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Research Article

Mortality Predictors in Patients with Cardiovascular Involvement by COVID-19

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Abstract

Introduction: SARS-CoV-2 is a new coronavirus responsible for one of the most evident diseases today, COVID-19, registering approximately 419,000 deaths until 2020. Some risk factors for infection and mortality must be assessed in clinical and research scenarios, such as the presence of cardiovascular diseases, with clinical and laboratory alterations. Objective: Our study aims to analyze the association between clinical and laboratory data and in-hospital mortality in patients with cardiovascular involvement by COVID-19 in Brazil. Method: This is a retrospective, observational, single-center cohort study. The sample consisted of patients admitted to a reference hospital from July 2020 to April 2021. We included patients over 18 years of age, hospitalized with COVID-19 infection, who developed heart involvement identified by clinical or laboratory findings. Patients who were pregnant or had negative serological tests for COVID-19 were excluded. Clinical variables such as gender, age, comorbidities, medications used during hospitalization, chest computed-tomography findings, need for intensive care unit, need for mechanical ventilation, and need for intravenous vasoactive drugs were analyzed. The laboratory variables analyzed were: troponin, NT-proBNP and D-dimer levels. The endpoint of the study was in-hospital death. Statistical analysis of the collected data was performed using Pearson's Chi-square test, Student's T test; p values < 0.05 were considered statistically significant. Results: 139 patients were included, and 30 (21.58%) patients died during hospitalization. The group that evolved to death, compared to the discharge group, was older (71 vs 65 years; p = 0.03), had more pleural effusion on chest computed-tomography (36% vs 17%; p = 0.023), had higher troponin levels (40% vs 20%; p = 0.02), more need for intensive care (83% vs 52%; p = 0.002), orotracheal intubation (83% vs 26%; p = 0.001), use of norepinephrine (76% vs 18%; p = 0.001), use of dobutamine (16% vs 4%; p = 0.023), and use of unfractioned heparin (46% vs 21%; p = 0.005). Conclusion: Advanced age was significantly associated with in-hospital death. In radiological patterns, despite the high incidence of ground-glass opacities, pleural effusion was the only finding associated with mortality. Increased troponin levels, but not NT-proBNP or D-dimer, was associated with in-hospital mortality. The need for norepinephrine and dobutamine, in addition to Intensive Care Unit admission and orotracheal

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Intubation, were also more frequent in the group that presented death during hospitalization, as wells as the use of unfractionated heparin rather than enoxaparin.

Keywords

COVID-19, SARS-CoV-2, Troponin T, Heart Diseases, Myocardial Ischemia, Indicators of Morbidity and Mortality

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a new coronavirus that causes an emerging infectious disease, with notable pulmonary involvement, known as COVID-19. Its pandemic emerged in late 2019 in China, and epidemiological data show about 270 million people infected and approximately 419 thousand deaths in 2020. It was noticed that patients with cardiovascular diseases exhibited a significantly higher mortality rate that was above 10%, in comparison to the general population, which presented mortality rates around 6.9% [1].

In addition to the hypothesis that patients with cardiovascular disease (CVD) or hypertension are more susceptible to COVID-19 infection due to dysregulation of angiotensin converting enzyme 2 (ACE2) receptors, preliminary reports have shown that patients with previous cardiovascular disease are at increased risk of adverse outcomes. Besides, patients who have any clinical or biological marker of acute cardiac outcome during COVID-19 infection are less likely to survive [1]. The mechanisms of myocardial injury in COVID-19 are not well established, but probably involve increased cardiac stress due to respiratory failure and hypoxemia, acute coronary syndrome (ACS), indirect injury caused by systemic inflammatory response, and direct myocardial infection by SARS-CoV-2 [2].

The cardiac manifestations of COVID-19 have been the subject of several studies. Despite the limited number of participants, the prevalence of acute cardiac injury in patients hospitalized for COVID-19 was as high as 12%. Likewise, cardiac biomarkers have been considered predictors of severity in patients with COVID-19 and cardiac injury, even with an undiagnosed CVD [3]. High troponin levels, even in an isolated setting, were associated with an increase of 71.0% in the risk of in-hospital death, and a six-fold increase in the number of cardiorespiratory arrests and myocardial infarctions [4]. However, these findings do not support a routine measurement of serum troponin levels to assess prognosis in COVID-19 worldwide. It is paramount to perform individualized therapeutic proposals and, thus, improve prognosis in patients with previous cardiovascular events or new cardiovascular findings resulting from the infection, due to a presumptive higher risk of poor outcomes in these groups.

