Cardiology in the Young

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Elevated cardiac biomarkers and outcomes in children and adolescents with acute COVID-19

Michael A. Fremed[1,2], Emma W. Healy[1], Nak Hyun Choi[1,2], Eva W. Cheung[1,2,3], Tarif A. Choudhury[1,2,3], Pengfei Jiang[1], Leonardo Liberman[1,2], Jason Zucker[2,4], Irene D. Lytrivi[1,2] and Thomas J. Starc[1,2]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA; [2]NewYork-Presbyterian Morgan Stanley Children's Hospital, New York, NY, USA; [3]Division of Pediatric Critical Care & Hospital Medicine, Department of Pediatrics, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA and [4]Division of Infectious Diseases, Department of Medicine, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

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Author for correspondence:
M. Fremed, Division of Pediatric Cardiology, NewYork-Presbyterian Morgan Stanley Children's Hospital, North Building, 2nd Floor, New York, NY 10032, USA. Tel: 212-305-6543; Fax: 212-342-5704.
E-mail: mf3032@cumc.columbia.edu

Irene D. Lytrivi and Thomas J. Starc contributed equally as senior authors.

Abstract

Cardiac involvement associated with multi-system inflammatory syndrome in children has been extensively reported, but the prevalence of cardiac involvement in children with SARS-CoV-2 infection in the absence of inflammatory syndrome has not been well described. In this retrospective, single centre, cohort study, we describe the cardiac involvement found in this population and report on outcomes of patients with and without elevated cardiac biomarkers. Those with multi-system inflammatory syndrome in children, cardiomyopathy, or complex CHD were excluded. Inclusion criteriaz were met by 80 patients during the initial peak of the pandemic at our institution. High-sensitivity troponin T and/or N-terminal pro-brain type natriuretic peptide were measured in 27/80 (34%) patients and abnormalities were present in 5/27 (19%), all of whom had underlying comorbidities. Advanced respiratory support was required in all patients with elevated cardiac biomarkers. Electrocardiographic abnormalities were identified in 14/38 (37%) studies. Echocardiograms were performed on 7/80 patients, and none demonstrated left ventricular dysfunction. Larger studies to determine the true extent of cardiac involvement in children with COVID-19 would be useful to guide recommendations for standard workup and management.

Cardiac involvement in patients with COVID-19 has been extensively described in the adult literature with evidence suggesting that elevations in cardiac biomarkers such as high-sensitivity troponin T and N-terminal pro-brain type natriuretic peptide are associated with more severe disease including mechanical ventilation and inotropic support.[1–7] Though cardiac findings have been well described in cases of multi-system inflammatory syndrome in children,[8,9] similarly robust data are not available for children with positive COVID-19 tests who do not have multi-system inflammatory syndrome in children. In this study, we describe the cardiac findings in children with acute COVID-19 who received care at a large tertiary care children's hospital in New York City, the initial epicentre in the United States of America, and describe outcomes in this population. Ultimately, we hope to use this information to standardise cardiac workup and monitoring in children with acute presentations of COVID-19 infection and guide early management decisions.

Methods

Study design and population

We performed a retrospective cohort study of patients under age 21 who presented to Morgan Stanley Children's Hospital emergency department or paediatric inpatient units and tested positive for SARS-CoV-2 on real-time polymerase chain reaction testing between 11 March 2020 (first positive paediatric case in our institution) and 17 May 2020. This period includes all patients from the start of the COVID-19 pandemic at our institution through approximately 1 month past our initial institutional peak caseload. Patients with complex CHD, cardiomyopathy, heart transplant, or multi-system inflammatory syndrome in children were excluded. This study was approved by the Columbia University Irving Medical Center Institutional Review Board with waiver of informed consent.

Diagnosis/testing

Samples for SARS-CoV-2 were collected via nasopharyngeal swabs and analysed via real-time polymerase chain reaction. Indeterminate polymerase chain reaction tests were considered positive as per institutional protocol. All diagnostic testing was done for clinical purposes

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and no additional testing was obtained solely for the purposes of this research. Testing availability, including SARS-CoV-2 polymerase chain reaction and cardiac serology, was limited early in the pandemic response, so patients who presented earlier may not have been tested, therefore may have been inadvertently excluded. Multi-system inflammatory syndrome in children was defined as per Centers for Disease Control case definition.[10] Comorbidities were determined based on documentation in the electronic medical record.

