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# Adult patients admitted to a tertiary hospital for COVID-19 and risk factors associated with severity: a retrospective cohort study

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## ABSTRACT

COVID-19 is a disease whose knowledge is still under construction, high transmissibility, with no consensual treatment available to everyone. Therefore, the identification of patients at higher risk of evolving to the critical form of the disease is fundamental. The study aimed to determine risk factors associated with the severity of COVID-19 in adults patients. This is an observational, retrospective study from a cohort of adult patients with COVID-19 admitted to a public hospital from March to August 2020, whose medical records were evaluated. For the association of possible severity predictors, a Poisson regression was used. The primary outcome was the critical form of the disease (need for admission to the Intensive Care Unit and/or invasive mechanical ventilation). We included 565 patients: mostly men; 55.5% of those who progressed to the critical form of the disease were over sixty years old. Hypertension, diabetes mellitus and obesity were the most frequent comorbidities. There were 39.8% of patients who progressed to the critical form of the disease. The hospital mortality rate was 22.1%, and that of critical patients was 46.7%. The independent factors associated with the severity of the disease were obesity [RR = 1.33 (95% CI 1.07 to 1.66; p = 0.011)], $SpO_2/FiO_2$ ratio ≤ 315 [RR = 2.20 (95% CI 1.79 to 2.71; p = 0.000)], C-reactive protein > 100 mg/L [RR = 1.65 (95% CI 1.33 to 2.06; p = 0.000)], and lymphocytes < 1,000/µL [RR = 1.44 (95% CI 1.18 to 1.75; p = 0.000)]. Advanced age and comorbidities were dependent factors strongly associated with the critical form of the disease.

**KEYWORDS**: COVID-19. SARS-CoV-2. Risk factors. Severity. Cohort study.

## INTRODUCTION

COVID-19 caused a sudden and substantial global increase in hospitalizations and mortality due to severe acute respiratory syndrome[1]. The flu-like syndrome, transmitted primarily through the respiratory tract[2] by asymptomatic, pre-symptomatic and symptomatic carriers[1], has heterogeneous clinical symptomatology, varying from asymptomatic to mild symptoms up to serious/critical cases[1,3].

The critical form of the disease consists of a severe acute respiratory syndrome (SARS) defined by hypoxemia that requires invasive mechanical ventilation (MV)[4]. Severe COVID-19 generally involves respiratory manifestations, although other systems can also affected. The critical form of the disease is usually followed by long term complications[5].

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Currently, COVID-19 is responsible for millions of cases and deaths worldwide[1]. The Brazilian Unified Health System (SUS), a global reference of universal health care[6], is fundamental for meeting the demands of the pandemic in the country, however, it has also faced difficulties. The beginning of 2021 was marked by the second wave of COVID-19 in Brazil, which presented characteristics that differed from the first wave[7]. The substantial increase in COVID-19 cases in different regions of the country caused a huge pressure on the health system, which was already overloaded after one year of pandemic and the likely dominance of new variants[8].

The clinical characteristics of patients with COVID-19 and the severity of the illness may vary between studies in different regions[1,9]. We still do not know how the pandemic will behave, therefore, promoting an observational study on patients hospitalized with COVID-19 in a public reference hospital in Southern Brazil represents an opportunity for the early identification of the worst outcomes related to COVID-19, in addition to guiding decision-making to reduce intra-hospital mortality. The study aimed to determine risk factors associated with the severity of COVID-19 in adult patients.

## MATERIALS AND METHODS

This is an observational, retrospective study from a cohort of adult patients with COVID-19 admitted to a large high-complexity tertiary public hospital[10] from March 1 to August 20, 2020, whose medical records were evaluated. Data were collected in the context of the multicentric study "National multicentric hospital record of patients with disease caused by SARS-CoV-2 (COVID-19)" conducted by the Federal University of Minas Gerais, Minas Gerais State, Brazil.

The eligible medical records belong to patients with COVID-19 diagnosis confirmed by RT-PCR or serology, who were admitted by spontaneous demand, were transferred or referred to our hospital by another service. Patients admitted to the institution for other reasons or who acquired COVID-19 during hospitalization, pregnant women and patients with COVID-19 diagnosis confirmed by other methods than RT-PCR and serology were deemed ineligible.

Data were collected at admission, during hospitalization and at the time of the disease outcome. The variables collected at admission (first 24 h) were related to the diagnostic method for COVID-19, demographic and clinical characteristics, previous health history, laboratory test results and imaging exams. During hospitalization, the following variables were described: drug therapy, vasoactive amines, prone position, non-invasive ventilation (NIV) at any moment, need for renal replacement therapy (RRT), and main complications during hospitalization. Among the clinical outcomes, we collected information on admission to the ICU, need for MV, hospital discharge or death. The primary outcome was the development of the critical form of the disease, characterized by admission to the ICU and/or need for MV.

