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Comparison of Adverse Clinical Outcomes in Children Hospitalized for Myocarditis with and without COVID-19

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Abstract

We used a nationally representative database of the United States, which included 1995 myocarditis cases, among whom 620 children had COVID-19. While the risk of in-hospital mortality was not higher, illness severity and length of hospital stay were higher in patients with myocarditis and COVID-19 than those without COVID-19.

Introduction

Myocarditis often results from a common cardiotropic viral infection that can be followed by active inflammatory destruction of the myocardium, leading to myocardial cell dysfunction and ventricular failure.[1–3] Patients can present with acute heart failure, ventricular arrhythmias, and cardiogenic shock leading to severe morbidity and mortality.

The COVID-19 pandemic has caused thousands of children to be hospitalized with complications, and recent studies have shown an association of COVID-19 with myocarditis.[4–6] SARS-CoV-2, the virus that causes COVID-19, occasionally targets the myocardium and causes myocarditis in children and adults.[3] A recent study reporting inpatient hospital data on adolescents and adults showed that patients with COVID-19 infection had on average 15.7 times the risk for myocarditis compared to those who were not diagnosed with COVID-19.[7] The risk of myocarditis from COVID-19 was highest for those <16 years and >75 years.[7] Studies comparing the outcomes of children with myocarditis and COVID-19 infection vs. myocarditis from other viral causes are lacking. Moreover, before vaccines became available, SARS-CoV-2 virus was associated with higher morbidity and mortality in 2020. We hypothesized that SARS-CoV-2 myocarditis would have worse clinical outcomes when compared to myocarditis from other causes. In this study, we sought to describe the outcomes

of children admitted for myocarditis with COVID-19 infection vs. myocarditis without COVID-19 using a nationally representative database in the United States (U.S.).

Methods

We used nationally representative National Inpatient Sample (NIS) data for the calendar year 2020 (from January 1, 2020, to December 31, 2020). Our sample included patients aged ≤20 years who were hospitalized for the primary and secondary admission diagnoses of myocarditis and COVID-19. The NIS is the largest publicly available all-payer inpatient healthcare database in the U.S. and contains anonymized data on primary and secondary discharge diagnoses and procedures. The NIS dataset is a multi-state dataset, estimated to represent more than 98% of hospitalizations in the U.S.

The primary aim was to compare in-hospital outcomes (mortality, cardiovascular, and non-cardiovascular complications) in individuals with myocarditis and COVID-19 infection vs. myocarditis and no COVID-19 infection.

Using the NIS complex survey design and accounting for clusters, strata, and weighting, we performed descriptive and inferential statistics. Regression models were created to calculate the risk of COVID-19 myocarditis versus non-COVID-19 myocarditis in children. We performed univariable analyses followed by a multivariable analysis incorporating additional variables (age, sex, race/ethnicity, asthma/chronic lung disease, congenital heart disease, obesity, and diabetes) to determine the effects of covariates and confounding variables on the outcomes of interest.

We also calculated the predicted model-adjusted mortality risks in the two groups, followed by differences in the probability of mortality between the two groups (myocarditis in COVID-19 vs. myocarditis without COVID-19), while controlling for the distribution of other covariates in the groups.

All statistical analyses were performed using Stata statistical software (version 15.1), R version 3.6.0[8], and R Studio 1.2.[9]

Results

Of the 5,138,171 hospitalized children in the calendar year 2020, we retrieved 1,995 who were admitted with a diagnosis of myocarditis (Table 1). Of these, 620 (31%) had concomitant COVID-19. A total of 105 children (5.3%) had CHD. Children with myocarditis and COVID-19 were younger than those with myocarditis and no COVID-19 [12 years (IQR:7-16) vs. 16 (IQR:9-18), P<0.001]. The sex distribution was similar between the two groups. The duration of hospitalization was longer in children with myocarditis and COVID-19 than in those with myocarditis in the absence of COVID-19 [7 days (IQR:4-9) vs. 4 (IQR:2-9), P<0.001]. We also identified 225 (11.3%) children with obesity and 45 (2.3%) with diabetes. The distribution of children with obesity and diabetes was similar between the group with myocarditis related to COVID-19 vs without COVID-19.

