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Predictors of in-hospital death in children with myocardial injury related to COVID-19

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Abstract

Introduction: Myocardial injury due to COVID-19 infection is associated with higher mortality rates, higher intensive care unit admissions, and greater levels of inflammatory and cardiac markers. However, given the smaller number of papers regarding pediatric patients, there is still scarce data about mortality predictors in this population. This study aims to identify independent predictors of in-hospital death among pediatric patients hospitalized with myocardial injury related to COVID-19.

Methodology: This is an observational, prospective, and longitudinal study of pediatric patients who were hospitalized between March 2020 and June 2021 in a tertiary pediatric hospital. A total of 1,103 consecutive pediatric patients tested positive for COVID-19, and 232 were admitted. All patients underwent cardiac evaluation with electrocardiogram, echocardiogram, and cardiac markers. Of these patients, 88 were diagnosed with myocardial injury but 1 patient refused to participate, therefore 87 patients were included in the study.

Results: The median age at the time of diagnosis was 2 years (0-18), 38% had pre-existing comorbidities, and the mortality was 12% (n = 11). Cardiac evaluation has revealed high levels of troponin I in 63%, and electrocardiogram and echocardiogram abnormalities in 81% and 22% respectively. We found that high levels of inflammatory markers had higher mortality, but they didn't emerge as significant predictors of mortality when adjusted for other variables. Patients without pre-existing comorbidities were less likely to die in both univariate and multivariate analysis.

Conclusions: Our findings may help healthcare providers better understand the cardiac implications of COVID-19 and define the necessity of cardiac surveillance amongst hospitalized pediatric patients.

Key words: Myocardial injury; COVID-19; SARS-CoV-2; death predictors.

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Introduction

Early data of the coronavirus disease 2019 (COVID-19) pandemic indicated that children were less susceptible to severe illness compared with adults [1–4]. However, subsequent studies revealed that pediatric patients could meet the criteria for severe disease, requiring mechanical ventilation and inotropic support, exhibiting higher mortality rates. These patients correspond to almost 14% in the United States, 40% in India, and 42% in Iran [5–7].

Afterward, it was described as a newly recognized syndrome related to SARS-CoV-2 infection characterized by hyperinflammation and multiorgan involvement in children (MIS-C) with a very high incidence of myocardial involvement (93%), shock (40%), and arrhythmia (35%) [8–11]. Elevated inflammatory markers levels in patients requiring admission to the intensive care are significantly higher compared to those managed exclusively on the ward [12,13].

Emerging clinical and epidemiological evidence suggests that metabolic disarray, hypoxia, and accentuated myocardial inflammation due to SARS-CoV-2 infection play a critical role in the pathophysiology of myocardial injury and the prevalence of arrhythmic complications [14]. Due to its mechanism of cellular invasion through the angiotensin-converting enzyme receptor 2 (ACE2), its heightened expression in the small intestine, heart, venous endothelial, and kidney tissues leads to a systemic response resulting in acute cardiopulmonary failure and coagulopathy. Furthermore, the overexpression of the ACE2 receptor can result in cardiovascular instability (renin-angiotensin system), acute inflammatory pulmonary edema (kinin-kallikrein system), and thromboembolism (coagulation system) [15–17].

Atrial fibrillation is the most common cardiac arrhythmia whereas sinus bradycardia is the most common bradyarrhythmia in adults. In hospitalized

COVID-19 patients, life-threatening ventricular arrhythmias may occur (sustained monomorphic ventricular tachycardia, polymorphic ventricular tachycardia/Torsade de Pointes, ventricular tachycardia/ventricular fibrillation arrest) [18]. In children, electrocardiographic changes lean towards the milder spectrum, commonly featuring sinus tachycardia, first-degree atrioventricular block, and nonspecific repolarization alterations as the primary observations. It's important to highlight, however, that both supraventricular and ventricular tachycardia have also been documented [12,19–21]. This myocardial injury can also lead to a reduction in systolic ventricular function and, therefore, heart failure. Other echocardiographic findings in children are mitral regurgitation, dilatation of the coronary arteries, and pericardial effusion [12].

