Cardiology in the Young

cambridge.org/cty

Cardiac injury in children with COVID-19

Joshua M. Herber[1], Samina S. Bhumbra[2], Michael W. Johansen[1], James E. Slaven[3] and Ryan M. Serrano[1]

[1]Pediatric Cardiology Department, Riley Hospital for Children, Indianapolis, IN, USA; [2]Ryan White Center for Pediatric Infectious Diseases and Global Health, Riley Hospital for Children, Indianapolis, IN, USA and [3]Department of Biostatistics and Health Data Science, Indiana University School of Medicine, Indianapolis, IN, USA

Original Article

Cite this article: Herber JM, Bhumbra SS, Johansen MW, Slaven JE, and Serrano RM (2024) Cardiac injury in children with COVID-19. *Cardiology in the Young* **34**: 62–66. doi: 10.1017/S1047951123000768

Received: 31 October 2022
Revised: 18 March 2023
Accepted: 22 March 2023
First published online: 16 May 2023

Keywords:
COVID-19; SARS-CoV-2; multisystem inflammatory syndrome in children; paediatrics; cardiology; cardiac biomarkers

Address for correspondence:
Dr. J. M. Herber, MD, 705 Riley Hospital Dr. RI 1134, Indianapolis, IN, USA. 46202. 260-415-6869. E-mail: jherber@iu.edu

Abstract

Background: There is little known about the spectrum of cardiac injury in acute COVID-19 infection in children. *Methods:* A single-centre, retrospective chart analysis was performed. The protocol was deemed IRB exempt. All patients under the age of 21 years admitted from 20 March, 2020 to 22 June, 2021 for acute symptomatic COVID-19 infection or clinical suspicion of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 were included. Past medical history, lab findings, echocardiogram and electrocardiogram/telemetry findings, and clinical outcomes were reviewed. *Results:* Sixty-six patients with MIS-C and 178 with acute COVID-19 were reviewed. Patients with MIS-C had more cardiac testing than those with acute COVID-19. Inflammatory markers were more likely elevated, and function was more likely abnormal on echocardiogram in those with MIS-C with testing performed. Among patients with MIS-C, 17% had evidence of coronary dilation versus 0% in the acute COVID-19 group. One (0.6%) patient with acute COVID-19 had clinically significant electrocardiogram or telemetry findings, and this was in the setting of prior arrhythmias and CHD. Four (6%) patients with MIS-C had clinically significant findings on electrocardiogram or telemetry. Among patients with acute COVID-19, extracorporeal membrane oxygenation support was required in 0.6% of patients with acute COVID-19, and there was a 2.8% mortality. There were no deaths in the setting of MIS-C. *Conclusions:* Patients with acute COVID-19 and clinical suspicion of cardiac injury had a lower incidence of abnormal laboratory findings, ventricular dysfunction, or significant arrhythmia than those with MIS-C.

COVID-19 was initially described in early 2020, and associations with cardiogenic shock or Kawasaki-like presentations in children were described in New York in March 2020.[1] By May 2020, the Centers for Disease Control and Prevention (CDC) published a case definition for the multisystem inflammatory syndrome in children (MIS-C).[2] In the setting of MIS-C, adverse cardiovascular events commonly include ventricular dysfunction, arrhythmia, and coronary artery aneurysms.[3,4,5] These findings, along with several other extracardiac signs/symptoms associated with MIS-C, have striking similarities to Kawasaki disease leading to treatment recommendations including intravenous immunoglobulin, corticosteroids, and biologics along with recommendations for cardiac observation and follow-up.[6] However, data on the cardiovascular effects of acute COVID-19 in hospitalised children are limited compared to what is known about MIS-C or what occurs in adults. Myocardial injury is present in a high proportion of hospitalised adults with COVID-19 infection, but outside of case reports/series, little is known about the frequency, characteristics, and type of cardiac injury seen in children.[7] Additionally, effects of cardiovascular involvement on length of stay, ICU admissions, utilisation of inotropic and/or extracorporeal membrane oxygenation (ECMO) support, and death rates have not been well delineated in acute COVID-19.