Regarding the above considerations, it has been suggested a correlation between cardiac biomarkers and the severity of the infection caused by SARS-CoV-2, emphasizing the importance of studying and discussing this topic in clinical and academic settings. However, the application of cardiac biomarkers as a prognostic tool is still not well understood and used internationally. Besides, cardiac involvement in COVID-19 may include several acute or preexisting conditions, and all those must be properly addressed in specific populations. Local data should be valued, and clinical manifestations must be carefully assessed in different countries and regions. This study aims to analyze the association between clinical data and laboratory biomarkers with in-hospital mortality in patients with cardiovascular involvement by COVID-19 in Brazil.

2. Method

2.1. Study Design and Population

This study is designed as a retrospective, observational, single-center cohort study. The sample was compound of patients admitted to a reference hospital from July 2020 to April 2021. We included patients older than 18 years, with acute COVID-19 infection who developed cardiac injury or clinical cardiac involvement. An acute cardiac decompensation of a previous heart disease was also considered as cardiac involvement. Pregnant women or patients with negative tests for COVID-19 were excluded from the analysis.

The diagnosis of COVID-19 was performed by either a positive result of a SARS-CoV-2 polymerase chain reaction (PCR) assay for nasal and pharyngeal swab specimens or positive serologic tests (IgM assay), according to local laboratories and practices at the time. To be enrolled, patients could have been admitted to general wards or to intensive care units (ICU).

Cardiac involvement was defined as present when at least one of the following conditions existed: troponin levels above the 99 percentile the upper reference value; brain natriuretic peptide (BNP) levels > 300 pg/ml; N-terminal-pro brain natriuretic peptide (NT-ProBNP) levels > 1,500 pg/ml; D-dimer levels > 3 times the upper limit of normal; new alterations in the echocardiogram (myocardial dysfunction, pericardial effusion or segmental dysfunction); alterations in the electrocardiogram suggestive of myocardial ischemia or pericarditis; occurrence of bradyarrhythmias, tachyarrhythmias, cardiogenic shock, heart failure or acute coronary syndromes.

2.2. Variables Analyzed

The clinical variables analyzed were: gender, age, comorbidities, medications used during hospitalization, and chest computed-tomography (CT) scan findings. The laboratory variables evaluated included: troponin, NT-proBNP, and D-dimer. Patients were followed from hospital admission until discharge or in-hospital death.

We compared clinical features, laboratory data and medical care administered to patients according to the outcome presented at the end of hospitalization (hospital discharge or in-hospital death).

2.3. Endpoints

The primary endpoints of the study were: in-hospital death, need for admission in the ICU, need for mechanical ventilation and need for vasoactive drugs.

2.4. Statistical Analysis

Statistical analysis was performed using Pearson's Chi-square and T student tests, and p values < 0.05 were considered statistically significant. The SPSS software version 23.0 was used.

2.5. Ethical Aspects

The study was approved by the Research Ethics Committee of the institution, under number 4,091,537. The standards of ethics in clinical research were respected, according to the Declaration of Helsinki.

3. Results

From July 2020 through April 2021, a total of 139 patients were hospitalized with COVID-19 infection associated with cardiac injury or other acute CVD. The average age of the included sample was 66.55 years ± 14.09, of which 63 (45.32%) were male and 76 (54.68%) were female. Among the total sample, 30 (21.58%) patients died during hospitalization. The average age of patients who died was 71.23 ± 12.54, 15 male (23.81% of the male group) and 15 female (19.74% of the female group). As for the group that evolved with hospital discharge, the average age was 65.35 (± 14.2) (p-value 0.03 when compared to the death group). No difference was observed for genders in the outcomes of death or hospital discharge ($p = 0.56$).

3.1. Clinical Profile of the Study Population

Regarding the clinical conditions in the population of the study, arterial hypertension was the most prevalent comorbidity and was present in more than half of the two groups (death and hospital discharge). Diabetes mellitus and chronic kidney disease (CKD) were also frequent and had a tendency to be more prevalent in the death group, whilst tobacco was more frequent in the discharge group, although without statistical significance. The clinical baseline characteristics are showed in Table 1.

