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REVISÃO

Cardiovascular comorbidity as a predictor of complications in patients hospitalized with Covid-19

Comorbidade cardiovascular como preditor de complicações em pacientes hospitalizados com Covid-19

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ABSTRACT

Objective: To evaluate the association between the clinical characteristics and the severity of Covid-19. **Methods:** We included hospitalized adults with Covid-19 confirmed by reverse transcriptase polymerase chain reaction (March to June 2020). We assessed patients' health status during their hospital stay. We collected demographic, clinical and laboratory data and performed multivariate linear regression analysis to determine predictive variables for the outcomes (length of stay, intensive care, and use of mechanical ventilation). For this study we defined cardiovascular comorbidity as those patients with coronary artery disease, atrial fibrillation, or valvular heart diseases. **Results:** The total sample of the study consisted of 221 patients with a mean age of 53.7 ± 16.0 years and 57% (n = 126) being male. After adjusting for age and oxygen saturation, individuals with cardiovascular disease had longer hospital stays (23.5 versus 13.5 days; p < 0.008; β = 0,175; 95%CI 2,33-17,14), longer intensive care unit stays (18.8 versus 7.7 days; p < 0.002; β = 0,195; 95%CI 3,47-16,67), and longer durations of mechanical ventilation (9.7 versus 4.0 days; p < 0.02; β = 0,148; 95%CI 0,64-10,58) compared to individuals without cardiovascular disease. The presence of cardiovascular disease and oxygen saturation was independently associated with adverse outcomes on a multivariate regression analysis. **Conclusion:** Patients with cardiovascular comorbidities have an increased risk of severe Covid-19. These findings can be useful in predicting complications and guiding personalized care for individuals with severe respiratory syndromes.

Keywords: Covid-19; Cardiovascular diseases; Hospitalization; Intensive care; Mechanical ventilation

RESUMO

Objetivo: Avaliar a associação entre as características clínicas e a gravidade da Covid-19. **Métodos:** Foram incluídos adultos hospitalizados com Covid-19 confirmada por reação em cadeia da polimerase com transcrição reversa (RT-PCR), entre março e junho de 2020. Avaliamos o estado de saúde dos pacientes durante a internação hospitalar. Coletamos dados demográficos, clínicos e laboratoriais e realizamos análise de regressão linear multivariada para determinar variáveis preditoras dos desfechos (tempo de internação, necessidade de terapia intensiva e uso de ventilação mecânica). Para este estudo, definimos comorbidade cardiovascular como a presença de doença arterial coronariana, fibrilação atrial ou valvopatias. **Resultados:** A amostra total do estudo consistiu de 221 pacientes, com média de idade de 53,7 ± 16,0 anos, sendo 57% (n = 126) do sexo masculino. Após ajuste por idade e saturação de oxigênio, indivíduos com doença cardiovascular apresentaram maior tempo de internação hospitalar (23,5 *versus* 13,5 dias; p < 0,008; β = 0,175; IC95% 2,33–17,14), maior tempo em unidade de terapia intensiva (18,8 *versus* 7,7 dias; p < 0,002; β = 0,195; IC95% 3,47–16,67) e maior duração de ventilação mecânica (9,7 *versus* 4,0 dias; p < 0,02; β = 0,148; IC95% 0,64–10,58) em comparação com indivíduos sem doença cardiovascular. A presença de doença cardiovascular e a saturação de oxigênio estiveram associadas, de forma independente, a desfechos adversos na análise de regressão multivariada. **Conclusão:** Pacientes com comorbidades cardiovasculares apresentam maior risco de desenvolver formas graves da Covid-19. Esses achados podem ser úteis na previsão de complicações e na orientação de cuidados personalizados para indivíduos com síndromes respiratórias graves.

Descritores: Covid-19; Doenças Cardiovasculares; Hospitalização; Cuidados Críticos; Respiração Artificial

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INTRODUCTION

In December 2019, several cases of pneumonia emerged in Wuhan, the capital and largest city of Hubei Province in China. Within days, Chinese authorities identified a new strain belonging to the broad coronavirus family. It spread quickly and it was rapidly clear that this was not merely another seasonal coronavirus responsible for the common cold. It would soon become the strain responsible for a severe respiratory illness and the first in the coronavirus family to cause a global pandemic, leading to more than 6.9 million deaths worldwide to date.[1,2]

