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RESEARCH

Long-Term Cardiovascular Outcomes of Multisystem Inflammatory Syndrome in Children Associated with COVID-19 Using an Institution Based Algorithm

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Abstract

Cardiovascular involvement is a major cause of inpatient and intensive care unit morbidity related to Multisystem inflammatory syndrome in children (MIS-C). The objective of this study was to identify long-term cardiovascular manifestations of MIS-C. We included 80 consecutive patients admitted to the intensive care unit with MIS-C who were evaluated for a year in our follow-up clinic using an institution protocol. The outcome measures were cardiac biomarkers (troponin and BNP), electrocardiogram changes, echocardiographic findings cardiovascular magnetic resonance (CMR) and graded-exercise stress test (GXT) findings. The cohort included patients aged between 6 months and 17 years (median 9 years; 48.8% females). At the peak of the disease 81.3% had abnormal BNP and 58.8% had troponin leak which reduced to 33.8% and 18.8% respectively at discharge with complete normalization by 6 weeks post-discharge. At admission 33.8% had systolic dysfunction, which improved to 11.3% at discharge with complete resolution by 2 weeks. Coronary artery abnormalities were seen in 17.5% during the illness with complete resolution by 2 weeks post discharge except one (1.9%) with persistent giant aneurysm at 1 year-follow up. CMR was performed at 6 months in 23 patient and demonstrated 4 patients with persistent late gadolinium enhancement (17.4%). Normal exercise capacity with no ectopy was seen in the 31 qualifying patients that underwent a GXT. There is significant heterogeneity in the cardiovascular manifestations of MIS-C. Although majority of the cardiovascular manifestations resolve within 6 weeks, diastolic dysfunction, CAA and myocardial scar may persist in a small subset of patients warranting a structured long-term follow-up strategy.

Keywords MIS-C · Echocardiogram findings · Long-term outcomes

Introduction

Coronavirus disease 2019 (COVID-19) has affected 82 million individuals throughout United States resulting in nearly 997,083 deaths [1]. Multisystem inflammatory syndrome in children (MIS-C) secondary to COVID-19 infection has been a major cause of hospitalization and intensive care unit (ICU) stay during the pandemic [2–4]. A total of 8210 cases with 68 deaths have been reported throughout the United States, based on CDC national surveillance data [4].

Cardiovascular involvement from MIS-C is a major cause of morbidity and ICU stay. This is usually manifested acutely during hospitalization as elevated cardiac biomarkers, prolonged PR interval and ST-T wave changes on electrocardiogram (ECG), left ventricular systolic and diastolic dysfunction, pericardial effusion, and coronary artery abnormalities on transthoracic echocardiogram (TTE). Specifically, left

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ventricular dysfunction has been reported in 31–100% [5–15] of the patients with MIS-C and coronary artery involvement in 6–46% [5–9, 11, 16–20] of cases. There is a growing pool of data on the acute cardiovascular manifestations related to MIS-C [5–15]. There is however significant paucity in our knowledge about medium and long-term cardiovascular outcomes of this condition. Limited, single center studies have described almost complete resolution of ventricular systolic dysfunction and coronary artery changes within 3–6 months following discharge [15, 19–21]. However, there is some evidence that subtle abnormalities in diastolic function on TTE and evidence of myocardial injury on cardiovascular magnetic resonance imaging (CMR) may persist longer [19–25]. We have previously described the CMR results in a subset of patients at 6-month follow-up who had initial presentation with significant troponin leak and/or left ventricular systolic dysfunction [25]. However, each of these studies is limited by the number of patients enrolled, the duration and compliance with follow-up and the considerable heterogeneity in testing. And although we have presented medium term results with the help of CMR in a subset of patients the utility of a more comprehensive study including follow up of all admitted patients with a battery of tests is extremely important given that majority of affected individuals have no pre-existing cardiovascular disease. Specifically, it poses a unique challenge for pediatricians and pediatric cardiologists to determine the duration and frequency of follow-up, the need for advanced testing and to provide recommendations or clearance for return to competitive sport. We believe that a standardized protocol with an algorithm-based advanced testing schedule in a dedicated MIS-C clinic would be helpful to investigate the course of cardiovascular outcomes, whilst providing additional insight into the cardiovascular prognosis of the condition.

Therefore, this study was undertaken with a primary objective of reporting long-term cardiovascular outcomes of patients with MIS-C using a comprehensive assessment protocol including clinical characteristics, cardiac biomarkers, ECG, TTE and advanced testing (exercise stress test and CMR). Secondary objectives were to determine any association of elevated cardiac biomarkers with ventricular dysfunction and coronary abnormalities.

Methods

Study Population

This is a single center retrospective study of all pediatric patients, aged less than 21 years, admitted with a diagnosis of MIS-C who had at-least 2 of the 4 outpatient follow-up visits over a span of a year between May 1, 2020, and February 28 2021, using our institutional algorithm (Fig. 1) at the University of Tennessee, Le Bonheur Children's Hospital. The scheduled outpatient visits to the MIS-C Clinic were 2 weeks (visit 1), 6–8 weeks (visit 2), 4–6 months (visit 3) and 12 months (visit 4) post-discharge. The clinical

