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CRITICAL CARE (R PIERCE, SECTION EDITOR)

Short-term Cardiovascular Complications of Multi-system Inflammatory Syndrome in Children (MIS-C) in Adolescents and Children

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Abstract

Purpose of Review We provide the readers with a review of cardiac complications in children with multi-system inflammatory syndrome in children (MIS-C) and its short-term outcomes.

Recent Findings Recent reports described the acute cardiac manifestations of MIS-C in children and provided a glimpse of the short-term outcomes.

Summary Children with MIS-C have been reported to acutely have variable degrees of cardiac findings including abnormal cardiac enzymes, abnormal electrocardiographs, decreased systolic function, coronary artery abnormalities from coronary dilation to giant aneurysms, mitral valve regurgitation, tricuspid valve regurgitation, aortic valve insufficiency, pericardial effusion, diastolic dysfunction, abnormal cardiac strain, and abnormal cardiac MRI. The majority of these abnormalities resolved during short-term follow-up. Further studies are needed to assess if transient or persistent cardiac complications are associated with long-term adverse cardiac events in children with MIS-C.

Keywords Myocarditis · Coronary artery aneurysm · Pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PMIS) · Multi-system inflammatory syndrome in children (MIS-C) · 2019 coronavirus disease (COVID-19) pandemic · Pediatric cardiology

Introduction

On 4/26/2020, a new illness emerged in children exposed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. This illness, categorized by severe inflammatory response, received multiple nomenclature including the multi-system inflammatory syndrome in children (MIS-C) [2•, 3•]. As we passed the first anniversary, we provide the readers with a review of cardiac complications in children with MIS-C and its short-term outcomes.

Early in the 2019 coronavirus disease (COVID-19) pandemic, previously healthy children were thought to have been spared from severe disease [4]. However, we quickly learned how unpredictable this illness can be as MIS-C emerged with reports of mortalities in the pediatric population [5–7, 8•, 9, 10]. Following early experience, centers and societies developed diagnostic and treatment algorithms to properly treat children with MIS-C [11••, 12••]. It is now considered prudent for providers to identify cases of MIS-C early in their illness and provide timely immune modulation therapy. Children with MIS-C have been reported to have variable degrees of cardiac findings including abnormalities of cardiac enzymes, electrocardiogram (EKG), echocardiogram, and cardiac Magnetic Resonance Imaging (MRI) (Fig. 1, Tables 1–2).

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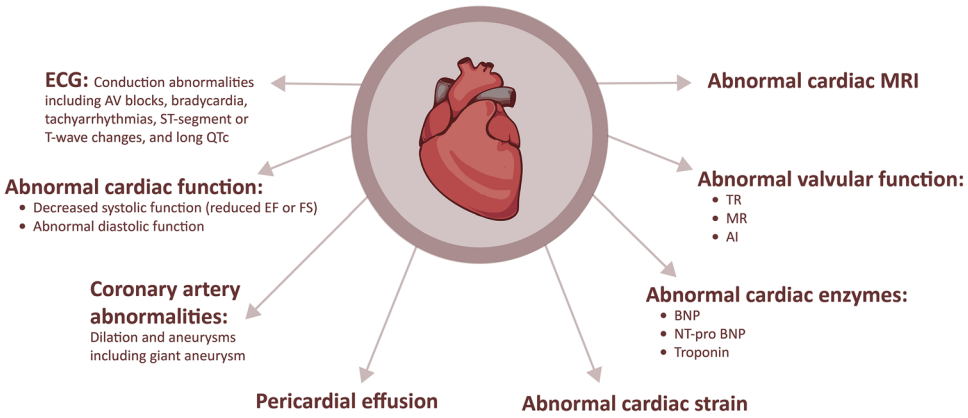

Fig. 1 Distribution of cardiac complications in children with multi-system inflammatory syndrome in children (MIS-C). AI, aortic insufficiency; AV, atrioventricular; BNP, B-type natriuretic peptide; FS, shortening fraction; ECG, electrocardiographic; EF, ejection fraction; MR, mitral regurgitation; NT-pro BNP, N-terminal B-type natriuretic peptide; TR, tricuspid regurgitation