The new coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for coronavirus disease (Covid-19), a disease with clinical manifestation ranging from asymptomatic to life-threatening complications, including severe acute respiratory syndrome and death. In more critical cases extrapulmonary complications are also observed in those who progress to the most critical stages of the disease[3] and can culminate in long-term Covid, a condition in which symptoms persist even after the resolution of the acute condition.[4] Factors such as age, underlying comorbidities and vaccination status affect the individual risk for hospitalization and serious outcomes.[5,6]

Multiple comorbidities have been linked to the severity of Covid-19, i.e., hospitalizations, intensive care unit (ICU) admission, need for invasive mechanical ventilation (IMV) and death.[7] In a report in New York City with more than 5,000 confirmed cases, a strong association was identified between heart failure, chronic kidney disease and obesity with hospitalization and risk of critical illness.[8]

In an analysis of 287,320 confirmed cases in the United States, hospitalization was six times higher and mortality 12 times higher among patients with reported underlying illnesses compared with those without comorbidities.[5]

Reflecting on the clinical characteristics of SARS-CoV-2-infected patients and their association with the stages of Covid-19 is crucial both during and after the pandemic. Understanding the impact of each risk factor allows for the prediction of various complications resulting from viral infection and guides individualized patient care. The primary objective of this study was to evaluate the association between the clinical characteristics and the severity of Covid-19.

METHODS

This retrospective cohort study was conducted at Hospital Santa Paula, a private hospital located in the city of São Paulo, Brazil (March to June 2020). This was a group of unvaccinated patients for Covid-19.

All hospitalized adult patients (n = 221) with a diagnosis of Covid-19 confirmed through nasal and oropharyngeal swab samples tested by reverse transcriptase polymerase chain reaction (RT-PCR) were included. Patients who were not admitted despite testing positive for SARS-CoV-2 were excluded from the study.

From the moment of hospital admission until the outcome of hospital discharge or death, demographic, clinical and laboratory data were collected. A previously trained team collected data by accessing the patients' electronic medical records and inserting them into a database. We collected four classes of variables: demographic variables (age, sex and smoking); clinical variables at admission (body mass index [BMI], respiratory rate [RR], oxygen saturation [SaO_2], ICU admission, symptoms and days of symptoms); clinical variables during hospitalization (results of laboratory tests, development of acute renal failure [ARF], need for renal replacement therapy [RRT], IMV, tracheostomy, prone ventilation, patient participation in clinical research of drug intervention, days of hospitalization, IMV days, ICU days, discharge and death); and underlying comorbidities (diabetes mellitus [DM], systemic arterial hypertension [SAH], chronic obstructive pulmonary disease [COPD], asthma, cardiovascular disease (coronary artery disease [CAD] heart failure, atrial fibrillation and valvular heart disease), hepatitis, neoplasia and

immunosuppression). Variable multimorbidity was defined as the presence of two or more chronic diseases in the same individual. The normality of the continuous variables was examined using the Kolmogorov-Smirnov test. Continuous data are expressed as mean and standard deviation, and categorical variables are expressed as numbers and percentages. The unpaired Student's t test was applied to compare the means of continuous variables between men and women in parametric data, and the Mann-Whitney U test for the non-parametric data. Comparison of proportions between men and women was performed using the Chi-squared test. The length of stay (LoS) in the hospital, in intensive care and using mechanical ventilation were compared between individuals with and without cardiovascular disease using analysis of covariance (ANCOVA), with adjustment for age and SaO_2. Multivariate linear regression analysis was performed to determine predictive variables for the outcomes: LoS, intensive care, and use of mechanical ventilation in the hospital. Statistical procedures were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, Illinois, USA). Statistical significance was set at $p < 0.05$.

Data collection respected the ethical precepts set out in Resolution 466/2012 of the National Health Council. The project was submitted and approved by the Research Ethics Committee of Hospital Santa Paula (CEP-HSP-4,328,290) which granted exemption from the term of free and informed consent to the research participants.

RESULTS

We enrolled 221 patients, mean age 53.7 ± 16.0 years, with 57% (n = 126) being male. Among them, 39.4% had multiple comorbidities, 9.5% had cardiovascular disease, and 11.8% died during the hospitalization period. The average hospital and ICU LoS, and mechanical ventilation duration was 14.5, 8.7, and 4.6 days, respectively (**Table 1**). Cardiovascular diseases identified in the studied group were CAD (38.1%), heart failure (33.3%), atrial fibrillation (23.8%) and valvular heart disease (4.8%).

