10.7)	175 (11.3)	0.797
Irritability	4 (0.2)	1 (0.2)	3 (0.2)	1.000
Neurological manifestations	44 (2.1)	16 (3.6)	24 (1.5)	**0.011**
Myalgia	551 (26.9)	69 (15.7)	473 (30.5)	< **0.001**
Nausea / vomiting	241 (11.7)	36 (8.2)	200 (12.9)	**0.007**
Skin rash	6 (0.3)	0 (0.0)	6 (0.4)	0.349
Productive cough	277 (13.5)	61 (13.9)	206 (13.3)	0.751
Dry cough	1075 (52.4)	183 (41.7)	863 (55.6)	< **0.001**
Clinical assessment at admission				
	(n = 1782)	**(n = 375)**	**(n = 1351)**	
Glasgow < 15	308 (17.3)	161 (42.9)	128 (9.5)	< 0.001
	(n = 2050)	**(n = 439)**	**(n = 1549)**	
Inotrope use	124 (6.0)	78 (17.8)	40 (2.6)	< 0.001
	(n = 1811)	**(n = 338)**	**(n = 1419)**	
SBP < 100 mmHg among the patients without inotrope	167 (9.2)	44 (13.0)	115 (8.1)	0.006
	(n = 1972)	**(n = 426)**	**(n = 1488)**	
HR > 100 bpm	436 (22.1)	125 (29.3)	304 (20.4)	< 0.001
	(n = 1607)	**(n = 365)**	**(n = 1242)**	
RR ≥ 24 irpm	503 (30.4)	135 (37.0)	347 (27.9)	0.001
	(n = 1264)	**(n = 261)**	**(n = 971)**	
Fever	186 (14.7)	32 (12.3)	151 (15.6)	0.203
	(n = 1964)	**(n = 405)**	**(n = 1502)**	
Peripheral oxygen saturation < 90%	263 (13.4)	105 (25.9)	151 (10.1)	< 0.001
Supplemental oxygen requirement	**(n = 2044)**	**(n = 437)**	**(n = 1547)**	
None	1157 (56.5)	157 (35.9)	973 (62.9)	< 0.001
1–6 L/min	606 (29.6)	105 (24.0)	476 (30.8)	
≥ 7 L/min	105 (5.1)	58 (13.3)	46 (2.9)	
Invasive mechanical ventilation	178 (8.7)	117 (26.8)	52 (3.4)	

Values in numbers (percentage).
HR: heart rate, SBP: systolic blood pressure, RR: respiratory rate.
[a] Of the 2,054 patients included in the analysis, 62 patients were transferred to another hospital. As the final survival status was unknown, they were not included in the stratified analysis. The total number of valid cases for each analysis is presented.

professionals who were not adequately trained in intensive care had to work in the ICU. This certainly may have contributed to higher mortality rates.

Reducing the mortality of hospitalized COVID-19 patients requires early medical intervention. Therefore, physicians need to quickly identify those patients who are at a higher risk of adverse outcomes. Easily assessed baseline parameters were associated with increased in-hospital mortality: age ≥ 65 years, male sex, chronic kidney disease, hypertension, CRP ≥ 100 mg/dL, blood platelet count < 100×10^9/L, oxygen saturation < 90%, supplemental oxygen requirement, and invasive mechanical ventilation. Old age, male sex, and the presence of comorbidities have previously been reported as important predictors of mortality in COVID-19 patients (Docherty et al., 2020; Liang et al., 2020; Zhou et al., 2020). Apart from the higher prevalence of comorbidities in the elderly, an age-related immune imbalance is believed to increase susceptibility to an unregulated inflammatory response (Sherwani and Khan, 2020).

The mortality rate of patients with at least one comorbidity was higher compared to those who had none, and the median number of comorbidities was higher among those who died compared to those who survived. Several previous studies have observed that patients with various comorbidities have a higher risk of in-hospital mortality due to COVID-19 (Gupta et al., 2020; Hajifathalian et al., 2020; Knight et al., 2020). Among these comorbidities, cardiovascular diseases (especially hypertension), DM, obesity, and respiratory diseases were the most prevalent. Interestingly, only CKD and hypertension were independent risk factors for mortality. The role of the kidney in COVID-19 is still under investigation, but it is well known that patients with chronic kidney disease tend to have less functional reserve and are therefore more commonly affected by a critical illness (Wang et al., 2020).

