ORIGINAL RESEARCH

Longitudinal Assessment of Cardiac Outcomes of Multisystem Inflammatory Syndrome in Children Associated With COVID-19 Infections

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BACKGROUND: In multisystem inflammatory syndrome in children, there is paucity of longitudinal data on cardiac outcomes. We analyzed cardiac outcomes 3 to 4 months after initial presentation using echocardiography and cardiac magnetic resonance imaging.

METHODS AND RESULTS: We included 60 controls and 60 cases of multisystem inflammatory syndrome in children. Conventional echocardiograms and deformation parameters were analyzed at 4 time points: (1) acute phase (n=60), (2) subacute phase (n=50; median, 3 days after initial echocardiography), (3) 1-month follow-up (n=39; median, 22 days), and (4) 3- to 4-month follow-up (n=25; median, 91 days). Fourteen consecutive cardiac magnetic resonance imaging studies were reviewed for myocardial edema or fibrosis during subacute (n=5) and follow-up (n=9) stages. In acute phase, myocardial injury was defined as troponin-I level ≥0.09 ng/mL (>3 times normal) or brain-type natriuretic peptide >800 pg/mL. All deformation parameters, including left ventricular global longitudinal strain, peak left atrial strain, longitudinal early diastolic strain rate, and right ventricular free wall strain, recovered quickly within the first week, followed by continued improvement and complete normalization by 3 months. Median time to normalization of both global longitudinal strain and left atrial strain was 6 days (95% CI, 3–9 days). Myocardial injury at presentation (70% of multisystem inflammatory syndrome in children cases) did not affect short-term outcomes. Four patients (7%) had small coronary aneurysms at presentation, all of which resolved. Only 1 of 9 patients had residual edema but no fibrosis by cardiac magnetic resonance imaging.

CONCLUSIONS: Our short-term study suggests that functional recovery and coronary outcomes are good in multisystem inflammatory syndrome in children. Use of sensitive deformation parameters provides further reassurance that there is no persistent subclinical dysfunction after 3 months.

Key Words: cardiac function ■ cardiac magnetic resonance imaging ■ coronary artery ■ echocardiography ■ multisystem inflammatory syndrome in children ■ strain

Multisystem inflammatory syndrome in children (MIS-C) is a newly described hyperinflammatory syndrome associated with antecedent COVID-19 exposure.[1] Cardiovascular involvement is frequent (80%–85% of cases), including shock, left ventricular (LV) dysfunction, coronary artery abnormalities, and biochemical evidence of myocardial injury.[2,3] Approximately 50% of children with MIS-C have decreased LV systolic function by conventional echocardiography during acute illness. Although LV ejection

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CLINICAL PERSPECTIVE

What Is New?

- We analyzed cardiac outcomes 3 to 4 months after initial presentation of multisystem inflammatory syndrome in children using conventional and speckle-tracking echocardiography and cardiac magnetic resonance imaging.
- All strain parameters, including left ventricular global longitudinal strain, peak left atrial strain, longitudinal early diastolic strain rate, and right ventricular free wall strain, improved quickly within the first week, followed by continued improvement and complete normalization by 3 months, suggesting absence of persistent subclinical dysfunction after 3 months.
- Reassuringly, there was no fibrosis in cardiac chambers in the few children who underwent follow-up cardiac magnetic resonance imaging; coronary outcomes were good during 3 to 4 months after initial presentation of multisystem inflammatory syndrome in children.

What Are the Clinical Implications?

- These findings may provide early guidelines for outpatient management strategies and recommendations for returning to competitive sports after 3 months.
- The echocardiographic parameters described in this study may form the basis of future long-term follow-up studies.

Nonstandard Abbreviations and Acronyms

CAA	coronary artery abnormality
EDSR$_L$	longitudinal early diastolic strain rate
GCS	systolic circumferential strain
GLS	global longitudinal strain
LAS	left atrial strain
MIS-C	multisystem inflammatory syndrome in children
RVFWS	right ventricular free wall strain

fraction (LVEF) improves rapidly before discharge from the hospital,[2,4] we have previously demonstrated that diastolic dysfunction measured by deformation parameters (strain) persists during the subacute phase.[5] In addition, because of similarities between MIS-C and Kawasaki disease, coronary abnormalities have garnered significant attention. The reported incidence of coronary abnormalities varies widely (4%–24%),[2,5] and includes cases of progressive coronary artery aneurysms following discharge.[6] Therefore, a detailed characterization of functional and coronary outcomes in this population is needed to generate follow-up guidelines and reduce ambiguity about follow-up.

