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Clinical profile and severity predictors of coronavirus disease 19 infection in a reference center from southern Brazil: a cross-sectional study

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SUMMARY

OBJECTIVES: The coronavirus disease pandemic has become a major global health crisis since 2019. Recent data show the association of diabetes, hypertension, and obesity with poor related outcomes in coronavirus disease infection. This descriptive study aimed to identify the clinical and laboratory parameters in patients with acute respiratory syndrome and confirmed severe acute respiratory syndrome coronavirus 2 infection.

METHODS: In this cross-sectional study, we analyzed data of 409 patients admitted to a referral hospital in Rio Grande do Sul, Brazil, with coronavirus disease infection confirmed by reverse transcription polymerase chain reaction. Clinical, laboratory, and imaging data were collected retrospectively from electronic medical records using a template with the variables of interest.

RESULTS: The average age was 64 years (52–73), and the body mass index was 27 kg/m² (22.1–31.2). Hypertension, diabetes, and obesity were observed in 58, 33, and 32% of the patients, respectively. Patients admitted to an intensive care unit were older [66 years (53–74) vs. 59 years (42.2–71.7)], with significantly higher impairment on chest computed tomography [75% (50–75) vs. 50% (25–60)] and received higher doses of corticosteroid therapy [39.4 mg (14.3–70.3) vs. 6 mg (6–14.7)]. Hematological parameters were lower in critically ill patients, with greater differences observed on the fifth day of hospitalization [hemoglobin 11.5 g/dL (9.5–13.1) vs. 12.8 g/dL (11.5–14.2), platelets 235,000 µL (143,000–357,000) vs. 270,000 µL (192,000–377,000), and lymphocytes 900 µL (555–1,500) vs. 1,629 µL (1,141–2,329)]. C-reactive protein levels and kidney function were also worse in intensive care unit patients. The mortality rate was significantly higher in the intensive care unit compared to the basic care unit (62.8 vs. 12.2%).

CONCLUSION: Our findings suggest that metabolic and cardiovascular comorbidities, as well as abnormal hematological parameters, are common findings among patients with severe respiratory syndrome related to coronavirus disease.

KEYWORDS: COVID-19. Severe acute respiratory syndrome. Hemoglobins. Blood platelets. Lymphocytes.

INTRODUCTION

Coronavirus disease 19 (COVID-19) first emerged as an unknown pneumonia in December 2019 in the city of Wuhan, China, quickly spreading to other regions of the world[1,2]. Coronaviruses are single-stranded RNA viruses that belong to the *Coronaviridae* family and are widely distributed in mammals and humans[3]. Although infections in humans are usually mild, there have been two epidemics in the past associated with respiratory syndrome, including SARS-CoV1 and MERS-CoV[4,5].

The World Health Organization (WHO) declared the disease COVID-19 as a pandemic in March 2020[6]—a pandemic unprecedented in scale and speed, reaching more than 188 countries, affecting countless individuals, and causing thousands of deaths. COVID-19 infection can lead to severe pneumonia, acute respiratory distress syndrome, acute kidney injury, and acute heart failure[3]. According to the COVID-19 panel of the Center for System Science and Engineering at Johns Hopkins University, until September 2021, almost 221 million cases were registered and 20 million cases were present only in Brazil.

As a rapidly spreading disease, SARS-CoV-2 infection transmits mainly by droplets and direct contact between people and is highly contagious. Although the incubation period averages 5.5 days, it is known to last up to 14 days[7]. The clinical manifestations of this disease vary; however, the typical symptoms

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of COVID-19 are fever, sore throat, fatigue, cough, and shortness of breath. Self-reported olfactory and taste disorders have also been reported[8]. In the acute phase, COVID-19 infection leads to a pronounced systemic increase in inflammatory mediators and cytokines, with high levels of pro-inflammatory interleukins (IL1B, IL6, IFNγ, IP10, and MCP1) and tumor necrosis factor-alpha (TNF-α). This cytokine storm leads to lymphocyte apoptosis, inflammation, and excessive lung damage, although the pathophysiology of the disease has not been fully elucidated[4]. Besides reduced lymphocyte counts, leukocytes, neutrophils, and platelets can also be affected and can be used as markers of systemic inflammation and possibly as prognostic indicators[5,9].

Considering the significant morbidity and mortality associated with COVID-19 infection, as well as the existence of viral variants and the unpredictability of the course of the SARS-CoV-2 pandemic, studies in different populations are needed to understand the behavior of the infection and identify markers capable of predicting patients at risk for a more severe course. This study aimed to describe and evaluate useful clinical (i.e., comorbidities, length of hospitalization, admission to intensive care, mechanical ventilation support, use of glucocorticoids and insulin therapy after hospital admission, and mortality rate), laboratory (i.e., glucose, renal function, and hematological and inflammatory parameters), and imaging predictors in patients with an unfavorable outcome in a population in southern Brazil.

