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Research paper

## COVID-19 in patients with cardiac disease: Impact and variables associated with mortality in a cardiology center in Brazil<sup>☆,☆☆</sup>



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### ABSTRACT

**Background:** Cardiovascular disease is associated with severe COVID-19. Our aim was to describe clinical and laboratory features (including electrocardiographic and echocardiographic ones) and outcomes of patients with cardiac disease hospitalized with COVID-19.

**Methods:** This is an observational retrospective study of consecutive adult patients admitted, between March and September of 2020, with confirmed SARS-CoV-2 infection. Data were collected as per the ISARIC case report form and complemented with variables related to heart disease.

**Results:** One hundred twenty-one patients were included. Mean age was 60 SD 15.2 years and 80/121 (66.1%) were male. Two-thirds of the patients (80/121, 66.1%) had COVID-19 at the time of hospital admission and COVID-19 was the reason for hospitalization in 42 (34.7%). Other reasons for hospital admission were acute coronary syndrome (26%) and decompensated heart failure (14.8%). Chronic cardiac diseases were found in 106/121 (87.6%), mostly coronary artery disease (62%) or valve disease (33.9%). A transthoracic echocardiogram was performed in 93/121 (76.8%) and enlarged cardiac chambers were found in 71% (66/93); admission ECG was done in 93 cases (93/121, 76.8%), and 89.2% (83/93) were abnormal. Hospital-acquisition of COVID-19 occurred in 20 (16.5%) of patients and their mortality was 50%. On bivariate analysis for mortality, BNP levels and troponin levels were NOT associated with mortality. On multivariate analysis, only C reactive protein levels and creatinine levels were significant.

**Conclusions:** COVID-19 impacted the profile of hospital admissions in cardiac patients. BNP and troponin levels were not associated with mortality and may not be good prognostic discriminators in cardiac patients.

### 1. Introduction

The World Health Organization (WHO) declared the new beta-coronavirus (SAR-CoV-2) infection a pandemic on 11th March 2020 and named the associated illness COVID-19. The outbreak of COVID-19 has caused serious disease in Brazil and globally [1,2,3]. As of 24

September 2021, there have been 230.418.451 confirmed cases of COVID-19, including 4.724.876 deaths, reported to WHO. Brazil is considered one of the new epicenters of this pandemic, having accumulated the third largest number of confirmed cases by country (21,283,567) and the second largest number of deaths (592,316) [3]. The majority (80%) of patients with COVID-19 develop mild symptoms,

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but some present a clinical picture of moderate severity which requires hospitalization (10–15%) and a smaller group (5–15%) has a severe illness with acute respiratory failure, septic shock and multiple organ failure [4,5].

Age above 60 years, male gender, high d-dimer levels, and comorbidities are risk factors for death and admission to ICU in patients with COVID-19 [1,6–14]. An important meta-analysis of 21 multinational studies, including 11,766 cases of COVID-19, showed that cardiovascular disease was an independent predictor of severe COVID-19, even after controlling for age and gender [15]. Early on in the pandemic, a Chinese study with 109 patients showed that 78% of patients admitted to ICU with COVID-19 had previous comorbidities, in which systemic arterial hypertension (HAS), cardiovascular disease (CVC), diabetes mellitus (DM), chronic renal disease, immunosuppression, obesity and chronic obstructive pulmonary disease (DPOC) were the most common [1,9,16]. A Spanish study with 15,110 cases showed that the most frequent comorbidities were systemic arterial hypertension (HAS) (50.9%), dyslipidaemia (39.7%), obesity (21.2%) and diabetes mellitus (19.4%) [17]. Another large study carried out in the UK with 20,133 patients showed that 30.9% bore some form of chronic cardiopathy; 10.7% were diabetic, 17.7% had chronic obstructive pulmonary disease (COPD) and 16.2% had chronic renal disease (CRF) [18]. In Brazil, cardiopathies and diabetes mellitus were the comorbidities most associated with deaths, and systemic arterial hypertension (HAS) was the most prevalent in all COVID-19 cases [9]. Furthermore, when someone bears multiple comorbidities, this significantly increases the risk of serious outcomes related to COVID-19. A systematic literature review with 202,005 patients with COVID-19, showed that the mortality rate when one comorbidity was present was 6%, and when six or more were present, this was 21% [19].