Data collection

Patients were identified by a search of the electronic medical record for all cases with positive SARS-CoV-2 polymerase chain reaction during the study period and entered into an electronic database.

Definitions

Elevated cardiac biomarkers were defined as any elevated high-sensitivity troponin T >14 ng/dL in females and >22 ng/dL in males (lab reference range) or any N-terminal pro-brain type natriuretic peptide > 450 pg/mL in children under age 4 or >300 pg/mL in patients 4 years of age and older.[11] Patients who did not have either high-sensitivity troponin T or N-terminal pro-brain type natriuretic peptide measured were not included in the cardiac biomarker analyses. Left ventricular dysfunction was defined as left ventricular ejection fraction <55% on any echocardiogram.[12,13] Baseline lab value was defined as values drawn at time of presentation and peak value was defined as the highest value obtained during admission during the study period. Lab values below the limits of detection (high-sensitivity troponin T <6 and N-terminal pro-brain type natriuretic peptide <5) were recorded as values just below the lower limit of detection. Lab values above the threshold for reporting (C-reactive protein > 300, N-terminal pro-brain type natriuretic peptide >70,000) were reported as values just over the upper reporting limit. For example, high-sensitivity troponin T values <6 were recorded as a value of 5. C-reactive protein > 300 was recorded as 301. Weight categories were determined by weight-for-height percentiles for patients under age 2,[14] BMI percentile for patients aged 2–20[15,16], and BMI for patients aged 20–21, with obesity staging assigned as per established standards.[17] Severe outcome was defined as treatment with advanced respiratory support (non-invasive positive pressure ventilation or invasive mechanical ventilation above baseline), treatment with inotropic or vasoactive agents, or death from any cause.

Electrocardiogram and echocardiogram analysis

Electrocardiograms for all patients were reviewed by a single experienced cardiologist (TJS), who also calculated the corrected QT intervals manually. All baseline ECGs were analysed. Echocardiographic data were extracted from the filed reports.

Statistics

Clinical and demographic variables were reported using standard summary statistics including medians and interquartile ranges for non-parametric data. Due to the small number of patients with elevated cardiac biomarkers, comparative statistics were not reported.

Results

Study population

During the study period, 103 patients had positive SARS-CoV-2 polymerase chain reaction. Of those, 17 were excluded for multi-system inflammatory syndrome in children, 4 were excluded for cardiomyopathy, and 2 for complex CHD including 1 with repaired Taussig–Bing anomaly and 1 with double outlet right ventricle who was in the immediate post-operative period following Fontan surgery. Eighty patients were included in the final analyses, 31/80 (39%) of whom were female, and the median age was 12.5 years (interquartile range 1.9–17.5). The median time from symptom onset to hospital presentation was 2 days (interquartile range 0–5) and from presentation to discharge was 3 days (interquartile range 1–8.5). There were 16/80 (20%) admissions to the paediatric intensive care unit, 41/80 (51%) to the medical ward, and 23/80 (29%) were discharged from the emergency department.

Comorbidities were present in 30/80 (38%) patients and included asthma, diabetes mellitus, chronic renal disease, oncologic disorder, sickle cell disease, and genetic syndromes, among others. One patient had recently undergone orthotopic liver transplant. Two patients had sickle cell disease. Genetic disorders were present in five patients including one with newly diagnosed Brugada syndrome with genetic testing notable for a variant of unknown significance in the SCN5A gene[18] (Table 1).

Severe outcomes

Severe outcomes were experienced by 17/80 (22%) patients overall and included 16/80 (20%) patients treated with advanced respiratory support, 10/80 (13%) treated with non-invasive positive pressure ventilation, 6/80 (8%) treated with invasive mechanical ventilation, 5/80 (6%) supported with inotropic or vasoactive agents, and 4/80 (5%) deaths from any cause. Two of these deaths were attributed to late-stage oncologic disease, one to acute chest syndrome in a patient with sickle cell disease and one to direct complications of COVID-19 after prolonged respiratory failure (Table 1).