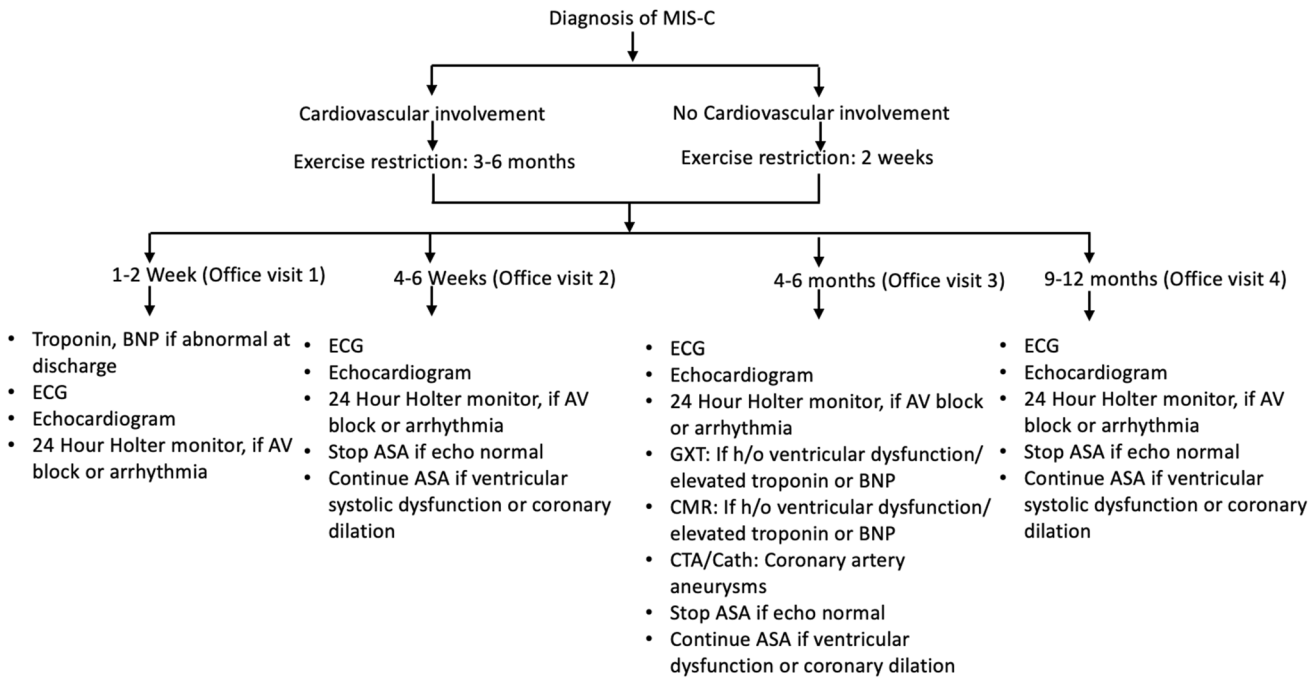

Fig. 1 Outpatient follow-up protocol for patients diagnosed with multisystem inflammatory syndrome in children (MIS-C)

diagnosis of MIS-C was based on criteria that was recommended by US Centers for Disease Control and Prevention [26, 27]. All patients included in this study were tested for the SARS-CoV-2 virus by polymerase chain reaction from the nasopharyngeal swab and/or chemiluminescent immunoassay for quantitative detection of immunoglobulin G (IgG) antibodies to the SARS-CoV-2. The patients diagnosed with MIS-C were positive for one or both tests in addition to meeting the clinical criteria. Patients with known primary cardiac diagnosis were excluded from the study.

Cardiac Biomarkers

The cardiac biomarkers evaluated were Troponin T (TnI) and Brain Natriuretic Peptide (BNP). Based on our institutional protocol, every patient admitted with MIS-C underwent measurement of TnI and BNP at the time of admission. Serial monitoring of the TnI and BNP was done depending on the clinical context and the trends of these biomarkers. In this study the TnI and BNP levels at admission, the peak levels and pre-discharge levels were recorded. At the first outpatient follow up, TnI and BNP levels were routinely measured. If these results were normal, the levels were not repeated at visit 2. Based on our laboratory standards Troponin > 0.034 pg/ml (99th percentile) and BNP > 100 pg/ml (99th percentile) were considered clinically significant. Abnormal TnI and BNP levels were compared with presence of ventricular systolic dysfunction and coronary artery abnormalities to determine any association.

ECG Parameters

Every patient underwent an ECG at the time of admission and then at least every 48 h. Additionally, an ECG was done at each of their outpatient follow-up visits per protocol. For the purposes of our study the following ECG parameters were recorded: prolonged PR interval (evaluated by age matched standards), presence of type 1 or type 2 s degree heart block, complete heart block, ST changes (> 2 mm elevation or depression from the isoelectric line) and T wave inversion in lateral precordial leads.

Echocardiographic Parameters

A TTE was obtained in every patient with the diagnosis of MIS-C within 24 h of admission. The frequency of the subsequent TTEs were dependent on the clinical picture of the patient and the findings of the initial echocardiogram. A TTE was obtained in all patients 24–48 h prior to discharge. As a part of the algorithm, TTEs were also obtained at each follow up visit.

The echocardiographic parameters evaluated were left ventricular systolic and diastolic function, presence of mitral regurgitation, pericardial effusion, and coronary artery abnormalities.

Left ventricular systolic function was graded based on the left ventricular ejection fraction (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 [28]. 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: 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 [29]. Presence of ventricular systolic dysfunction was compared with any coronary artery abnormalities to determine any association between the two.

Diastolic dysfunction was determined (yes or no) if atleast 2 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 [30]. The *E*′ velocity and *E*/*E*′ ratio with Z score > 2, either septal or lateral, were considered abnormal. Left atrial (LA) volume was calculated using area length method. An indexed left atrial volume of > 34 ml/m^2 was considered abnormal.

Advanced Testing

CMR was done between 4 and 6 months after discharge in patients with significant TnI leak (> 0.1) or depressed LVEF (< 55%) during their illness who were aged > 2 years. The age cut-off was utilized considering the potential benefit of CMR versus the risk of sedation that may be necessary for patients aged < 2 years. A total of 24 patients (30%) underwent CMR. GE Signa HDxt 1.5 Tesla magnet (General Electric Healthcare, Milwaukee, USA) was used to perform CMR using myocarditis protocol. Diagnosis of myocarditis by CMR was determined by The original Lake Louise Criteria was used to diagnose myocarditis [31]. T2 signal intensity ratio (SIR) of myocardium/skeletal muscle of ≥ 2.0 was considered abnormal. The volumetric parameters collected 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 [32]. LA volume was calculated by a

biplane area length obtained from the two-chamber and four chamber view at peak-systole [33]. An LVEF of < 55% and RVEF < 45% was considered abnormal. A LA volume of ≥ 34 ml/m^2 was considered abnormal.

A graded exercise stress test (GXT) was done between 4 and 6 months in patients with significant TnI leak, depressed LVEF during illness or abnormal ECG findings. Abnormal maximal exercise capacity and ECG findings during exercise were recorded for analysis. Twenty-nine patients (36.3%) underwent GXT.

The study was approved by the University of Tennessee Health Science Center institutional review board and in compliance with edicts of the Declaration of Helsinki (IRB Approval Number: UTHSC 20-07741-XP).