Table 1. *Clinical baseline characteristics of the study population.*

Clinical Data	Global (n= 139)	Deaths (n=30)	Hospital Discharge (n=109)	P value
Arterial hypertension	93 (66.90%)	23 (76.66%)	70 (64.22%)	0.19
Diabetes mellitus	46 (33.09%)	12 (40.00%)	34 (31.19%)	0.36
Chronic kidney disease	15 (10.79%)	4 (13.33%)	11 (10.09%)	0.61
Tobacco addiction	23 (16.54%)	4 (13.33%)	19 (17.43%)	0.59

The cardiologic involvement was mostly represented by laboratory data, with elevation of serum biomarkers. Cardiac arrhythmias, new findings in electrocardiogram or echocardiogram, acute coronary syndromes and decompensated heart failure were also represented as the acute cardiologic presentation. Only a few patients presented cardiogenic shock. The heart involvement of the sample is demonstrated in Table 2.

Table 2. *Cardiologic involvement due to covid-19 in the study population.*

Clinical Data	Global (n= 139)
Increased Troponin levels	93 (66.90%)

Clinical Data	Global (n= 139)
Increased D-dimer levels	105 (75.53%)
Increased NT-proBNP levels	57 (41.00%)
New electrocardiogram findings	2 (1.43%)
New echocardiogram findings	21 (15.1%)
Atrial fibrillation	3 (2.15%)
Other rhythm disturbances	4 (2.87%)
Decompensated heart failure	4 (2.87%)
Acute coronary syndrome (ACS)	11 (7.9%)
STEMI*	6 (4.31%)
Non ST-elevation ACS	5 (3.59%)
Cardiogenic shock	2 (1.43%)

*STEMI: ST-elevation myocardial infarction

3.2. Radiological Profile of the Study Population

Images of ground-glass opacities in CT scans were found in the majority of the sample. The only radiological finding with statistically significant difference in incidence between groups was pleural effusion, which was more common in the death group. Other radiological diagnoses are described in Table 3.

Table 3. *Radiological profile of the study population.*

Radiological Data	Global (n= 139)	Deaths (n=30)	Hospital Discharge (n=109)	P value
Ground glass opacities	139 (85.61%)	24 (80.00%)	95 (87.15%)	0.23
Consolidations	40 (28.77%)	8 (26.66%)	32 (29.35%)	0.77
Pleural effusion	30 (21.58%)	11 (36.66%)	19 (17.43%)	0.023
Cardiomegaly	17 (12.23%)	4 (13.33%)	13 (11.92%)	0.52
Pericardial effusion	4 (2.87%)	2 (6.66%)	2 (1.83%)	0.17

3.3. Medication Profile of the Study Population

Regarding drug therapy administered during hospitalization, different medications were used. The use of unfractionated heparin was more common in the death group. Administration of vasoactive drugs such as norepinephrin and dobutamine was also more frequent in the group of patients who evolved with in-hospital death. Other medications analyzed are described in Table 4.

Table 4. *Medication profile of the study population.*

Medications	Global (n= 139)	Deaths (n=30)	Hospital Discharge (n=109)	P value
Azithromycin	89 (64.02%)	16 (53.33%)	73 (66.97%)	0.17
Other antibiotics	118 (84.89%)	27 (90.00%)	91 (83.48%)	0.16

Medications	Global (n= 139)	Deaths (n=30)	Hospital Discharge (n=109)	P value
Corticosteroids	81 (58.27%)	18 (60.00%)	63 (63.30%)	0.82
Oseltamivir	48 (34.53%)	11 (36.66%)	37 (33.94%)	0.78
Norepinephrin	43 (30.93%)	23 (76.66%)	20 (18.34%)	0.0001
Dobutamine	10 (7.19%)	5 (16.66%)	5 (4.58%)	0.023
Enoxaparin	82 (58.99%)	10 (33.33%)	72 (66.05%)	0.001
Unfractionated Heparin	37 (26.61%)	14 (46.66%)	23 (21.10%)	0.005
Hydroxychloroquine	23 (16.54%)	2 (6.66%)	21 (19.26%)	0.06

3.4. Health Care of the Study Population

About the care given to patients, hospitalization in the ICU occurred in more than half of the cases of the total sample. Most of the patients who evolved to death needed admission in the ICU and orotracheal intubation. Nearly half of the patients who were intubated evolved with in-hospital death. These two features of medical care were strongly associated with the death group. The need of ICU admission and of orotracheal intubation with use of mechanical ventilation in the sample is showed in Table 5.

