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.

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Clinical characteristics and outcomes of hospital-manifested COVID-19 among Brazilians

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Abbreviations: COVID-19, Coronavirus disease 19; FiO_2, Fraction of inspired oxygen; GBD, Global Burden of Diseases; GHE, Global Health Estimates; ICU, Intensive care unit; IMV, Invasive mechanical ventilation; IQR, Interquartile range; NHS, National Health Service; SpO_2, Oxygen saturation; REDCap®, Research Electronic Data Capture; UK, United Kingdom.

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ABSTRACT

Objectives: To analyze the clinical characteristics and outcomes of admitted patients with the hospital-*versus* community-manifested COVID-19 and to evaluate the risk factors related to mortality in the first population.
Methods: This retrospective cohort included consecutive adult patients with COVID-19, hospitalized between March and September 2020. The demographic data, clinical characteristics, and outcomes were extracted from medical records. Patients with hospital-manifested COVID-19 (study group) and those with community-manifested COVID-19 (control group) were matched by the propensity score model. Logistic regression models were used to verify the risk factors for mortality in the study group.
Results: Among 7,710 hospitalized patients who had COVID-19, 7.2% developed symptoms while admitted for other reasons. Patients with hospital-manifested COVID-19 had a higher prevalence of cancer (19.2% vs 10.8%) and alcoholism (8.8% vs 2.8%) than patients with community-manifested COVID-19 and also had a higher rate of intensive care unit requirement (45.1% vs 35.2%), sepsis (23.8% vs 14.5%), and death (35.8% vs 22.5%) (P <0.05 for all). The factors independently associated with increased mortality in the study group were increasing age, male sex, number of comorbidities, and cancer.
Conclusion: Hospital-manifested COVID-19 was associated with increased mortality. Increasing age, male sex, number of comorbidities, and cancer were independent predictors of mortality among those with hospital-manifested COVID-19 disease.

Introduction

Since the beginning of the **coronavirus disease 2019 (**COVID-19) pandemic, a large part of the population avoided or delayed routine and nonemergency medical care for fear of in-hospital infection by **severe acute respiratory syndrome coronavirus 2 (**SARS-CoV-2) [1]. However, several patients admitted due to other conditions manifested COVID-19 during their hospital stay.

Despite an increasing understanding of COVID-19, establishing whether an infection is hospital-acquired remains challenging. For SARS-CoV-2, hospital-acquired infections are frequently defined by clinical assessment of the time of admission and the first positive test or symptom onset [2]. As the incubation period is very variable and the exact moment of infection is unknown, studying patients who manifested COVID-19 during the hospital stay for other reasons is essential, and studies on the topic are scarce. In addition, data on the prevalence of this condition and its prognosis in Latin American patients is still lacking. Thus, the aims of this study were (i) to analyze the clinical characteristics and outcomes of in-hospital patients with hospital- *versus* community-manifested

COVID-19, as well as (ii) to evaluate the risk factors related to mortality in the first population.

Methods

Study design and ethics

This study is part of a multicentric retrospective cohort, entitled the Brazilian COVID-19 Registry, which involved 34 Brazilian hospitals. The study protocol was approved by the National Commission for Research Ethics (CAAE: 30350820.5.1001.0008).

Study subjects

Consecutive adult patients (aged ≥18 years) with laboratory-confirmed COVID-19 [3] admitted to any of the participating hospitals from March 1 to September 30, 2020 were enrolled. The total duration of data collection was approximately seven months, although this duration varied for each hospital.

Hospital-manifested COVID-19 was defined as patients who were admitted for other reasons and had a positive test for COVID-19 at any moment of the hospital stay (study group). Community-manifested COVID-19 was defined as patients admitted due to COVID-19 (control group).

Data collection

Demographic data, clinical characteristics, and outcomes (for details, see Table S1) were collected from the medical records by trained researchers to the Research Electronic Data Capture (REDCap®) electronic platform [4,5], hosted at the Telehealth Center of the University Hospital of the *Universidade Federal de Minas Gerais* [6]. To ensure reliability and monitor data quality, the database was routinely audited.