Statistical Analysis

Categorical data were presented in the form of frequency distribution tables and percentages whereas continuous data were presented as median and interquartile range. Time trends were plotted using Kaplan–Meier survival curve analysis. Chi-square test (with Fischer's exact modification based on the size of the sample) was used as test of significance to determine association between categorical variables. p value < 0.05 was considered statistically significant. Statistical analysis was performed using, SPSS software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Eighty consecutive patients admitted with MIS-C aged between 6 months and 17 years (median age of 9 years (IQR 6–12.5 years) were evaluated using our institution-based algorithm (Fig. 1). They were equally distributed based on gender (female 51.2%). Sixteen were Caucasians (20%) and 52 African American (65%). There were 8 patients (10%) of Hispanic ethnicity. The duration of hospitalization ranged from 3 to 39 days (median duration 7 days; IQR 5–9.5 days). The median duration of ICU stay was 1 (IQR 1–3) day. The median duration of floor hospitalization was 5 (IQR 4–8) days. There was no mortality. One patient required extracorporeal membrane oxygenation (1.25%) for 7 days. The cardiovascular parameters over time during hospitalization and outpatient follow-up as per protocol are shown in Table 1.

Cardiac Biomarkers

On admission, TnI was elevated in 38.8% (> 1 ng/ml in 10%) and 58.8% at peak illness (> 1 ng/ml in 16.3%). Similarly, 55% had an elevated BNP on admission and 81.3% at peak illness (median 491.6 pg/ml—IQR 145.6–1384.2) with a maximum of 12,674 pg/ml. The median duration for TnI and BNP to peak were 1 day (IQR 1–2.5 days) and 3 days (IQR 1–4.5) after hospitalization respectively (Table 2). There was a temporal relation observed between administration of intravenous immunoglobulin (IVIG) and elevation of BNP.

ECG Changes

On admission prolonged PR interval was observed in 9 patients (11.3%) and 13 patients (16.3%) had ST-T wave changes. During hospitalization, a total of 16 patients (20%) went on to develop prolonged PR interval. Two patients had high-grade second-degree heart block which improved over the course of time and did not need any specific intervention. Prolonged PR interval at discharge was observed in 13.8%.

Echocardiographic Findings

Left ventricular dysfunction was seen in 22.5% of patients on admission and 33.8% during the course of the illness. The median time for maximum worsening of systolic function was 2 days (IQR 1–3 days). By discharge, there was significant improvement in systolic function (11.3% having persistent dysfunction- none with moderate or severe dysfunction).

There were 22 patients with MR (27.5%) at the time of admission. During the peak of illness, 28.7% had mild MR, and another 10% moderate MR. At the time of discharge 22.5% continued to have mild MR and 3.8% moderate MR.

On admission, 6 patients (7.5%) showed evidence of coronary artery changes and at peak illness 17.5%. At the time of discharge, coronary changes continued to be present in 12.5% including a giant aneurysm in 1 patient (Table 2).

On admission, 19 (23.8%) patients had LA enlargement with 25% ($n = 20$) of demonstrating abnormal diastolic function. During hospitalization, left atrial enlargement and diastolic dysfunction was seen in 23 (28.7%) and 27 (33.8%) patients respectively. At the time of discharge 20 patients (25%) demonstrated LA enlargement and 24 patients (30%) continued to demonstrate diastolic dysfunction (Table 3).

Outpatient-Follow Up and Longitudinal Trends

The first and second outpatient follow-up data were available in all 80 patients. The 6-month follow-up results were available in 68 patients, and 1-year outcomes were available in 62 patients. The median time required for normalization of each of the cardiovascular parameters is listed in Table 2. One patient continued to have elevated TnT at visit 1 although down trending from the time of discharge and normalized by visit 2. None of the patients had elevated BNP at visit 1 (Fig. 2a and b). The prolonged PR interval improved in most patients, after 2 weeks from discharge. However, there were 4 patients (5%) who continued to demonstrate prolonged PR

Table 1 Longitudinal trends of abnormal cardiovascular findings over time in patients with MIS-C

Cardiovascular parameters	Admission ($n=80$)	Peak of illness ($n=80$)	Discharge ($n=80$)	Office visit 1 2 weeks ($n=80$)	Office visit 2 6 weeks ($n=80$)	Office visit 3 4–6 months ($n=68$)	Office visit 4 1-year ($n=62$)
BNP levels							
Median with IQR (pg/ml)	136.1 (15.3–456.7)	491.6 (145.6–1384.2)	54.9 (11.1–205)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)
Elevated BNP	44 (55%)	65 (81.3%)	27 (33.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Troponin levels							
Median with IQR	0.015 (0.012–0.193)	0.0605 (0.012–0.385)	0.012 (0.012–0.018)	0.012 (0.012–0.012)	0.012 (0.012–0.012)	0.012 (0.012–0.012)	0.012 (0.012–0.012)
Elevated Troponin	31 (38.8%)	47 (58.8%)	15 (18.8%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Troponin levels > 0.1 ng/ml	25 (31.3%)	37 (46.3%)	8 (10%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Troponin > 1 ng/ml	8 (10%)	13 (16.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prolonged PR interval							
Present	9 (11.3%)	16 (20%)	11 (13.75%)	4 (5%)	4 (5%)	4 (5%)	2 (2.5%)
ST-T wave changes							
Present	13 (16.3%)	18 (34%)	12 (15%)	2 (2.5%)	2 (2.5%)	0 (0.0%)	0 (0.0%)
Ejection fraction							
Median and IQR	60 (54–62)	58 (50.25–60)	60 (58–64)	62 (60–65)	65 (62–66)	62 (60–64.75)	62 (60–64)
Abnormal systolic function							
Mild	12 (15%)	16 (20%)	9 (11.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	5 (6.3%)	7 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	1 (1.3%)	4 (5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	18 (22.5%)	27 (33.8%)	9 (11.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mitral regurgitation							
Trace	12 (15%)	9 (11.3%)	16 (20%)	14 (17.5%)	8 (10%)	3 (3.8%)	0 (0.0%)
Mild	16 (20%)	23 (28.7%)	18 (22.5%)	6 (7.5%)	3 (3.8%)	1 (1.3%)	0 (0.0%)
Moderate	6 (9.3%)	8 (10%)	3 (3.8%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total significant	22 (27.5%)	31 (38.8%)	21 (26.3%)	7 (8.8%)	3 (3.8%)	1 (1.3%)	0 (0.0%)
Coronary arterial abnormalities							
Prominent without dilation	3 (3.8%)	6 (7.5%)	3 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dilation	2 (2.5%)	5 (6.3%)	4 (5%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild aneurysm	1 (1.3%)	2 (2.5%)	2 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate aneurysm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Giant aneurysm	0 (0.0%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
Total	6 (7.5%)	14 (17.5%)	10 (12.5%)	2 (2.5%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
Pericardial effusion							
Trivial	16 (20%)	21 (35.8%)	18 (22.5%)	8 (10%)	3 (3.8%)	0 (0.0%)	0 (0.0%)
Mild	2 (2.5%)	4 (5%)	2 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate/Large	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

interval on 6 months follow-up and persisted in 2 patients (2.5%) at 1-year follow-up. Likewise, 3 patients (3.8%) continued to demonstrate ST-T wave changes at visit 1, all of which were resolved by 6 months follow-up visit (Fig. 2c and d).