The aim of this study is to describe cardiac outcomes during a 3-month follow-up period, to determine the short-term impact of acute myocardial injury caused by MIS-C. We hypothesize that children with MIS-C will have good functional recovery during this short-term follow-up period, regardless of biochemical evidence of myocardial injury in the acute phase.

METHODS

The data that support the findings of this study are not publicly available because of information that could compromise patient privacy. Requests to access a limited data set from qualified researchers trained in human subject confidentiality protocols may be sent to Dr Anirban Banerjee at the Children's Hospital of Philadelphia.

Study Design

This is a retrospective, longitudinal cohort study of cardiac outcomes in children with MIS-C.

Study Population

We included children aged ≤18 years admitted to the Children's Hospital of Philadelphia or its affiliate institution, St. Peter's University Hospital, meeting classification criteria for MIS-C from April 2020 to January 2021. The diagnosis of MIS-C was made according to the Centers for Disease Control and Prevention or World Health Organization definitions,[7,8] and secondarily adjudicated by a pediatric rheumatologist (J.C.) before inclusion. All subjects had confirmed SARS-CoV-2 exposure by nasopharyngeal reverse transcriptase polymerase chain reaction test or serum IgG antibody positivity. Exclusion criteria included a previous history of cardiac dysfunction, congenital heart disease, exposure to cardiotoxic agents, and chronic lung disease, and patients treated with extracorporeal membrane oxygenation. As controls, we included age-matched healthy children with structurally normal hearts, who underwent echocardiography at the same centers to evaluate benign heart murmurs, chest pain, syncope, or a family history of cardiac disease. Of the control subjects, 60% were chosen from the pre–COVID-19 pandemic era before January 2020. The remaining 40% of the control subjects were selected from patients who had echocardiograms performed under the strict infection-control regulations in our institution during the COVID-19 pandemic era after October 2020, which required the absence of any COVID-19–related symptoms. However, SARS-CoV-2 testing was not required, and therefore previous exposure status was unknown.

Study Procedures

This study was approved by the Institutional Review Boards of Children's Hospital of Philadelphia (20-018085) and St. Peter's University Hospital (20:95).

We retrospectively analyzed 2-dimensional transthoracic echocardiograms at the following 4 time points in MIS-C patients: (1) acute phase (initial hospitalization), (2) subacute phase (within 1 week of the first echocardiogram), (3) 1-month follow-up, and (4) 3- to 4-month follow-up. For patients with multiple echocardiograms in the acute phase, the study demonstrating the worst LV function was used for analysis. Subacute phase was defined as the period after the complete withdrawal of all vasoactive-inotropic support during the hospitalization. Because of lack of standardization of clinical protocols, the follow-up period exceeded 3 months in some patients.

Conventional Echocardiography

Two-dimensional echocardiography was performed by pediatric cardiac sonographers using Affiniti 70C (Philips Medical Systems, Andover, MA) or EPIQ CVx ultrasound system (Philips Medical Systems). Standard echocardiographic measurements of cardiac systolic and diastolic function were obtained according to American Society of Echocardiography guidelines.[9] LVEF was confirmed by 2 reviewers (A.B. and D.M.) in all studies.

Coronary artery abnormalities (CAAs) of right coronary or left main coronary artery or left anterior descending artery were evaluated in accordance with standard guidelines,[10] and measurements were rechecked by 3 investigators (D.M., A.B., and M.Q.; the latter 2 were blinded to the diagnosis). Left main coronary artery was measured with caution at the midpoint, away from the ostium and the bifurcation points. Coronary artery z-scores were derived from normative data (Boston z-score system) and classified as follows: normal, <2; dilatation, >2 to <2.5; and aneurysm, ≥2.5.