Considering the high mortality of COVID-19 patients with cardiovascular comorbidities, it is important to understand whether it is attributable to underlying cardiovascular disease or if it is the consequence of an inflammatory response to SAR-CoV-2 infection or severe respiratory symptoms [14]. Recent evidence suggests that any pre-existing medical conditions, myocardial injury, and inflammatory markers may predict death among COVID-19 patients [22–26], but given the smaller number of papers regarding pediatric patients, there is still scarce data about mortality predictors in this population.

Methodology

Study Design

In this retrospective, single-center, observational study, pediatric patients under 18 years with myocardial injury related to COVID-19 between March 2020 and June 2021 were included. All pediatric patients with COVID-19 infection who were hospitalized underwent cardiac evaluation with electrocardiogram, echocardiogram, and cardiac markers. SARS-CoV-2 infection was diagnosed based on a positive reverse transcription - polymerase chain reaction (RT-PCR) and/or rapid immunochromatographic antibodies test. This study included patients with a positive COVID test that presented abnormalities in their cardiac evaluation.

Table 1. Demographic characteristics.

Characteristic	
Male gender, n (%)	50 (57%)
Age (years), median (IQR)	2 (0 – 10)
Patients younger than 1 year, n (%)	33 (33%)
No pre-existing comorbidities, n (%)	54 (62%)
Admission in ICU, n (%)	45 (53%)
Length of stay at ICU (days), median (IQR)	7 (3-13)
Mechanic ventilatory support, n (%)	24 (28%)
Length of mechanic ventilatory support (days), median (IQR)	7 (3-13)
Inotropic support, n (%)	25 (29%)
Length of inotropic support (days), median (IQR)	5 (3-8)
Length of in-hospital stay (days), median (IQR)	10 (6-17)
Mortality, n (%)	11 (12%)

IQR: Interquartile Range; ICU: Intensive Care Unit.

Data Analysis

The demographic characteristics and clinical and laboratorial findings were analyzed. Troponin I and CK-MB were evaluated as cardiac markers and d-dimer, lactic dehydrogenase, creatinine, hemogram, lactate, ferritin and creatine kinase were also assessed. All electrocardiograms and echocardiograms performed were included. Myocardial injury was defined as blood levels of cardiac markers above reference levels, echocardiographic abnormalities and/or electrocardiographic abnormalities.

Statistical Analysis

R Software (Rstudio) was used for statistical analysis. Data were presented as means and interquartile ranges (IQR) for continuous variables whereas numbers (n) and percentages (%) for categorical ones. The normal distribution of variables was tested using the Shapiro-Wilk test. Categorical variables were compared by Fisher's exact test while continuous variables between two groups were tested using the Wilcoxon-Mann-Whitney test. The significance of each variable as a predictor of in-hospital mortality was assessed by univariate and multivariate logistic regression analysis. A P value less than 0,05 was considered statistically significant.

Ethics Approval

In December 2020, the Ethics and Research Committee of Hospital Pequeno Príncipe in Curitiba, Brazil (Approval No. 4.435.624) granted its approval to the study. To ensure the ethical integrity of the research, written informed consent was meticulously obtained from all legal representatives of the participating patients.

Results

A total of 1103 pediatric patients tested positive for COVID-19, and 232 were admitted between March 2020 and June 2021. Of these patients, 88 were diagnosed with myocardial injury but 1 patient refused to participate, therefore 87 patients were included in the study. The median age at the time of diagnosis was 2 years (0-18), 50 patients were male (57%) and 37 were female (43%). The median duration of in-hospital stay

was 10 days (1-57), 45 patients were admitted to the intensive care unit (53%), and they had a median duration in the intensive care unit of 7 days (1-57). 24 patients required mechanical respiratory support (28%), 25 required inotropic agents (29%), and the mortality was 12% (n = 11), as seen in Table 1.

On admission, 33 patients (38%) had pre-existing comorbidities. The most prevalent was neurological (15 patients) followed by cardiac (9 patients), oncological, and urological (5 patients each), while 54 patients were healthy.