METHODS

This is a cross-sectional and retrospective study based on electronic medical records. Hospitalized patients were analyzed at a reference hospital for COVID-19 from the metropolitan region of Porto Alegre, state of Rio Grande do Sul, from the period between September 2020 and July 2021. Data were collected from the medical records, using a template with the variables of interest previously established based on the available literature. All the medical records of patients with severe acute respiratory syndrome and suspected COVID-19 infection needing hospital admission were evaluated, using the hospital database for COVID-19 screening tests. All the patients were tested with reverse transcription polymerase chain reaction (RT-PCR) collected from upper airway samples through nasal swabs, and patients with negative RT-PCR tests for COVID-19 or aged less than 18 years were excluded. The study was approved by the Research Ethics Committee under protocol number 38815320.0.0000.5349 on October 14, 2020. All the participants signed the informed consent form.

Medical records were collected including clinical and anthropometric data, such as age, sex, ethnicity, body mass index (BMI), initial symptoms, vital signs (i.e., blood pressure, heart rate, and respiratory frequency), laboratory tests (i.e., creatinine, blood counts, electrolytes, C-reactive protein (CRP), and fasting glucose), ICU admission, oxygen supplementation, use of glucocorticoids and insulin therapy after hospital admission, and mortality rate. The presence of comorbidities such as diabetes mellitus, systemic arterial hypertension, cardiovascular disease (CVD), cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and history of malignancy and tobacco consumption were also evaluated. Biochemical tests including blood count, platelets, kidney function, electrolytes, and CRP were evaluated on the arrival and the fifth day of hospitalization. In addition, imaging studies such as chest X-ray, chest computed tomography (CT), and echocardiogram when needed were also included in the evaluation of these patients. Only CT exams performed in our hospital and analyzed by the same specialist (RGT) were considered in this study, assessing the findings of typical pulmonary involvement of COVID-19 infection and the extent of lung injury.

Statistical analysis

The results were presented as means±standard deviation or medians and interquartile range. The normality tests of each variable were performed using the Shapiro-Wilk test. Variables with non-Gaussian distribution underwent a logarithmic transformation for statistical analysis, being transformed back into their original units for data presentation. Differences between groups were analyzed using the t-test for independent samples, and the chi-square test was used to assess the association between categorical variables. Correlation analysis was performed using Pearson's test for variables with normal distribution and Spearman's test for variables with abnormal distribution. Values of $p<0.05$ will be considered significant. The IBM Statistical Package for Social Sciences 26.0 (SPSS, Chicago, IL, USA) software was used to analyze the present data.

RESULTS

We evaluated a total of 700 medical records, with 409 patients admitted to a referral hospital for acute respiratory syndrome related to COVID-19 infection (Figure 1). Regarding skin color, 75% of individuals were white and the remaining subjects were of mixed ancestry. More than half were men (51%), the average age was 64 years (52–73), and the BMI was 27 kg/m² (22.1–31.2). Previous or current use of tobacco was recorded in 25.9% of patients. Regarding medical conditions, about a

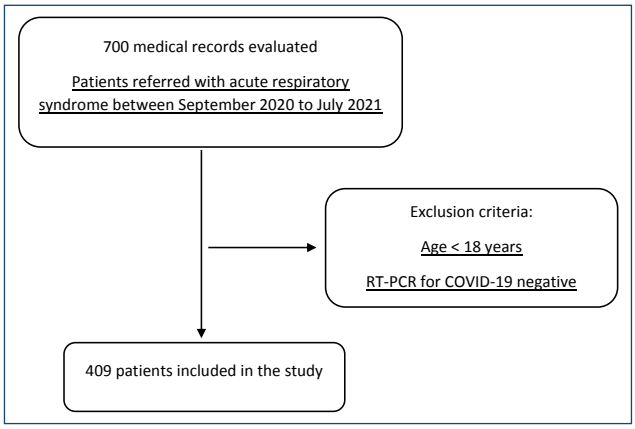

Figure 1. Patient selection flowchart. RT-PCR: reverse transcription polymerase chain reaction.

third presented previous diabetes (33%) and obesity (32%) and almost two-thirds (58%) had a diagnosis of arterial hypertension. Cardiovascular and cerebrovascular diseases were reported in 18 and 14% of the patients, respectively. Other conditions reported in less than 5% of the patients were COPD (8%), malignancies (4.6%), chronic kidney disease (CKD) (3.4%), and HIV infection (1%). The average length of stay in the hospital was 12 days (8–24).