The admission causes were stratified into categories based on both the Global Health Estimates [7] and the Global Burden of Diseases [8]. First, we created broad categories (*e.g.* malignant neoplasms and cardiovascular, infectious, and endocrine diseases) and subdivided these into specific diseases (Table S2). Then, each patient was assigned to one of these categories. Some patients were admitted for specific procedures (*e.g.* surgery, solid organ transplantation, or plasmapheresis), and others for propaedeutics or diagnostic evaluation due to several symptoms or syndromes (*e.g.* anasarca, fever of unknown origin, oliguria/anuria, and wasting syndrome). These categories were added as well (Table S2).

Statistical analysis

Patients with hospital-manifested COVID-19 (study group) were compared with matched controls (community-manifested) using the *t*- or Wilcoxon tests for continuous variables (according to data distribution) and chi-square or Fisher's exact tests for categorical variables. The descriptive analysis was presented by the median, interquartile range (IQR), numbers, and percentages.

For comparison purposes, the propensity score model was estimated by the logistic regression (including age, sex, number of comorbidities [hypertension, diabetes mellitus, obesity, coronary artery disease, heart failure, atrial fibrillation or flutter, cirrhosis, chronic obstructive pulmonary disease, cancer, and previous stroke], and hospital) to adjust for potential confounding variables and match the patients of the control group (1:1). The control group comprised those with the closest propensity score with patients with hospital-manifested COVID-19 (within 0.17 **standard deviations** of the logit of the propensity score on a scale from 0 to 1.00), using the MatchIt package in R software.

The demographic and clinical characteristics were assessed as risk factors for mortality among patients with hospital-manifested

Table 1
Demographic and clinical characteristics of the control group and study group.

Characteristics	Control group N = 537[a]	Study group N = 537[a]	*P*-value[b]
Age (years)	62.0 (48.0, 75.0)	62.0 (47.0, 74.0)	0.257
Male sex	252 (46.9%)	250 (46.6%)	0.903
Cardiovascular disease			
Hypertension	312 (58.1%)	295 (54.9%)	0.295
Heart failure	53 (9.9%)	50 (9.3%)	0.756
Coronary artery disease	49 (9.1%)	55 (10.2%)	0.536
Atrial fibrillation/flutter	30 (5.6%)	31 (5.8%)	0.895
Stroke	35 (6.5%)	45 (8.4%)	0.245
Respiratory disease			
Chronic obstructive pulmonary disease	37 (6.9%)	28 (5.2%)	0.249
Asthma	30 (5.6%)	15 (2.8%)	0.022
Metabolic disease			
Diabetes mellitus	181 (33.7%)	148 (27.6%)	0.029
Obesity (body mass index>30kg/m^2)	90 (16.8%)	48 (8.9%)	<0.001
Other conditions			
Chronic kidney disease	47 (8.8%)	74 (13.8%)	0.009
Cancer	58 (10.8%)	103 (19.2%)	<0.001
Rheumatologic disease	9 (1.7%)	19 (3.5%)	0.055
Cirrhosis	5 (0.9%)	14 (2.6%)	0.037
Previous transplantation	11 (2.0%)	18 (3.4%)	0.188
HIV infection	11 (2.0%)	11 (2.0%)	>0.999
Comorbidities (total number)			0.684
0	125 (23.3%)	133 (24.8%)	
1	145 (27.0%)	151 (28.1%)	
2	154 (28.7%)	139 (25.9%)	
3	72 (13.4%)	83 (15.5%)	
≥4	41 (7.6%)	31 (5.8%)	
Toxic habits			
Alcoholism	15 (2.8%)	47 (8.8%)	<0.001
Smoking	109 (20.3%)	129 (24.0%)	0.142

[a] n (%), median (interquartile range);
[b] Pearson chi-square test, Wilcoxon rank sum test, Fisher's exact test.

Table 2
Cause of admission for the study group (N = 537).

