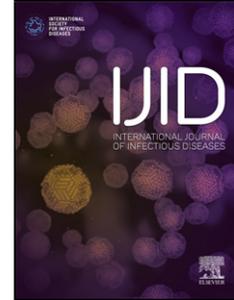Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof

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

Milena S. Marcolino, Patricia K. Ziegelmann, Maira V.R. Souza-Silva, Israel J. Borges do Nascimento, Luana M. Oliveira, Luanna S. Monteiro, Thaís L.S. Sales, Karen B. Ruschel, Karina P.M.P. Martins, Ana Paula B.S. Etges, Israel Molina, Carisi A. Polanczyk, Brazilian COVID- Registry Investigators

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

Authors: Milena S. Marcolino* PhD[1] (Marcolino MS - milenamarc@ufmg.br)

Patricia K. Ziegelmann PhD [2] (Ziegelmann PK- patricia.ziegelmann@ufrgs.br)

Maira V.R. Souza-Silva MD[1] (Souza-Silva MVR - mairavsouza@gmail.com)

Israel J. Borges do Nascimento[1] (Borges do Nascimento IJ - israeljbn@ufmg.br)

Luana M. Oliveira MSc[3] (Oliveira LM - luanalmo19.09@gmail.com)

Luanna S. Monteiro[1] (Monteiro LS - luannasmonteiro@gmail.com)

Thaís L.S. Sales MSc[4] (Sales TLS - thaislorennass30@yahoo.com.br)

Karen B. Ruschel PhD [2] (Ruschel KB - karenbruschel@gmail.com)

Karina P.M.P. Martins MSc[1] (Martins KPMP - kkpmprado2@gmail.com)

Ana Paula B.S. Etges PhD[2] (Etges APBS - anabsetges@gmail.com)

Israel Molina PhD [5] (Molina I - Israel.molina@fiocruz.br)

Carisi A. Polanczyk PhD [2] (Polanczyk CA - carisi.anne@gmail.com)

Brazilian COVID-19 Registry Investigators*

Affiliations:

[1] Medical School and University Hospital, Universidade Federal de Minas Gerais. Avenida Professor Alfredo Balena 190 sala 246, Belo Horizonte, Brazil

[2] Universidade Federal do Rio Grande do Sul and Institute for Health Technology Assessment (IATS/ CNPq). Rua Ramiro Barcelos, 2359. Prédio 21 | Sala 507, Porto Alegre, Brazil.

[3] Center for Research and Graduate Studies in Business Administration, Universidade Federal de Minas Gerais. Av. Presidente Antônio Carlos, 6627, Belo Horizonte, Brazil

[4] Universidade Federal de São João del-Rey. R. Sebastião Gonçalves Coelho, 400, Divinópolis, Brazil

[5] Vall d'Hebron University Hospital, PROSICS Barcelona. Passeig de la Vall d'Hebron, 119, 08035, Barcelona, Spain; Instituto René Rachou-FIOCRUZ Minas. Av. Augusto de Lima, 1715, Belo Horizonte, Brazil

* The full list of contributors (to be listed as coauthors) was provided at the end of the manuscript.

Running title: Characteristics and outcomes of patients hospitalized with COVID-19 in Brazil

Correspondence to: Milena Soriano Marcolino

University Hospital, Universidade Federal de Minas Gerais

Avenida Professor Alfredo Balena, 110 room 107. Ala Sul.

Santa Efigênia – Belo Horizonte – MG. Brazil.

CEP 30130-100

Highlights

- In-hospital mortality in COVID-19 Brazilian patients from 25 hospitals in 11 cities was 22·0%
- Among those who required invasive mechanical ventilation, mortality was 59.5%
- Easily assessed parameters at admission were associated with a higher risk of death
- Treatment included antibiotics in 87·1%
- Propagation of antimicrobial resistance may be a consequence of the pandemic

Abstract

Objectives: To describe clinical characteristics, laboratory and imaging findings, as well as in-hospital outcomes of COVID-19 patients admitted to Brazilian hospitals.

Methods: Cohort study of laboratory-confirmed COVID-19 patients hospitalized from March to September 2020 at 25 hospitals. Study data were collected from medical records using Research Electronic Data Capture (REDCap) tools. Multivariate Poisson regression model was used to assess risk factors for in-hospital mortality.

Results: Of 2054 patients (52.6% male, median age 58 [interquartile range 46-69] years old), in-hospital mortality was 22.0%, and 47.6% among those treated in the 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% 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 $\geq$65 years-old, chronic kidney disease, hypertension, C-reactive protein $\geq$100mg/dL, platelet count <100x10^9/L, oxygen saturation <90%, supplementary oxygen requirement 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 provides characteristics and in-hospital outcomes of consecutively hospitalized patients with confirmed COVID-19 in Brazil. 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.

Word count: 227

Keywords: COVID-19; SARS-CoV-2; hospitalizations; pandemic; Brazil; mortality; disease progression.

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 total number of COVID-19 cases and second in number of deaths. The impact of COVID-19 has been devastating on the country, with all regions and states being affected.(Barberia and Gómez, 2020, Cimerman et al., 2020) As of January 3, 2020, there are over 7.7 million confirmed cases and 195,000 deaths, and these figures are probably underestimated.(Lancet, 2020)

Clinical characteristics of COVID-19 patients and disease severity vary across studies from different countries.(Huang et al., 2020, Matsunaga et al., 2020, Munblit et al., 2020, Richardson et al., 2020) Recently, a lot of attention has been drawn to social and economic conditions as important determinants of COVID-19 infection and mortality rates.(Gutierrez and Bertozzi, 2020, Nayak et al., 2020) Difficulties in implementing public measures to mitigate virus spread are much higher in low- and middle- income countries. Socioeconomic disparities compromise access to adequate sanitation for part of the population, and there is a lower opportunity to work from home and a higher chance to live in crowded housing in those countries. They also usually have a greater number of coexisting non-communicable diseases (NCD), which are frequently more severe and experienced at a younger age.(Bambra et al., 2020, Lancet, 2020) Additionally, there are differences in access to healthcare, which tends to be delayed, intensive care unit (ICU) capacity and lower availability of diagnostic testing for the virus.

