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ORIGINAL ARTICLE

Cardiovascular Magnetic Resonance in Children with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19: Institutional Protocol-Based Medium-Term Follow-up Study

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) secondary to COVID-19 infection in previously healthy children often results in subtle but persistent echocardiographic abnormalities despite complete clinical recovery. This study was done to investigate medium-term cardiovascular outcomes of patients with MIS-C using cardiovascular magnetic resonance imaging (CMR). This is a single-center retrospective study of patients aged less than 21 years, diagnosed with MIS-C who received an outpatient CMR, around 6 months after discharge. CMR was done in patients with significant troponin leak or depressed LVEF. CMR performed on a GE Signa HDxt 1.5 Tesla magnet with a myocarditis protocol. Diagnosis of myocarditis was determined by the original Lake Louise Criteria. There were 21 patients with a median age of 11 years, (IQR 8–13 years), who underwent CMR at median follow-up duration of 6 months (IQR 5–7 months). At the peak of illness during admission, there were 95.2% patients with abnormal Troponin I and BNP. By echocardiogram, 76.2% had left ventricular systolic dysfunction and 9.5% had coronary ectasia, which all resolved by 6 months. By CMR, there were five patients (23.8%) with abnormal left atrial volume, one patient (4.8%) with an abnormal indexed left ventricular end-diastolic volume, and three patients (15%) with abnormal LVEF. There was no evidence of myocardial edema in T2-weighted image sequence. There were three patients with persistent late gadolinium enhancement (14.3%). Follow-up CMR is a useful tool in diagnosing subtle myocardial abnormalities and guide necessity for future follow-up.

Keywords MIS-C · COVID-19 · Cardiovascular magnetic resonance · Myocarditis

Introduction

The Coronavirus disease 2019 (COVID-19) has affected more than 340.5 million individuals and caused more than 5.5 million deaths across the globe [1]. In general, hospitalization rates and intensive care unit (ICU) stays related to acute respiratory distress syndrome (ARDS) from COVID-19 are less frequent in children compared to adults [2, 3]. However, multisystem inflammatory syndrome in children (MIS-C) secondary to COVID-19 infection has been a major cause of morbidity and ICU stay in children and adolescents during the pandemic [4–10].

Elevated biomarkers, left ventricular systolic and diastolic dysfunction, pericardial effusion, and coronary artery involvement are the most common cardiovascular manifestations of MIS-C [4–12]. There is a growing pool of data on

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the natural history and response to therapy during hospitalization [4–12]. However, there is a significant deficiency in our knowledge of medium- and long-term cardiovascular outcomes of this condition. Limited, single-center retrospective studies have demonstrated that although systolic ventricular dysfunction function and coronary artery abnormalities almost always recover within 3–6 months, subtle abnormalities in diastolic function possibly reflective of myocardial injury persist in a subset of patients [13–15]. In addition, Barris et al. demonstrated persistent abnormal T2-weighted signal ratio in 44% of the patients when cardiovascular magnetic resonance (CMR) was performed around 6 months after diagnosis of MIS-C [16]. Evidence of subtle myocardial injury is significant, considering that majority of these patients have no previous cardiovascular history. This is especially true with re-opening of school and sport events and poses a significant challenge for cardiologists and pediatricians in terms of return to play recommendations. Although, there is no single tool/test which can be used universally to determine presence and degree of myocardial injury, CMR has been used successfully in patients with acute viral myocarditis to detect inflammatory changes. It is unclear when the inflammatory process ends but in general, waiting at least 3–6 months to test before resumption of sports has been the general recommendation. In athletes with myocarditis even when the inflammation has resolved, they are still at risk for arrhythmias due to myocardial scar [17]. We postulate that since there is growing evidence that MIS-C is a type of post-infectious myocarditis, CMR could be an extremely valuable follow-up tool for the evaluation of subtle myocardial damage and scarring. We therefore aimed to investigate medium-term cardiovascular outcomes of MIS-C using CMR.