Abnormal Cardiac Enzymes

Cardiac enzymes including B-type natriuretic peptide (BNP) (pg/mL), N-terminal BNP (NT-pro BNP) (pg/mL), and troponins were noted to be elevated in some patients with MIS-C. In patients who developed shock, the median (interquartile (IQR)) troponin (ng/L) was 45 (8–294) and the median NT-pro BNP was 788 (174–10,548) [8•]. Other reports have also described similar elevation in cardiac enzymes [13••, 14–26]. Cardiac enzyme elevation has also been reported in other cardiac diseases. Troponin (ng/L) was noted to be elevated in children with acute myocarditis 80 (10–4930) [27]. NT-pro BNP (pg/mL) was shown to be elevated in children with cardiac disease (median: 548, range: 5–35,000) and helped differentiate them from other etiologies [28]. In some articles discussing MIS-C, the elevated cardiac enzymes were further stratified by clinical presentation. For example, the NT-pro BNP (ng/mL) and troponin were 2,148 ± 259 and 0.4 ± 0.5 in Kawasaki disease (KD), 7443 ± 15,975 and 1.0 ± 2.0 in incomplete KD, and 17,678 ± 39,609 and 1.0 ± 1.7 in shock presentations, respectively [29]. Matsubara et al. noted that median BNP of 596 (310–1,007) and median troponin I (ng/mL) (normal < 0.3) of 0.44 (0.09–1.46) correlated with the global longitudinal strain (GLS), global circumferential strain rate (GCSR), left atrial strain (LAS), and the right ventricular free wall longitudinal strain (RVFWLS) [30•].

Electrocardiographic Findings of MIS-C

MIS-C causes a variety of EKG changes. Conduction abnormalities including atrioventricular (AV) blocks, bradycardia, and tachyarrhythmias including ventricular arrhythmia, ST-segment or T-wave changes, and long QTc are all possible findings in MIS-C [8•, 16, 18, 20, 26, 29, 31] (Table 2). Further studies are needed to assess correlation of ECG changes with clinical outcomes or other cardiac findings.

Conventional Echocardiographic Findings of MIS-C

Multiple echocardiographic findings have been reported in children with MIS-C including decreased systolic function, coronary artery abnormalities, valve regurgitation, and pericardial effusion.

Decreased Systolic Function

Decreased systolic function was defined as left ventricular ejection fraction (LVEF) below 55% [32]. Decreased LVEF was reported in 13–100% of published cohorts [13••, 14–16, 19, 21, 22, 25, 29, 30•, 33••] (Table 2). In some MIS-C patients, LV systolic dysfunction was reported in those who developed shock [8•]. LV systolic dysfunction was not only reported on admission but also occurred later during admission emphasizing the importance of frequent echocardiogram assessment in this population [26]. In a study that recruited MIS-C children with decreased LV function, 25 (71%) had mild to moderate systolic dysfunction (an EF between 30 and 50%) and 10 (29%) patients had severe systolic dysfunction (EF below 30%) [31]. Clark et al. further categorized the degree of systolic function impairment with 11 (32%) patients with mild systolic dysfunction (EF 41–50%), and six (17%) patients with moderate to severe systolic dysfunction (an EF < 40%) [20]. One patient was reported by Kappanayil et al. to have a severely reduced EF of 10% [24]. What is lacking in these studies is the timing of echocardiogram to immune therapy and declaration of simultaneous inotropic or respiratory support at the time of obtaining the echocardiogram. As EF is known to be preload dependent, one wonders if frequency of systolic dysfunction

Table 1 Cardiac enzymes in patients with multi-system inflammatory syndrome in children (MIS-C)