Brazil is a middle-income country with continental dimensions, characterized by deep social and economic inequalities and a high prevalence of infectious diseases, such as dengue 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 in the country, based on scientific evidence and World Health Organization guidance. All 26 states

4

were encouraged to adapt the NCP based on local infrastructure and regional characteristics, as well as to provide for actions to combat the disease in 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, with measures aimed at protecting the community, setting guidelines for 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 to June 2020, and most teaching institutions have been closed since March 2020. Lockdowns were used as a strategy to attempt to contain the virus contamination in only a few cities.(Aquino et al., 2020)

The Brazilian health system is composed by of a complex network of service providers, in three subsectors: (i) the public one, which is free to all Brazilian citizens and whose services are financed and provided by governments at the federal, state, and municipal levels; (ii) the private one; and (iii) the private health insurance one, with different forms of health plans. People may use services in any of the three subsectors, depending on ease of access or their ability to pay.(Almeida-Filho, 2011, Uauy, 2011) The country is very heterogeneous in terms of climate, economic backgrounds, access to healthcare and population. Overall, Brazil's population is highly mixed, and there are wide varieties in the levels of ancestral contribution of African, European, Asian and Indigenous genetic ancestries.(Marson and Ortega, 2020) The pandemic has been impacting the public health system and the population in an uneven way, there is no medical support for all which takes into consideration 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 most populous cities. Sao Paulo, the biggest city in Brazil, was the epicenter of the pandemic in the country.

Due to differences in epidemiological profile, 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 severe disease in Brazil are the same observed in China and Europe.(Bambra et al., 2020) Knowing 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 to characterise clinical, laboratory and imaging features, as well as outcomes of patients with COVID-19 admitted to Brazilian hospitals. 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 among 36 Brazilian hospitals. At the moment this study was conducted, 25 of them were active. The 25 participating hospitals are located in 11 cities from three Brazilian states (Minas Gerais, Rio Grande do Sul, São Paulo). Of those, 12 are public hospitals; five are hospitals that provide exclusively private services; and eight are "mixed" hospitals that provide both public and private services. The 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 study was based on medical record review, so they started from the first COVID-19 patient admitted from March 1, 2020. COVID-19 diagnosis was confirmed through real time polymerase-chain reaction (RT-PCR) nasopharyngeal and oropharyngeal swab testing or anti-

SARS-CoV-2 IgM detected in serological assay in serum or plasma sample, according to World Health Organization guidance.(World Health Organization, 2020a)

For the purpose of the present study, patients who had completed hospitalization and were in the database by September 19, 2020 were included. Patients who were transferred to another hospital within the first three days after being admitted were only counted if data from the hospital they wound up at was available, otherwise they were excluded (Figure 1). Sample size was not calculated, as all patients who met the inclusion criteria were included.

Data collection

Medical records were reviewed to collect data on patients' characteristics, including age, sex and occupation (whether the patient was a healthcare professional); pre-existing comorbid medical conditions and home medications; COVID-19 associated symptoms at hospital presentation; clinical assessment at admission, third and fifth admission days; laboratory, imaging, electrocardiographic and echocardiographic data; inpatient medications, treatment and outcomes. The data collection instrument was designed considering COVID-19 guidelines from the World Health Organization and the Brazilian Ministry of Health. Definitions can be assessed in Supplementary Material 1.

Study data were collected 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*. To ensure reliable data collection from the medical records, all data abstractors went through online training, a coding manual guiding data collection of each variable was developed (Supplementary Material 1), and there was 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 data abstractors from each center, and asked them to review the data.

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), resource utilization (admission to the ICU, ICU length of stay, use of invasive and 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 per Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines.(Kellum et al., 2012) Acute hepatic injury was defined as an elevation in aspartate aminotransferase or alanine aminotransferase of more than 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 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.(von Elm et al., 2007)

Statistical analysis

Descriptive analyses were used to summarize all variables, stratified by in-hospital survival status. The Shapiro-Wilk normality test was performed to check for the normal distribution of continuous variables. As all variables had non-normal distribution, they were summarized using medians and interquartile ranges (IQR). Categorical variables were summarized with counts and percentages. The study population was divided into ten age groups sorted by age-dependent categories: 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, ≥90 years-old.

Fisher's Exact Test was used to compare proportions and Mann- Whitney U test to compare medians between patients who died and those discharged alive. A p-value lower than 0.05 was considered statistically significant.

Poisson regression model with robust variance estimation (relative risk [RR], 95% confidence interval [95%CI]) was used to investigate variables at hospital presentation as potential risk factors for in-hospital mortality. This model was chosen as it estimates relative risks, which are the parameters of primary interest, because of expected high event rate.(Zou, 2004) This analysis excluded patients who were determined to need palliative care (n=128).

Variables at hospital admission included: demographic characteristics; medical history data; outpatient medications; tobacco, alcohol and illicit drug use; symptoms and clinical characteristics at admission; laboratory values; X-ray, CT-scan, electrocardiographic and echocardiographic findings; and type of hospital (Supplementary material 1). Poisson regression model omits patients with missing values from the analysis (complete case analysis), so we opted to include in univariate analysis variables with less than 25% missing values. Univariate analysis was adjusted for age and sex. For the multivariate model, age, sex and variables with p<0.10 in univariate analysis were included. For continuous variables, cut-offs 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 daily as the proportion between deaths and hospitalized patients confirmed to COVID-19. Seven-day moving average was used to present those values, as well as number of hospital admissions, number of hospitalized patients and in-hospital deaths due to COVID-19.

Statistical analyses are 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 2129 patients in the database, 75 were transferred to another hospital in the first three days from hospital admission and the final status as discharged alive or dead was not available. Therefore, 2054 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 (IQR, 46-69) years-old, and women had a median age of 60 (IQR, 48-73) years-old (p=0.003). Baseline demographics, comorbidities and medications are summarized in Table 1 and Supplementary Table 1.

In-hospital mortality 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 admissions and mortality over time. The apparent higher mortality in September is due to the reduced number of cases who were hospitalized and in the database at that time.

In-hospital mortality and hospital length of stay for those who died or were discharged alive by 10-year age intervals and sex are presented in Supplementary Table 2. Overall, there was no difference in in-hospital mortality between men and women (22.9% vs. 21.1%, p=0.322), but it was higher for men compared with women at every 10-year age interval up to 69 years old.

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

Overall, 79.8% patients had at least one comorbidity. Mortality among those with at least one comorbidity was higher compared with those with none (25.5% vs 8.6%, p<0.001),

and the median number of comorbidities was higher among those who died when compared to those discharged alive (2 [IQR 1-3] vs. 1 [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 2054 patients, 52.8% were from public hospitals, 21.4% from private and 25.8% from mixed ones. Mortality was higher in mixed (26.2%) and public (24.7%) hospitals when compared to private ones (10.8%, p<0.001). Patients from private hospitals were younger (median age 55 [IQR 43-67] years-old) and had a lower number of comorbidities (1 [IQR 0-2]) than the ones from public (59 [IQR 47-71]) and mixed hospitals (median age 62 [IQR 49-74] years-old, p<0.001; median number of comorbidities 2 [IQR 1-3] for both, 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 hospital admission were more common among patients who died (Table 2).

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

Laboratory and imaging findings are presented in Table 3 and 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 and increased inflammatory response with significantly elevated C-reactive protein (CRP) levels.