Speckle-Tracking Echocardiography

Two-dimensional speckle-tracking analysis was performed offline to assess myocardial deformation using a vendor-independent software (2D CPA 1.3.0.91; TomTec Imaging Systems, Munich, Germany), as previously described.[5] Briefly, both systolic global longitudinal strain (GLS) and GLS rate from the endocardium were averaged from measurements from 4-, 3-, and 2-chamber views. LV segmental longitudinal strain values were calculated using the 17-segment model and averaged for basal, mid, and apical segments generated by the software. Longitudinal early diastolic strain rate ($EDSR_L$), peak global left atrial strain (LAS), and peak longitudinal strain of the right ventricular (RV) free wall were measured from 4-chamber images. Peak systolic circumferential strain (GCS), peak systolic circumferential strain rate, and circumferential early diastolic strain rate were obtained from midcavity short-axis views. $EDSR_L$, $EDSR_C$, and LAS were used as indexes of LV diastolic dysfunction.[11,12]

Clinical Data

We abstracted clinical data from medical records, including demographic factors (age, sex, race, and ethnicity); hospital outcomes (length of stay, intensive care, and respiratory support); treatment (inotropic and immunomodulatory agents); and laboratory data (acute phase reactants, troponin-I [Abbott Laboratories, Abbott Park, IL], and brain-type natriuretic peptide [BNP]). Biochemical evidence of myocardial injury was defined as maximum troponin-I level ≥0.09 ng/mL (>3 times the upper limits of normal values) or BNP >800 pg/mL.[13,14] All ECGs were reevaluated by the researchers from the acute to follow-up stages. New York Heart Association functional classification at the last visit was used as a clinical outcome.

Cardiovascular Magnetic Resonance Imaging

We retrospectively reviewed cardiac magnetic resonance imaging (CMR) studies obtained for clinical purposes to confirm the diagnosis of myocarditis along with assessment of ventricular function and coronary arteries during the acute stage. Patients with severe LV systolic dysfunction with highly abnormal baseline CMR during acute stage or with continued evidence of severe LV dysfunction by echocardiography during the follow-up stage were candidates for a repeated CMR. The CMR was performed on a 1.5-T Siemens Avanto FIT Whole Body MRI system (Siemens Medical Solutions, Erlanghen, Germany) using CVI42 software (Circle Cardiovascular, Calgary, Canada) and included (1) ventricular function with ejection fraction, (2) T1 mapping using the modified Look-Locker inversion recovery sequence (MOLLI) and late gadolinium enhancement to document fibrosis, (3) T2-weighted imaging and T2 mapping to document edema, and (4) gadolinium-enhanced 3-dimensional inversion recovery gradient echo coronary imaging for coronary visualization. Fibrosis was defined as exceeding upper limits of normal for native T1 relaxation time or increased extracellular volume or the presence of nonischemic patterns of late gadolinium enhancement. Myocardial edema was defined as an increased T2 relaxation time (>60 ms) or a ratio of the myocardial signal intensity divided by the skeletal muscle signal intensity >1.9 on T2-weighted imaging. Myocarditis was defined using the criteria based on expert recommendations.[15]

Study Measures
Functional Outcomes

Primary outcomes included strain parameters (GLS, $EDSR_L$, RV free wall strain [RVFWS], and LAS). Secondary outcomes included other conventional echocardiographic parameters i.e. LVEF, left ventricular fractional shortening (LVFS), ratio of peak early diastolic filling velocity (E) over early diastolic mitral annular velocity (e′), expressed as an average of septal and lateral annular velocities (E/e′), and tricuspid annular plane systolic excursion (TAPSE), and additional strain measures of LV systolic function (GCS, GLS rate, and GCS rate) and LV diastolic function (circumferential early diastolic strain rate). We defined LV and RV systolic dysfunction by GLS < −17% and RVFWS < −21%.[16,17] Because of the lack of normative pediatric reference data for $EDSR_L$ and LAS, we used the distribution in our controls to define abnormal cutoff values.

Structural Outcomes

We included the presence of CAAs as a binary outcome.

Myocardial Characteristics

The presence of myocardial edema or fibrosis by CMR.

Statistical Analysis

Baseline characteristics were summarized using standard descriptive statistics and compared using Fisher exact tests for categorical variables and Student t test or Wilcoxon rank-sum test for continuous variables, as appropriate. Normality was assessed using Shapiro-Wilk test.

To estimate changes in strain over time among subjects with MIS-C, we used linear mixed effects models, an extension of simple linear models that allow for both fixed and random effects, including within-subject correlation attributable to repeated measures. Mixed effects models use maximum likelihood methods for estimation, and introduce less bias in the presence of missing data. Subject-specific random effects were modeled using an autoregressive covariance structure to allow for unbalanced data and declining correlation between measures with increasing time. We assumed a random intercept to allow for variation in initial strain values. To determine whether rates of improvement over time differed between those with or without acute phase myocardial injury, we tested interactions between myocardial injury and time using Wald χ^2 tests. Patterns of missing follow-up echocardiograms were evaluated using χ^2 tests and t tests, as appropriate, and a missing at random mechanism was assumed.