Article	Number of MIS-C patients	Peak BNP (pg/mL)	Median BNP (pg/mL)	Peak NT-pro BNP (pg/mL)	Median NT-pro BNP (pg/mL)	Peak troponin	Median troponin	D-dimer (ug/mL)
Median (IQR) or mean ± SD								
Whittaker E et al. [8•]	58	N/A	N/A	N/A	788 (174–10,548)	N/A	Troponin (ng/L) 45 (8–294)	3.578 (2.085–8.235)
Belhadjer Z et al. [31]	35	4,256 (2,340–6,503)	5,743 (2,648–11,909)	N/A	41,484 (35,811–52,475)	High-sensitivity troponin I (ng/L) 408 (258–679)	N/A	5.284 (4.069–9.095)
Belay E et al. [13••]	1,733	599 (199.9–1,469)	N/A	2,789 (490.75–8,405)	N/A	Troponin (ng/mL, NL ≤ 0.1) 0.06 (0.01–0.3)	N/A	(Nl ≤ 0.4) 2.35 (1.25–4.38)
Valverde I et al. [14]	286	534 [48–2,494]	1,180 [248–3,510]	3,883 [955–12,354]	3,299 [802–12,622]	Troponin T (ng/mL, NL < 0.01) 12 [0.1–132]	Troponin T (ng/mL, < 0.01) 11 [0.1–80.3]	2,599 [1.244–4.803]
Caro-Paton GT et al. [15]	12	N/A	N/A	N/A	10,324	N/A	High-sensitivity cardiac troponin I (ng/L) (Nl ≤ 15.6) 56.4 (range, 3.6–5,992)	4.3
Vukomanovic V et al. [18]	3	N/A	N/A	> 5000	> 5000	Troponin I (ng/mL) Data presented by the 3 patients 1.14, 3.86, > 0.05	0.2	851
Bautista-Rodriguez C et al. [29] (international paper that included patients from the USA)	183 (14 from USA)	N/A	N/A	N/A	(NL, 0–300 pg/mL) KD-like presentation ($n = 27$) 2,148 ± 2,593 Incomplete KD-like presentation ($n = 78$), 7,443 ± 15,975 Shock presentation, ($n = 78$), 17,678 ± 39,609	N/A	Troponin (ng/mL) KD-like presentation ($n = 27$) 0.4 ± 0.5 Incomplete KD-like presentation ($n = 78$) 1.0 ± 2.0 Shock presentation, ($n = 78$) 1.0 ± 1.7	KD-like presentation ($n = 27$) 2,699 ± 1,465 Incomplete KD-like presentation ($n = 78$) 2,334 ± 2,055 Shock presentation, ($n = 78$) 4,594 ± 4,597
Mamishi S et al. [41]	45	N/A	N/A	N/A	N/A	N/A	Troponin (ng/mL) 0.6 (0.1–26)	3.9 (0.84–4.528)
Ramcharan T et al. [26]	15	N/A	N/A	(NL, < 400) 24,470 (17,212–26,655)	N/A	Troponin I (NL < 35 ng/L) 396 (100–1280)	N/A	2.06 (1.16–2.61)
Pouletty M et al. [19]	16	N/A	4,319 (2,747 to 6,493)	N/A	N/A	N/A	Troponin (ng/L, < 20) 58 (36 to 165)	N/A
Blondiaux et al. [43]	4	N/A	2,722.5 (19,58.25–31,58.5)	N/A	N/A	Troponin I* (ng/mL) 442 (286–1561)		N/A

Table 1 (continued)

Article	Number of MIS-C patients	Peak BNP (pg/mL)	Median BNP (pg/mL)	Peak NT-pro BNP (pg/mL)	Median NT-pro BNP (pg/mL)	Peak troponin	Median troponin	D-dimer (ug/mL)
Clark BC et al. [20] (international paper that included patients from the USA)	55 (16 from USA)	N/A	N/A	N/A	(NL, 5–1,121) 284.4 ± 25.8	N/A	Troponin 1.6 ± 0.9	N/A
Cattalini M et al. [21]	53	N/A	N/A	N/A	927 (701–1.734)	N/A	Troponin-T (ng/L) 82.5 (20–126)	2.514 (1.380–3.890)
Gaitonde M et al. [42]	12	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rojahn AE et al. [23]	1	N/A	N/A	30,000	N/A	Troponin T (ng/L) 453	N/A	N/A
Kappanayil M et al. [24]	1	N/A	N/A	N/A	157,000	N/A	Troponin T (ng/mL) 1.23	20
Bordet J et al. [25]	7	N/A	N/A	N/A	N/A	Initial troponin (ng/L), median (range) 338 [135–7,335]		N/A

*Authors did not clarify if this was peak or median value, *BNP*, B-type natriuretic peptide; *IQR*, interquartile; *KD*, Kawasaki disease; *MIS-C*, multi-system inflammatory syndrome in children; *N/A*, not available; *NL*, normal level; *NT-pro BNP*, N-terminal B-type natriuretic peptide; *USA*, United States; *SD*, standard deviation

was underestimated as most studies relied on the conventional EF [34••].