None of the patients had any evidence of left ventricular systolic dysfunction in the follow-up. Similarly, there was progressive improvement in MR over time with only 6 patients (7.5%), exhibiting mild MR and 1 patient (1.3%) with moderate MR at the time of the first outpatient visit.

Table 2 Longitudinal assessment of the biomarkers, EKG and heart function on echocardiogram

Parameters[a]	Time for maximal worsening	Time for recovery
Troponin	1 (1–2.5)	10 (3–22.5)
BNP	3 (1–4.5)	16 (6–21.5)
PR interval	1 (1–3)	22 (15.25–24)
ST-T wave changes	1 (1–2.5)	20.5 (16.75–25)
Systolic heart function	2 (1–3)	6 (4–16.25)
Mitral regurgitation	1 (1–3)	23 (17.25–28)
Coronary dilation	3 (1–3.5)	20 (8–27.5)

[a]All the values are measured in days and presented as median with interquartile range

At visit 2, only 3 patients (3.8%) had mild MR which completely resolved at the 1-year visit. The coronary artery abnormalities were all resolved by the first outpatient visit except one patient with the giant aneurysm that persisted even at the 1-year follow-up visit (Fig. 3).

At the first outpatient visit, 11 patients (13.8%) continued to have diastolic dysfunction. There were 6 patients (7.5%), with abnormal diastolic function at visit 2. At the 6-month visit, 5 patients continued to demonstrate diastolic dysfunction of which only one patient had persistent dysfunction at a year (Table 3).

The summary of CMR findings is demonstrated in Table 4. There were 24 patients who qualified for a CMR (TnI > 0.1 ng/ml or LEVF < 55% and age > 2 years) based on our protocol 4–6 months following discharge (median 6 months, IQR 5–7.5 months). There were 5 patients (20.8%) with an abnormal LA volume. There was 1 patient (4.2%) with an abnormal LVEDVi. The median LVEF calculated by CMR was 57.5% (IQR 55.6–60.7%). There were 3 patients (12.5%) with an abnormal LVEF by CMR. The median RVEF was 54% (IQR 51–57%). None of the patients had an abnormal RVEDVi 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. There were 4 patients (16.7%) with persistent LGE (Late Gadolinium Enhancement) on CMR (Fig. 3). The amount of LGE of the total myocardial mass for each patient was low (< 2% for all patients).

As per protocol, 29 patients (36.2%) qualified for a GXT 4–6 months post-discharge (median 6 months, IQR 5.5–7 months). None of the patients had an abnormal maximal exercise capacity or ventricular ectopy. There were 4 patients (5%) with an abnormal PR interval at baseline, each one of which showed normal shortening of the PR interval with exercise.

Interrelationship Between Elevated Cardiac Biomarkers, Ventricular Systolic Function, and Coronary Abnormalities

Elevated BNP levels at the time of admission were associated with systolic dysfunction at the time of admission (40.9% vs 0% $p < 0.001$) and at the peak of illness (54.5% vs 8.3% $p < 0.001$) in comparison to those with a normal BNP. Similar findings were seen with TnI (Table 5). None of the biochemical markers predicted persistence of systolic dysfunction at the time of discharge. There were no observed associations between elevated cardiac biomarkers and coronary artery abnormalities. Additionally, there was no correlation between systolic dysfunction at any time and presence of coronary artery abnormalities.

Table 3 Longitudinal trends of abnormal echocardiographic diastolic parameters over time in patients with MIS-C

Diastolic function parameters	Admission ($n = 80$)	Peak of illness ($n = 80$)	Discharge ($n = 80$)	Office visit 1 2 weeks ($n = 80$)	Office visit 2 6 weeks ($n = 80$)	Office visit 3 4–6 months ($n = 68$)	Office visit 4 1-year ($n = 62$)
Median LA volume (ml/m^2)	22 (IQR 22–29)	23.5 (IQR 21–31.75)	22 (IQR 21–28)	22 (IQR 20–26)	22 (IQR 18–24)	20 (IQR 18–22)	20 (IQR 18–22)
Left atrial enlargement	19 (23.8%)	23 (28.7%)	20 (25%)	10 (12.5%)	7 (8.8%)	3 (3.8%)	1 (1.3%)
Mitral E/A ratio	23 (28.7%)	29 (36.3%)	24 (30%)	13 (16.3%)	7 (8.8%)	6 (7.5%)	4 (5%)
Abnormal lateral or septal e' velocity	9 (11.3%)	13 (16.3%)	10 (12.5%)	3 (3.8%)	3 (3.8%)	5 (6.3%)	5 (6.3%)
Abnormal E/e' lateral or septal ratio	11 (13.8%)	14 (17.5%)	12 (15%)	5 (6.3%)	4 (5%)	2 (2.5%)	1 (1.3%)
Diastolic dysfunction	20 (25%)	27 (33.8%)	24 (30%)	11 (13.8%)	6 (7.5%)	5 (6.3%)	1 (1.3%)