Figure 1 shows the association of cardiovascular disease presence with LoS in the hospital, in the ICU, and on mechanical ventilation duration. Individuals with cardiovascular disease had longer hospital stays (23.5 *versus* 13.5 days; $p < 0.008$), longer ICU stays (18.8 *versus* 7.7 days; $p < 0.002$), and longer durations of mechanical ventilation (9.7 *versus* 4.0 days; $p < 0.02$) compared to individuals without cardiovascular disease. These analyses were adjusted for age and SaO_2.

Table 2 shows the coefficients and 95% confidence intervals (95%CI) of the multivariate linear regression models. The presence of cardiovascular disease and SaO_2 were associated with LoS in the hospital, in the ICU, and on mechanical ventilation. Oxygen saturation was the strongest predictor variable associated with all evaluated outcomes. These models accounted for 19 to 25% of the variability in the dependent variables.

DISCUSSION

Our findings showed that patients with cardiovascular disease had longer hospital stays, longer ICU stays, and longer durations of mechanical ventilation compared to individuals without cardiovascular disease, regardless of age and SaO_2. The presence of cardiovascular disease and SaO_2 were associated with the severity of Covid-19.

Our findings are consistent with the results of three meta-analyses, highlighting the importance of identifying and managing cardiovascular comorbidities in patients with Covid-19, as they are associated with a higher risk of disease severity and adverse outcomes. Understanding these associations is crucial for guiding prevention, screening, and appropriate treatment strategies, aiming to improve clinical outcomes and reduce the impact of Covid-19 or other SARS-CoV infections in patients with pre-existing cardiovascular comorbidities.[9-11]

Coronary artery disease was the most prevalent comorbidity among the cardiovascular diseases

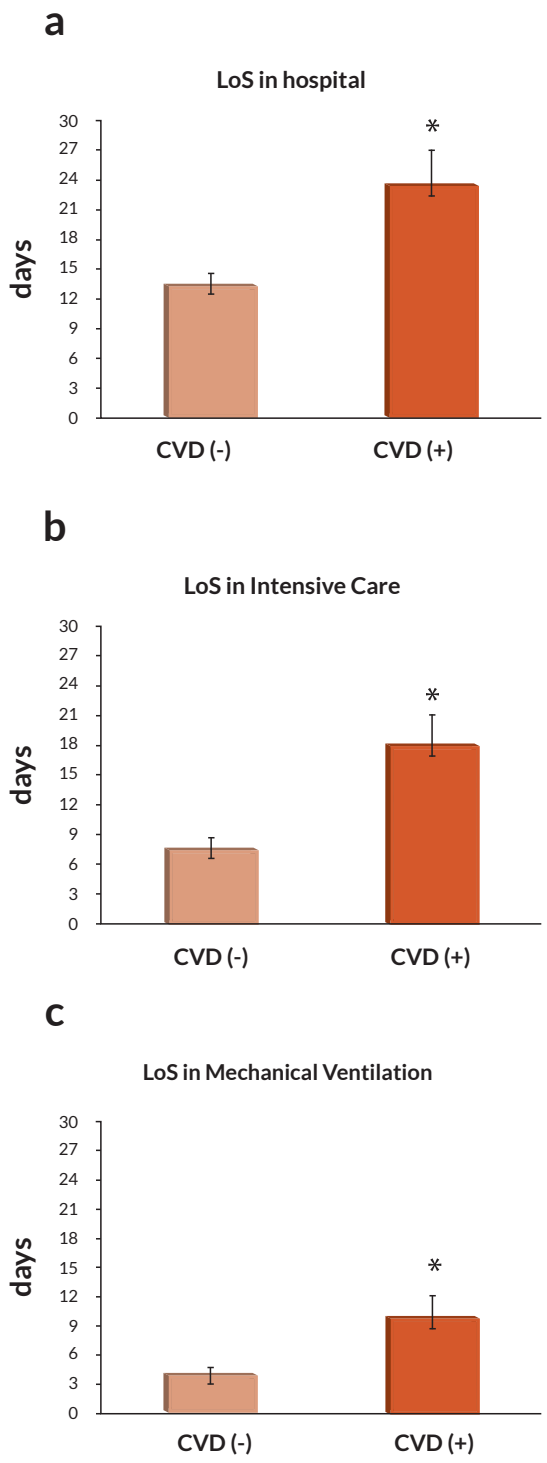
Table 1. Baseline characteristics and outcomes of the sample stratified by gender.