The prevalence of myocarditis in children admitted with COVID-19 was approximately 19 per 1,000 admitted children with COVID-19 (620 out of 33,220). The overall prevalence of myocarditis was higher in older children but lower in females.

In-hospital all-cause mortality associated with myocarditis in children with COVID-19 was <1% (n<11) vs. 4.4% (n=60) in children without COVID-19. In the multivariable regression model, the

risk of mortality was not significantly different between the COVID-19 and the non-COVID-19 groups, adjusted OR (aOR), 0.20 (95% CI: 0.02-1.4, P=0.10) (Table 2). The risk difference (differences in the probability of mortality) between myocarditis with COVID-19 and myocarditis without COVID-19 was 3.9%, P=0.056.

There were no significant differences in serious cardiovascular complications between myocarditis hospitalization with and without COVID-19: aOR for tachyarrhythmias was 0.6 (95% CI: 0.3-1.2, P=0.16); aOR for heart block was 0.8 (95% CI: 0.3-2.7, P=0.76); aOR for sudden cardiac arrest was 0.4 (95% CI: 0.1-1.6, P=0.21); aOR for the need for extracorporeal membrane oxygenation was 0.5 (95%CI: 0.1-2.0, P=0.31). For serious non-cardiovascular complications, the risk of acute respiratory failure and the need for noninvasive and invasive ventilation were similar between the groups (Table 2). In contrast, acute kidney injury was higher in the COVID-19 group than in the non-COVID-19 group, with an aOR of 1.9 (95% CI:1.1-3.3, P=0.020).

The risk of myocarditis was higher in black children with COVID-19 (3.1%, n=215) than in white children (1.3%, n=125). This difference was found to be significant in a multiple regression model, with an aOR of 2.4 (95% CI: 1.5-4.0, P=0.001). However, there were no significant differences in mortality and other adverse clinical outcomes that we studied between myocarditis with and without COVID-19 among racial/ethnic groups.

In a chi-square test, we found that mortality was higher in children with CHD and myocarditis, 15/105(14.2%) vs those without CHD, 50/1890(2.6%), P=0.004. However, after adjusting for our covariables in a multiple regression model, we did not find that the presence of CHD increased the risk of mortality in children with COVID-19 -related myocarditis [aOR:5.1(95% CI: 0.8-34), P=0.095].

Discussion

We report 620 children with myocarditis and concomitant COVID-19. Myocarditis with and without COVID-19 infection is uncommon in children; however, the risk of myocarditis in children with concomitant COVID-19 infection was approximately 19 per 1000 children admitted with COVID-19. While the risk of death was not higher with COVID-19, illness severity and length of hospital stay were higher in this group. When comparing in-hospital serious cardiovascular and non-cardiovascular outcomes, acute kidney injury was higher in children with myocarditis and COVID-19. Whether long-term sequelae will follow this pattern and whether vaccination will change the natural history of SARS-CoV-2 myocarditis in children is currently unknown and should be the subject of future studies.

This study's main limitation is the reliance on ICD-10 codes to identify cases of myocarditis, which does not allow for differentiation of the severity of the condition based on clinical or biomedical measures. The heightened awareness of the association between COVID-19 and myocarditis in young individuals may have influenced clinicians to have a lower threshold for diagnosing myocarditis in these patients.

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Table 1. Differences in characteristics and in-hospital complications in pediatric patients hospitalized with myocarditis(N=1995) with or without COVID-19 in calendar year 2020.