Conditions such as DM, hypertension, obesity, heart failure, and chronic obstructive pulmonary disease are frequent in patients with COVID-19, and they are also risk factors for the development of acute kidney injury (AKI) during the infection (Kovesdy et al., 2017; Nadim et al., 2020). These comorbidities are characterized by low-grade inflammation and increased immune senescence, although it remains unclear how this may affect the kidneys during a COVID-19 infection (Nadim et al., 2020). Recent studies have shown that a renin-angiotensin system imbalance due to COVID-19 can exacerbate the inflammatory state and result in a more severe clinical course of the disease (Lanza et al., 2020; Sanchis-Gomar et al., 2020).

Table 3
Laboratory parameters of the study population at admission[a].

Variable	Total N (n = 1986)	Died (n = 430)	Discharged alive (n = 1496)	*p* value
Hemoglobin (g/dL)	13.10 (11.85 – 14.30) **(n = 1967)**	12.35 (10.80 - 13.80) **(n = 427)**	13.20 (12.10 - 14.40) **(n = 1480)**	< 0.001
White blood cell count (x10^9/L)	6.90 (5.20 – 9.60) **(n = 1967)**	8.26 (6.07-12.18) **(n = 427)**	6.60 (5.00- 9.00) **(n = 1480)**	< 0.001
Neutrophils (x10^9/L)	4.99 (3.42 – 7.48) **(n = 1949)**	6.42 (4.43- 9.89) **(n = 417)**	4.62 (3.20-6.82) **(n = 1473)**	< 0.001
Lymphocytes (x10^9/L)	1.09 (0.76 – 1.54) **(n = 1954)**	0.91 (0.59-1.31) **(n = 424)**	1.13 (0.80- 1.60) **(n = 1470)**	< 0.001
Platelets (x10^9/L)	198.00 (153.00 – 259.75) **(n = 1904)**	180.50 (138.00- 238.00) **(n = 417)**	204.00 (158.00- 265.00) **(n = 1428)**	< 0.001
Creatinine (mg/dL)	0.90 (0.72 – 1.21) **(n = 1738)**	1.18 (0.87 - 2.00) **(n = 377)**	0.88 (0.70 - 1.09) **(n = 1309)**	< 0.001
Urea (mg/dL)	33.00 (24.00 – 49.00) **(n = 1373)**	51.00 (35.65 - 88.50) **(n = 335)**	29.42 (23.00 - 41.00) **(n = 989)**	< 0.001
Lactate (mmol/L)	1.40 (1.01 – 1.80) **(n = 1604)**	1.52 (1.20 - 2.00) **(n = 337)**	1.30 (1.00 - 1.70) **(n = 1224)**	< 0.001
C-reactive protein (mg/L)	80.00 (35.02 – 151.53) **(n = 1574)**	119.40 (64.00 - 200.95) **(n = 366)**	70.57 (31.10 - 132.50) **(n = 1157)**	< 0.001
Arterial pH	7.43 (7.39 – 7.46) **(n = 1542)**	7.40 (7.31 - 7.44) **(n = 354)**	7.44 (7.41 - 7.47) **(n = 1137)**	< 0.001
Arterial pCO2	35.30 (31.50 – 39.70) **(n = 1373)**	37.00 (31.00 - 45.70) **(n = 322)**	35.00 (31.70 - 39.00) **(n = 1010)**	< 0.001
Arterial pO2	75.50 (62.80 – 97.00) **(n = 1560)**	77.00 (59.58 - 102.25) **(n = 361)**	75.00 (64.00 - 94.10) **(n = 1150)**	0.899
Bicarbonate	23.10 (21.00 – 25.45)	22.20 (19.00 - 25.00)	23.50 (21.60 - 25.60)	< 0.001

Values in median (interquartile range) and numbers (percentage).
[a] Of the 2,054 patients included in the analysis, 62 patients were transferred to another hospital. As the final survival status was unknown, they were not included in the stratified analysis. The total number of valid cases for each analysis is presented.

Whereas in previous studies obesity was a risk factor for mortality (Docherty et al., 2020; Goyal et al., 2020; Jourdes et al., 2020; Matsunaga et al., 2020; Simonnet et al., 2020), this was not observed in our sample. This may be due to a limitation of the study, in that obesity was not directly measured by weight or body mass index, but rather was gathered from medical records, which may have ed to underreporting.

Concerning the laboratory results, patients who died from COVID-19 infection had higher mean white blood cell counts, higher absolute neutrophil counts, lower lymphocyte counts, and higher levels of CRP. A CRP $\geq$ 100 mg/dL was independently associated with mortality, which probably relates to the exaggerated inflammatory response and endothelial activation seen in severe cases (Girija et al., 2020).