Variables	Total	Genre		p-value
		Male n = 126 (57%)	Female n = 95 (43%)	
Age, years	53.7 ± 16.0	53.9 ± 15.9	53.5 ± 16.3	0.865
Body mass index, kg/m²	30.1 ± 6.1	29.9 ± 5.8	30.2 ± 6.5	0.646
Oxygen saturation, %	92.0 ± 6.7	91.8 ± 6.9	92.3 ± 6.3	0.604
LoS in hospital, days	14.5 ± 16.3	15.5 ± 18.3	13.0 ± 13.3	0.260
LoS in ICU, days	8.7 ± 15.2	10.0 ± 17.2	7.0 ± 11.8	0.155
LoS in mechanical ventilation, days	4.6 ± 11.2	5.3 ± 11.7	3.5 ± 10.5	0.241
Smoking	7 (3.2)	3 (42.9)	4 (57.1)	0.442
Obesity (≥ 30 kg/m²)	102 (46.2)	52 (51.0)	50 (49.0)	0.093
Dislipidemia	28 (12.7)	13 (46.4)	15 (53.6)	0.226
Chronic kidney disease	7 (3.2)	3 (42.9)	4 (57.1)	0.442
Cancer	21 (9.5)	11 (52.4)	10 (47.6)	0.652
Asthma	11 (5.0)	6 (54.5)	5 (45.5)	0.865
COPD	10 (4.5)	5 (10.0)	5 (10.0)	0.748
Hypertension	78 (35.3)	42 (53.8)	36 (46.2)	0.482
Diabetes	48 (21.7)	26 (57.8)	22 (42.2)	0.652
Multimorbidity	87 (39.4)	44 (50.6)	43 (49.4)	0.119
Cardiovascular disease	21 (9.5)	13 (61.9)	8 (38.1)	0.634
Outcomes				
LoS in hospital, days	14.5 ± 16.3	15.5 ± 18.3	13.0 ± 13.3	0.260
LoS in ICU, days	8.7 ± 15.2	10.0 ± 17.2	7.0 ± 11.8	0.155
LoS in mechanical ventilation, days	4.6 ± 11.2	5.3 ± 11.7	3.5 ± 10.5	0.241
Death from Covid-19	26 (11.8)	15 (57.7)	11 (42.3)	0.941

Results expressed as mean ± standard deviation for continuous variables and n (%) for categorical variables.
Calculated by Student's t-tests for continuous variables and Chi-squared tests for categorical variables.
Multimorbidity, two or more chronic diseases in the same individual.
LoS: length of stay; ICU: intensive care unit; COPD: Chronic Obstructive Pulmonary Disease.

identified in this cohort. A recent systematic review and meta-analysis highlighted those individuals who have CAD and Covid-19 simultaneously may have greater risks and complications from both diseases, especially men and the elderly.[12] In the meta-analysis conducted by Szarpak et al.,[13] CAD was identified as a risk factor for severe illness and mortality in patients with Covid-19. The researchers also reported that the occurrence of other cardiovascular comorbidities such as heart failure, arrhythmias and acute cardiac injury concomitant with Covid-19 were significantly associated with the need for intensive care, data also found in our research.

Although our findings are of a group of unvaccinated patients, the risk factors for worse outcomes described in the literature are like groups of vaccinated individuals, that is, multiple comorbidities and advanced age. Yek et al.[14] showed low rates of severe illness and mortality (1.5 and 0.3 per 10,000 respectively) in a study of more than one million individuals with completed primary vaccination.



*23.5, 18.8 and 9.7, respectively.

LoS: length of stay; CVD (-): individuals without cardiovascular disease; CVD (+): individuals with cardiovascular disease.

Figure 1. Association between cardiovascular disease and hospital length of stay (days), intensive care and mechanical ventilation in patients with Covid-19. Length of stay were compared between individuals with and without cardiovascular disease using analysis of covariance; (a) association between presence of cardiovascular disease and length of stay in hospital); (b) association between presence of cardiovascular disease and length of stay in intensive care; (c) association between presence of cardiovascular disease and length of stay in mechanical ventilation.