The in-hospital laboratory analysis has revealed high levels of troponin I in 63% (n = 53), CK-MB above reference levels in 65% (n = 46), high levels of C-reactive protein and D-dimer in 72% (n = 62), and 73% (n = 58) respectively.

Cardiac evaluation has revealed sinus tachycardia in 41% (n = 33), sinus bradycardia in 16% (n = 13), atrioventricular block in 3% (n = 2) and ventricular tachycardia in 3% (n = 2). Echocardiographic assessment has shown left ventricle systolic dysfunction in 11% (n = 9), hyper-refringent coronaries in 7% (n = 6), and coronary dilatation in 2% (n = 2). All cardiac abnormalities can be seen in Table 2.

Table 3 shows the bivariable comparison of patients who survived hospital discharge versus those who died. Patients with pre-existing comorbidities ($p = 0.02$), high levels of C-reactive protein ($p = 0.01$) and high levels of D-dimer ($p = 0.01$) had significantly higher mortality.

Binary logistic regression analysis has shown that only high C-reactive protein levels (odds ratio = 1.01; $p = 0.02$; 95% confidence interval = 1.00 – 1.01) and high levels of D-dimer (odds ratio = 1.00; $p = 0.01$; 95% confidence interval = 1.00 – 1.01) were statistically significantly associated with in-hospital deaths. Patients without pre-existing comorbidities were less likely to die in both univariate (odds ratio = 0.18; $p = 0.02$; 95% confidence interval = 0.04 – 0.75) and multivariate analysis (odds ratio = 0.14; $p = 0.02$; 95% confidence interval = 0.03 – 0.79) as seen in Figure 1.

Table 2. Cardiac abnormalities.

Electrocardiography	**N = 80**
Sinus Tachycardia (age-specific values)	33 (41%)
Supraventricular extrasystoles	12 (15%)
Supraventricular tachycardia	3 (4%)
Ventricular extrasystoles	5 (6%)
Ventricular tachycardia	2 (3%)
Sinus bradycardia (age-specific values)	13 (16%)
Atrioventricular block (first degree)	2 (3%)
ST-segment elevation	33 (41%)
ST-segment depression	11 (14%)
Non-specific T-wave abnormalities	26 (33%)
QT interval prolongation	7 (9%)
Any electrocardiogram abnormalities	65 (81%)
Echocardiography	**N = 85**
Left ventricular systolic disfunction	9 (11%)
Left ventricular diastolic disfunction	5 (6%)
Coronary dilatation	2 (2%)
Hyper-refringent coronary	6 (7%)
Any echocardiogram abnormalities	19 (22%)

Discussion

The present study addressed the importance of cardiac involvement in COVID-19 as a predictor of in-hospital death. The overall mortality from COVID-19 among hospitalized patients was 12%, with more than half (53%) being admitted to the ICU. Additionally, 28% required mechanical ventilatory support, and 29% needed inotropic agents. Oliveira *et al.* analyzed all COVID-19 cases in hospitalized children and adolescents in a Brazilian nationwide database and reported that 23.8% of patients were admitted to the ICU, while 10% required invasive ventilatory support, and the overall mortality rate was 7.5% [27]. A

Table 3. Bivariable association between patients' characteristics and in-hospital death.

Characteristics	**Survived (n = 76)**	**Died (n = 11)**	***p***
Male gender, n (%)	46 (61%)	4 (36%)	0.19
Age (years), median (IQR)	2.0 (0.0 – 10.0)	6.0 (4.5 – 12.5)	0.05
No pre-existing comorbidities, n (%)	51 (67%)	3 (27%)	0.02*
Length of stay at ICU (days), median (IQR)	7 (3 – 12)	7 (2 – 13)	0.93
Length of mechanic ventilatory support (days), median (IQR)	11 (5 – 15)	6 (3 – 12)	0.42
Length of inotropic support (days), median (IQR)	7 (3 – 9)	4 (2 – 6)	0.25
Troponin (I) (pg/mL), median (IQR)	50 (10 – 100)	120 (10 – 230)	0.09
D-dimer (ng/mL), median (IQR)	858 (437 – 2141)	3355 (2350 - 4537)	0.01*
C-reactive protein (mg/mL), median (IQR)	13 (5 – 107)	222 (72 – 245)	0.01*
Lactic acid (mmol/L), median (IQR)	2.5 (1.6 – 3.7)	3.4 (2.6 – 4.9)	0.17
CPK (U/L), median (IQR)	57 (29 – 110)	61 (20 – 276)	0.74
CKMB (U/L), median (IQR)	26 (10 – 41)	23 (11 – 86)	0.72
Lactic dehydrogenase (U/L)	360 (281 – 462)	782 (369 – 6192)	0.05
Any electrocardiogram abnormalities	60 (82%)	5 (71%)	0.61
Any echocardiogram abnormalities	15 (20%)	4 (44%)	0.11