Chest X-rays were done in 1219 patients (59.3%) at admission and it was abnormal in 98.7% the most common pattern being a reticular interstitial thickening in 53.0% and ground

glass opacity in 22.7%. Of the 913 patients (44.4%) who did a chest CT at admission, most had abnormal findings (94.2%). Ground glass opacities were the most frequent finding, in 89.2% of cases. Of 101 patients who had a normal chest X-ray and also performed a chest CT, 89.1% had abnormalities: 79.2% had ground glass opacities, 20.8% consolidation and 9.9% pleural effusion.

Only 23.0% of 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 (IQR, 6-16; range 0-63 days) days.

Although at the univariate analysis public and mixed hospitals were associated with higher mortality risk compared with private ones (RR 2.21; 95% CI 1.62-3.02), this association was not significant in multivariate analysis (1.34; 95% CI 0.89-2.04). In multivariate Poisson regression model (Table 5), age ≥65 years-old, male sex, CKF, hypertension, high CRP levels, low blood platelet count, supplementary oxygen requirement, invasive mechanical ventilation at admission and oxygen saturation <90% despite supplementary oxygen were independently associated with higher risk of death.

Discussion

This study reports clinical characteristics, laboratory, imaging findings and in-hospital outcomes of 2054 hospitalized patients with COVID-19, and it represents the experience of 25 Brazilian hospitals. Like other series already published, the most frequent symptoms of patients with COVID-19 were cough, shortness of breath and fever.(Borobia et al., 2020, Giacomelli et al., 2020, Goyal et al., 2020) Ageusia, anosmia, headache, rhinorrhea, dry cough, 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 deceased ones, but none of them were independent risk factors for mortality.

The overall mortality was 22.0%, which is similar to 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)

Mortality among patients requiring invasive mechanical ventilation during hospital stay was 59.5%, higher than what was observed in a recent metanalysis which included 57420 adult patients in 69 studies across 23 countries (45% [95% CI 38-52%]).(Lim et al., 2020) The majority of studies included in the metanalysis are from developing countries. We hypothesize that the higher mortality rate may be related to differences in access to healthcare, which tends to be delayed in developing countries such as Brazil, lower intensive care unit (ICU) availability of beds, lower provider: patient ratio and worse quality of ventilators. With the need for a rapid increase in the number of ICU beds, professionals who were not adequately trained in intensive care had to work in ICU. This certainly may have contributed to higher mortality.

13

Reducing mortality of hospitalized COVID-19 patients needs early medical intervention. Therefore, physicians need to quickly identify those patients at higher risk of adverse outcomes. Easily assessed baseline parameters were associated with in-hospital mortality: age ≥65 years-old, male sex, chronic kidney disease, hypertension, CRP ≥100 mg/dL, blood platelet count <100x10^9/L, oxygen saturation <90%, supplementary oxygen requirement and invasive mechanical ventilation. Old age, male sex and comorbidities have been reported as important predictors of mortality of COVID-19 patients.(Docherty et al., 2020, Liang et al., 2020, Zhou et al., 2020) Besides the higher prevalence of comorbidities in the elderly, age-related immune imbalance is believed to increase susceptibility to the unregulated inflammatory response.(Sherwani and Khan, 2020)

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

Additionally, other conditions such as DM, hypertension, obesity, heart failure and chronic obstructive pulmonary, which are frequent in patients with COVID-19, are also risk factors for the development of AKI in those patients.(Kovesdy et al., 2017, Nadim et al., 2020) Those comorbidities are characterized by low-grade inflammation and increased immune senescence, although how these impact the kidney in COVID-19 patients is still

unknown.(Nadim et al., 2020) Recent studies have shown that renin-angiotensin system imbalance due to COVID-19 exacerbates the inflammatory state and provides a more severe clinical course of the disease.(Lanza et al., 2020, Sanchis-Gomar et al., 2020)

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) the same was not observed in our sample. This may be due to a study limitation, as obesity was not directly measured by weight or body mass index, but rather gathered from medical records, which may have led to underreporting.

Per 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 CRP. A CRP ≥100 mg/dL was independently associated with mortality, probably related to exaggerated inflammatory response and endothelial activation in severe cases.(Girija et al., 2020)

Chest X-ray and chest CT findings were similar to what was observed in other series. Some rapid scoring systems have incorporated imaging findings.(Gupta et al., 2020) In contrast, a recent systematic review does not show any significant correlation between radiologic findings and mortality rates.(Mehraeen et al., 2020)

Our data points out the need to highlight the importance of having a baseline ECG assessment in COVID-19 patients to Brazilian doctors. In this series, only 23.0% of patients had an electrocardiogram recorded on admission and registered in the medical records, and patients who were deceased had a higher frequency of ECG abnormalities on baseline. Accumulated evidence suggests that cardiac involvement is common among hospitalized COVID-19 patients.(Basu-Ray et al., 2020, Chang et al., 2020) Acute cardiac injury, arrythmias, cardiomyopathy and heart failure are potential complications in those patients, associated with worse prognosis and higher mortality.(Basu-Ray et al., 2020) Electrolyte

disturbances and the use of mediations that can cause drug-induced long QT interval, such as hydroxychloroquine and azithromycin, which were frequently used in this series, may increase the risk of serious arrhythmic complications. Therefore, the current recommendation is to assess QTc in a baseline ECG and close monitoring of those patients.

Our findings are in line with a recent meta-analysis, which reported the prognostic value of decreased number of platelets in patients with COVID-19.(Bashash et al., 2020) Although the precise explanation is unknown, it is likely multifactorial. There are some hypothesis of direct infection of bone marrow cells by the virus, resulting in abnormal hematopoiesis; platelet destruction by the immune system; endothelial damage triggering platelet activation, aggregation and microthrombi in the lung; and deranged platelet defragmentation in the lungs.(Bashash et al., 2020)

Public or mixed hospitals had higher mortality rates compared with private ones (24.7% vs. 26.2% vs. 10.8%, p<0.001), and they were associated with higher mortality risk at univariate analysis. Those differences could be explained by the coexistence of other variables (age, comorbidities; delayed access to healthcare, different criteria for hospitalization). In fact, the average number of comorbidities was lower in patients from private hospitals (1 [IQR 0-2]) than the ones from public and mixed hospitals (2 [IQR 1-3] for both, p<0.001). Once eliminating the collinearity effect of those variables, no effect over prognosis was observed among the types of hospital. This factor is especially relevant in the Brazilian Healthcare System. Users of public or mixed hospitals could have different socio-economical profiles. A recent study conducted using data from the Brazilian Surveillance System also showed increased mortality in regions with a lower development index level, as well as among black populations, representing a regional and ethnicity effect, respectively.(Baqui et al., 2020) Additionally, low income has been associated with higher incidence of comorbidities such as hypertension, cardiovascular disease, chronic kidney disease and obesity.(Singu et al., 2020)

What could have been a pre-condition of poor prognosis might 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 for healthcare workers, the large number refers more to the high absolute number of cases than to a high mortality itself. (Domínguez-Varela, 2020) Mortality among healthcare workers was lower than the overall patients in our study, which may be associated to younger age, lower prevalence of comorbidities and awareness to identify early signs of deterioration.