The main presenting clinical findings were desaturation (64.6%), dyspnea (63.2%), cough (51.7%), and fever (47.8%). Other symptoms included myalgia (22%), headache (15.1%), fatigue (12.9%), vomiting (12.7%), anosmia (7.3%), and nasal congestion (7.1%). The average time from the onset of symptoms leading to hospital admission was 6 days (3–10). The laboratory and tomographic findings of all patients are detailed in Tables 1 and 2. The mortality rate was 29%.

A negative correlation was observed between lymphocytes on the fifth day of hospitalization and impairment on CT chest (p=0.037 r=-0.174), CRP (p=0.001 r=-0.210), and hospitalization time (p<0.001 r=-0.338).

DISCUSSION

In this study, approximately 30–60% of the patients admitted for COVID-19 infection presented with hypertension, diabetes, and obesity. In addition, we observed that patients admitted to ICU had lower hematological parameters and higher glucose levels and received corticosteroids in larger doses and for a longer period when compared to BCU patients. These results suggest that the clinical parameters can be used to predict unfavorable outcomes in patients with COVID-19 infection, in accordance with previously published data[10,11].

Table 1. Baseline characteristics of patients admitted to the referral hospital with coronavirus disease 19 (n=409).

Measures (unit)	All patients
Hemoglobin (g/dL)	12.8 (10.3–14.9)
Hematocrit (%)	38.8 (31.5–44.6)
Lymphocytes (μL)	1,410 (675–1,609)
Platelets (μL)	183,000 (131,500–244,000)
Urea (mg/dL)	36 (21.5–97.5)
Sodium (mEq/L)	138 (135.5–140.5)
Potassium (mEq/L)	4.6 (4.1–5.2)
Creatinine (mg/dL)	1.19 (0.70–2.05)
CRP (mg/L)	69.2 (17.3–175.8)
Supplemental oxygen therapy (%)	88.1
Oxygen therapy length in days	17 (9–25)
ICU admission (%)	34.2
ICU length of stay in days	12 (6–20)
Tracheal intubation (%)	29.2
Days to orotraqueal intubation	11 (6–17.5)
Systemic glucocorticoids use (%)	85.4
Systemic glucocorticoids therapy length in days	11 (6–17.5)
Daily dose of systemic glucocorticoid (mg)	39.4 (13.1–71.2)
Insulin therapy (%)	47.7
Left ventricle ejection fraction on echocardiogram (n=65) (%)	66.3 (53.7–69.2)
Impairment on chest CT (n=194) (%)	75 (37.5–82.5)
Pleural effusion on chest CT (%)	14.6

CRP: C-reactive protein; ICU: intensive care unit; CT: computed tomography. Median (interquartile range).

Both obesity and diabetes have been shown deleterious effects on host immunity, increasing the risk for infectious susceptibility and severity. These comorbidities are generally associated with low-grade chronic inflammation, which might intensify the cytokine storms, contributing to the severe outcomes of COVID-19[12]. The results of this study agree with this hypothesis, with approximately 30% of the subjects fulfilling diabetes and obesity criteria. In addition, more than half of the patients hospitalized for COVID-19 infection presented previous hypertension and 18% had established CVD. According to other published studies, the prevalence of hypertension and CVD is clinically relevant in patients with COVID-19, particularly the elderly, although the impact of these conditions on the outcome is still uncertain[13].

Table 2. Comparison of patients admitted to the intensive care unit and the basic care unit.

	ICU (n=140)	BCU (n=269)	p
Variables			
Age (years)	66 (53–74)	59 (42.2–71.7)	**<0.001**
Hospitalization length in days	19 (11–28)	8 (5.2–12)	**<0.001**
Days from symptoms to admission	7 (3–11)	7 (3–10)	0.608
BMI (kg/m²)	26.5 (23.7–31.0)	28.0 (23.6–32.4)	0.524
Glucose (mg/dL)	184 (133–241)	140 (118–200)	**<0.001**
Impairment on chest CT (%)	75 (50–75)	50 (25–60)	**<0.001**
Daily dose of systemic glucocorticoid (mg)	39.4 (14.3–70.3)	6 (6–14.7)	**<0.001**
Systemic glucocorticoids therapy length in days	11 (6–17)	6 (4–8)	**<0.001**
Laboratory findings on hospital admission			
Hemoglobin (g/dL)	13.0 (11.3–14.0)	13.1 (11.8–14.4)	**0.056**
Hematocrit (%)	38.6 (34.0–41.9)	39.2 (34.9–42.8)	0.141
Lymphocytes (µL)	983 (744–1,434)	1,313 (982–1,796)	**<0.001**
Platelets (µL)	217,000 (155,000–287,000)	238,000 (184,000–303,000)	**0.021**
Urea (mg/dL)	56 (37–104)	36 (25–54)	**<0.001**
Creatinine (mg/dL)	1.13 (0.88–1.70)	0.90 (0.70–1.17)	**<0.001**
CRP (mg/L)	234 (104–9,347)	172 (58–7,750)	0.183
Laboratory findings on the fifth day of hospitalization			
Hemoglobin (g/dL)	11.5 (9.5–13.1)	12.8 (11.5–14.2)	**<0.001**
Hematocrit (%)	35.3 (29.3–39.5)	37.5 (33.8–42.3)	**<0.001**
Lymphocytes (µL)	900 (555–1,500)	1,629 (1,141–2,329)	**<0.001**
Platelets (µL)	235,000 (143,000–357,000)	270,000 (192,000–377,000)	**0.005**
Urea (mg/dL)	90 (50–149)	45 (32–64)	**<0.001**
Creatinine (mg/dL)	1.16 (0.88–2.03)	0.95 (0.76–1.11)	**<0.001**
CRP (mg/L)	51.8 (22.6–133)	30.9 (10.3–88.4)	**0.001**
Death (%)	62.8	12.2	**<0.001**