Data were collected from July to December 2020 from electronic medical records and entered, according to a standardized protocol, in the online platform Research Electronic Data Capture - REDCap®. Clinical data were submitted to a univariate analysis; for the variables of interest at hospital admission, during hospitalization, and at the time of the study outcome, the reference values and measurement units of the tests followed the manufacturers' instructions. The $SpO_2/FiO_2$ ratio was calculated using data from the hospital admission on peripheral oxygen saturation ($SpO_2$) and oxygen flow in liters per minute (L/min) for patients in spontaneous ventilation. The oxygen flow was converted into the approximate fraction of inspired oxygen ($FiO_2$): no device - ambient air (0.21); nasal cannula 1 (0.24) 2 (0.28) 3 (0.32) 4 (0.36) 5 (0.40) 6 (0.44); simple mask (0.40) 6 (0.50) 7 (0.60); mask with reservoir 6 (0.60) 7 (0.70) 8-9 (0.80) 10-15 (0.95). For patients under NIV/MV, the $FiO_2$ described in the medical record was considered.

Continuous variables were expressed in medians and interquartile intervals (IQI), whereas categorical variables were expressed as absolute and relative frequencies. To compare the clinical complications during hospitalization of critical and non-critical patients, the Pearson chi-square test was used. The association of possible predictors with the severity outcome was carried out through the robust Poisson regression model for the estimate of prevalence ratios and 95% confidence intervals (CIs). In the multivariate analysis, a missing data percentage of 8.8% was considered for the inclusion of variables. Significant variables were selected and included in the multivariate model (age 60 to 69; age ≥ 70; $SpO_2/FiO_2$ ratio ≤ 315; hypertension; diabetes mellitus; obesity (BMI > 30 kg/m$^2$); malignant neoplasia; C-reactive protein > 100 mg/L; lymphocytes < 1,000/µL; urea > 50 mg/dL; use of vasoactive amines upon admission and altered level of consciousness upon admission). *P*-values of 0.05 or less were considered statistically significant. We excluded variables with missing data due to the high risk of bias, possibly not representing the population adequately. No other form of data entry was used. All analyses were carried out with the software SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA).

As data were collected from medical records, the free and informed consent form was waived. The study was approved by the local Research Ethics Committee and the National Research Ethics Commission under the number CAAE 30350820.5.0000.0008.

## RESULTS

The population was initially composed of 604 patients; 30 already hospitalized for other reasons, who contracted the virus during hospitalization were excluded, in addition to nine pregnant women. In the most critical period of the pandemic, 63 patients who did not require a high level of medical care were transferred to hospitals for less complex cases to continue their treatment, while two critical patients were transferred to another reference hospital due to lack of vacancy in the ICU. Information on their health outcomes was collected from the medical records of the institutions that took care of them. Therefore, 565 patients were included in the analysis.

The diagnostic method to confirm COVID-19 was the RT-PCR test for 94.3% (533) of the patients. Men represented 52.9% (299) of the sample, with an average age of 58 years (IQI 45 to 67). Patients over 60 years old progressed more often to the critical form of the disease [relative risk (RR) = 1.46 (95% CI 1.15 to 1.85)]. Likewise, there was no significant difference between genders. Demographic and clinical characteristics upon hospital admission in addition to laboratory and imaging tests results are shown in Table 1.

Regarding the health history of the patients, it was evinced that the average number of associated comorbidities was higher among those who presented with the worst prognoses. Patients with more comorbidities progressed to

**Table 1 -** Demographic characteristics, previous health history, clinical data, laboratory and imaging tests results upon hospital admission.