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

Due to the heavy burden experienced by the health systems during the pandemic, increasing the danger of abandoning good practices and attention was likely diverted away from monitoring for excess antimicrobial use and nosocomial infections.(Nori et al., 2021, World Health Organization, 2020b, 2020c) The overall use of antimicrobials in our cohort was roughly 90% of patients. That 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 over-use of antimicrobials in COVID-19 patients, even when evidence suggests bacterial co-infection is infrequent in these patients.(Rawson et al., 2020) The resemblance of clinical presentation of severe COVID-19 to bacterial or fungal sepsis is the likely factor driving the excess antimicrobial use.

Thus, a worrying 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 true bacterial coinfection. This overuse of antibiotics may have contributed to the observed increase in candidemia and more than 10% absolute increase in resistance of *K. pneumoniae, E. cloacae* and *P. aeruginosa* against several classes of antibiotics, when compared with 2019 at the same institution. Additionally, five patients admitted from the community during the pandemic developed infection with New Delhi metallo-β-lactamase (NDM)–producing *E. cloacae*, and 4 of them developed septic shock. The authors also observed a trend towards a higher mortality rate among patients who developed multidrug resistant infection (71 vs. 54%; p=0.12).(Nori et al., 2021) The potential impact on healthcare-associated infection rates is of high concern for hospitals.(Arshad et al., 2020) To address this situation, a comprehensive approach and international cooperation is required.(World Health Organization, 2020b, 2020c) It is vital to have national and international protocols to guide diagnostic and decision support in identifying secondary bacterial infection in COVID-19 and to encourage the use of stewardship principles when antimicrobials are necessary.(World Health Organization, 2019) Addtionally, infection prevention programs to monitor for nosocomial infections, excess antibiotic use, and multidrug resistance are highly necessary.(Arshad et al., 2020)

This study has limitations. It was a retrospective analysis subject to the drawbacks of a patient records review. Variables such as body mass index and the severity of the comorbidities could not be assessed. Some variables have missing data, specifically electrocardiographic, laboratory and imaging findings. However, it reflects the exams performed in clinical practice in those hospitals. Seventy-five patients were excluded from the study sample. It represents a small number compared with whole cohort, and no difference in baseline-variables were found compared with the remain participants. The sample of 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 participating hospitals may not be representative of the whole healthcare system in Brazil. One could argue that studies based on 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 (ie. it has a reduced set of comorbidities and symptoms, lack of laboratory data and no assessment of the proposed secondary outcomes).(Ministério da Saúde, 2013) Additionally, as it is based in a mandatory registration system, at patient admission to emergency departments the complete fulfillment of the notification form might be compromised due to the high demand (several incoming patients hourly), insufficient staffing with medical personnel and also the presence of severe cases, which requires more attention. Additionally, the data entry with free-text fields from multiple locations and professionals causes an inherent contrast on the use of medical terms and description, which also results in a heterogeneity of fulfilment. Therefore, the most complete and accurate medical history (including information about underlying diseases and a more detailed description of symptoms) is sometimes not possible to be achieved.(Nascimento et al., 2020)

One of the main strengths of the study was the fact that it is a real-life database, which included comprehensive data of a large sample size of patients from 25 hospitals in different Brazilian regions, able to ensure diversity of the population studied. Data were obtained by detailed medical record review, with higher degree of detail than electronic abstraction of structured data elements. 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 may be useful 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 based on the prediction model, to support frontline clinical decision making.

Brazilian COVID-19 Registry investigators (in alphabetical order): Alexandre Vargas Schwarbold; Amanda de Oliveira Maurílio; Ana Lara Rodrigues Monteiro de Barros; Ana Luiza Bahia Alves Scotton; Anderson Lacerda dos Reis; André Soares de Moura Costa; Argenil José Assis de Oliveira; Bárbara Lopes Farace; Carla Thais Cândida Alves da Silva; Carolina Marques Ramos; Christiane Corrêa Rodrigues Cimini; Cíntia Alcantara de Carvalho; Daniel Vitório Silveira; Daniela Ponce; Emanuele Marianne Souza Kroger; Euler Roberto Fernandes Manenti; Fernanda Barbosa Lucas; Fernanda d'Athayde Rodrigues; Fernando Anschau; Fernando Antonio Botoni; Frederico Bartolazzi; Gabriela Petry Crestani; Guilherme Fagundes Nascimento; Helena Carolina Noal; Helena Duani; Heloisa Reniers Vianna; Henrique Cerqueira Guimarães; Joice Coutinho de Alvarenga; Júlia Drumond Parreiras de Morais; Juliana Machado Rugolo; Lara Monalyza Gonçalves Franco; Leila Beltrami Moreira; Leonardo Seixas de Oliveira; Lílian Santos Pinheiro; Liliane Souto Pacheco; Luciane Kopittke; Luciano de Souza Viana; Luis Cesar Souto de Moura; Luisa Elem Almeida Santos; Máderson Alvares de Souza Cabral; Maíra Dias Souza; Marcela Gonçalves Trindade Tofani; Marconi Franco da Silveira; Marcus Vinicius Melo de Andrade; Maria Angélica Pires Ferreira; Maria Aparecida Camargos Bicalho; Maria Auxiliadora Parreiras Martins; Maria Clara Pontello Barbosa Lima; Mariana Balbinot Borges; Mariana de Braga Lima Carvalho Canesso; Matheus Carvalho Alves Nogueira; Meire Pereira de Figueiredo; Milton Henriques Guimarães Júnior; Mychelle Stefany Santos Almeida, Mônica Aparecida de Paula de Sordi; Natália da Cunha Severino Sampaio; Neimy Ramos de Oliveira; Paulo Tarso Lima Vianna; Pedro Guido Soares Andrade; Pedro Ledic Assaf; Rafael Fusaro Aguiar Oliveira; Rafael Lima Rodrigues de Carvalho; Rafaela dos Santos Charão de Almeida; Raphael Castro Martins; Reginaldo Aparecido Valacio; Ricardo Bertoglio Cardoso; Ricardo Braga Coelho; Roberta Pozza; Rodolfo Lucas Silva Mourato; Rodrigo Costa Pereira Vieira; Roger Mendes de Abreu; Rufino de Freitas Silva; Saionara Cristina Francisco; Silvana Mangeon Mereilles Guimarães; Silvia Ferreira Araújo; Talita

Fischer Oliveira; Tatiana de Vargas; Tatiani Oliveira Fereguetti; Thalita Martins Lage; Thulio Henrique Oliveira Diniz; Veridiana Baldon dos Santos.