Materials and methods

A retrospective chart analysis was performed on all patients admitted to a single centre with acute COVID-19 or who the met the CDC definition of MIS-C from 20 March, 2020 to 22 June, 2021. The study was reviewed by the institutional review board at Indiana University and deemed exempt. Acute COVID-19 was defined as any patient who tested positive for COVID-19 (positive SARS-CoV-2 polymerase chain reaction or positive antibody test during hospitalisation) and presented with COVID-19-associated symptoms such as respiratory distress, gastrointestinal concerns, and fevers. Patients incidentally found to be SARS-CoV-2-positive and not admitted for concern of acute COVID-19 or MIS-C were excluded. The diagnosis of MIS-C was made as per the published CDC criteria.[2]

Cardiac involvement was based on elevation of troponin or B-type natriuretic peptide (BNP)/N-terminal pro hormone BNP (NT-proBNP), cardiac arrhythmia identified on telemetry or electrocardiogram, ventricular dysfunction, significant pericardial effusion,

atrioventricular valve regurgitation, pulmonary hypertension, or coronary artery disease. Elevated cardiac inflammatory markers were defined as a troponin level > 0.03 ng/ml for troponin I testing, >12 ng/L for women, and > 20 ng/L for men based on 99th percentiles for each for high-sensitivity troponin, BNP > 100 pg/ml, or NT-proBNP > 125 pg/ml. When multiple inflammatory markers were drawn, the peak value was used. Clinically significant electrocardiogram or telemetry findings were defined as any arrhythmia that affected haemodynamic status or required additional therapies to return to baseline rhythm. Normal left ventricular systolic function was defined by an ejection fraction > 55%. Mildly, moderately and severely diminished function were defined as an ejection fraction of 44–55%, 35–44%, and < 35% respectively. Coronary dilation was defined as a maximum z-score of at least 2 for a given coronary artery. Small aneurysms were defined by z-scores of greater than or equal to 2.5 to less than 5. Medium aneurysms were defined by z-scores greater than or equal to 5, but less than 10 with absolute dimension less than 8 mm. Large aneurysms were defined by z-scores greater than or equal to 10 or with an absolute dimension greater than 8 mm. These definitions were based on the 2017 Kawasaki guidelines.[8] Signs of pericarditis on echo were defined as an effusion that was reported as more than trivial. For those patients with multiple echocardiograms, the study with the most severe dysfunction, maximal coronary dilation, and/or presence of pericarditis or pericardial effusion was used when evaluating these outcomes. Outcomes data including days in the ICU, level of respiratory support, days on ECMO, and mortality was also collected.

Statistical analysis

The clinical features, frequency of elevated cardiac inflammatory markers, arrhythmia data, significant echocardiographic findings, and outcomes data were compared between patients with MIS-C and COVID-19. Categorical variables were compared with Fisher's exact tests, due to small sample sizes, and continuous variables were analysed using Wilcoxon rank-sum tests, due to data being non-normally distributed. Significance was defined as $p < 0.05$. All analytic assumptions were verified, and all analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

Results

Data were collected on 276 patients hospitalised with acute COVID-19 infection or with concerns for MIS-C. Age upon admission ranged from 11 days to 22 years. Of these, 32 patients were excluded as they were asymptomatic or otherwise admitted for reasons not associated with acute COVID-19 or MIS-C. Of the 244 patients included in the study, 66 (27%) had MIS-C and 178 had acute COVID-19 (64%). Additionally, 54% were male and 46% were female.

MIS-C

Among patients with MIS-C, troponin was collected in 100% and BNP/NT-proBNP was collected in 50%. Troponin was elevated in 43/66 (65%) patients with MIS-C, and 30/43 (70%) patients with MIS-C and elevated troponin required ICU admission. Troponin was elevated in 28/35 (80%) patients with MIS-C requiring inotropic support. Only 30/43 (70%) patients with MIS-C and elevated troponin levels were admitted to the ICU. All patients requiring inotropic support were admitted to the ICU. Seven (11%) patients with MIS-C required inotropic support in the setting of normal troponin levels with a total of 35 (53%) of patients requiring inotropes. BNP/NT-proBNP was elevated in 30/33 (91%) of those patients with MIS-C who were tested (Table 1).