Table 5. *Health care of the study population.*

Variable	Global (n= 139)	Deaths (n=30)	Hospital Discharge (n=109)	P value
Intensive Care Unit	82 (58.99%)	25 (83.33%)	57 (52.29%)	0.002
Orotracheal intubation	54 (38.84%)	25 (83.33%)	29 (26.60%)	0.0001

3.5. Analysis of Biomarkers

Increased troponin levels were seen mostly in the death group. Among the three biomarkers, D-dimer was the one that showed the greatest alteration in both groups. Only troponin levels were associated with in-hospital death. Table 6 shows the analyzed biomarkers.

Table 6. *Analysis of biomarkers.*

Clinical Data	Global (n= 139)	Deaths (n=30)	Hospital Discharge (n=109)	P value
Increased Troponin levels	34 (24.46%)	12 (40.00%)	22 (20.18%)	0.02
Increased D-dimer levels	105 (75.53%)	20 (66.66%)	85 (77.98%)	0.2
Increased NT-proBNP levels	57 (41.00%)	10 (33.33%)	47 (43.11%)	0.33

4. Discussion

In the present study, clinical and laboratory data associated with negative outcomes in patients with cardiovascular involvement by COVID-19 were evaluated. High mortality was observed in this population, revealing the severity of the combination of COVID-19 and cardiac lesion or dysfunction. Previous studies observed that age, male gender, increased creatinine, C-reactive protein and natriuretic peptide levels, hypertension and coronary artery disease are factors that contribute to the severity of the disease caused by SARS-CoV2 [5]. We found that the in-hospital death group was more elderly than the discharge group ($p = 0.03$). According to the 2020 epidemiological bulletin of the Brazilian Ministry of Health, 90% of deaths from COVID-19 occurred in people over 60 years of age

[6]. A study published with retrospective data from two hospitals in Wuhan, China found that there was a significant association of advanced age with death from COVID-19 ($p < 0.001$), which can be explained by the higher incidence of comorbidities and the frailty of this group [7]. It should be noted that there was no difference between genders, corroborating the findings of the present study. However, previous studies observed higher mortality rates in males, independently of age, suggesting a possible protective role of high estrogen levels in females [8].

Most of the patients who died had arterial hypertension (76.66%) or diabetes mellitus (40.00%), but there was no statistical difference for these conditions between the groups discharge and death. Patients with comorbidities are considered to have a worse prognosis in COVID-19, with a greater chance of developing unfavorable outcomes, such as ICU admission, need for orotracheal intubation and even death, as observed in a meta-analysis [9]. One meta-analysis about the impact of cardiovascular diseases on COVID-19 revealed that hypertension and cerebrovascular diseases were associated with a statistically significant impact on ICU admission [10]. In our sample, one in every five patients died, which shows great severity of the clinical presentation and worse prognosis of COVID-19 in patients with acute or decompensated underlying cardiac disease.

Regarding radiographic findings on chest CT scans, 85.61% of all patients included in the study had ground-glass opacities. Similar data were observed in one of the first studies carried out in Wuhan, which showed that approximately 72% of COVID-19 patients had ground-glass opacities, while pericardial and pleural effusion were not common diagnoses [11]. However, the ground-glass pattern on chest CT was not statistically associated with higher mortality rate, supporting the clinical-radiological dissociation pattern found in viral pneumonias. From the CT data obtained in this study, pleural effusion was associated with in-hospital death (36.66% in the death group vs 17.43% in the hospital discharge group), and this finding, although unexpected, requests deeper investigation.

The inflammatory response generated from the viral infection leads to damage to the cardiovascular system and lungs, resulting in elevation of D-dimer, procalcitonin, C-reactive protein, ferritin, troponin and natriuretic peptide levels, and it is associated with cardiovascular complications and death [12]. Based on an Italian study that associated troponin levels with mortality, the analysis of myocardial markers can be useful in stratifying patients with COVID-19 at hospital admission, identifying patients with the greatest need for intensive care [4]. Furthermore, other studies have shown that factors such as increased NT-proBNP, troponin and C-reactive protein levels, which are markers of myocardial injury and inflammation, respectively, were significantly correlated with severe and critical illness [5]. Myocardial injury may represent a harmful cardiac damage in patients with COVID-19, and our results point to troponin levels as a strong mortality predictor, rather than NT-proBNP and D-dimer. In a retrospective Chinese study of 187 patients with COVID-19, 52 (27.8%) exhibited myocardial injury, demonstrated by elevated troponin levels, and mortality rate was markedly higher in patients with elevated troponin levels than in patients with normal troponin levels (59.6% vs 8.9%), in addition to a higher frequency of arrhythmias in patients with elevated troponin. Furthermore, it was also observed that, in patients who died, troponin and NT-proBNP increased during hospitalization. Another point worth mentioning is that, in the Chinese study, elevated levels of troponin associated with preexisting CVD were associated with greater mortality compared to preexisting CVD and normal troponin [3]. Natriuretic peptides may also have a role in prognosis for these cases, albeit our sample size was nor powered to investigate this association. D-dimer, in turn, is a nonspecific biomarker. Its importance in cardiac function may be explained by possible pulmonary embolism when severely increased. To balance the possible selection bias of including an isolated laboratory finding with the need to assess patients with subclinical pulmonary embolism, we used the inclusion criteria of D-dimer levels > 3 times the upper limit of normal.