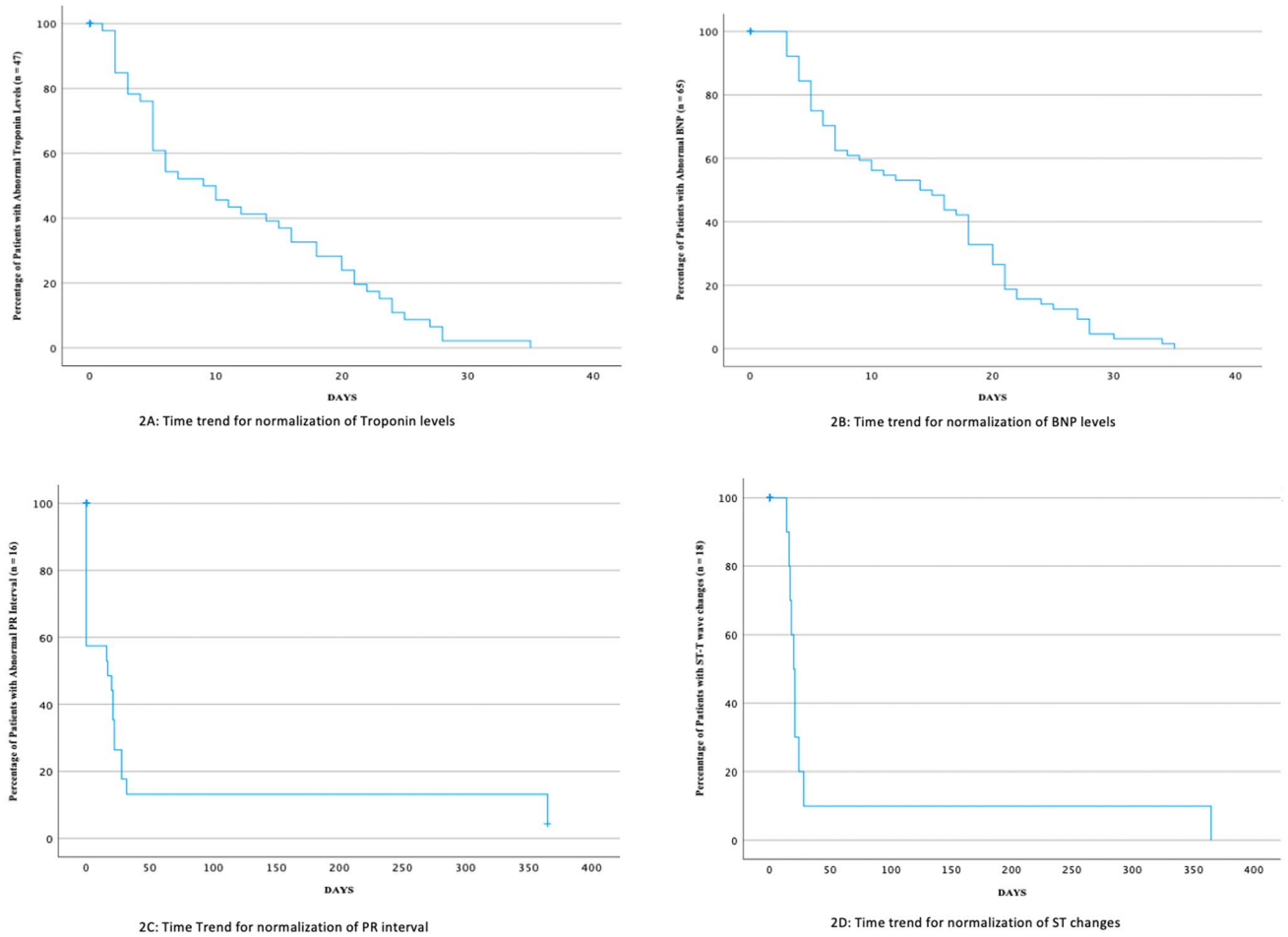

Fig. 2 Kaplan–Meier analysis plots representing trends for normalization of cardiac biomarkers (**a** and **b**) and EKG (**c** and **d**) findings in patients diagnosed with multisystem inflammatory syndrome in children (MIS-C)

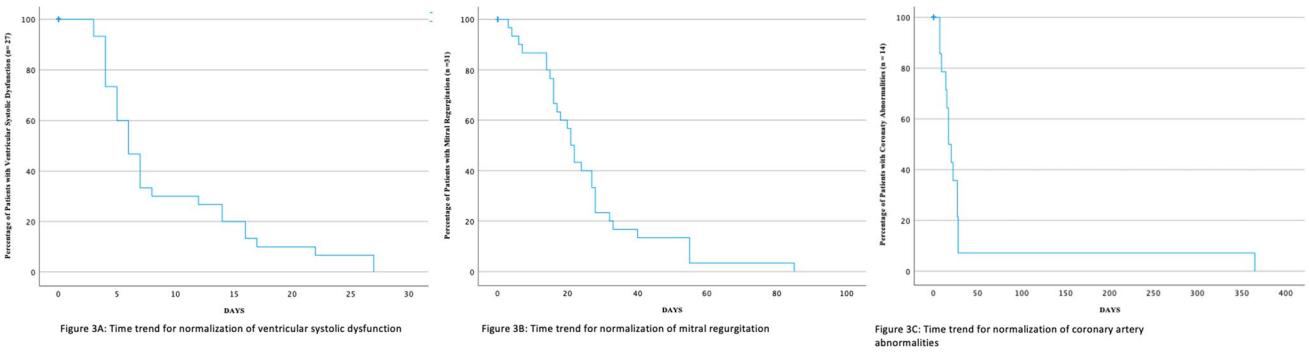

Fig. 3 Kaplan–Meier analysis plots representing trends for normalization of echocardiogram findings in patients diagnosed with multisystem inflammatory syndrome in children (MIS-C)

Discussion

This longitudinal study is a first of its kind which uses a comprehensive standardized protocol with tailored testing in the outpatient follow-up evaluation of patients with MIS-C. This study also describes the largest cohort of MIS-C patients who underwent 1-year follow-up and provides clinically relevant and practical data on the cardiovascular prognosis of the condition. The demographics

Table 4 Interrelations between cardiac biomarkers, systolic heart function and coronary artery changes