Chest X-ray and chest CT findings were similar to those observed in other studies. Some rapid scoring systems to predict in-hospital mortality have incorporated imaging findings (Gupta et al., 2020). However, a recent systematic review did not find any significant correlation between radiologic findings and mortality rates (Mehraeen et al., 2020).

Our data highlights the importance of having a baseline ECG assessment for COVID-19 patients. In this study, only 23.0% of the patients had an electrocardiogram recorded on admission and registered in the medical records. From these, it was found that there was a higher frequency of ECG abnormalities at baseline among those patients who died of COVID-19. Increasing evidence suggests that cardiac involvement is common among hospitalized COVID-19 patients (Basu-Ray et al., 2020; Chang et al., 2020). Acute cardiac injury, arrhythmias, cardiomyopathy, and heart failure are potential complications of COVID-19, and they are associated with poor prognosis and higher mortality (Basu-Ray et al., 2020). Electrolyte disturbances and the use of medication that can cause a drug-induced long QT interval, such as hydroxychloroquine and azithromycin (both frequently used in this study), may increase the risk of serious arrhythmic complications. For these patients, the current recommendation is to assess the corrected QT interval (QTc) in a baseline ECG and to closely monitor the patients.

Our findings are in line with a recent meta-analysis, which reported the prognostic value of a decreased number of platelets in patients with COVID-19 (Bashash et al., 2020). Although the precise explanation is unknown, the cause is likely to be multifactorial. There are hypotheses that the virus directly infects bone marrow cells, resulting in abnormal hematopoiesis; that platelets are destroyed by the immune system; that endothelial damage triggers platelet activation, aggregation, and microthrombi formation in the lungs; and that platelet defragmentation occurs in the lungs (Bashash et al., 2020).

Public and mixed hospitals had higher mortality rates compared to the private hospitals (24.7% vs. 26.2% vs. 10.8%, $p <$ 0.001), and a univariate analysis showed that the former were associated with a higher risk of mortality. These differences could be explained by other variables that relate to the type of hospital, such as patient age, the presence of comorbidities, delayed access to healthcare, and the criteria for hospitalization. For instance, the average number of comorbidities was lower in patients from private hospitals (1 comorbidity [IQR = 0–2]) than in the public and mixed hospitals (2 comorbidities [IQR = 1–3]; $p <$ 0.001 for both). Once the collinearity of these variables had been removed, the outcomes no longer differed according to the type of hospital. It is relevant to note that this factor is especially important in the case of the Brazilian healthcare system, where users of public and mixed hospitals may have different socio-economical profiles. A recent study conducted using data from the Brazilian Surveillance System showed increased mortality in regions with a lower development index, as well as among black populations, thus demonstrating regional and ethnicity effects, respectively (Baqui et al., 2020). In addition, a low income has been associated with a higher incidence of comorbidities, such as hypertension,

Table 4
In-hospital medication, supportive care, and secondary outcomes[a].