IQR: Interquartile Range; CKMB: Creatine-Kinase MB; CPK: Creatine Phosphokinase; *$p < 0.05$.

prospective cohort study conducted in the United States, which included children under 19 years of age, revealed that 13.9% met the criteria for severe disease, 7.8% underwent mechanical ventilation, and 8.5% needed inotropic support, with a mortality rate of only 1.3% [5].

Sharma *et al.* found a mortality rate of 9.9% in COVID-19 hospitalized patients aged zero to 12 years [6]. Similar to our study, their research included all hospitalized patients who tested positive for the virus, although not all of them died from symptoms directly associated with the virus. This may have led to an overestimation of the mortality rate. Additionally, this article is subject to underreporting of milder cases, where the population does not seek medical attention, making it difficult to compare with developed countries that have a more effective national policy for active case detection.

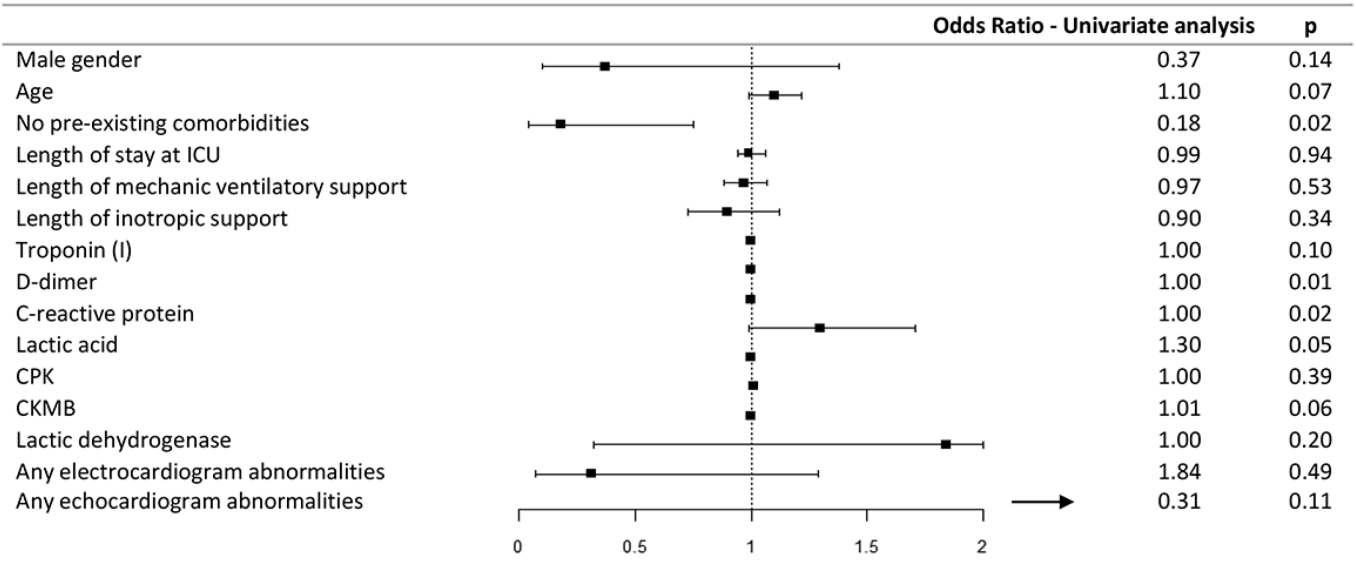
Sedighi *et al.* described the risk factors associated with severe illness in children with COVID-19 and found that the presence of comorbidity was correlated with higher ICU referrals [7]. Pre-existing medical conditions were also associated with an increased risk of death, and the risk of death increased with the number of pre-existing medical conditions [27]. In our study, we found that pre-existing comorbidities were an independent predictor of in-hospital mortality after adjusting for confounders.