Cardiac testing

Cardiac biomarkers

High-sensitivity troponin T was measured in 27/80 (34%) patients. The median baseline high-sensitivity troponin T was 5 (range 5–28) ng/L and was elevated in 3/27 (7%) patients. The median peak high-sensitivity troponin T was 6 (range 5–103) ng/L and was elevated in 3/27 (11%) patients. N-terminal pro-brain type natriuretic peptide was measured in 10/80 (13%) patients. The median baseline N-terminal pro-brain type natriuretic peptide was 92 (range 4–1351) and was elevated in 3/10 (30%) patients. The median peak N-terminal pro-brain type natriuretic peptide was 127 (range 4–1351) and was elevated in 2/10 (20%) patients. Both high-sensitivity troponin T and N-terminal pro-brain type natriuretic peptide were elevated in 3/5 (60%) of patients with elevated cardiac biomarkers. The decision to admit patients to the ICU or medical–surgical ward was made independent of the results of high-sensitivity troponin T and N-terminal pro-brain type natriuretic peptide testing and all patients admitted to the ICU met other criteria for intensive care admission (Table 2).

Electrocardiography

At least one ECG was performed in 38/80 (48%) patients. Abnormal findings on baseline ECG were present in 14/38

Table 1. Patient characteristics and testing

Demographics	Total (N = 80)	ICU (n = 16)	Ward (n = 41)	ED (n = 23)
Female	31 (39)	7 (44)	16 (39)	8 (35)
Age at presentation	12.5 [0.0–20.7]	14.2 [0.0–20.7]	10.7 [0.0–20.7]	12.4 [0.1–19.7]
Obese	18 (23)	5 (31)	10 (24)	3 (13)
Ethnicity				
Declined	6 (8)	0 (0)	6 (15)	0 (0)
Hispanic/Latino/Spanish origin	41 (51)	6 (38)	19 (46)	16 (70)
Not Hispanic/Latino/Spanish origin	33 (41)	10 (63)	16 (39)	7 (30)
Comorbidity	30 (38)	13 (81)	14 (34)	3 (13)
Asthma	10 (13)	3 (19)	5 (12)	2 (9)
Diabetes mellitus	5 (6)	4 (25)	0 (0)	1 (4)
Chronic renal disease	3 (4)	1 (6)	2 (5)	0 (0)
Oncologic disease	10 (13)	4 (25)	6 (15)	0 (0)
Sickle cell disease	2 (3)	2 (13)	0 (0)	0 (0)
Presenting symptoms				
Fever	45 (56)	11 (69)	23 (56)	11 (48)
Respiratory distress/tachypnoea	19 (24)	10 (63)	6 (15)	3 (13)
Chest pain	4 (5)	1 (6)	2 (5)	1 (4)
Time course				
Symptoms to presentation (days)	2 [0–31]	3 [0–9]	1 [0–30]	2 [0–31]
Presentation to discharge (days)	3 [0–60]	12.5 [2–60]	3.5 [0–43]	0 [0–15]
Severe outcome	17 (22)	13 (81)	4 (10)	0 (0)
Advanced respiratory support	16 (20)	13 (81)	3 (7)	0 (0)
Non-invasive positive pressure	10 (13)	7 (44)	3 (7)	0 (0)
Invasive mechanical ventilation	6 (8)	6 (38)	0 (0)	0 (0)
Inotropic/vasoactive support	5 (6)	5 (31)	0 (0)	0 (0)
Death*	4 (5)	3 (19)	1 (2)	0 (0)

Values represent N (%) for categorical variables and median [range] for continuous variables.
*Two deaths occurred after study period: one directly attributed to COVID-19 complications and the other due to complications from oncologic disease.

(37%) patients and included QRS-T angle >60° in 4/38 (11%) patients, QTc >450 ms in 3/38 (8%) patients, T wave flattening or inversion in 14/51 (24%) patients, and ST segment elevations or depressions in 4/38 (18%) patients. There were no patients with documented atrioventricular nodal block.