Table 1. Cardiac injury markers in patients with MIS-C versus acute COVID-19

	MIS-C	Acute COVID-19	p-value
Elevated troponin	43/66 (65%)	8/46 (17%)	< .0001
Elevated BNP/NT-proBNP	30/33 (91%)	14/25 (56%)	.0042
Inotropic support	35/66 (53%)	15/178 (8.4%)	< .0001
Diminished function	34/66 (52%)	11/60 (18%)	.0002
Inotropic support + Diminished function*	5/36 (13.9%)	26/178 (14.6%)	.5597

*Based on patients who had an echo performed. p-Values are from Fisher's exact tests.

Electrocardiograms were performed in 62/66 (94%) patients with MIS-C. Forty-nine (79%) were abnormal. However, only four of the abnormalities were clinically significant. The majority of the findings were non-specific T wave abnormalities, sinus tachycardia, and sinus bradycardia. One patient had ectopic atrial tachycardia, one patient had evidence of pericarditis with diffuse ST segment elevation, one patient had ST depression in the inferior and anterolateral leads, and one patient with worsening heart failure had prolonged pauses and asystolic episodes on telemetry.

Echocardiograms were completed in all patients with MIS-C (Table 1). Thirty-four (52%) of these patients had diminished LV function (Tables 1 and Fig 1). Of those with diminished LV function, 27 (79%) had an abnormal troponin, 16 out of 19 (88%) tested had an abnormal BNP or NT-proBNP, 27 (79%) were in the ICU, and 9 (26%) had CHD or another comorbid chronic medical condition. Eleven (17%) patients with MIS-C had coronary dilation with some patients exhibiting dilation/aneurysms of multiple coronary arteries. No patients had large aneurysms during the study period.

Of those patients admitted to the ICU, 30/39 (77%) had elevated troponin levels, 19/21 (90%) tested had elevated BNP/NT-proBNP, 27/39 (69%) had diminished function, and 25/39 (64%) had diminished function and required inotropic support. One (1.5%) patient with MIS-C required ECMO support. There were no deaths associated with MIS-C during the study period.

Acute COVID-19

Troponin was collected in 46/178 (26%) of patients with acute COVID-19 and was elevated in 8 (17%) of those patients tested (Table 1). Troponin was collected in 24/42 (57%) of patients with acute COVID-19 admitted to the ICU and was elevated in 7/24 (29%) of these patients. For patients with acute COVID-19 that required inotropic support, troponin was collected in 9/15 (60%) and was elevated in 6/9 (67%). Three patients with acute COVID-19 requiring inotropes had normal troponin and troponin was not collected in six patients requiring inotropes. A total of 15 (8.4%) of patients with acute COVID-19 required inotropic support. Troponin was collected in 3/5 (60%) patients with acute COVID-19 who died and was elevated in all three of these patients. BNP/NT-proBNP was collected in 25/178 (14%) of those with acute COVID-19 and elevated in 14 (56%) of those tested (Table 1). BNP/NT-proBNP was collected in 2/5 (40%) of acute COVID-19 patients who died and was elevated in both.

Electrocardiograms were completed in 78/178 (44%) patients with acute COVID-19. Of these, there were 53 (68%)

https://doi.org/10.1017/S1047951123000768 Published online by Cambridge University Press