Variables	Non-COVID-19 myocarditis	COVID-19 myocarditis	P-value
Total cases	1375	620	
Age, years(median)	16 (IQR 9-18)	12 (IQR 7-16)	<0.001
Length of stay(median)	4 (IQR 2-9)	7 (IQR 4-9)	<0.001
Female	415 (30.2%)	195 (31.5%)	0.81
Neighborhood Zip Codes according to family income			
0-24th	425 (31.6%)	175 (28.7%)	0.41
25-49th	325 (24.2%)	185 (30.3%)	
50-74th	290 (21.6%)	145 (23.8%)	
75th-100th	305 (22.7%)	105 (17.2%)	
Race			
White	525 (41.5%)	125 (22.3%)	0.001
Black	270 (21.3%)	215 (38.4%)	
Hispanic	320 (25.3%)	170 (30.4%)	
Other	150 (11.9%)	50 (8.9%)	
Prematurity <37 weeks	20 (1.5%)	†	>0.1
CHD	85 (6.2%)	20 (3.2%)	>0.1
Obesity	140 (10.2%)	85 (13.7%)	0.29
Diabetes	25 (1.8%)	20 (3.2%)	0.38
Respiratory anomalies	†	†	>0.1
Musculoskeletal anomalies	25 (1.8%)	†	>0.1
Chromosomal	20 (1.5%)	†	>0.1

anomalies			
Asthma/reactive airway disease	170 (12.4%)	90 (14.5%)	0.58
Acute respiratory failure	320 (23.3%)	205 (33.1%)	0.045
Acute kidney injury	270 (19.6%)	210 (33.9%)	**0.001**
Invasive MV	225 (16.4%)	105 (16.9%)	0.87
Non-invasive MV	75 (5.5%)	50 (8.1%)	0.36
Tachyarrhythmias	280 (20.4%)	90 (14.5%)	0.15
Heart block	105 (7.6%)	35 (5.6%)	0.44
Sudden cardiac arrest	55 (4.0%)	†	>0.1
MIS-C[§]	†	310 (50%)	<0.001
ECMO[§]	45(3.3%)	15 (2.4%)	0.63
In-hospital mortality	60 (4.4%)	†	>0.05
Hospital charges (US$)	65,058 (IQR 28,825-158,017)	127,878 (IQR 76,948-217,237)	<0.001

*Mechanical ventilation(MV)

[§]ECMO: Extracorporeal membrane oxygenation; MIS-C: Multisystem inflammatory syndrome in children

†Numbers <11 are not reportable as per Healthcare Cost and Utilization Project (HCUP) guidelines

Table 2. A multivariable logistic regression model to assess the risks of complications among children with myocarditis and COVID-19 compared to those with myocarditis without COVID-19.

Complications	**Unadjusted Odds ratio with 95% CI**	**P-value**	**Adjusted Odds ratio with 95% confidence interval**	**P-value**
Acute respiratory failure	1.6 (1.1-2.6)	0.038	1.3 (0.8-2.3)	0.29
Acute kidney injury	2.1 (1.3-3.4)	0.003	1.9 (1.1-3.3)	**0.020**
Invasive MV (IMV)	1.1 (0.6-1.8)	0.88	0.9 (0.5-1.7)	0.71
Non-invasive MV (NIMV)	1.5 (0.67-3.5)	0.31	1.2 (0.5-3.1)	0.68
Tachyarrhythmias	0.6 (0.4-1.2)	0.17	0.6 (0.3-1.2)	0.16
Heart block	0.7 (0.3-1.8)	0.48	0.8 (0.3-2.7)	0.76
Sudden cardiac arrest	0.4 (0.1-1.8)	0.23	0.4 (0.1-1.6)	0.21
ECMO	0.7 (0.2-2.8)	0.65	0.5 (0.1-2.0)	0.31
In-hospital mortality	0.18 (0.02-1.4)	0.10	0.2 (0.03-1.4)	0.10
Data presented as adjusted odds ratio (95% confidence interval) after being adjusted for age, sex, race/ethnicity, asthma/reactive airway disease, congenital heart disease, obesity and diabetes.				