Patient and public involvement

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

Role of the funder/sponsor

The sponsors had no role in 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.

References

1. Almeida-Filho N. Higher education and health care in Brazil. Lancet 2011;377(9781):1898-900.doi 10.1016/S0140-6736(11)60326-7

2. Aquino EML, Silveira IH, Pescarini JM, Aquino R, Souza-Filho JA, Rocha AS, et al. Social distancing measures to control the COVID-19 pandemic: potential impacts and challenges in Brazil. Cien Saude Colet 2020;25(suppl 1):2423-46.doi 10.1590/1413-81232020256.1.10502020

3. Arshad M, Mahmood SF, Khan M, Hasan R. Covid -19, misinformation, and antimicrobial resistance. BMJ 2020;371:m4501.doi 10.1136/bmj.m4501

4. Bambra C, Riordan R, Ford J, Matthews F. The COVID-19 pandemic and health inequalities. J Epidemiol Community Health 2020;74(11):964-8.doi 10.1136/jech-2020-214401

5. Baqui P, Bica I, Marra V, Ercole A, van der Schaar M. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. Lancet Glob Health 2020;8(8):e1018-e26.doi 10.1016/S2214-109X(20)30285-0

6. Barberia LG, Gómez EJ. Political and institutional perils of Brazil's COVID-19 crisis. Lancet 2020;396(10248):367-8.doi 10.1016/S0140-6736(20)31681-0

7. Bashash D, Hosseini-Baharanchi FS, Rezaie-Tavirani M, Safa M, Akbari Dilmaghani N, Faranoush M, et al. The Prognostic Value of Thrombocytopenia in COVID-19 Patients; a Systematic Review and Meta-Analysis. Arch Acad Emerg Med 2020;8(1):e75.

8. Basu-Ray I, Almaddah N, Adeboye A, Soos MP. Cardiac Manifestations Of Coronavirus. StatPearls. Treasure Island (FL); 2020.

9. Borobia AM, Carcas AJ, Arnalich F, Álvarez-Sala R, Monserrat-Villatoro J, Quintana M, et al. A Cohort of Patients with COVID-19 in a Major Teaching Hospital in Europe. J Clin Med 2020;9(6).doi 10.3390/jcm9061733

10. Chang WT, Toh HS, Liao CT, Yu WL. Cardiac Involvement of COVID-19: A Comprehensive Review. Am J Med Sci 2020.doi 10.1016/j.amjms.2020.10.002

11. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect 2020;80(5):e1-e6.doi 10.1016/j.jinf.2020.03.004

12. Cimerman S, Chebabo A, Cunha CAD, Rodríguez-Morales AJ. Deep impact of COVID-19 in the healthcare of Latin America: the case of Brazil. Braz J Infect Dis 2020;24(2):93-5.doi 10.1016/j.bjid.2020.04.005

13. Croda J, Oliveira WK, Frutuoso RL, Mandetta LH, Baia-da-Silva DC, Brito-Sousa JD, et al. COVID-19 in Brazil: advantages of a socialized unified health system and preparation to contain cases. Rev Soc Bras Med Trop 2020;53:e20200167.doi 10.1590/0037-8682-0167-2020

14. Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. Human Kidney is a Target for Novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. medRxiv 2020:2020.03.04.20031120.doi 10.1101/2020.03.04.20031120

15. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.doi 10.1136/bmj.m1985

16. Domínguez-Varela IA. High mortality among health personnel with COVID-19 in Mexico. Disaster Med Public Health Prep 2020:1-4.doi 10.1017/dmp.2020.382

17. Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: A prospective cohort study. Pharmacol Res 2020;158:104931.doi 10.1016/j.phrs.2020.104931

18. Girija ASS, Shankar EM, Larsson M. Could SARS-CoV-2-Induced Hyperinflammation Magnify the Severity of Coronavirus Disease (CoViD-19) Leading to Acute Respiratory Distress Syndrome? Front Immunol 2020;11:1206.doi 10.3389/fimmu.2020.01206 eCollection 2020.

19. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med 2020;382(24):2372-4.doi 10.1056/NEJMc2010419

20. Gregory KE, Radovinsky L. Research strategies that result in optimal data collection from the patient medical record. Appl Nurs Res 2012;25(2):108-16.doi 10.1016/j.apnr.2010.02.004

21. Gupta RK, Marks M, Samuels THA, Luintel A, Rampling T, Chowdhury H, et al. Systematic evaluation and external validation of 22 prognostic models among hospitalised adults with COVID-19: an observational cohort study. Eur Respir J 2020;56(6).doi 10.1183/13993003.03498-2020

22. Gutierrez JP, Bertozzi SM. Non-communicable diseases and inequalities increase risk of death among COVID-19 patients in Mexico. PLoS One 2020;15(10):e0240394.doi 10.1371/journal.pone.0240394

23. Hajifathalian K, Sharaiha RZ, Kumar S, Krisko T, Skaf D, Ang B, et al. Development and external validation of a prediction risk model for short-term mortality among hospitalized U.S. COVID-19 patients: A proposal for the COVID-AID risk tool. PLoS One 2020;15(9):e0239536.doi 10.1371/journal.pone.0239536

24. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019;95:103208.doi 10.1016/j.jbi.2019.103208

25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377-81.doi 10.1016/j.jbi.2008.08.010

26. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.doi 10.1016/S0140-6736(20)30183-5

27. Jourdes A, Lafaurie M, Martin-Blondel G, Delobel P, Faruch M, Charpentier S, et al. Clinical characteristics and outcome of hospitalized patients with SARS-CoV-2 infection at Toulouse University hospital (France). Results from the Covid-clinic-Toul cohort. Rev Med Interne 2020.doi 10.1016/j.revmed.2020.08.006

28. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney international supplements 2012;2(1):1-138.

29. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ 2020;370:m3339.doi 10.1136/bmj.m3339

30. Kovesdy CP, Furth SL, Zoccali C, World Kidney Day Steering C. Obesity and Kidney Disease: Hidden Consequences of the Epidemic. Can J Kidney Health Dis 2017;4:2054358117698669.doi 10.1177/2054358117698669eCollection 2017.