	Normal troponin	Elevated troponin	Significance level
Troponin level at admission and systolic function			
Systolic dysfunction on admission	2 (4.1%)	16 (51.6%)	**< 0.001**
Peak systolic dysfunction during admission	8 (16.3%)	19 (61.3%)	**< 0.001**
Systolic dysfunction at discharge	2 (4.1%)	7 (22.6%)	**0.015**
Systolic dysfunction at office visit 1	0 (0.0%)	0 (0.0%)	Not applicable
Systolic dysfunction at office visit 2	0 (0.0%)	0 (0.0%)	Not applicable
Peak troponin levels and systolic function			
Systolic dysfunction on admission	2 (6.1%)	16 (34%)	**0.003**
Peak systolic dysfunction during admission	4 (12.1%)	23 (48.9%)	**< 0.001**
Systolic dysfunction at discharge	1 (3%)	8 (17%)	0.05
Systolic dysfunction at office visit 1	0 (0.0%)	0 (0.0%)	Not applicable
Systolic dysfunction at office visit 2	0 (0.0%)	0 (0.0%)	Not applicable
Troponin levels at admission and coronary abnormalities			
Coronary abnormalities on admission	4 (7.3%)	2 (8%)	0.614
Coronary abnormalities during admission	6 (11.3%)	6 (11.3%)	0.420
Coronary abnormalities at discharge	5 (10.2%)	5 (16.1%)	0.327
Coronary abnormalities at office visit 1	1 (2%)	0 (0.0%)	0.612
Coronary abnormalities at office visit 2	1 (2%)	0 (0.0%)	0.612
Peak troponin levels and coronary abnormalities			
Coronary abnormalities on admission	1 (3%)	5 (10.6%)	0.204
Coronary abnormalities during admission	3 (9.1%)	11 (23.4%)	0.085
Coronary abnormalities at discharge	2 (6.1%)	8 (17%)	0.131
Coronary abnormalities at office visit 1	0 (0.0%)	1 (2.1%)	0.587
Coronary abnormalities at office visit 2	0 (0.0%)	1 (2.1%)	0.587
Coronary abnormalities on admission	1 (3%)	5 (10.6%)	0.204
	Normal BNP	Elevated BNP	
BNP level at admission and systolic function			
Systolic dysfunction on admission	**0 (0.0%)**	**18 (40.9%)**	**< 0.001**
Peak systolic dysfunction during admission	**3 (8.3%)**	**24 (54.5%)**	**< 0.001**
Systolic dysfunction at discharge	2 (5.6%)	7 (15.9%)	0.135
Systolic dysfunction at office visit 1	0 (0.0%)	0 (0.0%)	Not applicable
Systolic dysfunction at office visit 2	0 (0.0%)	0 (0.0%)	Not applicable
Peak BNP levels and systolic function			
Systolic dysfunction on admission	**0 (0.0%)**	**18 (27.7%)**	**0.014**
Peak systolic dysfunction during admission	**1 (6.7%)**	**26 (40%)**	**0.011**
Systolic dysfunction at discharge	1 (6.7%)	8 (12.3%)	0.464
Systolic dysfunction at office visit 1	0 (0.0%)	0 (0.0%)	Not applicable
Systolic dysfunction at office visit 2	0 (0.0%)	0 (0.0%)	Not applicable
BNP at admission and coronary abnormalities			
Coronary abnormalities on admission	3 (8.3%)	3 (6.8%)	0.562
Coronary abnormalities during admission	5 (13.9%)	9 (20.5%)	0.321
Coronary abnormalities at discharge	3 (8.3%)	7 (15.9%)	0.251
Coronary abnormalities at office visit 1	0 (0.0%)	1 (1.9%)	0.550
Coronary abnormalities at office visit 2	0 (0.0%)	1 (1.9%)	0.550
Peak BNP and coronary artery abnormalities			
Coronary abnormalities on admission	0 (0.0%)	6 (9.2%)	0.275
Coronary abnormalities during admission	2 (13.3%)	12 (18.5%)	0.484
Coronary abnormalities at discharge	2 (13.3%)	8 (12.3%)	0.600
Coronary abnormalities at office visit 1	0 (0.0%)	1 (1.5%)	0.812

Table 4 (continued)

	Normal BNP	Elevated BNP	
Coronary abnormalities at office visit 2	0 (0.0%)	1 (1.5%)	0.812
	Normal systolic function	Depressed systolic function	
Systolic heart function on admission and coronary artery abnormalities			
Coronary abnormalities on admission	5 (8.1%)	1 (5.6%)	0.592
Coronary abnormalities during admission	10 (16.1%)	4 (22.2%)	0.135
Coronary abnormalities at discharge	7 (11.3%)	3 (16.7%)	0.208
Coronary abnormalities at office visit 1	1 (1.9%)	0 (0.0%)	0.736
Coronary abnormalities at office visit 2	1 (1.9%)	0 (0.0%)	0.736
Trough of systolic heart function and coronary artery abnormalities			
Coronary abnormalities on admission	5 (8.1%)	1 (5.6%)	0.592
Coronary abnormalities during admission	7 (13.2%)	7 (25.9%)	0.135
Coronary abnormalities at discharge	5 (9.4%)	5 (18.5%)	0.208
Coronary abnormalities at office visit 1	1 (1.9%)	0 (0.0%)	0.698
Coronary abnormalities at office visit 2	1 (1.9%)	0 (0.0%)	0.698

Bold indicates statistically significant results

Table 5 Pertinent cardiovascular magnetic resonance features of patients with MIS-C on intermediate follow up

Serial no	Peak troponin, pg/ml	Peak BNP, pg/ml	Minimum echo LVEF, %	CMR LVEDVi, ml/m2	CMR LVEF, %	CMR RVEDVi, ml/m2	CMR RVEF, %	CMR LAVi, ml/m2	CMR LGE/T2 abnormality
1	2.45	1916	**54**	71	58	71.9	50	25	None
2	18.7	2959	**51**	67	56	72.3	47	14.5	None
3	0.677	6677	**25**	79.6	**54**	83.5	52	27	None
4	0.359	634.8	**40**	71	61	65.2	64	**34**	None
5	0.057	3393.8	**46**	66.2	64	69.1	55	30	None
6	0.012	24.7	**54**	80.3	55	74.5	55	25	None
7	0.244	761	56	76.5	56	69.3	58	22	None
8	0.11	120	63.2	65.3	56	66.8	50	28	None
9	5.46	361	**46.8**	54.6	**54**	53.7	52	19	**LGE+**
10	0.325	1070.8	60	57	59	69.1	54	24	**LGE+**
11	0.59	1375.7	62	76	64	80.5	53	30	None
12	0.191	1943	**35**	76.3	56	71.2	61	27	None
13	0.359	634	**44**	71	61	65.2	64	**35**	None
14	1.28	1354	**50**	79.8	57	73.9	54	20	None
15	0.05	600	**54**	65.6	55	63.3	51	21	None
16	1.22	7044	**32**	54.9	62	54.9	60	19	None
17	1.07	344	**48**	85.7	58	74.5	57	**47**	None
18	2.89	1245	**53**	**99.4**	56	102.8	54	4**0**	None
19	5.9	2137	**38**	71.4	65	87.1	57	**34**	**LGE+**
20	10.6	3010	**38**	94	**51**	100	45	27	None
21	0.12	314	57	79	58	79	51	28	None
22	1.06	5543	**45**	82.4	59	82.5	48	29	None
23	0.92	1234	58	78.6	56	78.3	54	25	**LGE+**
24	0.84	1100	**53**	58.6	57	69.7	53	24	None

Bold indicates statistically significant results

of the cohort of patient described by us is consistent with current available literature [6, 11, 13–15]. This study reiterates that there is no specific age or gender distribution and patients as young as 6 months could be affected. The median age correlates with contemporary large single and multicenter studies [5, 6, 8, 13–15, 34]. Although, some of the initial reports had shown increased prevalence of this diagnosis among the Hispanic population, larger single center and multicenter studies have confirmed increased prevalence among the non-Hispanic Black population [15]. This is true in our cohort as well, although ours being a single center study, the influence of general demographics of our city could influence the racial distribution of MIS-C patients in this cohort.