Moreover, cardiac complications of COVID-19 are frequent. The pathophysiology of cardiac injury involves infection via angiotensin-II converting enzyme receptors, causing systemic endotheliitis. This endothelial dysfunction occurs as a direct effect of SARS-CoV-2 tropism to the vascular tissue, inducing or potentiating a previous imbalance (as in patients with cardiovascular and metabolic diseases) of the intracellular Renin Angiotensin system. Atherosclerotic plaques may rupture, and stent thrombosis may occur. These phenomena, together with a pre-existing endothelial lesion that accompanies patients with comorbidities such as hypertension, diabetes, coronary artery disease (CAD) and obesity, can predispose to more severe presentations and a worse prognosis of COVID-19. These injuries result in organ dysfunction and circulatory collapse. Some pathological studies show infiltration of inflammatory mononuclear interstitial cells, suggesting myocardial inflammation as an underlying mechanism. Serious or fulminant myocarditis has also been reported [2,20]. COVID-19 decompensates cardiac failure in patients with pre-existing cardiac diseases and elevates serum troponin levels in critical patients [2]. In a study carried out in Germany with 138 patients admitted with COVID-19, 16.7% developed arrhythmia and 7.2% suffered an acute cardiac injury [21]. Another German study which included 100 patients showed that 78% of them had cardiac involvement when evaluated by MRI [2].

Patients with underlying cardiac conditions fare worse in COVID-19, and to understand variables associated with mortality in this subgroup could impact on clinical decisions and guide public health policies. The aim of this report was to describe the demographic, clinical and laboratory features (including electrocardiographic and echocardiographic ones) and outcomes of patients with cardiac disease hospitalized with COVID-19 in a reference cardiology institution in Brazil. Although patients with heart disease have been known to fare worse in COVID-19, no study specifically addressing this cohort of patients, in a specialized Cardiology institution has been published in Brazil or elsewhere to our knowledge. Therefore, it is important to understand how cardiac patients evolve when ill with COVID-19 and what are the prognostic markers for mortality in this particular set of patients.

## 2. Methods

This is an observational retrospective study of consecutive adult patients admitted, between March and September of 2020 with a diagnosis of SARS-CoV-2 infection confirmed by RT-PCR, to the National Institute of Cardiology (NIC), a public, quaternary-care hospital in the city of Rio de Janeiro, Brazil. Two information sheets were used to collect data, one of which was elaborated by the *International Severe Acute Respiratory and Emerging Infection Consortium* (CORE COVID-19 CASE REPORT FORM, available in the ISARIC site in several languages) [22] and the other form was created by our group, with an emphasis on variables related to cardiovascular illness. Data were collected from patients' electronic records using a secure online database (REDCap, Vanderbilt University, Nashville, TN, USA).

The ISARIC case report form, which was used for data collection, considers chronic cardiac disease separately from hypertension; other relevant comorbidities for cardiovascular diseases included in the CRF are diabetes mellitus, chronic kidney disease, obesity and smoking. Cardiovascular disease was defined as the presence of coronary artery disease, valvular heart disease, heart failure, congenital heart disease, cardiomyopathy, aortic diseases or arrhythmias.

Hospital admission occurred either due to COVID-19 symptoms or due to cardiovascular indications. Demographic and clinical characteristics, comorbidities, medications in use, clinical signs and symptoms related to COVID-19, complementary tests during hospitalization, treatment used, complications and outcome were obtained through electronic patient records. Variables related to severity of illness were admission to the intensive care unit (ICU), mechanical ventilation (MV), renal failure (IR), hemodialysis and death. Patients who were discharged or transferred from our centre to another hospital were followed up via telephone contact six months after hospital admission to find out their outcome (alive or dead).

Laboratory confirmation of the presence of SARS-CoV-2 was defined as a positive result on real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal- and oropharyngeal swab specimens using the U.S. Centre for Disease Control and Prevention (CDC) reagents and protocol [23]. Specimens were systematically collected from all patients on hospital admission; they were recollected if the patients were negative on admission but developed signs or symptoms of fever or respiratory disease, or if they had been in contact with another patient who tested positive for COVID-19. All patients were tested or re-tested prior to an invasive cardiac procedure or surgery.

COVID-19 was diagnosed based on the WHO interim guidance [24]. COVID-19 was considered hospital-acquired when the patient had a negative nasopharyngeal swab on admission and a positive one 14 or more days later. Lymphopenia was defined as less than 1000 cells/ $\mu$ l of peripheral blood. Comorbidities considered were those defined in the clinical notes; obesity was considered as per WHO definitions as body mass index greater than 30 [25]. Heart dysfunction was defined as a left ventricular ejection fraction <54% for females and <52% for males. Pulmonary hypertension was defined as a pulmonary artery systolic pressure greater than 35 mmHg.

The study was approved by the Ethics Committee under number: 4.048.557 on May 26, 2020; the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and its updates. Informed consent was obtained in written form or via digital media from the patients included prospectively or from a legally entitled next of kin.