Variable Medication	Total N (%) (n = 2037)	Died N (%) (n = 431)	Discharged alive N (%) (n = 1547)	*p* value
Antibiotic (except Azithromycin)	1790 (87.9)	412 (95.6)	1325 (85.6)	< **0.001**
Azithromycin	1569 (77.0)	301 (69.8)	1226 (79.3)	< **0.001**
Anticoagulant	1733 (85.1)	380 (88.2)	1304 (84.3)	**0.046**
Corticotherapy	1197 (58.8)	315 (73.1)	844 (54.6)	< **0.001**
Dexamethasone	825 (40.5)	186 (43.2)	609 (39.4)	0.25
Another corticoid	439 (21.6)	156 (36.2)	271 (17.5)	< **0.001**
Chloroquine	47 (2.3)	9 (2.1)	37 (2.4)	0.712
Hydroxychloroquine	183 (9.0)	47 (10.9)	132 (8.5)	0.129
Supportive care	**(n = 2037)**	**(n = 431)**	**(n = 1547)**	
Inotropes	540(26.5)	357 (82.8)	161 (10.4)	< **0.001**
ECMO	6 (0.3)	3 (0.7)	2 (0.1)	0.072
Prone position	344 (16.9)	180 (41.8)	150 (9.7)	< **0.001**
Volume resuscitation	346 (17.0)	213 (49.4)	117 (7.6)	< **0.001**
Noninvasive mechanical ventilation	185 (9.1)	75 (17.4)	106 (6.9)	< **0.001**
Secondary outcomes	**(n = 2054)**	**(n = 439)**	**(n = 1553)**	
Admission to the ICU	850 (41.4)	385 (87.7)	424 (27.3)	< **0.001**
Length of stay in the ICU	8 (4-15)	11.0 (6.0 - 17.0)	6.0 (3.0 - 13.0)	< **0.001**
Mechanical ventilation	667 (32.5)	377 (85.9)	257 (16.5)	< **0.001**
Number of days	9 (4-15)	10.0 (6.0 - 17.0)	7.0 (3.0 - 12.0)	< **0.001**
Failed extubation[b]	55 (8.2)	30 (8.0)	21 (8.2)	< **0.001**
Need for RRT	249 (12.1)	200 (45.6)	39 (2.5)	< **0.001**
Septic shock	308 (15.0)	235 (53.5)	60 (3.9)	< **0.001**
Disseminated intravascular coagulation	10 (0.5)	5 (1.1)	5 (0.3)	**0.048**
Bleeding	58 (2.8)	33 (7.5)	22 (1.4)	< **0.001**
Nosocomial infection	270 (13.1)	142 (32.3)	115 (7.4)	< **0.001**
HF	74 (3.6)	39 (8.9)	30 (1.9)	< **0.001**
AMI	19 (0.9)	9 (2.1)	7 (0.5)	**0.003**
Myocarditis	6 (0.3)	3 (0.7)	3 (0.2)	0.125
Thromboembolism	84 (4.1)	25 (5.7)	54 (3.5)	**0.036**
	(n = 1788)	**(n = 397)**	**(n = 1337)**	
Kidney injury	513 (28.7)	311 (63.5)	179 (13.4)	< **0.001**
	(n = 1074)	**(n = 284)**	**(n = 755)**	
Hepatic injury	29 (2.7)	21 (7.4)	7 (0.9)	< **0.001**

Values in numbers (percentage) or medians (interquartile range).
AMI: acute myocardial infarction, ECMO: extracorporeal membrane oxygenation, HF: heart failure, ICU: intensive care unit, RRT: renal replacement therapy.
[a] From the 2,054 patients included in the analysis, 62 patients were transferred to another hospital. As the final survival status was unknown, they were not included in the stratified analysis. The total number of valid cases for each analysis is presented.
[b] Percentage was calculated among patients who required invasive mechanical ventilation.

Table 5
Independent predictors of in-hospital mortality at hospital presentation.

Variables	Multivariate	
	RR (95% CI)	*p* value
Age ≥ 65 years	1.72 (1.31-2.26)	< 0.001
Male sex	1.35 (1.04-1.75)	0.026
Chronic kidney disease	1.59 (1.04-2.42)	0.032
Hypertension	1.42 (1.05-1.91)	0.021
Oxygen saturation < 90%	2.05 (1.52-2.78)	< 0.001
Supplemental oxygen requirement		
1-6 L/min	1.44 (1.02-2.04)	0.038
≥ 7 L/min	3.05 (1.98-4.7)	< 0.001
Invasive mechanical ventilation	4.96 (3.51-7.00)	< 0.001
CRP ≥ 100 mg/L	1.47 (1.12-1.94)	0.006
Platelets < 100×10^9/L	1.95 (1.23-3.10)	0.005

CI: confidence interval, CRP: C-reactive protein, IQR: interquartile range, RR: relative risk.

cardiovascular disease, chronic kidney disease, and obesity (Singu et al., 2020). It is plausible that factors that might have been indicative of a poor prognosis could have been compensated by excellent care in the public health system.

Although Brazil is a country with one of the highest COVID-19-related death tolls among healthcare workers, this relates to the absolute number of cases rather than to the mortality rate (Domínguez-Varela, 2020). In our study, the mortality of patients who were healthcare workers was lower than in the overall group of patients. This may relate to their younger age, lower prevalence of comorbidities, and ability to identify early signs of deterioration.

The analysis of secondary outcomes supports the growing body of evidence pointing to the multisystemic nature of COVID-19, which affects not only the respiratory system, but also the kidneys, cardiovascular system, and nervous system. Acute kidney injury was seen in almost a third of the patients and in over 68% of those who died. This is higher than in previous reports (Borobia et al., 2020, Richardson et al., 2020), which is to be expected given the higher prevalence of hypertension and chronic kidney disease in our sample. It is thought that the kidneys are directly affected by COVID-19 (Diao et al., 2020).