Coronary Artery Abnormalities

Coronary artery abnormality (CAA) was defined as a dilation if the *Z* score was 2 to < 2.5, small aneurysm 2.5 to < 5, moderate aneurysm 5 to < 10, and giant aneurysm referred to a *Z* score ≥ 10 or an actual measurement of ≥ 8 mm and has been described in children with MIS-C raising initial interest among the KD expert community [35••, 36–39, 40••]. The literature, consisting of single case reports to cohorts of up to 1733 patients, reported CAAs in 7 to 66% of children with MIS-C in the acute phase with variable CA involvement [13••, 15–21, 26, 29, 30•, 31, 41, 42] (Table 2). When excluding studies that included less than 50 patients, the reported incidence is 14–28%. While the majority of CAAs were either dilation or small aneurysms, some have reported cases of patients who developed giant aneurysms [8•]. Multivessel CAAs have also been reported [14, 33••].

Valvular Regurgitation

Variable degrees of atrioventricular valve regurgitation and aortic valve insufficiency (AI) have been described in children with MIS-C. When excluding studies that included less than 50 patients, the reported incidence of valvular regurgitation or insufficiency is 24–48% [16, 17, 20–22, 25, 26, 29, 30•, 42] (Table 2). On admission, Valverde et al. had 103 (38%) patients with mild mitral valve regurgitation (MR), 11 (4.2%) with moderate MR, and a single patient (0.3%) with severe MR. On the other hand, 10 (3.8%) patients had mild tricuspid valve regurgitation (TR) and six (2.1%) had moderate TR [14]. It is yet to be determined if valve regurgitation in children with MIS-C relates to inflammation of the valve itself (valvulitis) or secondary to ventricular dilation. In one report, the authors concluded that the MR seen in 2 (50%) patients was related to LV dilation [26].

Pericardial Effusion

Pericardial effusion occurred in 9–28% after excluding studies that included less than 50 patients (Table 2) [13••, 16–18, 20, 26, 29, 30•, 31, 33••, 41–43]. Valverde et al. described 80 (27.9%) patients to have a pericardial effusion upon admission to the hospital. While most papers did not include the degree of pericardial effusion and if it was hemodynamically significant, this study reported that 66 (23%) were mild, 8 (3%) were moderate, and none was severe effusions. At follow-up, pericardial effusion persisted in 59 (20.6%) patients [14].

Table 2 Conventional echocardiogram and electrocardiogram complications of patients with multi-system inflammatory syndrome in children (MIS-C)

Article	Cardiac complication present *n* (%)	CA aneurysm (*Z* score ≥ 2.5) *n* (%)	CAA (*Z* score > 2 to < 2.5) *n* (%)	EF < 55% *n* (%)	FS < 28% *n* (%)	MR *n* (%)	TR *n* (%)	AI *n* (%)	Pericardial effusion *n* (%)	ECG abnormalities and arrythmia *n* (%)
Whittaker E et al. [8•]	N/A	7 (12%)	1 (1.7%)	18 (62%)	N/A	N/A	N/A	N/A	N/A	1st degree AV block 1 (25%), intractable broad complex tachycardia 1 (25%), A fib 1 (25%), 2nd degree AV block 1 (25%)
Belhadjer Z et al. [31]	35 (100%)	0	6 (17%)	EF < 30% 10 (29%) EF 30–50% 25 (71%)	N/A	N/A	N/A	N/A	3 (8.5%)	Ventricular arrhythmia 1 (3%)
Belay E et al. [13••]	Cardiac dysfunction was reported in 484 (31.0%). Myocarditis in 300 (17.3%)	258 (16.5%)		484 (31%)	N/A	N/A	N/A	N/A	171 (10.3%)	N/A
Valverde I et al. [14]	266 (93%)	N/A	16 (26.7%)	71/208 (34%)	48/234 (20.6%)	Mild 103/270 (38.1%) Moderate 11/270 (4.2%) Severe 1/270 (0.3%)	Mild 10/272 (3.8%) Moderate 6/272 (2.1%) Severe none	N/A	80 (27.9%) at admission, decreased to 20.6% during hospitalization	101 (35.3%) as follows: abnormal ST- or T-wave segment 63 (22%), 1st degree block 18 (6.3%), bundle-branch block 11 (3.8%), prolonged QT interval 9 (3.1%), advanced AV block 6 (2.1%), tachyarrhythmias 5 (1.7%), abnormal Q waves 3(1%)
Caro-Paton GT et al. [15]	5 (42%)	0	1 (8%)	4 (33%)	N/A	N/A	N/A	N/A	N/A	0
Vukomanovic V et al. [18]	3 (100%)	Right CA 1 (33%)	2 (66%)	3 (100%)	N/A	N/A	N/A	N/A	2 (66%)	2 (66%) long Qtc