Massive inflammatory response in COVID-19 commonly lead to distributive shock, a severe condition that requires ICU admission and leads to high mortality. In the presence of shock, noradrenaline is the drug of choice for hemodynamic optimization, and the association of dobutamine in cases of cardiac dysfunction is suggested [13]. In our study, although not a specific treatment for SARS-CoV2, the use of norepinephrin and dobutamine were associated with in-hospital mortality. Obviously, patients who require the use of such drugs have life-threatening conditions, greater cardiovascular dysfunctions, worse prognosis and higher chances of negative outcomes. Thus, the important bias of this association must be considered, as well as orotracheal intubation.

Patients with COVID-19 are at high risk for venous thromboembolism due to mobility reduction and dysfunctional coagulation parameters [14]. Non-pharmacological interventions for the prevention of venous thromboembolism are recommended for every patient hospitalized for COVID-19. Pharmacological strategies, such as the use of low molecular weight or unfractionated heparins, should be instituted when the patient does not have any contraindication [12]. In our study, the death group was treated more frequently with unfractionated heparin instead of enoxaparin than the hospital discharge group. Despite the well-known differences between the two types of heparin, this study was not powered to properly assess this difference. We must recall that resources and supplies were scarce in some periods of the pandemic, and this required alternatives for medical care in many countries, such as using unfractionated heparin when enoxaparin was not widely available.

In our sample, 82 patients required ICU admission, of

which 25 died (p=0.002), possibly due to the greater severity of these patients' diseases. The development of acute heart injury in COVID-19 requiring ICU admission was previously associated with higher mortality [15]. Besides, 54 patients underwent orotracheal intubation and 25 (46.29%) of them died. Most of the patients who died had been intubated during hospitalization. This association is certainly influenced by the severity of the cases, although errors in mechanical ventilator adjustments may also cause serious iatrogenic and risk of death. These malpractice complications were reported in different countries due to difficulties to manage the COVID-19 pandemic, with scarcity of resources and professionals. The appropriate use of mechanical ventilation in COVID-19 patients with acute respiratory distress, although challenging, reduces mortality, the occurrence of complications, length of stay in the ICU and hospital costs [16], and must be pursued in all health systems.

5. Conclusion

Advanced age was associated with higher mortality in patients with COVID-19 and cardiovascular involvement, whilst gender, arterial hypertension and diabetes mellitus were not significantly associated with in-hospital death. As for radiological patterns, despite the high prevalence of ground-glass opacities in the total sample, the only finding associated with mortality was pleural effusion. Myocardial injury evidenced by increased troponin levels, but not D-dimer and NT-proBNP, was associated with higher mortality. The use of unfractionated heparin rather than enoxaparin was significantly associated with in-hospital death. The necessity for norepinephrin and dobutamine was associated with higher mortality, probably due to the critical patients' status, as well as the need for ICU admission and orotracheal intubation. This study highlights the association between cardiovascular involvement and severity of COVID-19. Although health systems may vary from one country to another and the pandemic situation is constantly changing, troponin raise clearly impacts in-hospital mortality for patients with COVID-19.

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

CVD: Cardiovascular Disease

ACE2: Angiotensin Converting Enzyme 2

ACS: Acute Coronary Syndrome

PCR: Polymerase Chain Reaction

ICU: Intensive Care Unit

BNP: Brain Natriuretic Peptide

NT-ProBNP: N-terminal-pro Brain Natriuretic Peptide

CT: Computed-Tomography

CKD: Chronic Kidney Disease

Conflicts of Interest

The authors declare no conflicts of interest.

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