Statistical analysis: Data were expressed as frequency and percentages (categorical variables), mean  $\pm$  standard deviation (continuous variables with normal distribution) or median and interquartile range (continuous variables with non-normal distribution). The categorical variables were analyzed using the Chi-square and Fisher's exact tests. The T-Student and Mann-Whitney tests were used to compare continuous variables. The survival curve was calculated using the Kaplan-Meier method. A p level less than 0.05 was considered of significance. A model of logistic regression was developed using the stepwise

methodology, where variables were included in the model until exhaustion and significant statistical of the component variables in the model was reached. Data were analyzed using Jamovi 1.6 e R 4.0.1 statistical software.

### 3. Results

One hundred twenty-one patients with a confirmed diagnosis of COVID-19 were included from March to September 2020 at our cardiac referral hospital. Median age was 64 years (IQR: 33–72 years) and male gender corresponded to 80/121 (66.1%).

Two-thirds of the patients (80/121, 66.1%) were suspected of infection by SARS-CoV-2 at the time of hospital admission. Most of the patients, 69 (57%), acquired the disease in the community; 20 patients (16.5%) were infected at our center, while 31 (25.6%) were transferred from other hospitals with the infection. COVID-19 was the reason for hospital admission in 42 (34.7%), and 96/114 (84.2%) had symptoms related to the infection. Other reasons for hospital admission were acute coronary syndrome (26%), decompensated heart failure (14.8%), complete atrioventricular block (4.1%), heart surgery (coronary artery bypass, valve surgery or aortic surgery, 4.1%), pacemaker dysfunction (2.5%), valve disease (3.3%), endocarditis (2.5%), supraventricular arrhythmias (2.5%), and other causes (stroke, hematologic disease, or exogenous intoxication, 2.5% each).

A large proportion of patients (84/108, 78.5%) took angiotensin-receptor blockers or angiotensin receptor inhibitors; 64/108 (59.3%) used aspirin on a regular basis, 22/108 (18.2%) took clopidogrel, and 23/108 (21.3%) used anticoagulants prior to COVID-19 diagnosis. Demographic and clinical characteristics are described in [Table 1](#).

Regarding comorbidities, chronic cardiac diseases (excluding systemic hypertension) were found in 106/121 (87.6%), mostly coronary artery disease (62%) or valve disease (33.9%). Among the former, 49.2% had a history of myocardial infarction. Diseases of the aorta were found in 9 (7.4%) of the patients. Other common comorbidities were systemic hypertension (83.5%), dyslipidemia (52.9%), diabetes with end-organ damage (24.8%), chronic kidney disease (18.2%), or chronic obstructive pulmonary disease (11.6%). Among 67 patients with available information, 43.3% were former smokers and 19.4% were current smokers. Obesity was found in 26/84 (31%) of the patients in whom the data were registered. Further details are presented in supplementary Fig. 1.

In our study, 87.6% of patients were classified as having chronic cardiac disease and 15/121 (12.4%) were not. However, among these 15 patients, 13/15 (86.7%) had systemic arterial hypertension, 6/15 (40%) had dyslipidemia, 2/15 (13.3%) had chronic renal failure, 2/15 (2%) were diabetic, 6/14 (42.9%) were obese and 3/12 (40%) were smokers. Therefore, we feel confident that our cohort was representative for cardiovascular disease.

Median length of hospitalization was 19 days (IQR: 8–33 days). During hospitalization, 35/119 (29.4%) underwent an invasive cardiology procedure: 31.4% coronary artery bypass surgery, 17.1% pacemaker implantation, 11.4% valve surgery and 5.7% aortic surgery. Regarding clinical manifestations (supplementary Fig. 2), the most frequent symptoms were dyspnea (65.3%), fatigue (62.8%), fever (43.3%), cough (42.5%), and chest pain (42.5%).

Complications and clinical interventions are described in supplementary Table 1. ICU admission occurred in 89/121 (66.1%) of the cases; 63/121 (52.1%) of the patients needed supplementary oxygen; 37/121 (30.6%) needed mechanical ventilation and 38 (31.4%) used vasoactive drugs, and 31.4% (38/121) needed dialysis. Viral pneumonia was present in 64/121 (52.9%) of the patients, and acute severe respiratory syndrome occurred in 28/121 (23.1%). The worsening of heart failure and cardiac arrhythmias occurred in 43% and 37.2%, respectively. During illness, 77/121 (63.6%) of the patients received antibiotics, 40/121 (33.1%) used steroids, and 55/119 (46.2%) received full anticoagulation.

**Table 1**

Demographic and clinical features of 121 hospitalized patients with cardiac disease and COVID-19, March–September 2021.