Due to the heavy burden experienced by healthcare systems during the pandemic, there was an increased danger of abandoning good practice, and attention was likely to have been diverted away from monitoring for excess antimicrobial use and nosocomial infections (Nori et al., 2021; World Health Organization, 2020b, 2020c). In our cohort, antimicrobials were administered to around 90% of the patients. This proportion is even higher than the 72% found in a recent rapid review of 18 studies (Rawson et al., 2020). This concerning fact points to an overuse of antimicrobials in COVID-19 patients, even when evidence suggests that bacterial coinfection is infrequent in these patients (Rawson et al., 2020). The resemblance between the clinical presentation of severe

COVID-19 and bacterial or fungal sepsis is likely to underlie this excessive antimicrobial use.

Given these findings, a worrying potential consequence of the current pandemic is the propagation of antimicrobial resistance (Vincent et al., 2020). A recent study in a hospital in New York City has shown that 71% of COVID-19 patients received antibiotics, while only 4% had a true bacterial coinfection (Nori et al., 2021). This overuse of antibiotics may have contributed to the observed increase in candidemia, as well as to the increase (> 10% absolute increase) in the resistance of *K. pneumoniae*,*E. cloacae*, and *P. aeruginosa* to several classes of antibiotics, which was found by comparing the results of 2020 with those for 2019 at the same institution. In addition, five patients admitted during the pandemic became infected with New Delhi metallo-β-lactamase-producing *E. cloacae*, and four of them developed septic shock. The authors also observed a trend towards a higher mortality rate among patients who developed a multidrug-resistant infection (71% vs. 54%; $p = 0.12$; Nori et al., 2021). The potential impact on healthcare-associated infection rates is of much concern (Arshad et al., 2020). To address this situation, a comprehensive approach and international cooperation are required (World Health Organization, 2020b, 2020c). It is vital to have national and international protocols to guide diagnoses and decisions concerning secondary bacterial infections in COVID-19 and to encourage the implementation of stewardship principles when antimicrobials are necessary (World Health Organization, 2019). Additionally, infection prevention programs are greatly needed in order to monitor nosocomial infections, excess antibiotic use, and multidrug resistance (Arshad et al., 2020).

This study has a number of limitations. It was a retrospective analysis subject to the drawbacks of a patient records review. Certain variables could not be determined, such as the body mass index and the severity of the comorbidities. Some of the variables had missing data, in particular electrocardiographic data, as well as laboratory and imaging findings. This reflects the examinations performed in clinical practice in the hospitals. Seventy-five patients were excluded from the study sample. This represents a small percentage of the whole cohort, and they were not found to differ in terms of the baseline variables. The hospitals participating in the study were not randomly chosen. An invitation was sent by social media, radio, and through the National Institute of Science and Technology for Health Technology Assessment (*Instituto de Avaliação de Tecnologias em Saúde – IATS*) website, so the participating hospitals may not be representative of the whole healthcare system in Brazil. One could argue that studies based on the Influenza Surveillance Information System (SIVEP-Gripe) dataset could provide a more representative account of hospitalized patients in Brazil. However, the SIVEP-Gripe dataset has a restricted number of variables (i.e., it has a reduced set of comorbidities and symptoms, a lack of laboratory data, and no assessment of the proposed secondary outcomes; Ministério da Saúde, 2013). Additionally, as it is based on a mandatory registration system, the completion of the notification form might be compromised when patients are admitted to emergency departments due to the high demand (several incoming patients hourly), insufficient staffing, and the presence of severe cases that require more attention. Furthermore, the data entry with free-text fields from multiple locations and professionals causes an inherent contrast in the use of medical terms and descriptions, which leads to a lack standardization of data collection. Therefore, a complete and accurate medical history (including information about underlying diseases and a more detailed description of symptoms) is not always obtained (Nascimento et al., 2020).

One of the main strengths of the study is the fact that it is based on a database of real-life cases, which includes comprehensive data from a large number of patients in 25 different hospitals. As the hospitals are located in different regions of Brazil, this ensures the diversity of the population studied. The data were obtained by means of a detailed medical record review, which results in a higher degree of detail than would the electronic abstraction of structured data elements. The data was submitted to periodic auditing to ensure data quality and the analysis provided a thorough assessment of various outcomes in hospitalized COVID-19 patients. The data could be used to inform healthcare planning in preparation for the next phase of the pandemic. The next step would be to create and validate a prediction tool for in-hospital mortality to support frontline clinical decision making.

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Patient and public involvement

This was an urgent public health research study in response to a Public Health Emergency of International Concern. Patients and the public were not involved in the design, conduct, interpretation, or presentation of the results of this research.

Role of the funder/sponsor

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

Data are available upon reasonable request.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.01.019.

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