Table 2 (continued)

Article	Cardiac complication present *n* (%)	CA aneurysm (*Z* score ≥ 2.5) *n* (%)	CAA (*Z* score > 2 to < 2.5) *n* (%)	EF < 55% *n* (%)	FS < 28% *n* (%)	MR *n* (%)	TR *n* (%)	AI *n* (%)	Pericardial effusion *n* (%)	ECG abnormalities and arrythmia *n* (%)
Bautista-Rodriguez C et al. [29] (international paper that included patients from the USA)	121 (66.1%)	N/A	38 (20.7%)	81 (44%)	N/A	undefined Valvulitis 39 (21%)			38 (20.7)	Arrythmia 14 (7.7%), QTc > 500 ms 4 (2%), abnormal repolarization 12 (6.5%)
Mamishi S et al. [41]	25 (56%)	N/A	14 (31%)	N/A	N/A	N/A	N/A	N/A	1 (2%)	N/A
Ramcharan T et al. [26]	15 (100%)	1 (6.6%)	6 (40%)	12 (80%)	8 (53%)	10 (66.6%)	3 (20%)	N/A	8 (53%)	9 (60%) as follows: 1st degree AV block 1 (6.6%), abnormal T-wave 7 (46.6%), 1 (6.6%) had both
Pouletty M et al. [19]	16 (100%)	3 (18%) with median *Z* score of 2.6 (1.7 to 3.7)		16 (100%)	N/A	N/A	N/A	N/A	N/A	N/A
Blondiaux et al. [43]	4 (100%)	0	0	2 (50%)	1 (25%)	2 (50%)	N/A	N/A	3 (75%)	1 (25%) ST-segment depression
Clark BC et al. [20] (international paper that included patients from the USA)	N/A[#]	3 (8.3%)	11 (20%)	11 (32%) patients had LVEF of 41–50% and 6 (17%) patients had LVEF < 40%	N/A	8 (22%)	5 (13.8%)	2 (5.5%)	9 (25%)	6 (11%) Complete AV block, 2nd degree AV block, sinus pause, ventricular tachycardia
Cattalini M et al. [21]	32 (60.4%)	N/A	7 (13.2%)	19 (35.8%)	N/A	undefined valvular insufficiency 13 (24.5%)			N/A	N/A
Gaitonde M et al. [42]	N/A[#]	0	1 (8%)	8 (67%)	N/A	Mild or greater 6 (50%)	Mild or greater 4 (33%)	N/A	5 (42%)	N/A
Rojahn AE et al. [23]	1 (100%)	0	0	N/A	1 (100%)	N/A	N/A	N/A	N/A	N/A
Kappanayil M et al. [24]	1 (100%)	0	0	1 (100%)	N/A	N/A	N/A	N/A	N/A	N/A
Bordet J et al. [25]	7 (100%)	0	0	6 (86%)	N/A	7 (100%)	N/A	N/A	N/A	N/A

[#]Authors did not clarify how many patients had combined versus isolated cardiac complications, *A fib*, atrial fibrillation; *AI*, aortic insufficiency; *AV*, atrioventricular; *CAA*, coronary artery abnormality; *ECG*, electrocardiogram; *EF*, ejection fraction; *FS*, shortening fraction; *GLS*, global longitudinal strain; *GCS*, global circumferential strain; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation; *MS*, milliseconds; *N/A*, not available; *TR*, tricuspid regurgitation

Advanced Cardiac Imaging Findings of MIS-C

Cardiac Magnetic Resonance Imaging (CMR)