Characteristics	N (%)
Cardiovascular diseases	104 (20.0%)
Propaedeutics/diagnostic evaluation	101 (19.5%)
Gastrointestinal diseases	52 (10.0%)
Procedures	52 (10.0%)
Genitourinary diseases	42 (8.1%)
Malignant neoplasms	31 (6.0%)
Injuries	30 (5.8%)
Musculoskeletal diseases	26 (5.0%)
Skin and soft tissue diseases	19 (3.7%)
Neurological conditions	17 (3.3%)
Diabetes mellitus	16 (3.1%)
Respiratory diseases	15 (2.9%)
Mental and substance use disorders	7 (1.3%)
Infectious and parasitic diseases	5 (1.0%)
Endocrine, blood, immune disorders	2 (0.4%)

Median (interquartile range).

COVID-19 using the logistic regression analysis. In the first model, the variable “number of comorbidities” was included. In the second model, we considered the different comorbidities separately and did not include the variable “number of comorbidities”. In both models, we excluded the duplicates of the cause of hospitalization to prevent the comorbidity from being entered twice in the model.

All statistical analyses were performed using R software (version 4.0.2). The significance level for the two-tailed *P*-value was set at ≤0.05.

Results

From 7,710 hospitalized patients with COVID-19, 537 (7.2%) had hospital-manifested COVID-19, and 537 were selected as matched controls. The median age was 62 (interquartile range 47.2-74.0) years, and the majority of patients were female (53.3%). Patients with hospital-manifested COVID-19 had a higher prevalence of cancer (19.2% vs 10.8%, *P*<0.001), alcoholism (8.8% vs 2.8%, *P*<0.001), chronic kidney disease (3.5% vs 1.7%, *P*= 0.009), and cirrhosis (2.6% vs 0.9%, *P*= 0.037) than patients with community-manifested COVID-19 (for more details, see Table 1).

The most common causes of hospitalization (Table 2) in the study group were cardiovascular diseases (20.0%), propaedeutics evaluation (19.5%), gastrointestinal diseases (10.0%), and procedures (10.0%). Regarding the clinical outcomes, the patients in this group had a higher mortality rate (35.8% vs 22.5%, *P*<0.001), intensive care unit admission rate (45.1% vs 35.2%, *P*<0.001), frequency of sepsis (23.8% vs 14.5%, *P*= 0.010), and bleeding (4.1% vs 1.5%, *P*= 0.010) than the control group (Table 3). On the other hand, there were no statistically significant differences in the need for invasive mechanical ventilation and dialysis, as well as the incidence of venous thromboembolism and acute heart failure, between groups (Table 3).

In the first multivariable logistic regression analysis for in-hospital mortality (Table 4), the following variables were shown to be independent predictors: older age (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02-1.05) and a higher number of comorbidities (OR 1.34, 95% CI 1.1-1.64). In the second analysis (Table 5), the factors independently associated with mortality were increasing age (OR 1.04, 95% CI 1.02-1.05), male sex (OR 1.51, 95% CI 1.01-2.27), and underlying cancer (OR 2.34, 95% CI 1.33-4.15).

Discussion

In this study from a large cohort of Brazilian patients, 7.2% had hospital-manifested COVID-19. The patients with hospital-manifested symptoms had a higher prevalence of cancer, alcoholism, chronic kidney disease, and cirrhosis than the controls. Cardiovascular diseases, propaedeutics, gastrointestinal diseases, and procedures were the most common causes of hospitalization in that group. Furthermore, patients with hospital-manifested COVID-19 were associated with a higher rate of admission to the intensive care unit, frequency of sepsis, bleeding, and in-hospital mortality. Increasing age, male sex, number of comorbidities, and cancer were independent predictors of mortality among patients with hospital-manifested COVID-19.