| Variable | Total - N (%) / N = 595 |
|---|---|
| **Gender** | |
| Male | 299 (52.9) |
| **Age (years)** | |
| < 60 | 303 (53.6) |
| 61 to 69 | 135 (23.9) |
| > 70 | 127 (22.5) |
| **Most frequent comorbidities** | |
| Hypertension | 265 (46.9) |
| Diabetes mellitus | 163 (28.8) |
| Obesity | 90 (15.9) |
| Asthma | 47 (8.3) |
| COPD | 47 (8.3) |
| Neoplasia | 44 (7.8) |
| Coronary artery disease | 42 (7.4) |
| Chronic kidney disease | 35 (6.2) |
| **Living Habits** | |
| Use of illicit drugs | 10 (1.8) |
| Alcoholism | 28 (5.0) |
| Current smoking | 33 (5.8) |
| Formersmoker | 114 (20.2) |
| **Most prevalent clinical manifestations** | |
| Dyspnea | 372 (65.8) |
| Fever | 329 (58.2) |
| Dry cough | 299 (52.9) |
| Myalgia | 189 (33.5) |
| Adynamia | 133 (23.5) |
| Anosmia (loss of smell) | 99 (17.5) |
| Headache | 99 (17.5) |
| **Clinical alterations upon hospital admission** | |
| Altered level of consciousness | 64 (11.3) |
| BP ≤ 90/60 mmHg | 13 (2.8) |
| Vasoactive amines | 30 (5.3) |
| HR ≥ 100 bpm | 145 (30.9) |
| RRt ≥ 20 mipm | 240 (56.5) |
| Tax ≥ 37.8°C | 106 (27.5) |
| SpO2 < 93% | 115 (21.1) |
| SpO2/FiO2 Ratio ≤ 315 | 115 (21.1) |
| Supplemental $O_2$ requirement | 206 (36.5) |
| **Laboratory and imaging test results upon admission** | |
| C-Reactive Protein > 100 mg/L | 249 (45.9) |
| D-dimer ≥ 1,000 ng/mL FEU | 254 (49.1) |
| Platelets ≤ 15,0000/uL | 79 (14.5) |
| Lactate (ABG) ≥ 1.6 mmol/L | 137 (26.9) |
| Troponin ≥ 14 ng/L | 171 (40.9) |
| Lymphocytes < 1,000/uL | 235 (42.0) |
| Urea ≥ 50 mg/dL | 154 (27.2) |
| Creatinine > 1.2 mg/dL | 144 (25.8) |
| GOT/AST ≥ 37 U/L | 248 (60.6) |
| GPT/ALT ≥ 41 U/L | 165 (40.6) |
| INR ≥ 1.3 | 116 (25.3) |
| $pO_2$ (ABG) < 83 mmHg | 351 (70.5) |
| Hemoglobin < 12.8 g/dL | 201 (36.0) |
| Chest x-ray | 535 (94.7) |
| Altered x-ray | 434 (81.1) |
| Chest CT | 101 (17.9) |
| Altered chest CT | 96 (95.0) |
| Involvement > 25% of lung parenchyma | 30 (65.2) |

Frequency (percentage) or median (interquartile interval); BP = blood pressure; HR = heart rate; RRt = respiratory rate; Tax = axillary temperature; SpO2 = peripheral oxygen saturation; SpO2/FiO2 ratio = the ratio between the peripheral oxygen saturation and the fraction of inspired oxygen; ABG = arterial blood gas; CT = computerized tomography.

the critical form of the disease up to twice as often (Table 2). Just over half of the patients (51.5%, 291) presented with some associated cardiovascular disease and 46.4% (135) of them were admitted to the ICU or required MV. Oncology patients progressed to the critical form of the disease nearly twice as often [RR = 1.41 (1.05 to 1.90)]. The most prevalent comorbidities were systemic hypertension, diabetes mellitus (DM) and obesity. Comorbidities behave as age-dependent factors - the older the individual, the greater the number of associated preexisting diseases. Chronic kidney disease (CKD) was not associated with the severity of COVID-19. Respiratory system diseases such as asthma and chronic obstructive pulmonary disease (COPD) proved to behave as protective variables for the severity ofCOVID-19.

In 15.9% (90) of the patients, obesity was characterized as an independent variable for the severity of COVID-19. Hospitalized obese patients were on average 49 years old (IQI 23 to 84), 62.2% (56), presented with two or more comorbidities and 52.5% (47) were admitted to the ICU. The mortality rate among obese patients was 17.8% (16),