In light of these clinical cardiac complications from MIS-C, multiple centers are proactively utilizing CMR to follow up these patients in prospective observational studies [44–46]. Such efforts are critical, as CMR findings from published case series are generally limited by inconsistent timing of CMR in relation to onset of disease (in some centers, CMR was performed during acute phase, whereas others waited at least 6 weeks to 3 months). In general, CMR findings include pericardial effusion, abnormal T2 myocardial values/hyperintense myocardium on T2-weighted imaging (representing myocardial edema), early gadolinium enhancement (representing capillary leak/hyperemia), and late gadolinium enhancement (representing myocardial necrosis/fibrosis) [47]. For example, Valverde et al. reported CMR results in 42/286 (14.7%) patients; T2 hyperintensity was found in 14 (33.3%), pericardial effusion in 10 (23.8%), early gadolinium enhancement in 1 (2.4%), and late gadolinium enhancement in 6 (14.3%) [14]. This is of importance as late gadolinium enhancement was found to correlate with worse composite outcome of all-cause mortality, cardiac mortality, and/or major adverse cardiovascular events in adults with acute myocarditis [48]. Although pediatric data is very limited, late gadolinium enhancement correlated with increased risk of worse outcomes [49, 50]. There is also ongoing assessment of native T1/T2 changes by parametric mapping which are now encouraged in CMR evaluation of nonischemic myocardial inflammation [47, 51].

Abnormal Myocardial Strain and Abnormal Diastolic Function

Abnormal myocardial strain and abnormal diastolic function have been described in children with MIS-C. Myocardial strain takes into account the heterogenous motion of the myocardial wall, providing an angle-independent quantification of deformation in radial, circumferential, and longitudinal directions. In general, the more negative a strain value, the better it corresponds to myocardial function. However, interpreting the significance of myocardial strain across MIS-C studies is challenged by interobserver variability that is vendor dependent (machine used for acquisition, and software used for strain analysis) [52]. Reference ranges have been developed for left ventricular strain values based on age and vendor [53], and Valverde et al. used this to identify that 5/44 (11.4%) had reduced LVGLS[14].

Other studies have opted to compare MIS-C patients against other historical cohorts such as healthy controls or KD patients. For example, Matsubara et al. reported that the median LVGLS in MISC was worse at − 16.2 (IQR − 19.5 to − 13.6), compared to healthy controls at − 22.5 (IQR − 23.7 to − 21.1, $p < 0.001$) and classic KD at − 20.1 (− 21.8 to − 18.1). Other systolic strain parameters such as global circumferential strain (GCS), LAS, and RVFWLS also demonstrated similar patterns. Interestingly, diastolic parameters such as circumferential/longitudinal strain rate in early diastole and peak pulsed wave tissue Doppler diastolic velocities in lateral mitral annulus were different and persisted despite subsequent improvement in systolic function [30•, 54, 55].

Despite the potential variability in measurements, MIS-C studies have demonstrated the potential value of strain in determining clinical course. Matsubara et al. demonstrated that worse LVGLS, GCS, LAS, and RVFWLS were associated with clinical myocardial injury (elevated serum biomarkers) [30•]. Both Sanil et al. and Kobayashi et al. reported that patients with worse LVGLS had higher serum biomarkers and disease severity, i.e., more likely to present in shock, require intensive care unit (ICU) stay/inotropic support and mechanical life support, and longer hospital length of stay [55, 56••]. Early strain quantification may identify a sub-group to intensify monitoring and therapy to help prevent clinical deterioration.

Progression of Cardiac Complications of MIS-C

As we commemorated the 1-year anniversary of the first report of MIS-C, several publications have reported the short-term outcomes of cardiac complications in children with MIS-C. Although rare, mortality occurred in 1–2% of patients with MIS-C [13••, 57]. Of the 286 children with MIS-C, one patient died after developing ventricular arrhythmia and another patient developed dilated cardiomyopathy and was listed for heart transplantation [14]. In Bautista-Rodriguez et al.'s report, a patient died after suffering a massive myocardial infarction after developing giant coronary artery aneurysms in all three vessels, another patient died while on ECMO due to cerebral injury, and a third patient died after several cardiac arrests [29].