Materials and Methods

This is a single-center retrospective study of all pediatric patients aged less than 21 years, who were admitted with a diagnosis of MIS-C between May 1, 2020 and April 30, 2021 who received an outpatient CMR as a part of cardiovascular follow-up using our institutional algorithm at the Le Bonheur Children's Hospital. Patients with Troponin levels > 0.1 ng/ml or left ventricular ejection fraction (LVEF) < 55% at any time during hospital underwent CMR. Patients aged less than 2 years did not undergo CMR. The study was approved by our institutional review board (IRB Approval Number: UTHSC 20-07741-XP). US Centers for Disease Control and Prevention (CDC) criteria was used for diagnosis of MIS-C [18]. Patients with prior history of congenital heart disease, myocarditis, or cardiomyopathy were excluded from our study.

Apart from basic demographic data, which included age, sex, race, and ethnicity, cardiovascular data extracted for this study included cardiac biomarker levels, echocardiogram, and CMR findings.

Cardiac biomarkers evaluated were Troponin I (TnI) and brain natriuretic peptide (BNP). Based on our laboratory standards, Troponin > 0.034 ng/ml (99th percentile) and BNP > 100 pg/ml (99th percentile) were considered abnormal. Peak value of these cardiac biomarkers during admission, and levels at 6 weeks and 6 months post-discharge were collected.

The echocardiographic parameters evaluated were left ventricular systolic function, the presence of mitral regurgitation, pericardial effusion, coronary artery abnormalities, and the presence of diastolic dysfunction. Each of these echocardiographic parameters were collected at peak of illness during admission, at 6 weeks and 6 months following discharge. Left ventricular systolic function was graded in this study based on the LVEF as follows: normal function – LVEF > 55%, mild dysfunction LVEF 45–54%, moderate dysfunction LVEF 35–44% and severe dysfunction < 35%. This was measured using the Simpson's bi-plane method [19]. Mitral regurgitation (MR) was classified as none, trivial, mild, moderate, and severe based on qualitative assessment and the width of the vena contracta. Pericardial effusion was similarly graded as none, trace (< 3 mm), mild (3–10 mm), moderate (10–20 mm), and large (> 20 mm). The coronary abnormalities were graded as follows: normal coronaries, prominent without ectasia (borderline *Z* scores ranging between 1.8 and 2, with prominent echogenic walls), dilation (*Z* score 2–2.5), mild aneurysm (*Z* score > 2.5–5), moderate aneurysm (*Z* score 5–10), and giant aneurysm (*Z* score > 10) based on AHA/ACC guidelines for management of patients with Kawasaki Disease [20]. A patient was considered to have diastolic dysfunction (yes or no) if at least two parameters (*E*/*A*, *e*', *E*/*e*', or left atrial volume) were abnormal. The mitral inflow *E*/*A* Doppler profile was considered abnormal if the *E* and *A* waves were fused or if the *E*/*A* ratio had a Boston Children's Hospital *Z* score > 2.0 [21]. The *e*' velocity and *E*/*e*' ratio, either septal or lateral, were considered abnormal if had a Boston Children's Hospital *Z* score > 2.0. Left atrial volume was calculated using area length method. An indexed left atrial volume of > 34 ml/m^2 was considered abnormal.

CMR was done around 6 months after discharge in patients with significant troponin leak or depressed LVEF during their illness. All CMR performed on a GE Signa HDxt 1.5 Tesla magnet (General Electric Healthcare, Milwaukee, USA) with a myocarditis protocol (standard cine steady state free precession (SSFP) imaging planes (short axis stack, two chamber left, three chamber left, four chamber), T2-weighted short axis stack, early gadolinium enhancement short axis stack (post contrast T1 double

inversion recovery), late gadolinium enhancement short axis stack, and long axis images (segmented GRE post contrast)). Diagnosis of myocarditis by CMR was determined by the original Lake Louise Criteria [22]. T2 signal intensity ratio (SIR) of myocardium/skeletal muscle of ≥ 2.0 was considered abnormal. All patients who had a CMR completed the entire myocarditis protocol, and all CMR interpreted by a cardiologist with expertise in CMR (AM or JNJ). T1 mapping, T2 mapping, and extracellular volume (ECV) not available at our center. The volumetric parameters collected for this study from the cine SSFP short axis stack included indexed left ventricular end-diastolic volume (LVEDVi), indexed left ventricular end-systolic volume (LVESVi), LVEF, indexed right ventricular end-diastolic volume (RVEDVi), indexed right ventricular end-systolic volume (RVESVi), and right ventricular ejection fraction (RVEF). These volumetric parameters were compared with historical standards [23]. Left atrial volume was calculated by a biplane area length calculated from the two-chamber left and four chamber view at peak-systole [24]. An LVEF of < 55% and RVEF < 45% was considered abnormal. *A* left atrial volume of ≥ 34 ml/m^2 was considered abnormal.