This study is innovative in assessing the most frequent causes of hospital admission, prognosis, and risk factors for mortality in patients with hospital-manifested COVID-19 in Latin America. However, the cut-off to define hospital-acquired COVID-19 is still a matter of debate. Hospital-acquired COVID-19 is frequently defined by comparing the time of admission and the first positive laboratory test or the symptom onset [2]. National Health Service, for example, classifies hospital-acquired infections as ‘indeterminate’, ‘probable’, or ‘definite’ for symptom onset or a positive test after 3-7 days, 8-14 days, and >14 days after admission, respectively [9]. If the delay is much greater than the incubation period, the infection is likely hospital-acquired [1,2]. Thus, the number of patients with hospital-acquired SARS-CoV-2 infection will depend on the definition used, with imprecision driven by the unobservable nature of the infection and the wide variation in the incubation periods [2].

Table 3
Clinical outcomes of control and study groups.

Characteristics	Control group N = 537[a]	Study group N = 537[a]	*P*-value[b]
Hospital length of stay	8.0 (5.0, 15.0)	12.0 (5.0, 21.0)	<0.001
ICU	189 (35.2%)	242 (45.1%)	<0.001
Time of ICU admission	1.0 (0.0, 3.0)	1.0 (0.0, 5.0)	0.026
Days in the ICU	9.0 (4.0, 19.0)	7.0 (3.0, 15.0)	0.100
Mechanical ventilation	145 (28.0%)	166 (32.7%)	0.103
Dialysis	68 (12.7%)	85 (15.8%)	0.138
Sepsis	78 (14.5%)	128 (23.8%)	<0.001
Disseminated intravascular coagulation	2 (0.4%)	4 (0.7%)	0.687
Acute cardiac insufficiency	17 (3.2%)	24 (4.5%)	0.265
Acute myocardial infarction	5 (0.9%)	10 (1.9%)	0.194
Myocarditis	2 (0.4%)	1 (0.2%)	>0.999
Hemorrhage	8 (1.5%)	22 (4.1%)	0.010
Vascular thrombosis	19 (3.5%)	26 (4.8%)	0.286
Venous thromboembolism	18 (3.4%)	24 (4.5%)	0.345
Arterial thrombosis	1 (0.2%)	2 (0.4%)	>0.999
In-hospital mortality	121 (22.5%)	192 (35.8%)	<0.001

[a] n (%); Median (interquartile range);
[b] Pearson chi-squared test; Wilcoxon rank sum test; Fisher’s exact test. ICU, intensive care unit.

Table 4
Risk factors for in-hospital mortality of the patients with hospital-manifested COVID-19 (study group, first multivariate logistic regression model).

Characteristics	Odds ratio (95% confidence interval)	*P*-value
Male sex	1.43 (0.97-2.13)	0.0735
Age (years)	1.04 (1.02-1.05)	<0.0001
Number of comorbidities	1.34 (1.1-1.64)	0.0035
Causes of hospital admission		
Malignant neoplasms	1.79 (0.71-4.44)	0.2126
Musculoskeletal diseases	1.83 (0.73-4.72)	0.2030
Digestive diseases	0.79 (0.37-1.66)	0.5394
Cardiovascular diseases	1.14 (0.61-2.13)	0.6871
Procedures	0.79 (0.33-1.82)	0.5874
Injuries	2.04 (0.8-5.18)	0.1320
Respiratory diseases	1.09 (0.32-3.57)	0.8825
Neurological conditions	1.05 (0.34-3.16)	0.9361
Skin and soft tissue diseases	1.38 (0.42-4.18)	0.5740
Genitourinary diseases	1.01 (0.44-2.26)	0.9893
Diabetes mellitus	0.54 (0.14-1.75)	0.3296
Mental and substance use disorders	0.48 (0.02-3.73)	0.5422
Infectious and parasitic disease	0.75 (0.04-5.83)	0.8055

Table 5
Risk factors for in-hospital mortality of the patients with hospital-manifested COVID-19 (study group, second multivariate logistic regression model).