**Table 2 -** Significant variables for the severity of the patients admitted due to COVID-19 in the bivariate analysis.

| Variable | ICU/MV N (%) N = 225 (39.8) | RR (95% CI) | *P-value* |
|---|---|---|---|
| **Age (years)** | | | |
| < 60 | 100 (33.0) | 1 | |
| 61 to 69 | 65 (48.1) | 1.46 (1.15 to 1.85) | 0.004 |
| > 70 | 60 (47.2) | 1.43 (1.12 to 1.83) | 0.002 |
| **Comorbidities** | | | |
| Hypertension | 122 (46.0) | 1.34 (1.09 to 1.64) | 0.005 |
| Diabetes mellitus | 78 (47.9) | 1.31 (1.07 to 1.61) | 0.010 |
| Obesity | 48 (53.3) | 1.43 (1.14 to 1.79) | 0.002 |
| Neoplasia | 24 (54.5) | 1.41 (1.06 to 1.89) | 0.020 |
| **Number of comorbidities** | | | |
| None | 46 (26.3) | 1 | |
| 1 | 70 (42.7) | 1.62 (1.20 to 2.20) | 0.002 |
| ≥ 2 | 109 (48.2) | 1.84 (1.38 to 2.43) | < 0.001 |
| **Clinical alterations upon admission** | | | |
| Altered level of consciousness | 45 (70.3) | 1.96 (1.61 to 2.38) | < 0.001 |
| Vasoactive amines | 29 (96.7) | 2.64 (2.32 to 3.00) | < 0.001 |
| $SpO_2$ < 93% | 82 (71.3) | 2.21 (1.85 to 2.65) | < 0.001 |
| $SpO_2/FiO_2$ Ratio ≤ 315 | 97 (84.3) | 2.93 (2.48 to 3.47) | < 0.001 |
| Supplemental $O_2$ requirement | 130 (63.1) | 2.39 (1.95 to 2.92) | < 0.001 |
| **Laboratory and imaging tests upon admission** | | | |
| C-Reactive Protein > 100 mg/L | 141 (56.6) | 2.13 (1.71 to 2.66) | < 0.001 |
| Lactate (ABG) ≥ 1.6 mmol/L | 74 (54.0) | 1.44 (1.17 to 1,76) | < 0.001 |
| Troponin ≥ 14 ng/L | 92 (53.8) | 1.58 (1.27 to 1.98) | < 0.001 |
| Lymphocytes < 1,000 /Ul | 123 (52.3) | 1.70 (1.38 to 2.08) | < 0.001 |
| Urea ≥ 50 mg/dL | 83 (53.9) | 1.55 (1.27 to 1.90) | < 0.001 |
| Creatinine > 1.2 mg/dL | 76 (52.8) | 1.48 (1.21 to 1.81) | < 0.001 |
| GOT/AST ≥ 37 U/L | 106 (42.7) | 1.32 (1.01 to 1.73) | 0.039 |
| INR ≥ 1.3 | 64 (55.2) | 1.44 (1.17 to 1.78) | 0.001 |
| Altered chest x-ray | 189 (43.5) | 2.00 (1.36 to 2.94) | < 0.001 |
| Need of NIV at some time during hospitalization | 21 (87.5) | 2.32 (1.93 to 2.80) | < 0.001 |

Frequency (percentage); RR = Relative risk; CI = Confidence interval; $O_2$ = oxygen; $SpO_2$ = peripheral oxygen saturation; $SpO_2/FiO_2$ Ratio = the ratio between the peripheral oxygen saturation and the fraction of inspired oxygen; ABG = arterial blood gas; NIV = non-invasive ventilation.

with the acute respiratory distress syndrome (ARDS) as the primary complication associated with severity (23.3%, 21).

Predominant symptoms upon hospital admission were dyspnea, fever, dry cough and myalgia (Table 1). The mean time from the beginning of the symptoms until hospital admission was seven days (IQI 3 to 10) for non-critical patients and five days (IQI 2 to 7) for patients who required ICU and/or MV. However, the symptoms did not prove to be statistically significant to discriminate the severity of the outcome.

On admission, clinical manifestations that proved to be significantly associated with the critical form of the disease are shown in Table 2. In the multivariate analysis, we used the $SpO_2/FiO_2$ ratio [RR = 2.93 (2.48 to 3.47)] instead of the isolated $SpO_2$ [RR = 2.21 (1.85 to 2.65)] because there was a higher relative risk for severity of COVID-19. Among the patients who presented with $SpO_2/FiO_2$ ratios ≤ 315 upon admission, 84.3% (97) were admitted to the ICU or required MV.

Critically ill patients had lower lymphocyte counts, higher serum levels of troponin, international normalized ratio (INR), creatinine, urea, glutamic oxaloacetic transaminase/aspartate aminotransferase (GOT/AST), C-reactive protein (CRP) and arterial blood gas (ABG) lactate (Table 2). Despite showing a significant association with severity ($p < 0.001$), troponin was not included in the multivariate analysis due to the absence of available data. Likewise, GOT/AST, a significant variable for the severity of the illness ($p = 0.039$), was altered in more than 60.6% (248) of the samples collected upon admission, even so with a high rate of lost data. The chest x-rays upon admission were altered in 81.1% (434) of the patients. The main alterations were the presence of diffuse infiltrates in 36.3% (194), opacities in 28.2% (151) and consolidations in 23% (123). Altered chest x-rays upon admission were associated with the critical form of the disease [RR = 2.00 (1.36 to 2.94)] (Table 2).