BNP and Troponin levels were compared between patients with and without late gadolinium enhancement on CMR, with normal and abnormal left atrial volumes on CMR and those with normal and abnormal LVEF on CMR. In addition, indexed volumes and ejection fractions were correlated with peak Troponin and BNP levels. Continuous variables were presented in the form of median and interquartile range, and discrete variables were represented by frequency tables and percentages. Kruskal–Wallis test with box plots were used to compare the medians of continuous variable across two groups. Spearman rank correlation was used to establish any relationship between continuous variables. Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

There were 80 patients admitted with diagnosis of MIS-C in the study period, of which 23 (28.4%) met clinical criteria for undergoing CMR (Troponin > 0.1 ng/ml or LVEF < 55% and age > 2 years). Two patients were lost to follow-up and a total of 21 patients were included in this study. The median duration for the follow-up CMR was 6 months (IQR 5–7.5 months). The demographic, biochemical, and echocardiogram findings are presented in Table 1. The median age of patients at the time of diagnosis was 11 years (IQR 8–13 years), with 61.9% ($n = 13$) female patients. This included 23.8% Caucasian ($n = 5$), 66.7% African American ($n = 14$), and 9.5% ($n = 2$) Hispanic patients. The median length of hospital stay in this cohort of patients was 7 days (IQR 5.5–12.5 days). ICU admission was required in 71.4% of patients ($n = 15$). The median length of ICU stay in that population was 3 days (IQR 1.0–5.0 days).

This cohort of patients included 95.2% ($n = 20$) with either an abnormal troponin or BNP levels at the peak of illness. This included 85.7% patients ($n = 18$) with Troponin levels > 0.1 ng/ml and 42.9% ($n = 9$) with troponin level > 1 ng/ml. The median peak troponin level was 0.59 (IQR 0.15–2.67). The median BNP at the peak of illness was 1245 (IQR 480.5–2548) pg/ml. There were no patients with abnormal troponin or BNP 6 weeks after MIS-C diagnosis.

The median EF by echocardiography at peak of illness during admission was 50% (IQR 39–55%). There were 9 (42.9%) patients with mild left ventricular systolic dysfunction, 5 (23.8%) patients with moderate left ventricular systolic dysfunction, and 2 (9.5%) patients with severe left ventricular dysfunction, with an overall prevalence of at least mild dysfunction at 76.2%. There was complete recovery of left ventricular systolic function at 6 weeks with a median LVEF by echocardiography of 64% (IQR 60.5–65%). Similarly at 6 months, all the patients continued to have normal left ventricular systolic function with medial LVEF of 64% (IQR 61–65%) on echocardiogram. At the peak of illness during hospitalization, there were 15 patients (71.4%) with mitral regurgitation. This included eight patients (38.1%) with mild mitral regurgitation and seven patients with (33.3%) moderate to severe mitral regurgitation. At the 6 weeks visit, there were four patients (19%) with mild regurgitation, and none with moderate or severe regurgitation. By 6 months from discharge, none of the patients had more than trivial mitral regurgitation. At the peak of illness, in this cohort, there were three patients with prominent coronaries (14.3%) and two patients with coronary ectasia (9.5%). None of the patients had persistence of these abnormalities at the 6-weeks or 6-months visit. Two patients (9.5%) had evidence of diastolic dysfunction at 6-months follow-up. The median left atrial volume measured by echocardiogram was 23 ml/m^2 (IQR 21–27 ml/m^2), with two patients having an abnormal left atrial volume by echocardiogram (9.5%). Both patients had an abnormal LAVi on CMR.