Echocardiography

At least one echocardiogram was performed during admission for 7/80 (9%) patients, all of which demonstrated normal left ventricular function. Follow-up studies were performed during admission for 2/7 (29%) patients. The median left ventricular ejection fraction on initial echocardiogram was 60% (range 56–65) and on follow-up echocardiogram was 63% (range 60–66). Of the five patients who had echocardiograms performed during admission and survived to discharged, 4/5 had post-discharge echocardiograms performed. Of these, one had a left ventricular ejection fraction of 55% (performed post-chemotherapy) and the rest had left ventricular ejection fractions >55%.

Cardiac biomarkers and outcomes

Elevation in cardiac biomarkers was present in 5/27 (19%) patients for whom high-sensitivity troponin T or N-terminal pro-brain type natriuretic peptide was obtained (Table 3). Underlying comorbidities were present in all five patients with elevated cardiac biomarkers and included diabetes mellitus, Trisomy 21, seizure disorder, Hashimoto's thyroiditis, spastic quadriplegia, obesity, and obstructive sleep apnoea. All required advanced respiratory support and were admitted to the ICU (Table 4). Severe outcome was experienced by 14/27 (52%) patients for whom cardiac biomarkers were obtained including all 5/5 (100%) patients with elevated cardiac biomarkers. When individual components of severe outcome were analysed for the elevated cardiac biomarker group, 5/5 (100%) received advanced respiratory support, 2/5 (40%) received inotropic or vasoactive support, and 1/5 (20%) died following prolonged respiratory failure. All 5/5 (100%) patients with elevated cardiac biomarkers were admitted to the ICU compared to 8/22 (36%) of those with normal biomarker values.

Table 2. Results of cardiac testing by location

Test	Total (N = 80)	ICU (n = 16)	Ward (n = 41)	ED (n = 23)
High-sensitivity troponin T	27 (34)	13 (81)	11 (27)	3 (13)
Elevated	3	3	0	0
Baseline	5 [5–28]	9 [5–28]	5 [5–9]	5 [5–5]
Peak	6 [5–103]	13 [5–103]	5 [5–9]	5 [5–5]
NT-pro-BNP	10 (13)	4 (25)	4 (10)	2 (9)
Elevated	2	2	0	0
Baseline	92 [4–1351]	301 [108–1351]	8[4–38]	163 [76–250]
Peak	127 [4–1351]	469 [169–1351]	8 [4–80]	168 [85–250]
Electrocardiography	38 (48)	11 (69)	13 (32)	14 (61)
PR interval (ms)	132 [86–170]	128 [102–154]	138 [86–164]	145 [104–170]
QRS-T angle >60	4 (11)	2 (18)	2 (15)	0 (0)
Prolonged QTc >450 ms	3 (8))	1 (9)	2 (15)	0 (0)
T wave inversion or flattening	9 (24)	5 (45)	3 (20)	1 (7)
ST elevation or depression	4 (11)	2 (18)	0 (0)	2 (14)
Any abnormality	14 (37)	6 (55)	5 (38)	3 (21)
Echocardiography	7 (9)	4 (25)	3 (7)	0 (0)
LV dysfunction (EF < 55%)	0 (0)	0 (0)	0 (0)	0 (0)
Baseline LVEF (n = 6)	60 [68–65]	58 [58–62]	64 [56–65]	N/A
Follow-up LVEF (n = 3)	63 [60–66]	62 [60–63]	66 [66–66]	N/A

Values represent N (%) for categorical variables and median [range] for continuous variables.

Death occurred in 1/5 (20%) of patients with elevated cardiac biomarkers after a prolonged admission for respiratory failure. Echocardiogram performed on the day of death demonstrated right ventricular hypertension and decreased right ventricular systolic function with preserved left ventricular function.

Among those with elevated cardiac biomarkers who survived to discharge, two returned to baseline clinical status. One patient with acute lymphocytic leukaemia went on to undergo bone marrow transplant 6 months post-discharge, subsequently complicated by graft-vs-host disease. One patient with biliary atresia status post-liver transplant had significant hepatitis during admission and was found on biopsy following discharge to have evidence of liver cirrhosis as well as early stages of post-transplant lymphoproliferative disorder.