During hospitalization due to COVID-19, 39.8% (225) of the patients progressed to the critical form of the disease and 36.8% (208) were admitted to the ICU, 35.9% (203) progressing to MV, 11.7% (66) needing RRT (10 were already dialysis patients before hospitalization), 31.7% (179) received vasoactive amines, 18.9% (107) required the prone position and 4.2% (24) used NIV at some point during hospitalization. The average duration of MV in the patients was 11 days (IQI 7 to 21). The main clinical complications related to the severity of COVID-19 during hospitalization are shown in Table 3.

Eighty-three patients were admitted to the ICU, and other 17 could not find an ICU vacancy in the institution. The average age of these 17 patients was 73 years (IQI 58 to 80). The hospital mortality rate was 22.1% (125) and among critically ill patients it was 46.7% (105). Regarding the patients admitted to the ICU, 49.3% (100) required MV and 42.3% (88) died. Three patients died within the first six hours of their admission, eight patients kept waiting for ICU beds in the emergency department until their deaths were confirmed, and four patients progressed to palliative care after the aggravation of COVID-19. The mortality of patients not admitted to the ICU was 100%.

The average hospitalization time was nine days (IQI 5 to 17). The average hospitalization time was 19 days for critically ill patients, (IQI 11 to 30), and the average ICU stay was 12 days (IQI 7 to 23). For non-critical patients, the average hospitalization time was six days (IQI 4 to 9).

In the multivariate Poisson regression model (Table 4), some factors were independently associated with a higher risk of COVID-19 severity: obesity [RR = 1.48 (95% CI 1.19 to 1.84)], $SpO_2/FiO_2$ ratio ≤ 315 upon admission [RR = 2.20 (95% CI 1.79 to 2.71)], CRP > 100 mg/L upon admission [RR = 1.73 (95% CI 1.40 to 2.15)], and lymphocytes < 1,000 /uL upon admission [RR = 1.40 (95% CI 1.15 to 1.70)].

**Table 3 -** Main clinical complications during the hospitalization of patients with COVID-19.

| | Sample (n = 565) | Critical (n = 225) | Non-critical (n = 340) | *P-value* |
|---|---|---|---|---|
| ARDS | 98 (17.3) | 95 (42.2) | 3 (0.9) | < 0.001 |
| Nosocomial infection | 94 (16.6) | 82 (36.4) | 12 (3.5) | < 0.001 |
| Septic shock | 86 (15.2) | 82 (36.4) | 4 (1.2) | < 0.001 |
| Hyperglycemia | 88 (15.6) | 68 (30.2) | 20 (5.9) | < 0.001 |
| Pulmonary thromboembolism | 40 (7.1) | 29 (12.9) | 11 (3.2) | < 0.001 |
| Peripheral venous thrombosis | 13 (2.3) | 12 (5.3) | 1 (0.3) | < 0.001 |
| Hemorrhage | 11 (1.9) | 10 (4.4) | 1 (0.3) | < 0.001 |

Frequency (percentage); *P* = Pearson chi-square test; ARDS = Acute respiratory distress syndrome.

**Table 4 -** Independent variables for severity in patients with COVID-19.

| Variable | Multivariable | |
|---|---|---|
| | RR (95% CI) | *P-value* |
| Obesity | 1.48 (1.19 to 1.84) | < 0.001 |
| $SpO_2/FiO_2$ Ratio ≤ 315 | 2.20 (1.79 to 2.71) | < 0.001 |
| Lymphocytes < 1,000/uL | 1.40 (1.15 to 1.70) | < 0.001 |
| C-Reactive Protein > 100 mg/L | 1.73 (1.40 to 2.15) | < 0.001 |

RR = Relative risk; CI = confidence interval; *P* = multivariate Poisson regression model.

## DISCUSSION

In the present study, patients over 60 years old had nearly twice the risk of developing the critical form ofCOVID-19. Comorbidities behave as an age-dependent factor. Half of the patients reported associated cardiovascular diseases, and half of them were admitted to the ICU. Two or more preexisting comorbidities were present in 40% of the patients and showed a significant association with worse outcomes. Obesity was an independent variable for the severity of the illness. Patients with $SpO_2/FiO_2$ ratios ≤ 315 upon admission were up to three times more often admitted to the ICU or required MV. Lower lymphocyte counts and higher CRP levels upon admission were independent factors for the critical form of the disease and altered chest x-rays upon admission and the use of NIV at some point during hospitalization were also associated with unfavorable outcomes. Four in every ten patients with COVID-19 presented with the critical form of the illness.

Most of the patients (94.3%, 533) were diagnosed by a positive reverse transcription polymerase chain reaction (RT-PCR) amplification, which, according to Kumar *et al.*[11], is still the gold standard for diagnosing COVID-19.