BMI: body mass index; CRP: C-reactive protein; ICU: intensive care unit; BCU: basic care unit; CT: computed tomography. Median (interquartile range). Bold values indicate statistical significance at the p<0.05 level.

The difference found in this study between the hematological parameters of ICU and BCU patients was confirmed in other studies. A meta-analysis, including 21 studies, found significantly lower lymphocytes, platelets, and hemoglobin in patients with severe disease[11]. Several factors may be involved in the pathogenesis of these findings, including the presence of hypoxia in critically ill patients, which may have contributed to dysfunctional hematopoiesis. Despite the medulla being a naturally hypoxic tissue, hematopoietic cells require high levels of oxygen. Another factor that may have contributed to these results is the activation of the immune system, which may contribute to the senescence of hematopoietic stem cells. In this study, the CRP values did not show a significant difference between the groups, demonstrating that perhaps inflammation does not play a central role in bone marrow suppression and a direct effect of viral on hematopoiesis should be considered[11,14]. Our results suggest that hematological parameters could be used for monitoring prognosis in COVID-19 patients over the course of hospitalization.

In this study, 85% of the patients were submitted to systemic therapy with corticosteroids and 34% of them were admitted to the ICU. In this group, the mean dose and duration of the therapy were higher compared to BCU patients, although ICU patients had higher CRP levels and greater lung involvement in thorax CT. Importantly, almost half of the patients evaluated required insulin therapy during hospitalization. However,

only 33% of all patients had a previous history of diabetes mellitus. Corticosteroids are a class of anti-inflammatory and immunosuppressive drugs, with a high risk of adverse effects, which are time- and dose-dependent. These drugs increase hepatic gluconeogenesis and reduce peripheral glucose use, which have direct effects on glycemic control and hyperglycemia. This explains the higher use of insulin therapy in critically ill patients receiving systemic glucocorticoid[15,16], as recommended by the American Diabetes Association (ADA) in order to achieve better glycemic control. Huang et al., describe the importance of using corticosteroids in the treatment of critically ill patients with COVID-19, based on the justification that the damage caused by the disease is related to the intense inflammatory response that is triggered[4]. However, previous studies demonstrate that hyperglycemia and insulin resistance should be considered in the decision of dose and duration of corticosteroid therapy, especially in the setting of uncontrolled or drug-induced diabetes (depending on the dose and time of use)[17]. The available literature recommends attention to blood glucose monitoring in patients with a previous diagnosis of diabetes who will be undergoing corticosteroid therapy or in patients with iatrogenic hyperglycemia, considering early intervention (insulin therapy) to avoid the complications of poorly controlled blood glucose[16].

This study had some limitations. We can highlight the temporality of the condition studied, the retrospective collection of data from electronic medical records, and missing data, common within this design of the study. As the strengths of the study, all included patients had COVID-19 infection confirmed by RT-PCR and a significant number of patients performed thorax CT, all of them evaluated by a single medical professional.

In conclusion, this study showed that patients with acute respiratory syndrome related to COVID-19 infection presented an elevated prevalence of comorbidities such as obesity, diabetes, hypertension, and CVD. In addition, critically ill patients who needed intensive care presented a significant decrease in hemoglobin, lymphocytes, and platelet parameters compared to BCU patients. Taking together, our findings suggest that patients with metabolic and cardiovascular diseases are at higher risk of worse outcomes in COVID-19 infection and that simple and accessible hematological parameters may be helpful in identifying the severity of the disease.

AUTHORS' CONTRIBUTIONS

RGT: Conceptualization, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **TMF:** Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **GCB:** Data curation, Investigation, Writing – original draft. **GLF:** Data curation, Investigation, Writing – original draft. **ISR:** Data curation, Investigation, Writing – original draft. **MLCC:** Data curation, Investigation, Writing – original draft. **TBSC:** Data curation, Investigation, Writing – original draft. **LKML:** Data curation, Investigation, Writing – original draft.

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