The CMR findings for each patient are detailed in Table 2. The median LA volume indexed was 27.0 (IQR 21.5–31.5) ml/m^2. There were five patients (23.8%) with abnormal LA volume. The median LVEDVi was 71.4 (IQR 65.9–79.7) ml/m^2. There was one patient (4.8%) with an abnormal LVEDVi. The median LVESVi was 29.7 (26.5–35.4) ml/m^2. The median LVEF calculated by CMR was 57% (IQR 55.5–61.0%). There were three patients (14.3%) with an abnormal LVEF by CMR. The median RVEDVi was 71.9 (IQR 66–79.6) ml/m^2. The median RVESVi was 32.1 (IQR 28.4–38.1) ml/m^2. The median RVEF was 54% (IQR 51–57.5%). None of the patients had an abnormal RVEDVi,

Table 1 Demographic, biochemical, and echocardiogram findings of patients with MIS-C on intermediate follow-up

Serial number	Age/sex (years)	Race/ethnicity	Weight (kg)	Peak trop (pg/ml)	Peak BNP (pg/ml)	Minimum Echo LVEF (%)	Diastolic dysfunction at 6 months	LAVi at 6 months (ml/m^2)
1	13/F	AA/NH	**54**	2.45	1916	54	None	16
2	14/F	Cau/NH	**51**	18.7	2959	51	None	18
3	7/F	Cau/NH	25	0.677	6677	25	None	24
4	3/F	AA/NH	40	0.359	634.8	40	None	26
5	3/F	AA/NH	**46**	0.057	3393.8	46	None	28
6	16/M	AA/NH	**54**	0.012	24.7	54	None	22
7	13/F	AA/NH	56	0.244	761	56	None	16
8	13/M	AA/NH	63.2	0.11	120	63.2	None	20
9	14/F	AA/NH	**46.8**	5.46	361	46.8	None	22
10	10/M	AA/NH	60	0.325	1070.8	60	None	14
11	10/M	AA/NH	62	0.59	1375.7	62	None	22
12	13/M	Cau/NH	35	0.191	1943	35	None	28
13	3/M	AA/NH	44	0.359	634	44	None	24
14	8/F	Cau/NH	**50**	1.28	1354	50	None	29
15	8/F	Oth/H	**54**	0.05	600	54	None	22
16	9/F	AA/NH	32	1.22	7044	32	None	23
17	11/M	AA/NH	48	1.07	344	48	None	26
18	13/F	AA/NH	**53**	2.89	1245	53	Yes	36
19	11/F	AA/NH	38	5.9	2137	38	Yes	34
20	14/F	Oth/H	38	10.6	3010	38	None	24
21	14/M	Cau/NH	57	0.12	314	57	None	23

The bold values indicate abnormal values

AA African American, *BNP* b-type natriuretic peptide, *Cau* Caucasian *Echo* echocardiogram, *F* female, *H* Hispanic, *M* male, *NH* non-Hispanic, *Oth* Other, *Trop* troponin

or RVEF by CMR. None of the patients had any coronary abnormalities. There was no evidence of myocardial edema in T2-weighted image sequence in any of the patients. The median T2 SIR was 1.58 (IQR 1.39–1.65). There were three patients with persistent LGE on CMR. The first patient had focal epicardial LGE in the lateral wall of apical left ventricle, the second patient had epicardial LGE in the anterior mid left ventricular wall, and the third patient had epicardial LGE in the anteroseptal and apical region of the left ventricle (Fig. 1). The amount of LGE of the total myocardial mass for each patient was quite low (< 2% for all patients). Overall, the prevalence of decreased LVEF or the presence of LGE by CMR was 23.8% ($n=5$). None of the patients met Lake Louise Criteria for acute myocarditis.

There were no differences in the Troponin levels across patients with and without LGE ($P=0.409$), normal and abnormal LAVi ($P=0.322$), and normal and abnormal LVEF ($P=0.108$). Likewise, there were no differences in the BNP levels between patients with and without LGE ($P=0.269$), normal and abnormal LAVi ($P=0.763$), and normal and abnormal LVEF ($P=0.366$). In addition, there was no correlation between Troponin levels and LVEDVi ($P=0.457$), LVESi ($P=0.615$), RVEDVi (0.087) and RVESi ($P=0.098$). BNP levels were not correlated with LVEDVi ($P=0.964$), LVESi ($P=0.621$), RVEDVi (0.205), and RVESi ($P=0.337$) (see Fig. 2).