The results of this study demonstrated that patients over 60 years old with associated comorbidities had worse COVID-19 prognosis, as in the study by Li *et al.*[12], Schuelter-Trevisol *et al.*[13] and Tan *et al.*[14]. In the systematic review by Tan *et al.*[14], critically ill patients with COVID-19 had an average age of 62.6 years. Our findings agree with the evidence found in several studies that pointed out a more significant occurrence of the critical form of the disease in older patients[15-19]. The decreased cardiopulmonary reserve in old patients increases the risk of complications, and the aging of the immune system (immunosenescence), leads to a pro-inflammatory trend, contributing to an exacerbated response to SARS-CoV-2[16,20].

However, in this study, the age factor did not prove to be independently associated with a more serious outcome. This finding may suggest that the use of a criterion of age for the prioritization of patients in cases of a scarcity of ICU beds, is not the most appropriate considering that other criteria can be evaluated concomitantly such as the existence of associated comorbidities, the irreversible impairment of cognitive functions and the application of fragility scales, according to screening guidelines in catastrophe situations and the particularities of the COVID-19 pandemic by AMIB[2]. Recent systematic reviews[12,21] have identified results similar to ours, in which the most associated comorbidities with severity were diseases of the cardiovascular system, with a higher prevalence of systemic hypertension. According to Liang *et al.*[22], a cancer history proved to be an independent factor in their study. A systematic review with 16,561 critically ill patients in 17 countries and four continents identified that advanced age and comorbidities such as obesity, systemic hypertension, DM and cardiovascular diseases were the main risk factors for severe COVID-19[12].

This study suggests that the higher the number of preexisting comorbidities, the higher the risk of developing the critical form of the disease, in agreement with the results by Cheng *et al.*[23], Suleyman *et al.*[24], and Giri *et al.*[25]. In Brazil, one in every five Brazilian adults has two or more comorbidities[26]. A study in Sergipe, in Northeastern Brazil, pointed out a mortality 1.5 times higher associated with systemic hypertension or DM in patients over 65 years old[26]. The study by Li *et al.*[12] suggested that patients with subjacent diseases are more vulnerable to pneumonia and have weaker immunity systems and a higher probability of falling seriously ill. The effects of SARS-CoV-2 on the immune system, T cells and on the production of cytokines seem to further aggravate the pro-inflammatory trend in patients with cardiovascular comorbidities[16,20]. Andrade *et al.*[27] analyzed data from public Brazilian hospitals and identified that the behavior of the Charlson and Elixhauser indices (comorbidity assessment indices) was consistent with the hypothesis of a higher risk of the critical form of the disease and death by COVID-19 in patients with comorbidities, with obesity as an independent factor.

Similarly, in this cohort, the only comorbidity identified as an independent factor for severity of COVID-19 was

obesity. A growing body of evidence suggests that obesity and the increase in visceral adiposity are strongly and independently associated with adverse outcomes, the critical form of the disease, and death due to COVID-19[28]. Some studies highlighted other characteristics of obesity such as alteration of respiratory mechanics, hampered pulmonary function and coexistence of metabolic disorders such as diabetes and cardiovascular diseases in a single individual that also increase the risk of severe COVID-19[29]. The main complication associated with the severity of the disease in obese individuals in this study was ARDS. Obesity itself is a comorbidity generally associated with other health problems; according to this study, 62.2% (56) of obese patients had two or more comorbidities. Although the mean age of the cohort patients was 49 years, according to Gonçalves *et al.*[30], the immunological imbalance in obesity does not depend on age to impair the response. Gonçalves *et al.*[30] have also claimed that obesity is associated with an increase in ICU hospitalizations and a more considerable need for ventilation support in hospitalized obese patients, which we also identified in this study. Despite the greater need for ICUs and MV, the mortality was lower (17.8%) in obese patients compared to the general mortality (22.1%) due to COVID-19, which may be justified by the lower average age of obese patients, disagreeing with Gonçalves *et al.*[30]. Obesity complicated their health conditions, but they died less for being younger and had more significant organic reserves. In the Brazilian National Vaccination Plan against COVID-19[31], obesity is only considered a comorbidity when it is morbid obesity (BMI ≥ 40). However, according to this study, obese individuals with BMI ≥ 30 are already in the risk group for the critical form of the disease, and it is important and necessary to take this finding into account.