Characteristics	Odds ratio (95% confidence interval)	*P*-value
Male sex	1.55 (1.01-2.27)	0.0465
Age (years)	1.04 (1.02-1.05)	<0.0001
Manifest		
Malignant neoplasm	1.94 (0.76-4.89)	0.159
Musculoskeletal diseases	2.03 (0.8-5.3)	0.1378
Digestive diseases	0.76 (0.35-1.62)	0.4782
Cardiovascular diseases	1.18 (0.58-2.41)	0.6412
Procedures	0.7 (0.28-1.66)	0.4255
Injuries	2.03 (0.79-5.24)	0.1405
Respiratory diseases	1.05 (0.3-3.45)	0.9415
Neurological conditions	1.16 (0.36-3.57)	0.8004
Skin and soft tissue disease	1.37 (0.41-4.22)	0.5939
Genitourinary diseases	1.11 (0.48-2.51)	0.8068
Diabetes mellitus	0.54 (0.13-1.81)	0.3395
Mental and substance use disorders	0.6 (0.03-4.44)	0.6598
Infectious and parasitic disease	0.87 (0.04-6.95)	0.9085
Comorbidities		
Hypertension	1.47 (0.88-2.44)	0.1384
Coronary artery disease	1.15 (0.46-2.88)	0.7615
Heart failure	0.88 (0.35-2.13)	0.7688
Atrial fibrillation/flutter	1.34 (0.45-4.08)	0.6011
Stroke	1.11 (0.45-2.77)	0.8136
Chronic obstructive pulmonary disease	1.23 (0.52-2.95)	0.6406
Diabetes mellitus	1.34 (0.85-2.11)	0.2119
Obesity (body mass index>30 kg/m^2)	1.32 (0.65-2.63)	0.4354
Cirrhosis	1.05 (0.3-3.4)	0.9397
Cancer	2.34 (1.33-4.15)	0.0034

In the absence of universal testing of all patients at admission, we opted to use the cautious definition of hospital-manifested COVID-19.

In fact, it is quite probable that we have had anecdotal information of patients (from different studies) who were infected before hospital admission and those patients were misclassified as hospital-acquired COVID-19. A recent study considered nosocomial those patients who developed symptoms and had a positive SARS-CoV-2 polymerase chain reaction test results more than 7 days after admission. In this study, only 5.7% of patients tested positive for COVID-19 after 14 days from hospital presentation [10]. On the other hand, in low-income countries, such as Brazil, there is no standardized protocol for testing inpatients for COVID-19. This heterogeneity has made it even more challenging to identify positive COVID-19 cases because many institutions only test hospitalized patients who developed symptoms or have been in close contact with a confirmed COVID-19 case (*e.g.*, in the same ward) [11]. This may explain the prevalence (7.2%) of patients with hospital-manifested COVID-19 in our cohort.

The exact explanation for the number of patients infected in these hospital settings is still unknown and probably multifactorial, which could be related to the large numbers of inpatients, limited facilities for isolation of cases, reduced capacity for rapid and reliable diagnostic testing, and inadequate use of personal protective equipment, in addition to no suspicion of COVID-19, in patients with atypical symptoms or those who are asymptomatic [12].

Our results showed that patients with hospital-manifested COVID-19 had a greater prevalence of cancer, alcoholism, chronic kidney disease, and cirrhosis than controls. Elkrief et al. [13] described a high rate of hospital-acquired COVID-19 in patients with cancer. Our study also identified that patients with cancer are at a particularly increased risk for mortality from COVID-19, possibly due to the use of immunosuppressants and other associated factors, such as undernutrition and prolonged time of hospitalization.

The main causes of hospitalization unrelated to COVID-19 observed in our study, including cardiovascular diseases, propaedeutics, procedures, and gastrointestinal diseases, are possibly related

to the fact that the majority of the centers are general hospitals, with the exception of one specialized hospital in trauma. However, there are no studies with a similar hospital profile to ours to enable a direct comparison of the frequency of the causes of hospitalization.