Discussion

There are limited data on mid-term outcome of MIS-C. Multiple studies have demonstrated that a vast majority of patients have recovery of systolic ventricular function by echocardiogram at the time of hospital discharge [4–12]. However, there is growing evidence that diastolic dysfunction persists even in 6-months follow-up studies [13–15]. This probably represents either ongoing subtle myocardial damage or results of previous scarring, resulting in abnormal myocardial tissue characteristics. CMR is an excellent tool for diagnosis of either of these processes and is helpful not only in terms of prognosis but also to provide novel insights into the pathophysiology.

We report the largest cohort of patients with MIS-C ($n=21$) who underwent CMR as a part of mid-term evaluation of cardiovascular outcomes. CMR as a part of 6-months evaluation has also been reported by Barris et al. [16]. This

Table 2 CMR findings of patients with MIS-C on intermediate follow-up

Serial no.	LVEDVi (ml/m^2)	LVEDVi (*Z* score)	LVESVi (ml/m^2)	LVESVi (*Z* score)	LVEF (%)	RVEDVi (ml/m^2)	RVEDVi (*Z* score)	RVESVi (ml/m^2)	RVESVi (*Z* score)	RVEF (%)	LAVi (ml/m^2)	LGE/T2 abnormality
1	71	0	29.9	0.8	58	71.9	− 1.2	35.9	0.6	50	25	None
2	67	− 0.5	29.5	0.8	56	72.3	− 1.2	38.2	0.9	47	14.5	None
3	79.6	1.1	36.9	1.9	**54**	83.5	1.2	39.8	1.1	52	27	None
4	71	0	27.5	0.4	61	65.2	− 1.7	23.2	− 1.3	64	34	None
5	66.2	− 0.6	23.5	− 0.3	64	69.1	− 1.4	30.9	− 0.2	55	30	None
6	80.3	0.1	36.2	1.9	55	74.5	− 0.9	33.5	0.2	55	25	None
7	76.5	− 0.7	23.5	− 0.3	56	69.3	− 1.4	29.1	− 0.4	58	22	None
8	65.3	− 1.2	28.5	0.6	56	66.8	− 1.6	33.7	0.2	50	28	None
9	54.6	− 2	25.4	0.1	**54**	53.7	− 2.7	25.9	− 0.9	52	19	**LGE+**
10	57	− 2	23.6	− 0.2	59	69.1	− 1.4	32.1	0	54	24	**LGE+**
11	76	0.6	27.5	0.4	64	80.5	− 0.5	37.5	0.8	53	30	None
12	76.3	0.6	33.3	1.4	56	71.2	− 1.2	27.7	0.6	61	27	None
13	71	− 0.7	27.5	0.4	61	65.2	− 1.7	23.2	− 1.2	64	34	None
14	79.8	1.1	34.5	1.6	57	73.9	− 1	31.1	− 0.1	54	20	None
15	65.6	− 0.7	29.7	0.8	55	63.3	− 1.9	31.3	− 0.1	51	21	None
16	54.9	− 2	21.1	− 0.6	62	54.9	− 2.6	21.8	− 1.4	60	19	None
17	85.7	0.6	36.2	1.9	58	74.5	− 0.9	32.1	0	57	**47**	None
18	99.4	3.5	43.6	3.1	56	102.8	1.4	47.5	2.2	54	**40**	None
19	71.4	0.1	25	0	65	87.1	0.1	37.9	0.8	57	**34**	**LGE+**
20	94	1.9	45.7	3.4	**51**	100	1.2	54.9	3.2	45	27	None
21	79	1	33	1.3	58	79	− 0.6	38	0.9	51	28	None

The bold values indicate abnormal values

CMR cardiovascular magnetic resonance, *LAVi* left atrial volume indexed, *LGE* late gadolinium enhancement, *LVEDVi* left ventricular end-diastolic volume indexed, *LVEF* left ventricular ejection fraction, *LVESVi* left ventricular end-systolic volume indexed, *RVEDVi* right ventricular end-diastolic volume indexed, *RVESVi* right ventricular end-systolic volume indexed, *RVEF* right ventricular ejection fraction