Variables	N (%)
Age, years	
Median (IQR)	64 (33–72)
Range	19–90
<60	46 (38)
60–74	55 (45.5)
≥75	20 (16.5)
Sex	
Male	80 (66.1)
Female	41 (33.9)
Drugs in use	
ACE <sup>a</sup> inhibitors and ARBs <sup>b</sup>	84 (69.4)
β blockers	74 (61.2)
Aspirin	64 (52.9)
Diuretic	51 (42.1)
Calcium channel blockers	27 (22.3)
Anticoagulants	23 (19)
Vasodilator	23 (19)
Clopidogrel	22 (18.2)
Statins	79 (65.3)
Anticoagulant types	
Warfarin	16 (13.2)
Enoxaparin	6 (5.0)
NOAC <sup>c</sup>	1 (0.8)
Cardiac disease	106 (87.6)
Systemic arterial hypertension	101 (83.1)
Coronary artery disease	75 (62)
Multiarterial coronary artery disease	51 (42.1)
Dyslipidemia	64 (52.9)
Myocardial infarction	59 (48.8)
Aortic disease	9 (7.4)
Valvulopathy	41 (33.9)
Mitral regurgitation	19 (15)
Aortic stenosis	13 (10.7)
Aortic regurgitation	10 (8.3)
Mitral stenosis	9 (7.4)
Tricuspid regurgitation	5 (4.1)
Past cardiac surgery	
Coronary artery by-pass graft	13 (10.7)
Aortic and/or mitral valve replacement	11 (9.1)
Other	5 (4.1)
Past cardiac procedures	
Stent angioplasty	33 (27.3)
Implantable cardioverter-defibrillator	4 (3.3)
Other	3 (2.5)

<sup>a</sup> Angiotensin converting enzyme inhibitors.

<sup>b</sup> Angiotensin II receptor blockers.

<sup>c</sup> Novel oral anticoagulants.

Results of laboratory tests, including echocardiogram and ECG, are presented in [Table 2](#). Among 85 patients who had troponin evaluation, 27.1% had elevated levels; BNP was measured in 28 patients, and the median value was 1046 pg/ml. The median lymphocyte count was 1324/μl (IQR 762–1985), and 31.4% of the patients had lymphopenia. The medians of C-reactive protein and d-dimer were, respectively, 6.25 mg/dl (IQR 1.5–14) and 1180 ng/ml (IQR 547–2172). D-dimer was evaluated in 62 patients, among whom 77.4% had levels above 500 ng/ml. Ferritin was over 341 ng/ml in 39/ 54 (72%) individuals.

A transthoracic echocardiogram was performed in 85% of the patients (93/121, 76.8%), as shown in [Table 2](#). Enlarged cardiac chambers were found in 71% (66/93), left ventricular systolic dysfunction was found in 54.8% (51/93), left ventricular diastolic dysfunction was found in 52.7% (49/93), and 20.4% (19/93) had right ventricular dysfunction. Heart valve abnormalities were found in 54.8% (51/93), 45.2% (42/93) had left ventricular hypertrophy, 18.3% (17/93) had pulmonary hypertension, 11.8% (11/93) had pericardial effusion and 5.4% (5/93), pleural effusion.

Data on the admission ECG was found in 93 cases (93/121, 76.8%), among which 89.2% (83/93) were abnormal; 34.4% (32/93) had any abnormality of cardiac rhythm, 20.4% (19/93) had bundle branch

**Table 2**

Selected laboratory features in 121 hospitalized patients with cardiac disease and COVID-19.

Laboratory tests*	
Atrial natriuretic peptide (n = 28; pg/ml; mean. ±SD)	1303.82 (±995.19)
Troponin (n = 85)	62 (72.9%) negative
Ferritin (n = 54; ng/ml; median.IQR)	755 (271–2839)
D-dimer (n = 62; ng/mL; median. IQR)	1180 (547–2172)
C-reactive protein (n = 106; mg/dL; median. IQR)	6.25 (1.5–14)
Leukocyte count (n = 121; /μL; median. IQR)	7150 (5160–9670)
Lymphocyte count (n = 121; /μL; median. IQR)	1324 (762–1985)
Neutrophil count (n = 121; /μL; median. IQR)	4604 (3146–7.259)
Hemoglobin (n = 121; g/dL; mean. ±SD)	12.3 (±1.8)
Creatinine (n = 119; mg/ dL; median.IQR)	1.08 (0.85-1.56)
Chest tomography findings n = 97	
Ground-glass opacity <25%	n = 32 (33%)
Ground-glass opacity:25% a 50%	n = 20 (20.6%)
Ground-glass opacity >50%	n = 21 (21.6%)
Pleural effusion	n = 23 (23.7%)
Consolidations	n = 15 (15.5%)
Pericardial effusion	n = 3 (3.1%)
Normal	n = 6 (6.2%)