31. Lancet T. COVID-19 in Brazil:"So what?". Lancet (London, England) 2020;395(10235):1461.doi 10.1016/S0140-6736(20)31095-3

32. Lanza K, Perez LG, Costa LB, Cordeiro TM, Palmeira VA, Ribeiro VT, et al. Covid-19: the renin-angiotensin system imbalance hypothesis. Clin Sci (Lond) 2020;134(11):1259-64.doi 10.1042/CS20200492

33. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med 2020;180(8):1081-9.doi 10.1001/jamainternmed.2020.2033

34. Lim ZJ, Subramaniam A, Reddy MP, Blecher G, Kadam U, Afroz A, et al. Case Fatality Rates for COVID-19 Patients Requiring Invasive Mechanical Ventilation: A Meta-analysis. Am J Respir Crit Care Med 2020.doi 10.1164/rccm.202006-2405OC

35. Lorenz C, Dias Bocewicz AC, Corrêa de Azevedo Marques C, Reis Santana LM, Chiaravalloti-Neto F, Alves Gomes AH, et al. Have measures against COVID-19 helped to reduce dengue cases in Brazil? Travel Med Infect Dis 2020;37:101827.doi 10.1016/j.tmaid.2020.101827

36. Marson FAL, Ortega MM. COVID-19 in Brazil. Pulmonology 2020;26(4):241-4.doi 10.1016/j.pulmoe.2020.04.008

37. Martins-Melo FR, Ramos AN, Alencar CH, Heukelbach J. Prevalence of Chagas disease in Brazil: a systematic review and meta-analysis. Acta Trop 2014;130:167-74.doi 10.1016/j.actatropica.2013.10.002

38. Matsunaga N, Hayakawa K, Terada M, Ohtsu H, Asai Y, Tsuzuki S, et al. Clinical epidemiology of hospitalized patients with COVID-19 in Japan: Report of the COVID-19 REGISTRY JAPAN. Clin Infect Dis 2020.doi 10.1093/cid/ciaa1470

39. Mehraeen E, Karimi A, Barzegary A, Vahedi F, Afsahi AM, Dadras O, et al. Predictors of mortality in patients with COVID-19-a systematic review. Eur J Integr Med 2020;40:101226.doi 10.1016/j.eujim.2020.101226

40. Ministério da Saúde. [Sistema de Informação de Agravos de Notificação - SINAN Influenza Web]. [Secretaria de Vigilância em Saúde]; 2013. p. 17.

41. Munblit D, Nekliudov NA, Bugaeva P, Blyuss O, Kislova M, Listovskaya E, et al. StopCOVID cohort: An observational study of 3,480 patients admitted to the Sechenov University hospital network in Moscow city for suspected COVID-19 infection. Clin Infect Dis 2020.doi 10.1093/cid/ciaa1535

42. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. JAMA 2020;323(21):2195-8.doi 10.1001/jama.2020.7202

43. Nachega JB, Ishoso DK, Otokoye JO, Hermans MP, Machekano RN, Sam-Agudu NA, et al. Clinical Characteristics and Outcomes of Patients Hospitalized for COVID-19 in Africa: Early Insights from the Democratic Republic of the Congo. Am J Trop Med Hyg 2020.doi 10.4269/ajtmh.20-1240

44. Nadim MK, Forni LG, Mehta RL, Connor MJ, Jr., Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020;16(12):747-64.doi 10.1038/s41581-020-00356-5

45. Nascimento IJBd, Pinto LR, Fernandes VA, Romero IM, Oliveira JAdQ, Marcolino MS, et al. Clinical characteristics and outcomes among Brazilian patients with severe acute respiratory syndrome coronavirus 2 infection: an observational retrospective study. Sao Paulo Medical Journal 2020.doi 10.1590/1516-3180.2020.00365.r1.08092020

46. Nayak A, Islam SJ, Mehta A, Ko YA, Patel SA, Goyal A, et al. Impact of Social Vulnerability on COVID-19 Incidence and Outcomes in the United States. medRxiv 2020.doi 10.1101/2020.04.10.20060962

47. Neiva MB, Carvalho I, Costa Filho EDS, Barbosa-Junior F, Bernardi FA, Sanches TLM, et al. Brazil: the emerging epicenter of COVID-19 pandemic. Rev Soc Bras Med Trop 2020;53:e20200550.doi 10.1590/0037-8682-0550-2020

48. Nikpouraghdam M, Jalali Farahani A, Alishiri G, Heydari S, Ebrahimnia M, Samadinia H, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. J Clin Virol 2020;127:104378.doi 10.1016/j.jcv.2020.104378

49. Nori P, Cowman K, Chen V, Bartash R, Szymczak W, Madaline T, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infect Control Hosp Epidemiol 2021;42(1):84-8.doi 10.1017/ice.2020.368

50. Quisi A, Alıcı G, Harbalıoğlu H, Genç Ö, Er F, Allahverdiyev S, et al. The CHA2DS2-VASc score and in-hospital mortality in patients with COVID-19: A multicenter retrospective cohort study. Turk Kardiyol Dern Ars 2020;48(7):656-63.doi 10.5543/tkda.2020.03488

51. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis 2020.doi 10.1093/cid/ciaa530

52. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323(20):2052-9.doi 10.1001/jama.2020.6775

53. Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, Henry BM, Lippi G. Angiotensin-Converting Enzyme 2 and Antihypertensives (Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors) in Coronavirus Disease 2019. Mayo Clin Proc 2020;95(6):1222-30.doi 10.1016/j.mayocp.2020.03.026 Epub 2020 Apr 4.

54. Sherwani S, Khan MWA. Cytokine Response in SARS-CoV-2 Infection in the Elderly. J Inflamm Res 2020;13:737-47.doi 10.2147/JIR.S276091 eCollection 2020.

55. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring) 2020;28(7):1195-9.doi 10.1002/oby.22831

56. Singu S, Acharya A, Challagundla K, Byrareddy SN. Impact of Social Determinants of Health on the Emerging COVID-19 Pandemic in the United States. Front Public Health 2020;8:406.doi 10.3389/fpubh.2020.00406

57. Teixeira MG, Costa MDCN, Paixão ESD, Carmo EH, Barreto FR, Penna GO. The achievements of the SUS in tackling the communicable diseases. Cien Saude Colet 2018;23(6):1819-28.doi 10.1590/1413-81232018236.08402018

58. Uauy R. The impact of the Brazil experience in Latin America. Lancet 2011;377(9782):1984-6.doi 10.1016/S0140-6736(11)60437-6

59. Vincent JL, Sakr Y, Singer M, Martin-Loeches I, Machado FR, Marshall JC, et al. Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017. JAMA 2020;323(15):1478-87.doi 10.1001/jama.2020.2717

60. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335(7624):806-8.doi 10.1136/bmj.39335.541782.AD

61. Wang X, Fang X, Cai Z, Wu X, Gao X, Min J, et al. Comorbid Chronic Diseases and Acute Organ Injuries Are Strongly Correlated with Disease Severity and Mortality among COVID-19 Patients: A Systemic Review and Meta-Analysis. Research (Wash D C) 2020;2020:2402961.doi 10.34133/2020/2402961. eCollection 2020.

62. Wolff R, Moons K, Riley R, Whiting P, Westwood M, Collins G, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Annals of Internal Medicine 2019;170(1):51-8.doi 10.7326/m18-1376 %m 30596875

63. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. 2019.