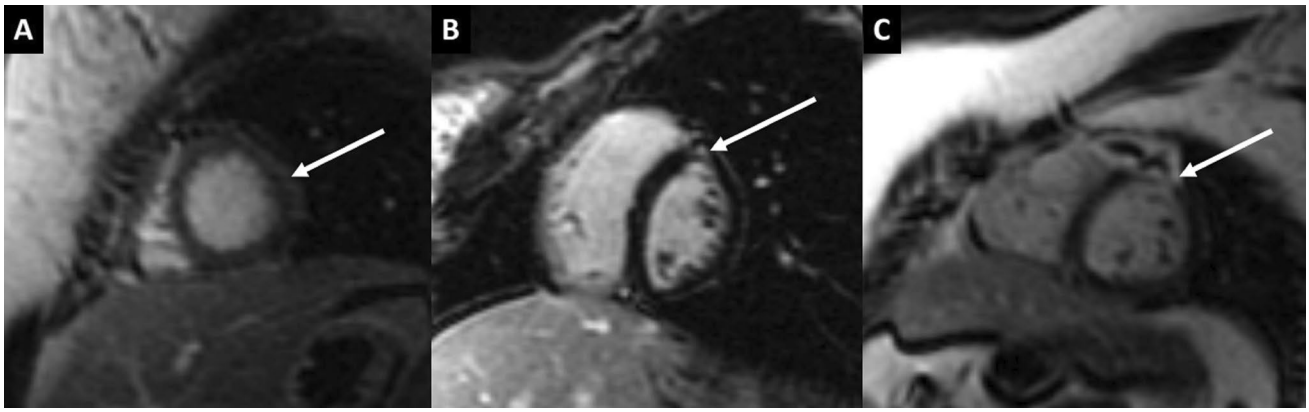

Fig. 1 Cardiovascular magnetic resonance short axis late gadolinium enhancement in three separate patients. **A** Patient 1. Apical segment with epicardial enhancement in the lateral wall (arrow). **B** Patient 2. Mid segment with mid myocardial enhancement in the anteroseptal wall (arrow). **C** Patient 3. Mid segment with epicardial enhancement in the anterior wall (arrow)