Reference values: atrial natriuretic peptide: <100 pg/dL; troponin negative (below reference value of 0,16 ng/ml); ferritin: <341 ng/ml; D-dimer: <500 ng/mL; leukocyte count: 4000 to 10,000/μL; lymphocyte count: 800 to 4500/μL; neutrophil count: 1600 to 7500/μL; hemoglobin: 11.5 to 16.4 g/dL; C-reactive protein: <0.5 mg/dL.

block, 21.5% (20/93) had ST segment abnormalities, 11.8% (11/93) left ventricular overload and 6.5% (6/93) QT interval abnormalities. The most frequent arrhythmia was atrial fibrillation (14/93, 15.1%), followed by sinus tachycardia, sinus bradycardia and supraventricular tachycardia, which occurred in 3/93(3.2%) of patients each. At the time of data analysis, overall mortality was 24% and 68.6% were discharged from hospital.

As shown in Table 3, on bivariate analysis, mortality related to COVID-19 was significantly associated with diabetes with end-organ damage, dyslipidemia, echocardiographically-defined pulmonary hypertension, elevated C-reactive protein and creatinine, longer ICU admission and the presence of dyspnea at admission. The use of the following medications was also associated with mortality: antibiotics, steroids, vasoactive drugs, neuromuscular blockers ( $p < 0.001$ ), aspirin and/or clopidogrel ( $p < 0.057$ ), anticoagulants, antivirals, and antifungals. The following complications were associated with increased mortality: viral or bacterial pneumonia, the presence of pleural effusions on CT scans, heart failure, arrhythmias, cardiac ischemia, coagulation disorders, anemia, acute renal failure, hyperglycemia, and hypoglycemia. Moreover, mortality was higher in patients who needed ICU treatment, underwent hemodialysis, needed mechanical ventilation or non-invasive ventilation. Prior heart disease (either coronary artery disease, valve disease, or aortic disease), systemic hypertension, smoking, chronic kidney failure or obesity were not associated with mortality. Table 4 shows laboratory features associated with mortality. Most interestingly, BNP levels and troponin levels were NOT associated with mortality in this group of cardiac patients.

On multivariate analysis for mortality associated to COVID-19 in cardiac patients, only CRP protein levels and creatinine levels remained significant. For each 1 mg/dL increase in CRP, there was a 10% increase in mortality risk (OR 1.1, CI 0.0497–0.141); for each 1 mg/dL increase in serum creatinine levels, mortality increased by 53.46% (OR 1.5346, CI 0.0307–0.826).

We compared patients who acquired COVID-19 during hospital admission in our center to those that had the diagnosis of COVID-19 on admission. Patients who developed COVID-19 while in hospital had as reasons for admission: decompensated heart failure (35%), acute coronary syndrome (20%), heart surgery (CABG, valve replacement or aortic

**Table 3**

Features associated with mortality in 121 hospitalized patients with cardiac disease and COVID-19. March to September 2020.