Discussion

Previously, we described our approach to the cardiac evaluation of children with COVID-19 based on expert opinion. In this institutional protocol, we recommended obtaining at minimum a baseline high-sensitivity troponin T and N-terminal pro-brain type natriuretic peptide in addition to basic inflammatory markers (as per institutional protocol) for these patients. Should any cardiac concerns arise based on history, exam, or other clinical findings, an ECG should be performed, and cardiology consulted, with performance of echocardiography left to the discretion of the consulting cardiologist.[19] Patients with suspected multi-system inflammatory syndrome in children should undergo more complete cardiac workup based on institutional protocol. This protocol was based on expert opinion and was not uniformly implemented at our institution at the time.

We found that among those for whom cardiac biomarkers were measured, these markers were elevated in 19% of patients. Those with elevated cardiac biomarkers were all admitted to the ICU and all experienced severe outcomes including advanced respiratory support. There was one death in the elevated cardiac biomarker group that occurred well after the study period and was attributed to prolonged respiratory failure secondary to COVID-19. We also found electrocardiographic abnormalities in 37% of the total patient population. No patients demonstrated left ventricular dysfunction on echocardiogram, though relatively few underwent echocardiography during that time. Importantly, all patients with elevated cardiac biomarkers had significant comorbidities. Given the incidence of cardiac involvement in these patients and its association with severe outcome even in the absence of multi-system inflammatory syndrome in children, we continue to advocate for the inclusion of cardiac workup as a standard part of the initial evaluation of children and adolescents presenting to the hospital with positive SARS-CoV-2. More extensive workup should be considered based on clinical circumstance and the results of the initial testing.

Adult studies have shown evidence of cardiac involvement in up to 30% of cases[20] including potentially 20% of asymptomatic to mild cases,[21] as well as an association of cardiac involvement with severe outcomes.[3–5,22,23] Similar studies of children with acute COVID-19 have shown elevated pro-brain type natriuretic peptide but have not focused specifically on cardiac biomarkers.[24,25] The association of cardiac involvement and elevated cardiac biomarkers with multi-system inflammatory syndrome in children

Table 3. Characteristics and outcomes of patients with and without elevated cardiac biomarkers

	All (n = 27)	Elevated cardiac biomarkers (n = 5)	Normal cardiac biomarkers (n = 22)
Demographics			
Female	12 (44)	3 (60)	9 (41)
Age at presentation (years)	12.5 [1.9–17.5]	14.3 [14.3–18.6]	15.0 [9.8–19.10]
Obese	10 (37)	2 (40)	8 (36)
Ethnicity			
Declined	1 (4)	0 (0)	1 (5)
Hispanic/Latino/Spanish origin	15 (56)	2 (40)	13 (59)
Not Hispanic/Latino/Spanish origin	11 (41)	3 (60)	8 (36)
Comorbidity	17 (63)	5 (100)	12 (55)
Asthma	5 (19)	1 (20)	4 (18)
Diabetes mellitus	4 (15)	3 (60)	1 (5)
Chronic renal disease	1 (4)	0 (0)	1 (5)
Oncologic disease	5 (19)	1 (20)	4 (18)
Presenting symptoms			
Fever	17 (63)	3 (60)	14 (64)
Respiratory distress/tachypnoea	14 (42)	4 (80%)	10 (45)
Chest pain	3 (11)	1 (20)	2 (9)
Location			
ICU	13 (48)	5 (100)	8 (36)
Medical ward	11 (41)	0 (0)	11 (50)
Emergency department	3 (11)	0 (0)	3 (14)
Symptoms to presentation (days)	2 [0–5]	3 [0–4]	3 [2–7]
Presentation to discharge (days)	3 [1–8.5]	18.5 [18–24]	7 [2.5–11]
Labs			
C-reactive protein (mg/L)			
Baseline	9.1 [0.2–214.6]	47.6 [5.5–99.3]	8.7 [0.5–209.9]
Peak	24.6 [0.2–246.5]	89.8 [46.3–246.5]	10.5 [0.5–246.5]
Creatinine (mg/dL)			
Baseline	0.5 [0.2–1.2]	0.61 [0.2–1.2]	0.5 [0.2–1.0]
Peak	0.6 [0.2–1.9]	1.02 [0.2–1.5]	0.6 [0.2–1.9]
Lymphocyte %	22 [2.6–93.0]	21 [3–39.8]	22 [4–93]
Severe outcome (composite)	14 (52)	5 (100)	9 (41)
Advanced respiratory support	13 (48)	5 (100)	8 (36)
Non-invasive positive pressure	8 (30)	3 (60)	5 (23)
Invasive mechanical ventilation	5 (19)	2 (40)	3 (14)
Inotropic support	5 (19)	2 (40)	3 (14)
Death	4 (15)	1 (20)	3 (14)