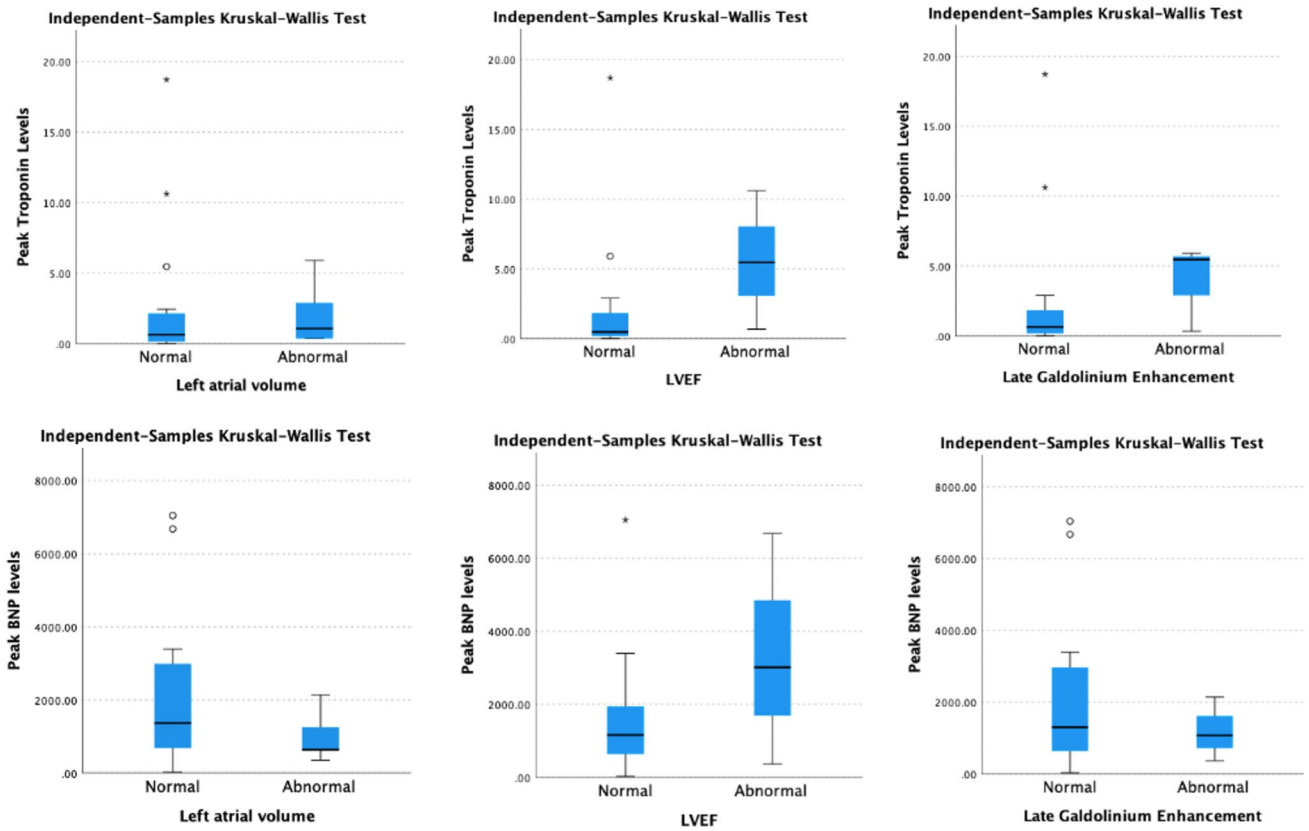

Fig. 2 Relationship with cardiac biochemical markers with abnormal CMR findings. *BNP* b-type natriuretic peptide; *LGE* late gadolinium enhancement; *LVEF* left ventricular ejection fraction; *TropMax* troponin maximum

study included CMR evaluation in 9 patients with median follow-up of 7 (IQR 6–8.4) months. The cardiovascular manifestations of the selected cohort are very similar to ours with the CMR being performed only in patients with significant troponin leak or decreased LVEF. The study reports complete resolution of the systolic ventricular function in all patients. However, abnormal T2-weighted signal ratio suggestive of myocardial edema was present in as many as 44% ($n=4$). The reason for this large number of patients having persistent abnormal T2-weighted signal ratio is unclear from

the study. In contrast to our study, none of the patients had abnormal T2 imaging.

Short-term CMR results after MIS-C have been reported by Webster et al. and more recently in a multicentric study by Aeschlimann et al. [25, 26]. Webster et.al describes 6 patients with MIS-C and 11 patients with COVID-19 infection [25]. The patient cohort consisted of two patients with mild-moderate LV dysfunction and two patients with abnormal troponin levels. LVEF was reported as normal in all the patients. Mean native global T1, global T2, and segmental T2 maximal values were compared with a control group. Unlike Barries et al. and similar to our study, none of the patients had any abnormalities of tissue characterization. Gadolinium contrast was not used in this study. The study by Aeschlimann et al. on the other hand reports CMR results in a more acute phase of the illness (median = 28 days from illness onset) [26]. This study included a cohort consisting of 65% with abnormal systolic function by echocardiogram. Myocarditis was diagnosed by CMR in 18% of this group and LGE was found in 16%.

Similarly, Capone et al. also reported their short-term CMR results at 8 weeks follow-up after MIS-C in 11 patients [13]. All of the patients in the CMR cohort had history of troponin leak and/or left ventricular systolic dysfunction. Although the details of the CMR technique are not available in this study, the authors report the absence of persistent edema or evidence of fibrosis. Short-term CMR results have also been reported in 19 patients with MIS-C by Bartozsek. et al. with a median follow-up of 3 months [27]. The cohort consisted of patients with either troponin leak or decreased LVEF. No evidence of abnormal T1 or T2 signal values using parametric mapping was reported in this study. However, using T2 signal intensity ratio, one patient was diagnosed with myocardial edema. In addition, no evidence of LGE was seen.