Left ventricular systolic dysfunction has been described in 31 to 100% of patients with MIS-C depending on the definition and inclusion criteria [5–15, 35–37]. Most of the studies, describe a combination of mild, moderate, and severe dysfunction, except Grimaud et al. who describes a case series of 20 patients with cardiogenic shock (every patient has LVEF < 35%) from Paris [7]. The largest multicenter case series by Feldstein et al. describes myocardial depression in 34.2% patients, with mild depression in 55.2% of them and severe depression in 22.1% [6]. Using similar criteria for grading systolic dysfunction, our results are comparable with 33.8% presenting with depressed myocardial function during the course of illness. It is interesting to note that, whereas 33.8% of the patients had myocardial dysfunction during the study, 87.5% of these patients had abnormal LVEF in the first echocardiogram (done within 24 h of admission), although a significant number of patients had progressive worsening of LVEF during the course of illness. This underscores the importance of obtaining the first echocardiogram, within 24 h of admission but also illustrates that subsequent echocardiogram are useful to follow any abnormal LVEF and the need and frequency can be dictated by this first echocardiogram. At the time of discharge mild dysfunction persisted in 11.3% of the patient, similar to contemporary literature which describes persistence of ventricular dysfunction in 6–14% [6, 8, 16].

The natural history of this persistent systolic dysfunction is available in only a handful of studies. Feldstein et al. describes resolution of myocardial dysfunction in 91%, within 30 days and 99.4% within 90 days [6]. Similarly, Belhadjer et al. described residual mild to moderate dysfunction in 14.8%, with a median follow up of 12 days [8]. Penner et al. in a large single center study from UK, described resolution of LV dysfunction in all patients by 6 months [38]. Similar inferences were drawn from studies by Capone et al., Aziz et al. and Dove et al. [19, 23, 24] Most of the other studies describe near complete resolution of myocardial dysfunction with 4–18 days at the time of discharge [7, 13, 14, 17, 35, 36]. Our study specifically investigates the natural history of the myocardial dysfunction. There was complete resolution of the depressed myocardial systolic function by 2 weeks following discharge in all patients and none of the patients had any recurrence of systolic dysfunction at their 1-year follow-up.

Subclinical myocardial damage presenting in the form of diastolic dysfunction and abnormal speckled tracking, or strain pattern is even more sparse and complicated by lack of uniform standards in measuring such data in children as well as considerable variability in the parameters used by each one of the authors. Capone et al. describes persistence of diastolic dysfunction, (measured by conventional Doppler indices similar to our study), in 11% of the patients at 2 weeks following discharge and in 4% at 6 months following discharge [19]. This is comparable to our results of 13.8% and 6.3% at 2 weeks and 6 months respectively. Matsubara et al. in their cohort of 28 patients with MIS-C describe abnormal global longitudinal strain, global circumferential strain, peak left atrial strain and peak longitudinal strain of the right ventricular free wall [39]. In this study both systolic and diastolic dysfunction during the acute and subacute phase was demonstrated in patients with MIS-C when compared with a control group. During early follow (5.2 ± 3 days), the authors also describe resolution of systolic dysfunction but persistence of abnormal global longitudinal strain and diastolic dysfunction. In a recent follow-up study by Matsubara et al. conventional echocardiograms and echo derived deformation parameters followed longitudinally in 60 patients with MIS-C in the acute phase and 25 of them were followed up to 4 months [20]. This study again demonstrated slow recovery of diastolic function and normalization by 3–4 months. Despite the use of different methods to assess diastolic function across these studies it is reasonable to infer, diastolic dysfunction persists longer in a limited number of patients for at least 4–6 months. Our study further confirms this hypothesis in a larger patient population and reiterates that a small percentage of patients (6.3%) continue to have diastolic dysfunction, till 6 months and almost completely normalizes by 1-year. This gradual resolution of diastolic dysfunction in contrast to rapid resolution of systolic dysfunction, probably emphasizes the heterogeneity in the degree of myocardial damage associated with MIS-C, and although clinical resolution of cardiac manifestation is the norm, subclinical myocardial injury may persist in a small group of patients with longer time to recovery.

It is noteworthy that although some patients had a trace or small pericardial effusion, a clinically significant pericardial effusion needing intervention or pericarditis, was not a clinical manifestation of MIS-C with spontaneous resolution of the small pericardial effusion in majority of the patients, consistent with contemporary studies. The development of MR in vast majority of the patients closely followed

development of myocardial dysfunction. Once again, the natural history of MR is unclear from contemporary studies. Clinically significant myocardial dysfunction was present in almost every patient with an abnormal LVEF. However, it is probably more imperative to point out that whereas only 15.1% patients, had abnormal LVEF at discharge, a significantly larger number (30.2%), continued to have a significant MR at the time of discharge. Thus, it can be inferred that resolution of MR lags the resolution of systolic dysfunction to a significant extent. However, almost all patients had complete resolution of MR by 6-months without any intervention. This further strengthens the hypothesis there may be subtle long-term cardiac injury from MIS-C which takes a longer time to recover [5, 6, 20, 39, 40].

Coronary artery abnormalities have been described in 6–46% of the patients with MIS-C, based on the definition of coronary involvement [5, 6, 9, 16–18]. Similar to our results, the coronary artery involvement has been described as dilation or mild aneurysm in most of the published studies. Giant aneurysm although extremely rare, have been described [14, 23, 37, 38]. Feldstein et al. identified 93% of the coronary abnormalities as mild aneurysm and 4% as a moderate aneurysm without any giant or large aneurysm [6]. The same study describes 100% resolution of these abnormalities within 90 days although the number of patients in which this follow-up data was available was limited. Whittaker et al. in a multicenter study from UK, describes giant aneurysm in 3.5%, whereas Riphagen et al. describes 1 patient with a giant aneurysm [14, 37]. The natural history of this giant coronary aneurysm is unknown. Our study, similar to the contemporary studies illustrates the persistence of coronary aneurysms in 10% of the patients. The natural history of these coronary artery abnormalities was available in all our patients with complete resolution in all patients except the one with a giant aneurysm, who continued to have the giant aneurysm at the 1-year follow-up visit. Similar persistent coronary aneurysm in a small minority of patients at 6-months have been reported by Aziz et al. and Penner et al. [23, 38]. Importantly, our study shows that cardiac biomarkers and abnormal left ventricular function do not predict neither development of coronary artery abnormalities nor their persistence. This probably highlights two important inferences. One is that these cardiac biomarkers should not be used to predict coronary artery abnormalities. And two, the ventricular dysfunction and coronary artery abnormalities probably represent two different pathophysiological processes.