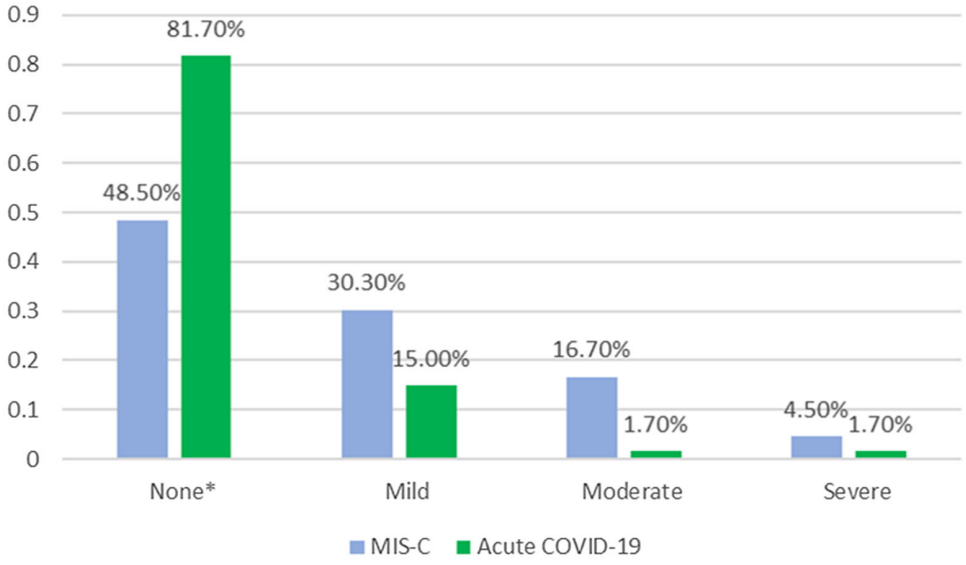

Figure 1. Percentage of patients with LV systolic dysfunction.

electrocardiogram abnormalities, but only one was clinically significant. One of these patients had atrial flutter with known prior history of atrial flutter and CHD.

Echocardiograms were performed in 60/178 (34%) patients with acute COVID-19. Among those, 11/60 (18%) patients had diminished LV systolic function (Table 1 and Fig 1). Of the 11 patients with abnormal function in the setting of acute COVID-19, 2 (18%) had an abnormal troponin, 1 (9%) had an abnormal BNP or NT-proBNP, 8 (73%) were in the ICU, and 10 (91%) had CHD or another comorbid chronic medical condition. There was no evidence of coronary dilation in patients with acute COVID-19.

Of those patients with acute COVID-19 requiring admission to the ICU, 7/24 (29%) tested had elevated troponin levels, 11/16 (69%) tested had elevated BNP/NT-proBNP, 8/23 (35%) with echocardiograms performed had diminished function, and 6/23 (26%) with echocardiograms performed had diminished function and required inotropes. One (0.6%) patient with acute COVID-19 required ECMO support and five (2.8%) patients in this group died. Three out of five (60%) deaths were in the setting of CHD. One of these patients had single-ventricle physiology status post extra-cardiac Fontan, history of protein S deficiency and a middle cerebral artery stroke. Another had a chromosome nine partial duplication and partial deletion on 9p, double-outlet right ventricle, an atrioventricular canal defect with a cleft mitral valve and no primum atrial septal defect, and an inlet ventricular septal defect who was status post-pulmonary arterial band and patent ductus arteriosus ligation followed by pulmonary artery debanding. The third patient who died with CHD had trisomy 21, pulmonary hypertension, atrioventricular canal defect status post complete biventricular repair, post-surgical heart block status post-pacemaker, hypothyroidism, type 2 diabetes, and obstructive sleep apnoea. Of those who died without history of CHD, one patient had aplastic anaemia with multiple infections and one patient was a 3-year-old with no known significant past medical history.