Our study adds to the growing pool of data on mid-term cardiovascular outcomes of patients with MIS-C. In contrast to Barries et al. and Bartozsek et al. our study does not report any evidence of ongoing myocardial edema. We postulate that most of the patients are expected to have resolution of acute myocardial injury and edema by the time CMR is performed 6 months after the diagnosis. It is however difficult to derive an inference with a small number of patients in each cohort. In addition, there is variability in the CMR techniques used with some of the studies using parametric mapping and others using T2 signal intensity ratio. Absence of a control, such as in ours, is also a recognizable contributor in differences in the results of abnormal tissue characterization across the studies. Nevertheless, it would not be unreasonable to assume that a vast majority of patients in whom there is no evidence of active myocardial injury by biochemical markers or echocardiogram findings, the presence of myocardial edema would not be very unlikely and false positives should be considered.

About 15% of the patients in our study had mildly abnormal LVEF in contrast to previous studies. In each one of these patients the LVEF was 54% and might be labeled as low normal or borderline abnormal and this variability across the studies is probably not very clinically significant. It is interesting to note each one of these patients had moderate to severe LV systolic dysfunction in acute phase. More importantly, although there is echocardiographic evidence of normalization of LVEF within 6–8 weeks of diagnosis, true volumetric measurements of systolic function may be slower to recover than we think, with subtle abnormalities lasting up to 6 months.

One of the highlights of our study is persistent epicardial LGE in as many as 15% of the patients at 6 months. This did not correlate with the degree of troponin elevation during the illness. We postulate that this represents scarring from previous myocardial injury, analogous to acute viral myocarditis. None of the other studies reporting short-term and mid-term outcomes based on CMR results have reported LGE. Blondiaux et al. report CMR findings in four patients during hospitalization or within 2 weeks of discharge and even in this subgroup, LGE was not observed [28]. The authors of this paper go further to postulate that this is due to the fact that LGE is observed usually in acute viral myocarditis where there is evidence of myocardial necrosis followed by scarring as opposed to MIS-C which is a post-infectious myocarditis, and there is no significant component of cytotoxic myocardial necrosis. Rather inflammation and edema manifest as abnormal tissue characterization on CMR without clear focal fibrosis by LGE. We believe that although this may be true in a subset of patients, this does not completely explain the paradigm of cardiovascular manifestations in MIS-C. There is a significant number of patients with slow recovery of systolic ventricular function and abnormal diastolic function and this group may have direct cytotoxic myocardial injury and present as abnormal LGE findings, as described by Aeschlimann et al. [26]. In addition, whether in this inflammatory milieu, abnormal myocardial perfusion from coronary artery abnormalities/coronary steal contributes to additional myocardial damage is not clear. And these findings highlight the importance of the 6-months follow-up CMR, in diagnosing subclinical myocardial damage, and provides new insights into the natural history of MIS-C. In addition, we believe that although there is no strong evidence to adequately guide clinician based on CMR findings in MIS-C, patients who have evidence of myocardial fibrosis, and particularly with systolic or diastolic function might benefit from a longer and closer follow-up than patients with normal CMR. Interestingly, level of troponinemia or LV dysfunction in the acute phase had no relationship LGE in the follow-up CMR.

Our study had several limitations. Firstly, it is a retrospective single-center of study with relatively small number of patients. Secondly, our center does not utilize CMR myocardial mapping techniques that could have made the CMR more sensitive to detect myocardial abnormalities. Thirdly, no control group was present in our study and clinical significance of the findings can only be compared with historical cohorts. Finally, since CMR findings are only available for patients with abnormal troponin or LV systolic dysfunction and are not generalizable to the entire MIS-C cohort.

In conclusion MIS-C has a heterogenous cardiovascular manifestation and a spectrum of underlying pathophysiology that needs further study. Follow-up CMR is a useful tool in diagnosing subtle myocardial abnormalities and guide necessity for future follow-up.

Author Contributions AC: Conceptualization, collection of relevant data, initial manuscript generation, critical review, and modification of subsequent versions of manuscript. RP: Conceptualization, critical review, and modification of subsequent versions of manuscript. MS: Conceptualization, collection of relevant data, critical review, and modification of subsequent versions of manuscript. RN: Conceptualization, critical review, and modification of subsequent versions of manuscript. AM: Conceptualization, critical review, and modification of subsequent versions of manuscript. JJ: Conceptualization, critical review, and modification of subsequent versions of manuscript.

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Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical Approval The study was approved by our IRB (University of Tennessee Health Sciences Center).

Informed Consent Since the study encompassed retrospective data and minimal risk to human subjects a waiver of consent was approved by IRB.

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