With evidence of persistent diastolic dysfunction in a subgroup of patients up to 6-months, and suspicion of ongoing subclinical damage or previous scarring, CMR is an additional armament to help distinguish between these two processes and potentially provides novel insights into prognosis and pathophysiology. Since our last publication on mid-term CMR results from the same cohort, CMR was available in 3 more patients [25]. The most important findings from CMR were identification of LGE in 18% of the patients during medium-term follow-up. Aeschlimann et al. described CMR findings in MIS-C patients within 4 weeks of diagnosis and report diagnosis of myocarditis in 18% and LGE in 16% [41]. In contrast Webster et al. ($n=6$) reported normal tissue characteristics, in the absence of gadolinium use shortly after MIS-C [42]. In the short-term follow-up outcomes reported by Bartozsek et al., and Capone et al. LGE were not demonstrated [19, 43]. Medium-term outcomes have been described by Barris et al. ($n=9$), Dilorenzo et al. ($n=13$) and Dove et al. ($n=51$) [24, 44, 45]. Myocardial edema on T2 weighted image was reported by Barris et al. in 44%, the reason for this large number of patients having persistent abnormal T2 weighted signal ratio, long after initial insult is unclear [44]. In contrast, Dilorenzo et al. and Dove et al. similar to our study did not report any myocardial edema but presence of LGE in 7.6% and 3.9% respectively [24, 45]. We postulate this presence of LGE during mid-term follow in these multiple single center studies represents scarring from previous myocardial injury, analogous to acute viral myocarditis. This further highlights the importance of obtaining CMR at least in a selected group of patients, to detect subclinical myocardial damage as well as to provide new insights into the natural history of the disease. We further believe that patients who have evidence of LGE, particularly with systolic or diastolic dysfunction might benefit from a longer and closer follow-up than the ones with normal CMR.

Elevated troponin and BNP levels have been described in 25 to 100% of the patients [5, 6, 12, 16, 17, 36, 46]. This study, like most of the contemporary studies illustrate that normalization of the Troponin and BNP levels lag behind resolution of ventricular dysfunction [5, 6, 8, 16, 35]. Hence, isolated residual abnormalities in these cardiac biomarkers should not preclude discharge as long as the levels are serially down-trending. The study further highlights that although a small Troponin leak and BNP abnormality may be present at the time of discharge, complete resolution within 2 weeks in general was the rule. In our opinion the most significant role of the Troponin and BNP was found in predicting ventricular dysfunction. Specifically, an elevated Troponin and BNP at the time of admission was highly predictive of ventricular dysfunction. Our study did not find any prognostic value of either peak Troponin or BNP values. Therefore, excessive blood draws to measure these biomarkers frequently is probably not indicated. Our study was also unique in time trending these cardiac biomarkers and it is apparent that the median time for troponin to peak was day 1 of admission and BNP on day 3 of admission. This further highlights the relative futility of serial measurements once the downtrend is demonstrated. It was interesting to note that a significant

number of patients had a rise in their BNP levels after administration of IVIG. This is most likely representative of the volume load that accompanies the infusion, as many patients without any troponin leak or elevated BNP throughout admission also had transient BNP elevations after the IVIG was administered.

Although there has been occasional description of sustained arrhythmias leading to hemodynamic collapse related to this condition [14, 37], the vast majority of rhythm abnormalities have been described as benign and present in 7–60% of patients. This included ST-T wave changes, QTc prolongation, premature atrial and ventricular beats, and heart block [6, 8, 14, 16, 36, 37]. Our study is in concurrence with contemporary studies with a prolonged PR interval in 22.6% of patients and ST-T wave changes in 34%. It is interesting to know that these changes persisted through discharge in majority of patients. However, most of these changes were resolved within 2 weeks of discharge. Intriguingly there were 4 patients with sustained PR prolongation at 1-year follow up. Each of these patients showed improvement in the PR interval with exercise. The natural history of these changes was not available from contemporary studies.

Our study also describes the largest and only available literature on exercise stress tests in patents with MIS-C. It is reassuring to note that all 36.2% of patents who underwent a GXT had normal results. This is also the population of patients with highest Troponin leaks and depressed LVEF during hospitalization. We believe that this suggests although a minority of patients may present with evidence of subclinical myocardial injury long after clinical recovery, the overall clinical prognosis is favorable.

The existential question for the clinician on when to return to play after a COVID-19 infection continues to be answered [45] but the general recommendations for MIS-C is to follow myocarditis guidelines of exercise restriction for 4–6 months guided by advanced testing with an exercise stress test ± a CMR [47, 48]. This further re-iterates the importance of a systematic protocol-based outpatient follow-up of this cohort. It provides reassurance and practical guidance to pediatricians and families on return to competitive sport with shared decision making. In a pandemic where clinicians and hospital systems are fraught with limited resources, longitudinal natural history follow-up studies of this nature offer insight to the clinician on the duration of follow up needed, risk stratification guidance and may potentially help tailor advanced testing to only a high-risk sub-set of MIS-C patients.

Limitations

This is a single-center study, and the results cannot be generalized. As a reflection of the general population that is served in the region, there was an unequal racial and ethnic distribution which precluded the study comparison of outcomes based on race and ethnicity. The time-gap in testing between discharge from hospital to the first 2-week follow-up appointment, limits our ability to predict the exact timeline for normalization of cardiac biomarkers. CMR techniques of T1 mapping, T2 mapping, and extracellular volume are not available at our center. Since a risk-based tailored approach was used for advanced cardiac testing (CMR and GXT), the true incidence of LGE or an abnormal GXT may be under-represented.

Conclusions

In conclusion MIS-C is a complex and heterogenous cardiovascular disease and has a spectrum of underlying pathophysiology, that needs further investigation. While clinical recovery is a norm, there is a small subset of patients with sequelae of subclinical myocardial damage. The successful use of an institutional outpatient follow-up protocol provides natural history data and potentially paves the way towards development of a universal protocol for the outpatient cardiovascular management of this condition.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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