In accordance with the literature, an intense inflammatory response was found in most of the patients. We observed high lactic dehydrogenase levels in 92% of the patients and high d-dimer levels in 73%, but only C-reactive protein levels were significantly high in our univariate analysis. However, it is important to note that none of the inflammatory markers emerged as significant predictors of mortality when adjusted for other variables.

Initial reports revealed a myocardial injury rate among adults of 20% to 25%, despite a variable incidence of confounding factors like pre-existing cardiac disease or renal disease [26]. A multicenter study gathered data from 32 hospitals in Spain and evaluated the role of cardiac troponin in COVID-19 infection. It found that both types of cardiac troponin, T and I, were independent predictors of 30-day mortality [28]. In our study, the median troponin level of patients who died was higher than those who survived (120 pg/mL versus 50 pg/mL), but neither troponin nor CKMB were significant predictors.

Currently, limited information is available regarding arrhythmic manifestations associated with COVID-19 in pediatric patients. In a multicenter study

Figure 1. Logistic regressions analysis of the incidence of in-hospital death.



	Odds Ratio (95% CI) - Multivariate analysis	p
No pre-existing comorbidities	0.19 (0.02 – 0.79)	0.02
D-dimer	1.00 (0.99 – 1.01)	0.10
C-reactive protein	1.00 (0.99 – 1.01)	0.21

CI: Confidence interval; CKMB: Creatine-Kinase MB; CPK: Creatine Phosphokinase.

of 286 children, Valverde *et al.* reported arrhythmias in 35% of hospitalized patients, with a return to normal during hospitalization in 72% [12]. Hersh *et al.* described electrocardiographic abnormalities in 40% of pediatric patients (0-21 years), with nonspecific ST-T wave patterns being the most common findings [21]. We found electrocardiographic abnormalities in 81% of our patients, with the most common being sinus tachycardia (41%), ST-segment elevation (41%), and non-specific T-wave abnormalities (33%). Guo *et al.* described a high incidence of malignant arrhythmia (59%) as a major cause of death among severe or critically ill adult patients [29]. In our study, most of our patients showed benign abnormalities, and only 2 patients (3%) presented non-sustained ventricular tachycardia.

Among COVID-19 patients, echocardiographic abnormalities are diverse and include global left ventricle dysfunction, regional wall motion abnormalities, diastolic dysfunction, right ventricle dysfunction, and pericardial effusions [4]. In children with MIS-C, coronary abnormalities have also been described without association with higher mortality [8,13,30]. In our study, we found left ventricle systolic dysfunction in 11% and coronary dilatation in only 2 patients (2%), but without statistical correlation with in-hospital mortality.

This study had some limitations. We had a significant amount of missing data for certain laboratory markers, specifically CPK and LDH. However, these data were missing at random, given the rapidly evolving institutional protocols for patients admitted with COVID-19 during this period. Furthermore, our patients were enrolled upon admission; therefore, the disease state may be different, and in some cases, clinical data were missing, restricting our analysis regarding MIS-C. Also, subsequent cardiac evaluation with treadmill exercise tests and cardiac magnetic resonance imaging were not included in the in-hospital evaluation protocol and could have improved our analysis. Finally, our results should be substantiated in a larger patient cohort to increase predictive power.

Conclusions

In conclusion, our findings indicate that pre-existing comorbidities are independent predictors for in-hospital death, and high levels of inflammatory markers are associated with higher mortality, although they did not emerge as significant predictors of mortality when adjusted for other variables. Our findings may help healthcare providers better understand the cardiac implications of COVID-19 and define the necessity of cardiac surveillance among hospitalized pediatric patients. Finally, more studies are required to determine mortality predictors in the pediatric population.

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