Variables	Dead (n = 29)	Alive (n = 92)	OR (95% CI)	P value
Age				
>60	15 (51.7%)	39 (42.4%)	1.4 (0.6–3.3)	0.378
Male gender	20 (69%)	60 (65.2%)	0.8 (0.3–2.0)	0.710
Diabetes with end-organ damage	12 (41%)	18 (19.6%)	2.9 (1.1–7.1)	0.018
Dyslipidemia	23 (79.3%)	41 (44.6%)	4.7 (1.7–12.8)	0.001
Cardiac disease	27 (93.1%)	79 (85.9%)	2.2 (0.4–10.5)	0.518
COPD	4 (13.8%)	10 (10.9%)	1.31 (0.3–4.5)	0.741
CRF	14 (15.2%)	8 (27.6%)	2.1 (0.7–5.7)	0.132
Arterial hypertension	27 (93.1%)	74 (80.4%)	3.2 (0.7–15.1)	0.153
Coronary heart disease	18/28 (64.3%)	57/91 (62.6%)	1.7 (0.4–2.5)	0.874
Obesity	7/20 (35%)	19/64 (29.7%)	1.2 (0.4–3.7)	0.654
Previous clopidogrel and/or aspirin use	19/24 (79.2%)	47/84 (56%)	2.99 (1.0–8.7)	0.057
Previous Statin use	17/29 (58.6%)	62/92 (67.4%)	0.68 (0.2–1.6)	0.387
Any COVID-19 symptom	28/28 (100%)	68/86 (79%)	0.06 (0.003–1.1)	0.006
Fatigue	24 (82.8%)	52 (56.5%)	3.6 (1.2–10.5)	0.015
Shortness of breath	27 (93.1%)	52 (56.5%)	10.4 (2.3–46.3)	<0.001
Chest pain	14 (48.3%)	37 (40.7%)	1.3 (0.5–3.1)	0.470
Pleural effusion	11/27 (40.7%)	12 (13.0%)	4.5 (1.7–12.2)	0.004
Lung consolidation on CT scan	7 (24.1%)	8 (8.7%)	2.3 (0.7–7.3)	0.028
Viral pneumonia	23 (79.3%)	41 (44.6%)	4.7 (1.7–12.8)	0.001
Bacterial pneumonia	19 (65.5%)	21 (22.8%)	6.4 (2.5–15.9)	<0.001
Heart failure	21 (72.4%)	31 (33.7%)	5.1 (2.0–13.0)	<0.001
Arrhythmia	22 (75.9%)	23 (25.0%)	9.4 (3.5–24.9)	<0.001
Myocardial ischaemia	13/28 (46.4%)	10/91 (11.0%)	7.0 (2.6–18.9)	<0.001
Coagulation disorder	11 (37.9%)	3 (3.3%)	18.1 (4.5–71.6)	<0.001
Anemia	20 (69.0%)	15 (16.3%)	11.4 (4.3–29.8)	<0.001
Acute renal injury	23 (79.3%)	14 (15.2%)	21.4 (7.3–61.9)	<0.001
Hyperglycaemia	18 (62.1%)	21 (22.8%)	5.5 (2.2–13.5)	<0.001
Hypoglycaemia	5/28 (17.9%)	3 (3.3%)	6.45 (1.4–29.0)	0.017
Admission to intensive care	27 (93.1%)	53 (57.6%)	9.9 (2.2–44.3)	<0.001
Mechanical ventilation	22 (75.9%)	15 (16.3%)	16.1 (5.8–44.5)	<0.001
Non-invasive ventilation	9 (33.3%)	5 (9.6%)	4.7 (1.3–15.9)	0.013
Oxygen therapy	21 (72.4%)	31 (33.7%)	5.1 (2.0–13.0)	<0.001
Neuromuscular blocking agents	12 (41.4%)	1 (1.1%)	64.2 (7.8–527)	<0.001
Nitric oxide	2 (6.9%)	0%	16.8 (0.7–361)	0.056
Pronation	22.2%	5.5%	4.9 (1.3–17.7)	0.017
Hemodialysis		9 (9.8%)		<0.001

(continued on next page)



**Table 3** (continued)

Variables	Dead (n = 29)	Alive (n = 92)	OR (95% CI)	P value
	15 (51.7%)		9.8 (3.6–26.9)	
Vasoactive drugs	24 (82.8%)	14 (15.2%)	26.7 (8.7–81.9)	<0.001

**Table 4**

Laboratory features associated with mortality in 121 hospitalized patients with cardiac disease and COVID-19.

Variables	Alive	Dead	OR (95% CI)	P value
Leukocyte count (cells/ $\mu$ l)	6740 (5120–8993)	8530 (6610–11,010)	1.0 (1.0–1.0)	0.037
Lymphocyte count (cells/ $\mu$ l)	1451 (1029–1999)	720 (570–1940)	0.9 (0.9–1.0)	0.008
Glucose (mg/dl)	110 (94.5–147)	157 (117–207)	1.0 (1.0–1.0)	0.008
AST (IU)	26.5 (19.8–44.3)	52 (41–79)	1.0 (0.0–1.0)	0.001
Creatinine (mg/dl)	1.04 (0.8–1.39)	1.46 (1.05–2.25)	1.4 (1.0–2.0)	<0.001
CRP levels (mg/dl)	3.4 (1.2–9.2)	17 (7–31)	1.0 (1.0–1.1)	<0.001
Ferritin levels ( $\mu$ g/l), n = 54	585 (197–1066)	1488 (654–2106)	1.0 (1.0–1.0)	0.007
D-dimer (ng/ml), n = 62	1130 (498–1893)	1545 (785–3945)	1.0 (1.0–1.0)	NS
BNP (pg/ml), n = 28	1298 $\pm$ 1069	1332 $\pm$ 635	1.0 (0.9–1.0)	NS
Troponin <sup>a</sup> (n = 85)	46/59 (78%)	16/26 (61.5%)	0.452 (0.166–1.23)	NS
Echocardiogram (n = 93)				
Pulmonary hypertension	6 (9.2%)	11 (40.7%)	6.7 (2.1–21.1)	<0.001
Enlarged cardiac chambers	43 (66.2%)	22 (81.5%)	2.2 (0.7–6.7)	0.2092
Left ventricular systolic dysfunction	32 (49.2%)	18 (66.7%)	2.0 (0.8–5.2)	0.126
Right ventricular dysfunction	9 (13.8%)	10 (37.0%)	3.6 (1.2–10.5)	0.012
Heart valve abnormalities	35 (53.8%)	14 (51.9%)	0.9 (0.3–2.2)	0.861
Left ventricular hypertrophy	28 (43.1%)	14 (51.9%)	1.4 (0.5–3.5)	0.442
Pericardial effusion	9 (13.8%)	2 (7.4%)	0.4 (0.1–2.4)	0.386
Electrocardiogram (n = 93)				
Any abnormality of cardiac rhythm	18 (26.5%)	14 (56%)	3.5 (1.3–9.2)	<0.008
Atrial fibrillation	8 (11.8%)	5 (20%)	1.8 (0.5–6.3)	0.310
Bundle branch block	14 (15.2%)	5 (17.2%)	1.1 (0.3–3.5)	0.775
ST segment abnormalities	15 (22.1%)	5 (20%)	0.8 (0.2–2.7)	1.000
QT interval abnormalities	4 (5.9%)	2 (8.0%)	1.3 (0.2–8.1)	0.658