ECG abnormalities normalized prior to discharge in 22–100% of patients at a median of 5 days in some patients [14, 20, 26]. LV dysfunction resolved in 58–100% of those with initial systolic dysfunction at a median time of only 2 days in some cohorts [14, 17, 18, 24, 31, 58]. Others also reported that all cardiac findings, including any ECG abnormalities (including 3rd degree AV block), reduced LVEF, MR, and CAAs resolved within 2 weeks [16, 18, 20]. In Feldstein et al.'s article, during hospitalization, 172 patients (34.2%) had LV systolic dysfunction. Most patients (91.0%

of cohort) normalized their LVEF by 30 days, and 99.4% of cohort had normal LVEF by 90 days. The last patient had a normal LVEF at 142 days [57].

In some cohorts, cardiac complications persisted at time of last follow-up [21, 33••]. One study found that, at the time of discharge, cardiac complications persisted in 3 (25%) patients [15]. One patient had persistent LAD prominence [17]. As mentioned earlier, GLS remained low and the RV dysfunction persisted despite normalization of LVEF [30•]. Follow-up for patients in Ramcharan et al. revealed that atrioventricular valve regurgitation persisted in 7/13 (54%) patients. The patient with the lowest EF (28%) (severely reduced) improved to 53% (mildly reduced) at discharge. Mildly decreased systolic function persisted in 1/8 (12.5%) patients [26]. Some studies provided follow-up data on the patients with worst disease (i.e., admitted to ICU). Only two patients out of the 7 who were admitted to the ICU had persistent mild LV dysfunction [19].

CAAs persisted in few patients with MIS-C. Although cardiac systolic dysfunction, MR, and AI resolved, mild CA enlargement and a small aneurysm in the right CA persisted in one patient [22]. In Gaitonde et al., 2 (16%) had persistent CA dilation at time of last follow-up [42]. Sanil et al. reported resolution of CAAs in 5/6 patients at the 3- and 10-week follow-up visits. The only patient with persistent CAA had CA *Z* score of 2.4 (dilation) [56••]. In a study that focused on follow-up of patients with MISC, after 6 months, one patient had a medium CA aneurysm (*Z* score 9.8) that was stable [58]. These reports highlight that although mortality did occur in children with MIS-C, it is very rare. More importantly, during the short-term follow-up, most of the cardiac findings resolved.

Demographics, Clinical Features, Laboratory Evaluation, and Clinical Outcome of Children With MIS-C

Supplemental tables 3 to 7 display the demographics, clinical presentations, laboratory evaluation therapies received, clinical course, and outcomes of children with MIS-C. To help ensure we did not double count in the tables, we excluded any US-based study that included patients prior to 1/11/2021 as they were included in Belay et al.'s manuscript [13••] (supplemental Fig. 2).

Future Direction

As our community expands its investigations of this relatively new illness, we ought to work collaboratively to answer:

1- Why do some children with MIS-C develop cardiac complications? What are the demographics, clinical, laboratory, and therapeutic items associated with developing cardiac complications? In a small single center observational cohort study, children with cardiac complications were more likely to present with conjunctival injection, have higher NT-pro BNP, higher white blood cell count, higher neutrophil count, severe lymphopenia, use of milrinone, and intensive care requirement [33••]. Can artificial intelligence be utilized to predict which patients are at increased risk for developing cardiac abnormalities? Is there a learning curve in managing children with MIS-C? If so, is it associated with development of cardiac complications? Case in point, patients seen after 7/1/2020 were more likely to receive immune therapy and less likely to develop cardiac complications compared to those evaluated prior to 07/01/2020 [13••].
2- What are the factors favoring resolution of cardiac findings in children with MIS-C? What is the role of immune therapy choice and/or timing in resolving the cardiac findings? Is there a "Golden hour" for initiating therapy? [7].
3- What are the long-term cardiac findings in children with MIS-C? Are the cardiac changes seen in the acute phase, transiently or persistently, associated with long-term cardiac abnormalities including cardiomyopathy?

Conclusions

Cardiac complications in children with MIS-C are not uncommon and have been reported across the globe. Although mortality has occurred, it is very rare and the majority of children with MIS-C had resolution of their cardiac complications. Further studies are needed to assess if transient or persistent cardiac complications are associated with long-term adverse cardiac events.

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Availability of Data and Material Data will be available upon a reasonable request.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Clinical Trial Registration Not applicable.

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