Comparison of MIS-C and acute COVID-19

In patients with testing completed, inflammatory markers were more likely to be elevated among those with MIS-C (Table 1). In both groups, the most common electrocardiogram abnormalities were non-specific T wave abnormalities (acute COVID-19 25/78 (32%), MIS-C 13/62 (21%); $p = 0.3208$) and sinus tachycardia (acute COVID-19 18/78 (23%), MIS-C 41/62 (66%); $p < 0.0001$. %). Diminished function was more commonly present in patients with MIS-C (Fig 1). In those patients with diminished function, associated comorbidities were more commonly present in those patients with acute COVID-19 compared to those with MIS-C (91% versus 26%, $p = 0.002$). Inotropic support was required in 50 patients and was more frequently required in patients with MIS-C compared to acute COVID-19 (Table 1). However, only 31 of these patients had evidence of diminished function on echocardiogram (5/36 (13.9%) MISC, 26/178 (14.6%) acute COVID-19; $p = 0.9111$). No patient in either group had evidence of significant pericardial effusions. Ninety-six patients required respiratory support (MISC 33/66 (50%), acute COVID-19 n = 63/178 (35%); $p = 0.0404$). Data on the cardiac injury markers in these patients are outlined in Table 2. The total length of stay was similar in both groups (MIS-C: median – 5, range 1–32; acute COVID-19: median – 2, range 1–48) but, when ICU admission was required, the length of ICU stay was longer in patients with acute COVID-19 (median – 4.5 days, range 1–42) compared to those patients with MIS-C (median – 2 days, range 1–30).

CHD

Eleven patients in this study had CHD. One of these patients had MIS-C, and the remainder had acute COVID-19. Six of these patients (55%) required an ICU stay and five (45%) required inotropic support. Eight (73%) required additional respiratory support. Three patients with CHD (27%) had died.

Discussion

Our study identified that an elevation of cardiac biomarkers, abnormal electrocardiograms, diminished function, and coronary dilation were more commonly seen in the group with MIS-C

https://doi.org/10.1017/S1047951123000768 Published online by Cambridge University Press

Table 2. Cardiac injury markers in patients requiring respiratory support

	MIS-C	Acute COVID-19	p-Value
# requiring respiratory support	33/66 (50%)	63/178 (35%)	.0404
Troponin collected	33/33 (100%)	26/63 (41%)	< .0001
Elevated troponin	27/33 (82%)	8/26 (31%)	< .0001
BNP/NT-proBNP collected	17/33 (52%)	16/63 (25%)	.0135
Elevated BNP/NT-proBNP	17/17 (100%)	11/16 (69%)	.0184
Inotropic support	27/33 (82%)	15/63 (24%)	< .0001
Echo performed	33/33 (100%)	33/63 (52%)	< .0001
Diminished function	22/33 (63%)	9/33 (27%)	.0028
Inotropic support + diminished function*	20/33 (61%)	6/33 (18%)	.0009

*Based on patients who had an echo performed. p-Values are from Fisher's exact tests.

compared to those with acute COVID-19 reaching statistical significance ($p < 0.05$).

Prior studies comparing children with MIS-C to those with acute COVID-19 did not evaluate the presence of elevated cardiac biomarkers.[9] Our study showed that testing was more common in patients with MIS-C and, of those patients tested, there was a statistically significant difference with more patients having troponin and BNP elevations in the MIS-C group compared to those with acute COVID-19. Rodriguez-Gonzalez et al. found that 73.6% and 86.8% of patients with MIS-C had elevated troponin levels and natriuretic peptide levels (N-terminal (NT)-proBNP or proBNP), respectively.[4] Our findings were similar, with the exception that 100% of our patients with MIS-C had elevated natriuretic peptide levels, when tested. However, only 52% of our patients were tested which may be a lower percentage than those tested at other centres. This selectivity may have increased the percentage of patients with elevated natriuretic peptide levels.

Diminished function was seen in both groups, but at a higher frequency in the MIS-C population compared to the acute COVID-19 population (52% versus 18%, $p = 0.0002$). A study by Feldstein et al found that 34.2% of patients had depressed left ventricular ejection fraction (LVEF) on echocardiograms performed on 503 patients with MIS-C. This study also showed a lower percentage of patients with acute COVID-19 and depressed LVEF (6/111 (5.4%).[9] While inotropic support was also utilised more frequently in the MIS-C group, this was often not related to diminished cardiac function, but likely due to non-cardiac causes such as septic shock. Patients with MIS-C requiring inotropic support were more likely to also have diminished function when compared to patients with acute COVID-19 who required inotropic support.