<sup>a</sup> Troponin levels considered positive or negative with a cut-off value of 0,16 ng/ml; P levels calculated by the Mann-Whitney test, except for BNP (t-Student test); D-dimer levels were obtained in 62 patients; ferritin in 54 and BNP in 28 patients.

surgery) in 25%, complete AV block (5%), pacemaker dysfunction (5%), stroke (5%) and hematologic disease (5%). Most (18/20, 90%) were symptomatic when diagnosed with COVID-19. Median age and IQR was 64 years (61.8–69.3) for those with hospital-acquired COVID-19 whilst it was 63 (52–72) for those who acquired it outside our hospital. There was no difference between patients with hospital-acquired COVID-19 and those who acquired COVID-19 outside our center regarding the presence of heart disease [18/20(90%) vs 88/101 (87,1%)],  $P = 1$ ,

COPD [4/20 (20%) vs 10/101 (9,9%),  $P = 0,246$ ], obesity [7/13 (53.8%) vs 19 /71 (26.8%),  $P = 0,098$ ], complicated diabetes mellitus [5/20 (25%) vs 25/101 (24.8%),  $P = 1$ ], uncomplicated diabetes mellitus [4/20 (20%) vs 19/101 (18.8%),  $P = 0,902$ ], heart valve disease (7/19 (36.8%) vs 34/100 (34%),  $P = 0,811$ ], coronary artery disease [14/20 (70%) vs 61/99 (61.6%),  $p = 0.479$ ], systemic arterial hypertension [18/20 (90%) vs 83/101 (82.8%),  $P = 0,39$ ]. However, the 2 groups were different regarding the frequency of dyslipidemia (15/20 (75%) vs 49/101 (48,5%),  $P = 0,030$ ) and chronic renal failure [7/20 (35%) vs 15/101 (15%),  $p = 0.033$ ], and most importantly, mortality was significantly different [10/20 (50%) vs 19/101 (18.8%),  $p = 0.003$ ].

#### 4. Discussion

Our study focuses on aspects of COVID-19 in hospitalized patients in a high-complexity Brazilian Cardiology hospital in the first semester of 2020. This is a different scenario compared to most studies on COVID-19 to date, since the study population represents a highly selected group of patients with significant cardiac abnormalities, mainly coronary artery, and valve disease.

Most patients were male and older than 60 years, similarly to other series [18,26]. Over half were admitted due to decompensated heart failure, and the reason for clinical deterioration was infection by SARS-Cov-2, illustrating the impact of the pandemic in the study period. On the other hand, nosocomial transmission of the virus occurred in nearly a fifth of our patients (20 [16.5%]), highlighting the risk of acquisition of COVID-19 for those admitted for cardiac surgery or other routine procedures. Importantly, patients who acquired COVID-19 in hospital had a much higher mortality (50%) than those who had the diagnosis of COVID-19 on admission (18.8% mortality), highlighting the danger nosocomial COVID-19 represented, despite the fact our center was not to receive COVID-19 patients and was to remain COVID-free.

Other clinical features reported by several groups were frequently seen, such as shortness of breath, fatigue, and cough [6,12,15,17–19,27,28]. However, we noticed a high rate of chest pain, which was the main complaint in over a third of patients. Since a large part of this population consisted of patients with coronary artery disease, chest pain might be viewed as a manifestation of prior cardiac disease, possibly worsened by the current infection. Interestingly, pleural effusions occurred in a quarter of patients, probably due to heart failure. This radiological feature is not usual in COVID-19, and in a systematic review of chest imaging findings in COVID-19, pleural effusions were described in 0.9 to 10.3% of included studies with more than 100 patients [29]. We highlight that the presence of pleural effusions on CT scans, of heart failure, of arrhythmias, and of cardiac ischemia, were significantly associated to mortality in this cohort of patients with cardiovascular diseases, as were pulmonary hypertension and right ventricular dysfunction.