However, all patients who progressed to severe disease had at least one of the eight risk factors assessed, including previous cardiovascular diseases. Furthermore, evidence suggests that, regardless of the severity of Covid-19 and the patient's vaccination status, acute infection can trigger significant, long-lasting cardiovascular complications. New events such as arrhythmias, ischemic heart disease, pericardial and myocardial inflammation disorders, cerebrovascular diseases and thromboembolism may appear for at least 12 months after the acute condition, leading to a significant increase in cardiovascular diseases with an impact on health systems in the long-term.[15,16]

In our results, SaO_2 was also strongly associated with length of hospital stay, intensive care and mechanical ventilation. In a prospective multicenter study of over 800 hospitalized patients conducted by Cordova et al.,[17] $SaO_2 \leq 93\%$ was one of the independent factors associated with ICU admission and 30-day mortality. Hypoxemia at presentation portends extensive pulmonary compromise and a severe disease course. It is associated with unchecked systemic inflammation and could potentially also be a mechanisms of myocardial injury.[18] Despite this, our findings suggest that there is an association between the presence of cardiovascular disease and the severity of Covid-19 regardless of SaO_2.

The present study did not identify an association between age and gender variables with severity. It is possible that we had limited statistical power due to the sample size and distribution of representation for these two variables. However, age and gender are considered risk factors for the severity of Covid-19. Studies have shown that older patients, especially those aged 65 or older, have a higher risk of developing severe or fatal complications due to SARS-CoV-2 infection. Additionally, men appear to have a slightly higher risk compared to women, with higher rates of hospitalization and mortality.[19,20]

Zhou et al.[21] conducted a retrospective cohort study in Wuhan, China, and identified risk factors

Table 2. Factors associated with hospital length of stay, intensive care unit admission, and mechanical ventilation in patients with Covid-19

Variables	LoS in hospital		LoS in ICU		LoS in mechanical ventilation	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Age, years	0.022 (-0.11-0.16)	0.747	0.001 (-0.12-0.13)	0.990	-0.020 (-0.11-0.08)	0.769
Gender	0.056 (-2.13-5.84)	0.359	0.077 (-1.21-5.89)	0.195	0.057 (-1.39-3.97)	0.343
Smoking	-0.035 (-14.95-7.98)	0.569	0.000 (-10.06-9.99)	0.994	- 0.039 (-10.02-0.09)	0.520
CVD	0.175 (2.33-17.14)	0.010*	0.195 (3.47-16.67)	0.003*	0.148 (0.64-10.58)	0.027*
Comorbidities	0.009 (-4.00-4.62)	0.889	0.019 (-3.26-4.43)	0.763	-0.002 (-2.95-2.85)	0.973
Oxygen saturation, %	-0.367 (-1.21--0.59)	<0.001*	-0.433 (-1.26--0.72)	<0.001*	-0.434 (-0.94--0.53)	<0.001*

* Statistically significant values (p < 0.05).

LoS: length of stay; ICU: intensive care unit; 95%CI: 95% of confidence interval; CVD: cardiovascular disease.

for mortality in adult inpatients. They found that older age, high Sequential Organ Failure Assessment (SOFA) score, and d-dimer levels were associated with higher mortality rates. Docherty et al.[22] conducted a prospective observational cohort study in the United Kingdom, focusing on the clinical characteristics of hospitalized patients. They reported that older age, male gender, and comorbidities such as diabetes, obesity, and chronic kidney disease were associated with increased mortality. Petrilli et al.[8] conducted a prospective cohort study in New York City and identified factors associated with hospital admission and critical illness. They found that older age, male gender, and comorbidities such as obesity, hypertension, and diabetes were associated with higher risks of hospitalization and critical illness.

The present study has some limitations that must be considered. First, this is a single-center retrospective study with a relatively small sample size. Some laboratory tests were not collected in the cut-off periods determined in our study, compromising the statistical analysis of the data and, consequently, the evaluation of the associations of these parameters with the studied outcomes. Second, it involves a selection of patients without vaccination (at the beginning of the pandemic) and with an evolutionary understanding of best practices. The dynamic nature of the disease, the current immunization status, and the rapid evolution of the epidemiological scenario may make the data just a reflection of previous conditions. However, this current association may provide insights for prevention in patients with other viruses capable of causing severe respiratory syndrome.

CONCLUSION

Various cardiovascular comorbidities, including coronary artery disease, atrial fibrillation, and valvular heart diseases are associated with an increased risk of severe Covid-19, resulting in longer hospital stays, intensive care needs, and mechanical ventilation. These findings can be useful in predicting complications and guiding personalized care for individuals with severe respiratory syndromes.

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