We used Kaplan-Meier survival curves to estimate median time to recovery of normal function for subjects with MIS-C with abnormal strain at baseline.

To compare strains between MIS-C cases at follow-up and controls, we used linear regression models adjusted for body mass index percentiles for age and sex. We tested other potential confounders, including heart rate, age, race, and ethnicity, and retained them in the models only if strain estimates changed by >10%. To account for multiple comparisons, we used the Benjamini-Hochberg procedure to control the false discovery rate at 5%.

All statistical analyses were performed using STATA 15.0 (College Station, TX) using a 2-sided significance level of 0.05.

Reliability

Intraclass correlation coefficients were used to assess intraobserver and interobserver reliability for GLS, $EDSR_L$, and LAS. We randomly selected 14 patients for de novo measurement for these parameters by 2 investigators (A.B. and D.M.). For intraobserver reliability, one observer (D.M.) repeated each measurement after 4 weeks. We have previously shown excellent intraobserver and interobserver reliability of RVFWS in our laboratory, which were not repeated in this study.[18]

RESULTS
Subject Characteristics

We identified 60 controls and 61 MIS-C cases, of which 1 patient with MIS-C was excluded because of the incidental discovery of a congenital coronary artery anomaly, by subsequent CMR (total MIS-C=60). In the acute phase, all 60 subjects with MIS-C had evaluable echocardiograms. During the subacute phase (median, 3 days after initial echocardiography), 50 had repeated echocardiograms attributable to clinical indications, 39 returned for 1-month follow-up (median, 22 days), and 25 had 3- to 4-month follow-up (median, 91 days). One patient had 3-month follow-up study without subacute and 1-month follow-up studies (schematically depicted in Figure 1).