Intensive care admission was necessary for 2/3 of our cohort, a rate much higher than seen in Spain (18.5%) [28], the USA (14.2%) [26], China (14.8%) [5] and the United Kingdom (17%) [18]. This is not unexpected, as our cohort was particularly represented by patients with a variety of severe heart conditions.

In the current literature, severe complications of COVID-19 such as respiratory failure and acute renal failure are reported to occur in 14 to 19% of cases [5,15]; however, in our study, incidences were 23.1% and 30.6% respectively, highlighting, once more, the harsh course of disease in patients with cardiac disease. Despite this, overall mortality was 24%, which is similar to mortality reported for hospitalized patients in Spain (28%), the USA (21%) and England/Wales (26%) [26,28,18], but higher than that reported in a Brazilian series from a private hospital (6.4%) and China (2.3%) [9,5].

Patients with diabetes with end-organ damage, those who developed heart failure or cardiac ischemia had greater mortality; this has also been reported by others [5,6,19,11,28,30]. Zhou et al. showed that 51.9% of patients who developed heart failure died, compared with

11.7% of those who did not present heart failure [6]. It is not clear if heart failure occurred because of worsening previous left ventricular failure (LVF) or because of new-onset LVF [13]. Moreover, patients with dyslipidemia and pulmonary hypertension had higher mortality. The former may overlap to some degree with coronary artery disease patients, as dyslipidemia is one of the most important risk factors for this condition, and that might explain their worse prognosis. Regarding the latter, it is known that pulmonary hypertension (in this population, most likely found in patients with valve disease or heart failure) is associated with poorer outcomes in general, and especially when challenged by infectious states.

Cardiac arrhythmias are another common CV manifestation described in patients with COVID-19. In our study, the most prevalent arrhythmia was atrial fibrillation. An American study with 9,564 patients showed that atrial fibrillation increased the risk of mortality in patients hospitalized for COVID-19. The prevalence and incidence of AF during hospitalization for COVID-19 is unclear; however, one should expect similarities with other systemic inflammatory response syndromes and sepsis [31]. We did not find atrial fibrillation was associated with mortality in our study of cardiac patients. Though nonspecific, palpitations were part of the presenting clinical features in 7.3% of patients in a cohort of 137 patients admitted for COVID-19 disease [32]. In hospitalized COVID-19 patients, cardiac arrhythmia was noted in 16.7% of 138 patients in a Chinese cohort and was more common in ICU patients than in non-ICU patients (44.4% vs. 6.9%) [21]. A high rate of cardiac arrhythmias may be due to metabolic disorder, hypoxemia, neuro-hormonal stress or inflammation resulting from SARS-CoV-2 infection and was associated to mortality. Malignant tachyarrhythmias, associated with high troponin levels, however, are often associated with underlying myocarditis [13].

Laboratory features associated with greater mortality were increased creatinine and CRP levels, similarly to other studies [28,33]. Interestingly, BNP levels and troponin were not associated with mortality, differently from other reports [7,34]. We hypothesize that, in patients with cardiac disease, these cardiac injury markers may not be as important as prognostic indicators as in the general patient population. Nonetheless, this inference may be limited by the small number of patients with available data for these laboratory markers.

Other limitations of our study are its single-center characteristic, and the fact that laboratory and imaging tests were not uniformly applied to all patients but were ordered at the discretion of the attending physicians, what derives from the “real-world” scenario of the study. Notwithstanding, these drawbacks offer a picture of current practice in the setting of the COVID-19 pandemic at a public, specialized Cardiology healthcare institution of a developing country.

## 5. Conclusions

Cardiac patients hospitalized with COVID-19 often presented with dyspnea, chest pain and signs or symptoms of congestive heart failure. Tomographic images showed ground-glass opacities in nearly ¾ of patients and pleural effusions in a quarter of cases. Nearly a fifth of hospitalized patients acquired COVID-19 while being cared for other cardiac conditions, and this group had a particularly high mortality of 50%. Mortality for the whole group of patients with COVID-19 was high, at 24%, but like other series of hospitalized patients with COVID-19. On bivariate analysis, BNP levels and troponin levels were not associated with mortality, suggesting these are not good discriminators of prognosis in cardiac patients, and on multivariate analysis, only CRP and creatinine levels were significant.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ahjo.2021.100069>.

## Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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