64. World Health Organization. Diagnostic testing for SARS-CoV-2: interim guidance, 11 September 2020. Geneva: World Health Organization; 2020a.

65. World Health Organization. Stop the COVID-19 pandemic from becoming an AMR catastrophe. Copenhagen: World Health Organization. Regional Office for Europe; 2020b.

66. World Health Organization. World Antimicrobial Awareness Week; 2020c. Available from: https://www.who.int/campaigns/world-antimicrobial-awareness-week/2020. [Accessed 04 Jan 2021].

67. Yu C, Lei Q, Li W, Wang X, Liu W, Fan X. Clinical Characteristics, Associated Factors, and Predicting COVID-19 Mortality Risk: A Retrospective Study in Wuhan, China. Am J Prev Med 2020;59(2):168-75.doi 10.1016/j.amepre.2020.05.002

68. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054-62.doi 10.1016/S0140-6736(20)30566-3.Epub 2020 Mar 11.

69. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. American Journal of Epidemiology 2004;159(7):702-6.doi 10.1093/aje/kwh090

Figures

Figure 1. Flowchart of COVID-19 patients included in the study
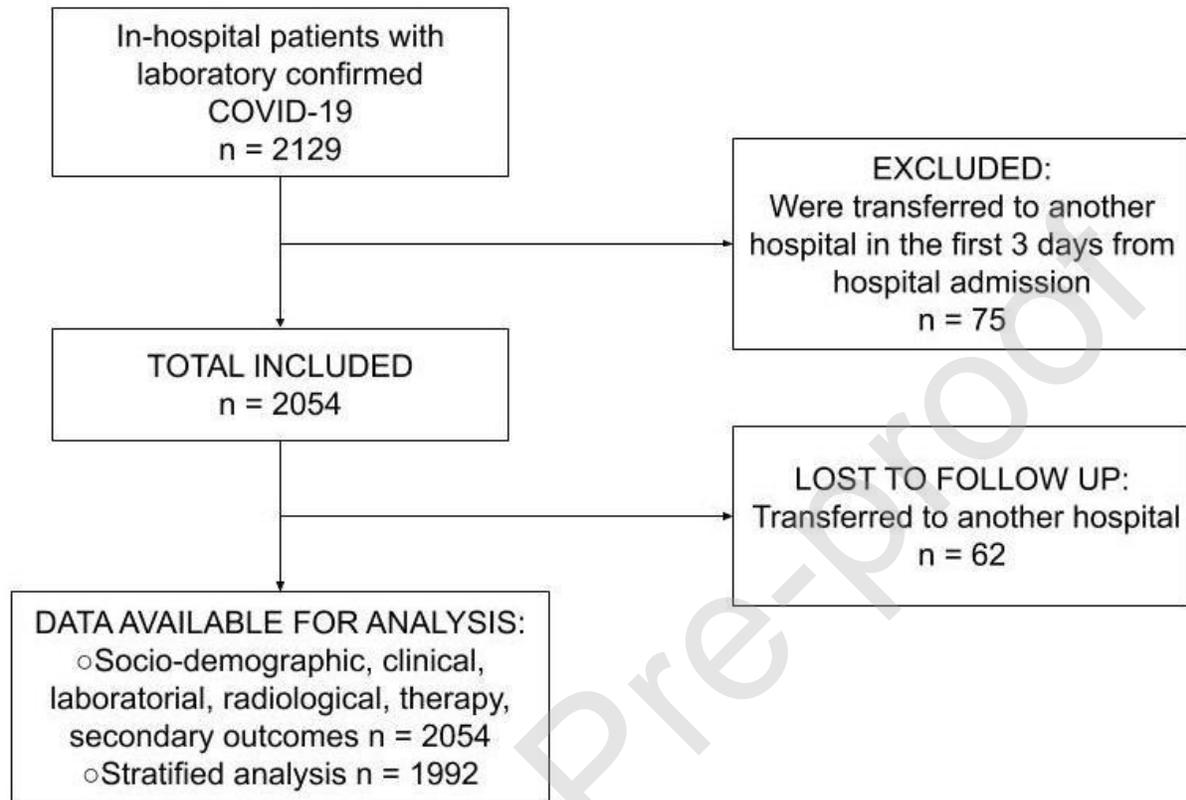
Figure 2. Seven-day moving average of (A) COVID-19 inpatient hospital admissions; (B) number of patients hospitalized for COVID-19; (C) number of COVID-19 deaths; (D) mortality among COVID-19 patients hospitalized (number of deaths/number of patients hospitalized).