While coronary dilation and aneurysms were present in the MIS-C group and these findings have been well described, no coronary dilation was seen in the acute COVID-19 group.[3,5,6,10] Similar coronary findings were seen in the study by Feldstein et al with 1/111 (0.9%) patients with acute COVID-19 having coronary aneurysms versus 57/424 (13.4%) with MIS-C.[9]

Respiratory support was more frequently required in those patients with MIS-C. The majority of patients with MIS-C requiring respiratory support had elevated cardiac biomarkers, required inotropic support, and had diminished function on echo. These signs of cardiac injury were less frequent in patients with acute COVID-19 who required respiratory support (Table 2).

Clinically significant electrocardiogram/telemetry findings were more common in patients with MIS-C. The one patient with acute COVID-19 was in atrial flutter and had a prior history of atrial flutter and CHD. None of the patients with MIS-C and clinically significant arrhythmias had a prior history of arrhythmia or CHD. In a study by Rodriguez-Gonzalez et al, 27% of patients with MIS-C had electrocardiogram alterations. This differed from our study which found that 79% of patients with MIS-C had electrocardiogram abnormalities, but only four of which were clinically significant.

While the sample size of patients with CHD is small in this study, it does suggest that patients with CHD and acute COVID-19 are at increased risk for use of inotropic support, ICU admission, need for additional respiratory support, and mortality.

Cardiovascular involvement in patients with acute COVID-19 was highest among those patients with associated comorbidities and those who were most critically ill with longer ICU stays, more respiratory support required and higher mortality.

Limitations to this study include its relatively small sample size. Additionally, the completion of testing in patients with acute COVID-19 was dependent on the provider's clinical suspicion of cardiac disease, and it is possible that some cardiac injury was missed in those patients who were not tested. Future studies should be performed to assess the length of time required for cardiac function recovery in MIS-C and acute COVID-19 patients and how this timing is affected by medical management.

Acknowledgements. None

Financial Support. The authors would like to thank the Susan P. Murphy fund of the Riley Children's Foundation for their financial support.

Conflicts of Interest. None.

References

1. 2020 health alert #13: pediatric multi-system inflammatory syndrome potentially associated with COVID-19 (n.d.), https://picsociety.uk/wp-.
2. Centers for disease control and Prevention. Emergency preparedness and response: HAN00432, 2020. https://emergency.cdc.gov/han/2020/han00432.asp, Accessed December 3, 2020.
3. Valverde I, Singh Y, Sanchez-De-Toledo J, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation 2021; 143: 21–32. DOI 10.1161/CIRCULATIONAHA.120.050065.
4. Rodriguez-Gonzalez M, Castellano-Martinez A, Cascales-Poyatos HM, Perez-Reviriego AA. Cardiovascular impact of COVID-19 with a focus on children: a systematic review. World J Clin Cases 2020; 8: 5250–5283. DOI 10.12998/wjcc.v8.i21.5250.
5. Feldstein LR, Tenforde MW, Friedman KG, et al. characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-c) compared with severe acute COVID-19. JAMA-J Am Med Assoc 2021; 325: 1074–1087. DOI 10.1001/jama.2021.2091.
6. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr 2021; 180: 307–322. DOI 10.1007/s00431-020-03766-6.

https://doi.org/10.1017/S1047951123000768 Published online by Cambridge University Press

7. Metkus TS, Sokoll LJ, Barth AS, et al. Myocardial injury in severe COVID-19 compared with non–COVID-19 acute respiratory distress syndrome. Circulation 2021; 143: 553–565. DOI 10.1161/CIRCULATIONAHA.120.050543.
8. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American heart association. Circulation 2017; 135: e927–e999. DOI 10.1161/CIR.0000000000000484.
9. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA-J Am Med Assoc 2021; 325: 1074–1087. DOI 10.1001/jama.2021.2091.
10. Cantarutti N, Battista V, Adorisio R, et al. Cardiac manifestations in children with sars-cov-2 infection: 1-year pediatric multicenter experience. Children 2021; 8: 717. DOI 10.3390/children8080717.

https://doi.org/10.1017/S1047951123000768 Published online by Cambridge University Press