This study has also identified clinical markers upon admission associated with the critical form of the disease, including the $SpO_2/FiO_2$ ratio, which proved to be an independent predictor factor associated with severity. We compared the clinical relevance with the severity of the patients' $SpO_2/FiO_2$ ratio, $SpO_2$ and partial pressure of oxygen ($PaO_2$) of the ABG and identified the $SpO_2/FiO_2 \leq 315$ as the best predictor for the critical form of the disease [RR = 2.93 (2.48 to 3.47)]. The $SpO_2/FiO_2$ ratio is a low-cost, non-invasive, painless, quick and safe method available in most health services and a reliable predictor for ARDS, as described in the literature and corroborated in this study, becoming a differential method in facing the pandemic. The $PaO_2$ of the ABG, even with hypoxemia, did not prove to be a significant factor for severity. In the study by Choi *et al.*[32], the $SpO_2/FiO_2$ ratio upon admission presented an area under the receiver operating characteristic curve (ROC) around 85.7%, characterizing the $SpO_2/FiO_2$ ratio as a strong predictor for the occurrence of ARDS. The WHO[33] recommended the $SpO_2/FiO_2$ ratio when PaO2 is not available, considering values ≤ 315 as suggestive of SARS, including non-ventilated patients. According to Catoire *et al.*[34], the $SpO_2/FiO_2$ ratio may be a reliable tool to screen for hypoxemia in patients admitted to the emergency department, particularly during the COVID-19 pandemic. Considering the current pandemic scenario, in which there is a shortage of supplies and hospital overcrowding, studies aimed at predicting the factors associated with the severity of COVID-19 through fast, available low and low-cost methods are very relevant. In the analysis of biomarkers, low lymphocytes count and high CRP levels were independent risk factors for severity. According to Li *et al.*[12], CRP is a common inflammation marker in COVID-19 with high RR in critical groups. According to their results, lymphopenia and high CRP were intimately associated with severe pneumonia. To Malik *et al.*[35], CRP may be the most effective and sensitive marker in predicting the progression of COVID-19, suggesting that one of the pathophysiological signatures of COVID-19 could be the sustained inflammatory response and the cytokine storm, similar to those found in patients infected with SARS-CoV and MERS-CoV, and severe inflammation would lead to immunological impairment, liver, myocardial and kidney damages in addition to activation of coagulation.

Altered chest x-ray upon admission was strongly associated with severity; these patients are almost three times more likely to be at risk than others, similar to the findings of a cohort that studied 1,590 patients[22] in whom the chest x-ray was an independent predictive factor included in the risk score for chest x-ray abnormality. In 10 studies focused on chest x-ray findings, bilateral infiltrates were observed in 72% of the patients[14]. These results evinced that radiological abnormalities are the most direct diagnostic method for severe pneumonia[12].

The WHO[33] recommends the balanced use of all non-invasive respiratory support strategies, justified by the insufficient evidence base. During the pandemic, the concern that such strategies could cause more damage to the patients has emerged, by means of late tracheal intubation that could exacerbate the lung injury; for health professionals who could acquire nosocomial infections and for health systems, due to the high level of oxygen demand to ventilate a high number of ventilated patients[36]. In this cohort, 4.2% (24) of the patients used NIV; among them, 87.5% (21) were admitted to the ICU and 83.3% (20) progressed to MV. The variable time was not assessed, therefore, we cannot tell in what moment the patients used these procedures during hospitalization. Considering that NIV was only recommended when negative pressure

systems are available due to the risk of aerosolization, we can assume that many patients only used NIV admission to the ICU due to the availability of adequate conditions. Currently, a better conduction of the patients with NIV support has been reported[37] facilitated by the availability of more considerable evidence, so that it is possible that some admissions to ICUs and use of MV could have been avoided in the past.

The need for MV in this cohort was 35.9% (203), totaling 89.4% (186) of the patients admitted to the ICU. Suleyman *et al*.[24] reported that 80.8% of their critically ill patients required MV. These estimates are higher than those pointed out by a private hospital in the city of Sao Paulo in which MV was necessary in 65% of the ICU patients. In the systematic review by Tan *et al.*[14], 67.7% of the patients needed MV. Facing an unknown and very dynamic pandemic, medical protocols were updated quickly, and, initially, early intubation was indicated, that this procedure can perhaps justify this high percentage of MV at the institution.

The need for intensive treatment observed in the study was 36.8% (208), and this rate is higher than those found in the systematic review by Li *et al.*[38], who estimated a 23% rate of critical COVID-19. According to Suleyman *et al.*[24], 39.7% of their patients needed ICU hospitalization in a New York hospital, similar to the percentage found in this study. In another hospital with similar characteristics[13], 29% of the patients needed to be admitted to the ICU; in a private hospital, the need for ICU hospitalization was 33%[8]. Some factors are considered to be associated with the slightly superior percentage found in this study, such as factors related to the higher incidence of comorbidities in our patients because they are socioeconomically disadvantaged, being dependent on the Brazilian Unified Health System (SUS), therefore facing more significant challenges in getting medical care and treatments. Marcolino *et al.*[15] corroborated that the average number of comorbidities was smaller in patients from private hospitals than in patients from public and mixed hospitals.