COVID−19 inpatient hospital admissions

Number of patients hospitalized for COVID−19

Number of COVID−19 deaths

Mortality among COVID−19 patients hospitalized

35
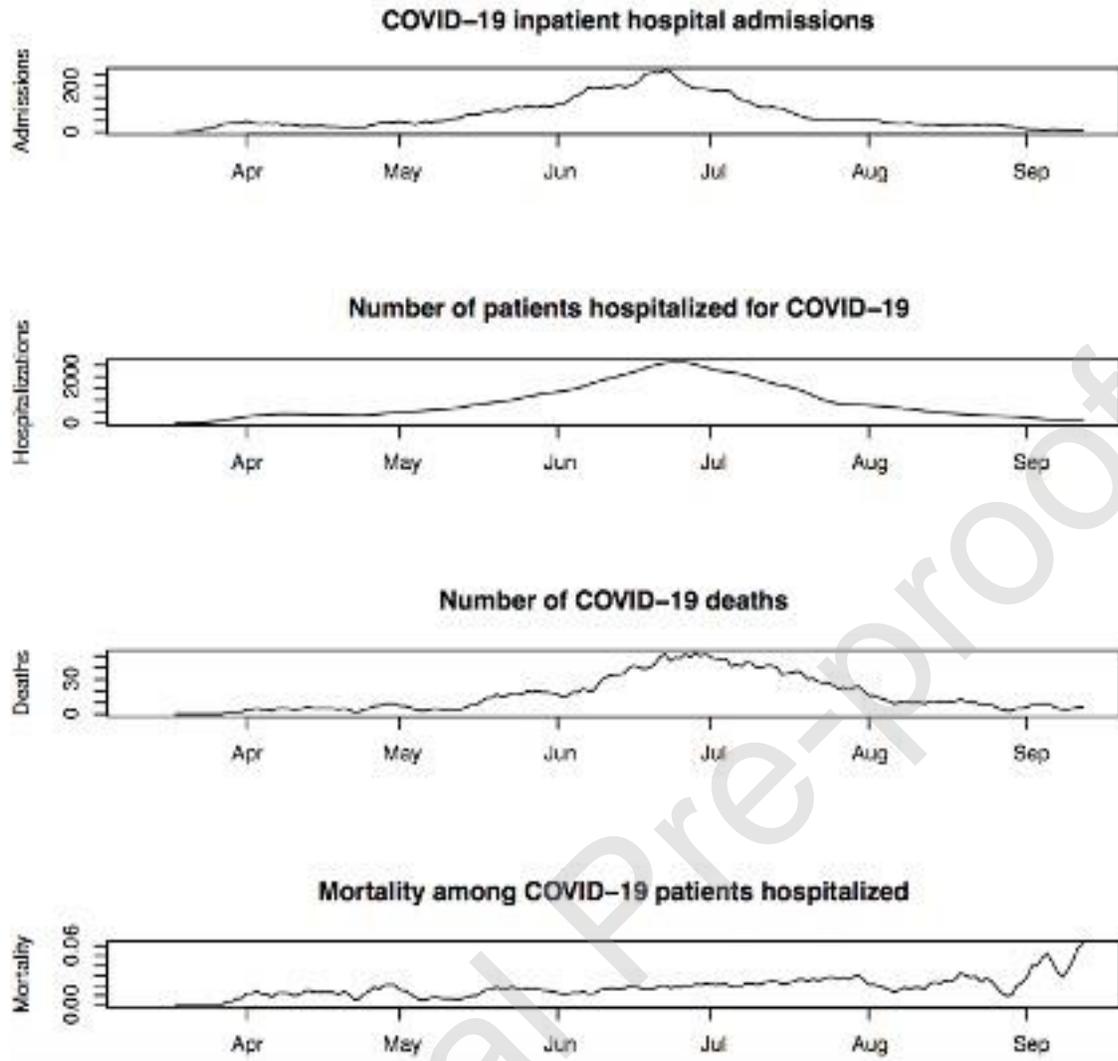
Tables

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

Variable	Total	Died	Discharged alive	p-value
	N (%)	N (%)	N (%)	
	(n = 2054)	(n = 439)	(n = 1553)	
Age	59 (47-71)	70 (59 - 81)	56 (44 - 68)	<0.001
Age ≥65 years-old	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				
Ilicit 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 smoking	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).

* From the 2054 patients included in the analysis, 62 patients were transferred to another hospital. As final survival status was unknown, they were not included in the stratified analysis.

COPD: chronic obstructive pulmonary disease

Table 2. Clinical data at presentation of the study population*

Variable	Total	Died	Discharged alive	p-value
	N (%)	N (%)	N (%)	
Symptoms	**(n = 2052)**	**(n = 439)**	**(n = 1551)**	
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<100mmHg 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
Supplementary 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)	
≥7L/min	105 (5.1)	58 (13.3)	46 (2.9)	
Invasive mechanical ventilation	178 (8.7)	117 (26.8)	52 (3.4)	

* From the 2054 patients included in the analysis, 62 patients were transferred to another hospital. As final survival status was unknown, they were not included in the stratified analysis. Total number of valid cases for each analysis is presented.

Values in numbers (percentage).

HR: heart rate, SBP: systolic blood pressure, RR: respiratory rate.

Table 3. Laboratory parameters of the study population at admission*

Variable	Total	Died	Discharged alive	p-value
	N			
	(n = 1986)	**(n = 430)**	**(n = 1496)**	
Hemoglobin (g/dL)	13.10 (11.85 – 14.30)	12.35 (10.80 - 13.80)	13.20 (12.10 - 14.40)	<0.001
	(n = 1967)	**(n = 427)**	**(n = 1480)**	
White blood cell count $(x10^9/L)$	6.90 (5.20 – 9.60)	8.26 (6.07-12.18)	6.60 (5.00- 9.00)	<0.001
	(n = 1967)	**(n = 427)**	**(n = 1480)**	
Neutrophils $(x10^9/L)$	4.99 (3.42 – 7.48)	6.42 (4.43- 9.89)	4.62 (3.20-6.82)	<0.001
	(n = 1949)	**(n = 417)**	**(n = 1473)**	
Lymphocytes $(x10^9/L)$	1.09 (0.76 – 1.54)	0.91 (0.59-1.31)	1.13 (0.80- 1.60)	<0.001
	(n = 1954)	**(n = 424)**	**(n = 1470)**	
Platelets $(x10^9/L)$	198.00 (153.00 – 259.75)	180.50 (138.00-238.00)	204.00 (158.00-265.00)	<0.001

	(n = 1904)	(n = 417)	(n = 1428)	
Creatinine (mg/dL)	0.90 (0.72 – 1.21)	1.18 (0.87 - 2.00)	0.88 (0.70 - 1.09)	<0.001
	(n = 1738)	(n = 377)	(n = 1309)	
Urea (mg/dL)	33.00 (24.00 – 49.00)	51.00 (35.65 - 88.50)	29.42 (23.00 - 41.00)	<0.001
	(n = 1373)	(n = 335)	(n = 989)	
Lactate (mmol/L)	1.40 (1.01 – 1.80)	1.52 (1.20 - 2.00)	1.30 (1.00 - 1.70)	<0.001
	(n = 1604)	(n = 337)	(n = 1224)	
C-reactive protein (mg/L)	80.00 (35.02 – 151.53)	119.40 (64.00 - 200.95)	70.57 (31.10 - 132.50)	<0.001
	(n = 1574)	(n = 366)	(n = 1157)	
Arterial pH	7.43 (7.39 – 7.46)	7.40 (7.31 - 7.44)	7.44 (7.41 - 7.47)	<0.001
	(n = 1542)	(n = 354)	(n = 1137)	
Arterial pCO2	35.30 (31.50 – 39.70)	37.00 (31.00 - 45.70)	35.00 (31.70 - 39.00)	<0.001
	(n = 1373)	(n = 322)	(n = 1010)	
Arterial pO2	75.50 (62.80 – 97.00)	77.00 (59.58 - 102.25)	75.00 (64.00 - 94.10)	0.899

43

	(n = 1560)	(n = 361)	(n = 1150)	
Bicarbonate	23.10 (21.00 – 25.45)	22.20 (19.00 - 25.00)	23.50 (21.60 - 25.60)	<0.001

* From the 2054 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. Total number of valid cases for each analysis is presented.

Values in median (interquartile range) and numbers (percentage).

Table 4. In-hospital medications, supportive care and secondary outcomes*

Variable	Total	Died	Discharged alive	p-value
	N (%)	N (%)	N (%)	
Medications	**(n = 2037)**	**(n = 431)**	**(n = 1547)**	
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**

45

Number of days	9 (4-15)	10.0 (6.0 - 17.0)	7.0 (3.0 - 12.0)	**<0.001**
Failed extubation**	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**

* From the 2054 patients included in the analysis, 62 patients were transferred to another hospital. As final survival status was unknown, they were not included in the stratified analysis. Total number of valid cases for each analysis is presented.

** Percentage was calculated among patients who required invasive mechanical ventilation.

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.

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

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
Supplementary 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 <100x10^9/L	1.95 (1.23-3.10)	0.005

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