Values represent N (%) for categorical variables and median [range] for continuous variables.

has been more clearly detailed and cardiac involvement may be present in up to 80% of cases.[8] Similar to the adult literature, we found increased rates of respiratory support above baseline and admission to the ICU. Unlike adult findings, however, there was no difference in inotropic support or intubation rates. This is likely due to the relatively low occurrence of these events in children even in severe cases. Death was rare when compared to adult outcomes and we likely had too small of a sample size to determine if those with elevated cardiac biomarkers are at increased mortality risk. Interestingly, unlike previous work[24,25] which showed worse outcomes in obese patients, elevation in cardiac biomarkers was not associated with obesity in our study.

This study had several limitations. Early in the pandemic, testing was limited due to shortages of resources, incomplete

Table 4. Characteristics of patients with elevated cardiac biomarkers

Case	Age (years)	Sex	Comorbidities	Location	Hospital course	Cardiac workup	Follow-up
1	14	F	Spastic quadriplegia, gastrostomy, tracheostomy, diabetes mellitus	ICU	Intubated. Pulmonary haemorrhage. Arrest requiring CPR and epinephrine	Elevated hsTrpT	Return to baseline. No cardiology follow-up
2	19	M	Acute lymphocytic leukaemia	ICU	Intubated with inotropic support. Severe hypertriglyceridaemia. Infected pancreatic pseudocyst	Elevated NT-pro-BNP	Bone marrow transplant 6 months post-discharge. EF 55 % 2 months post-discharge (post-chemotherapy), improved on subsequent echos. Course complicated by graft versus host disease
3	14	M	Lennox–Gastaut syndrome, cerebral palsy, obstructive sleep apnoea, baseline BiPAP, moderate persistent asthma, diabetes mellitus	ICU	Acute hypoxic respiratory failure requiring increased BiPAP settings above baseline	Elevated NT-pro-BNP, T wave abnormality	Return to baseline
4	0.6	F	Biliary atresia status post-orthotopic liver transplant	ICU	Respiratory distress requiring CPAP. COVID-19 hepatitis	Elevated hsTrpT	Liver cirrhosis, post-transplant lymphoproliferative disorder
5	19	F	Trisomy 21, type 2 diabetes mellitus, Hashimoto's thyroiditis, autism spectrum disorder, ADHD, asthma, h/o PDA status post ligation, obesity, obstructive sleep apnoea	ICU	Intubated throughout 2.5-month admission, treated with inhaled nitric oxide and inotropes. Right ventricular hypertension and systolic dysfunction on echocardiogram on day of in-hospital death	Elevated hsTrpT, Elevated NT-pro-BNP	N/A

knowledge on the full extent of disease involvement, and need to limit exposure. For this reason, it is likely that several milder cases were missed. Cardiac testing was also not consistently done early on as the extent of cardiac involvement with this disease was unclear and our institution limited echocardiography to only the most severe cases or those with other signs suggestive of cardiac involvement. Additionally, sicker patients such as those admitted to the ICU may have been more likely to have undergone comprehensive laboratory and imaging workups necessary to determine cardiac status as compared to those admitted to the medical/surgical unit or discharged from the emergency department. It is likely that those patients who were not sick enough to undergo cardiac workup did not have significant cardiac involvement, though larger studies with standardised workup protocols would be necessary to determine if this were true. Our definition of elevated cardiac biomarkers was also reliant on adult reference ranges as no normal values for high-sensitivity troponin T and N-terminal pro-brain type natriuretic peptide have been clearly established for children. Due to our small sample size in elevated cardiac biomarker group, definitive conclusions regarding risk factors for severe outcomes compared to those with normal cardiac biomarkers are difficult to make.