The ICU mortality in the study by El Aidaoui *et al.*[39] in South Africa was 31.1%, lower than that found in this study (46.7%, 105). Wiersinga *et al.*[1] described a lethality of 40% in patients admitted to ICUs. There was a marked heterogeneity in the global mortality rate for patients with COVID-19 admitted to ICUs and the average was 28%, according to Tan *et al.*[14].

In the 17 patients who needed MV but were not admitted to the ICU due to the lack of vacant beds, the mortality rate was 100%. Even if the patients in this condition being only 17 with an average age of 73 years old, we can infer that the management of critically ill patients by teams not qualified for the work in the ICU environment may have influenced this unfavorable clinical outcome.

Regarding the intra-hospital mortality, the percentage found in this study was 22.1% (125), similar to that of the city of New York, with 21%[40] and slightly lower than that of the one found in the study carried out in Sergipe State, of 29.2%[26]. Andrade *et al.*[27] reported a 24.4% mortality and suggested that there was a wide variation in hospital mortality by COVID-19 in the many services belonging to the Brazilian Unified Health System (SUS), and these differences were associated with demographic and clinical factors, social inequality and differences in the infrastructure of the services and the quality of the healthcare provided. According to Marcolino *et al.*[15], public and mixed hospitals presented with higher mortality rates than private hospitals (24.7% vs. 26.2% vs. 10.8%, $p < 0.001$). In the systematic review by Tan *et al.*[14] assessed the mortality rates at a global scale, and the percentages varied from 23.4% to 33.0%.

Among the limitations of this study, we highlight the data collection in a public hospital, which may represent only a specific and disadvantaged portion of the population. Moreover, this is a retrospective study. Important social determinants such as family income and education level were not collected. The absence of data on some variables upon hospital admission was also a limiting factor. We believe that the unavailable data could be related to the absence of hospital guidelines specific for COVID-19 at that time of the pandemic, and current protocols were heterogeneous and divergent. In addition, the level of control or decompensation of preexisting comorbidities was not measured. We used data from the patients' hospital admission to identify the factors associated with the severity of COVID-19; data referring to the period of hospitalization were also not considered.

The importance of this cohort stems from the need for rapid and effective identification of patients at higher risk of developing the critical form of the disease through simple and objective parameters upon hospital admission, allowing prioritizing care for such patients and directing clinical management. The early identification of such factors associated with severity is essential in the attempt to reduce ICU admissions and, consequently, the morbimortality. This study includes s many variables, and a thorough review of medical records enabled the reliability of the results. Moreover, all data were submitted to periodical audits. The patients were monitored from admission to hospital discharge or death. The outcome of the cases transferred to other institutions were included in the study as we performed an active search, and retrieved information on the clinical profile of patients and associated factors upon admission and the hospital outcomes. We employed a methodology based on STROBE, a quality tool widely

used in cohort studies. The collected data and the obtained conclusions are important considering that there are few studies on the subject in Latin America and in Brazil, so they can serve as subsidies for the development of clinical guidelines and help the allocation of supplies, teams and public resources, as well as for future research.

## CONCLUSION

The results of this study provide important data on patients with COVID-19 admitted to a public hospital, their clinical profile and factors associated with progression of the disease. The advanced age and subjacent comorbidities are dependent factors associated with the critical form of the disease, as much as altered chest x-rays upon hospital admission and the need for NIV at some time during the hospitalization. The main clinical complication among the critically ill patients was ARDS. The following were identified as independent factors for the severity of the disease: obesity, the $SpO_2/FiO_2$ ratio ≤ 315, CRP > 100 mg/L, and lymphocytes < 1,000/μL upon admission. We found easily measurable results even in small centers with limited healthcare resources. However, considering that the epidemic curve is dynamic and that associated factors may diverge among regions for various reasons, in addition to the discovery of new variants, constant studies on the profile of infected patients and factors associated with the severity of the disease are necessary.

## AUTHORS' CONTRIBUTIONS

VBS: literature search, study design, data collection, data analysis, data interpretation, writing; EIW, ATS and SLSB: literature search, study design, data analysis, data interpretation, writing; AFG, RCA, DRC, FCS, RL, IHG and KMM: literature search and data collection; AK: data analysis, data interpretation and writing.

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