As aforementioned, the few available evidence refer to hospital-acquired SARS-CoV-2 infection using different criteria. Although the results are useful to understand the problem in several settings, they cannot be used to directly compare with our data. Shiwani et al. [14], for example, demonstrated that despite the baseline characteristics of hospital-acquired and community-acquired COVID-19 in the United Kingdom displaying significant differences, the rates of mortality were similar between these patients. Khan et al. [15] identified that among 173 patients, 19 (11.0%) had nosocomial infection, and in line with this, Shiwani et al. [14] did not observe differences in 30-day mortality rates (*e.g.*, patients admitted with suspected COVID-19 [21.1%] vs patients with incidental COVID-19 [17.6%] vs patients with nosocomial COVID-19 [21.6%], $P = 0.755$). In contrast, in the current analysis, patients with hospital-manifested COVID-19 had a higher mortality rate than controls (35.8% vs 22.5%, $P < 0.001$). Our findings are in accordance with the initial hypothesis that patients who manifest COVID-19 while admitted for other conditions would have a higher risk for severe outcomes and subsequent mortality because of the delayed medical assistance in a pandemic scenery and the presence of underlying comorbidities, which makes these patients more vulnerable to COVID-19.

Overall, age and the presence of underlying diseases are established predictors of severity and mortality in patients with community-manifested COVID-19. In a previous analysis, our group reported a higher in-hospital mortality risk in older adults, those with a higher number of comorbidities, those with lower oxygen saturation-fraction of inspired oxygen ratio, and those with higher levels of C-reactive protein and platelet count, in addition to higher heart rate and blood urea nitrogen [16].

These factors have also been shown to be associated with those defined as hospital-acquired COVID-19. Carter et al. [17] described a higher mortality rate in older patients with frailty, renal failure, and increased C-reactive protein levels. In addition, Kuderer et al. [18] observed that the independent factors associated with increased mortality were increasing age, male sex, smoking, number of comorbidities, and active cancer. Elkrief et al. [13] observed older age and higher cancer stage to be independent risk factors for mortality in this population. All these findings are in agreement with ours, which indicated that advancing age, male sex, number of comorbidities, and cancer as risk factors for mortality in the study group.

To the best of our knowledge, there is a lack of studies comparing community-manifested *versus* hospital-manifested in Latin America. A large breadth of our understanding of COVID-19 comes from studies performed in Europe or North America, despite Brazil having been an important epicenter of the pandemic. It is known that scientific information is a critical source for directing medical practice, as well as guiding the national government policy, but the differences in the demographics between the populations and the health systems' characteristics largely influenced the results [14]. Thus, this study is an important part of such data in Latin America. It also has other strengths, such as its multicenter design, sample size, and matched analysis.

Regarding the study limitations, the primary cause for hospitalization might have been a COVID-19 manifestation that was not acknowledged at admission in some instances (or atypical symptoms attributed especially to the presence of chronic diseases [19]). COVID-19 also may cause decompensation of baseline medical conditions contributing to hospitalization, even when it is not considered the primary cause [19]. Future studies with larger sample sizes should include the aforementioned National Health Service surveillance criteria for hospital-acquired infections [9].

Conclusion

Hospital-manifested COVID-19 was associated with worse outcomes than community-acquired COVID-19. Older age, male sex, a higher number of comorbidities, and cancer are risk factors for in-hospital mortality in patients with hospital-manifested COVID-19. Our findings reinforce the importance of early diagnoses, show the necessity of maximizing the prevention of intra-hospital infection, and emphasize the clinical care for those with hospital-manifested COVID-19.

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Ethics: informed consent

Individual written informed consent was waived due to the severity of the situation and the use of deidentified data, based on medical chart review only.

Author contributions

Substantial contributions to the conception or design of the work: PDP, MCP, and MSM. Substantial contributions to the acquisition, analysis, or interpretation of data for the work: PDP, VMRG, MCAN, MCPBL, MCP, TCAF, and MSM. Drafted the work: PDP, VMRG, MCAN, MVRSS, TCAF, and MSM. Revised the manuscript critically for important intellectual content: all authors. Final approval of the version to be published: all authors.

Consent for publication

All authors gave consent for publication of the work.

Availability of data and materials

Data is available upon reasonable request.

Declaration of competing interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.02.012.

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