At our institution, cardiac biomarkers were elevated in 19% of children and adolescents with COVID-19 who had these markers measured during the initial peak of the pandemic, though overall rates of testing for cardiac biomarker levels were low. All patients in the elevated cardiac biomarker experienced severe outcomes. Electrocardiographic abnormalities were present in over one-third of cases. Based on these findings, larger studies to determine the true incidence of cardiac involvement in children with COVID-19 in the absence of multi-system inflammatory syndrome in children in the broader population would be useful to guide recommendations for standard workup and management and characterise long-term cardiac sequelae.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Columbia University Irving Medical Center Institutional Review Board. Waiver of informed consent was granted by the Institutional Review Board of Columbia University Irving Medical Center in the setting of the ongoing global COVID-19 pandemic.

References

1. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020; 382: 2372–2374. DOI 10.1056/NEJMc2010419.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–1062. DOI 10.1016/S0140-6736(20)30566-3.

3. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol 2020; 5: 751. DOI 10.1001/jamacardio.2020.1105.
4. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020; 5: 802. DOI 10.1001/jamacardio.2020.0950.
5. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 811–818. DOI 10.1001/jamacardio.2020.1017.
6. Tersalvi G, Vicenzi M, Calabretta D, et al. Elevated troponin in patients with coronavirus disease 2019: possible mechanisms. J Card Fail 2020; 26: 470–475. Retrieved July 7, 2020, from, https://www.onlinejcf.com/article/S1071-9164(20)30357-2/fulltext
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061–1069. DOI 10.1001/jama.2020.1585.
8. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020; 383: 334–346. DOI 10.1056/nejmoa2021680.
9. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to covid-19 in previously healthy children and adolescents in New York City. JAMA, 324: 294–296. DOI 10.1001/jama.2020.10374.
10. CDC. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Retrieved January 4, 2021, from https://www.cdc.gov/mis-c/hcp/
11. Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. Pediatr Cardiol 2012; 33: 1295–1300. DOI 10.1007/s00246-012-0306-8.
12. Lopez L, Colan SD, Frommelt PC, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010; 23: 465–495. DOI 10.1016/j.echo.2010.03.019.
13. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440–1463. DOI 10.1016/j.echo.2005.10.005.
14. WHO.Weight-for-length/height. WHO.Published online 2015.
15. CDC. BMI calculator child and teen | Healthy weight. Retrieved October 20, 2020, from https://www.cdc.gov/healthyweight/bmi/calculator.html
16. CDC. Defining childhood obesity | Overweight & obesity. Retrieved October 20, 2020, from https://www.cdc.gov/obesity/childhood/defining.html
17. CDC. Defining adult overweight and obesity | Overweight & obesity. Retrieved October 20, 2020, from https://www.cdc.gov/obesity/adult/defining.html
18. Hyun Choi N, Silver ES, Fremed M, Liberman L. COVID-19 reveals Brugada pattern in an adolescent patient. Cardiol Young 2020; 30: 1735–1737. DOI 10.1017/S1047951120002619.
19. Fremed MA, Lytrivi ID, Liberman L, et al. Cardiac workup and monitoring in hospitalised children with COVID- 19. Cardiol Young 2020; 30: 907–910. DOI 10.1017/S1047951120001778.
20. Smilowitz NR, Jethani N, Chen J, et al. Myocardial injury in adults hospitalized with COVID-19. Circulation 2020; 142: 2393–2395. DOI 10.1161/CIRCULATIONAHA.120.050434.
21. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 1265–1273. DOI 10.1001/jamacardio.2020.3557.
22. Li X, Pan X, Li Y, et al. Cardiac injury associated with severe disease or ICU admission and death in hospitalized patients with COVID-19: a meta-analysis and systematic review. Crit Care 2020; 24: 468. DOI 10.1186/s13054-020-03183-z.
23. Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID-19 and cardiovascular disease. Circulation 2020; 141: 1648–1655. DOI 10.1161/CIRCULATIONAHA.120.046941.
24. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. J Pediatr 2020; 223: 14–19.e2. DOI 10.1016/j.jpeds.2020.05.006.
25. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr 2020; 174: e202430. DOI 10.1001/jamapediatrics.2020.2430.