Most were treated with intravenous immunoglobulin (90%) and/or systemic steroids (92%). Of the 60 subjects with MIS-C, 42 had evidence of myocardial injury at the time of presentation (isolated elevated BNP, n=6; isolated elevated troponin, n=13; elevation of both, n=23). It is noteworthy that the BNP levels in these 6 patients greatly exceeded the 97.5 percentile values in children by many fold.[14] Although 70% had biochemical evidence of myocardial injury at their initial presentation, in most of them their cardiac markers returned to normal levels in the subacute stage before discharge. There were no deaths or unexpected cardiac events during follow-up. All subjects were classified as New York Heart Association
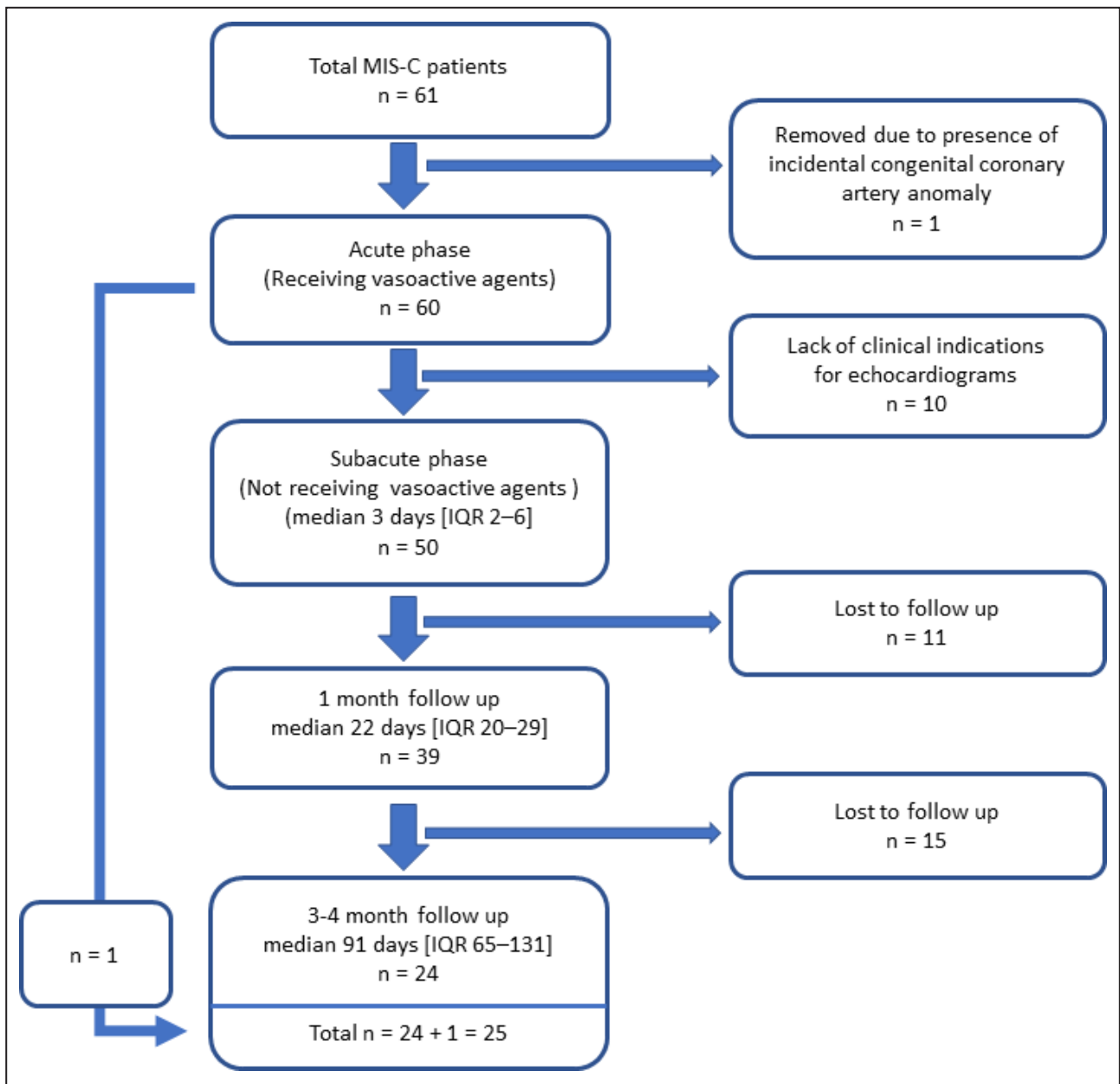
Figure 1. Schematic representation of our study population from the acute to the follow-up stages.
IQR indicates interquartile range; and MIS-C, multisystem inflammatory syndrome in children.

class I at their last clinical visit without cardiac symptoms, fatigue, or other symptoms suggestive of the prolonged post–COVID-19 syndromes described in adults (Table 1).

Patterns of Improvement in Cardiac Function Over Time

Mean strain values over time estimated from linear mixed effects models are illustrated in Figure 2. There was a rapid initial improvement in LVEF, GLS, RVFWS, and LAS within the first week, followed by continued gradual improvement through the 3-month follow-up period (Table 2, Figure 3, and Table S1). It is notable that 81% of patients with myocardial injury lost the left atrial (LA) contraction phase during the acute phase of illness (Figure 3B, white arrow). In the immediate subacute stage, 52% lost the contraction phase; and at the 1-month interval, 30% continued to manifest loss of LA contraction phase. Finally, the LA contraction phase normalized in all patients by 3 to 4 months. Diastolic function by $EDSR_L$ did not show rapid initial improvement within the first week compared with the other strain parameters, but still normalized by 3 months (Figure 2D and Table S2). Compared with controls, subjects with MIS-C had significant impairments across all strain parameters

**Table 1. Demographics in MIS-C and Control Groups**

Variables	MIS-C (n=60)	Control (n=60)	*P* value
Age, mean±SD, y	10.0±4.3	11.5±3.9	0.10
Men, n (%)	36 (60)	33 (55)	0.58
BMI, median (IQR), percentile for age and sex	92 (75–98)	79 (49–93)	0.01
Race, n (%)			<0.01
White	16 (27)	37 (62)	
Black	29 (48)	16 (27)	
Asian	2 (4)	2 (3)	
Other/unknown	13 (23)	5 (8)	
Hispanic ethnicity, n (%)	9 (15)	4 (7)	0.15
Hospital outcomes and treatment exposure			
Hospital length of stay, median (IQR), days	6 (4–9)		
ICU admission, n (%)	42 (70)		
Vasoactive-inotropic agents, n (%)	30 (50)		
Need for invasive ventilation, n (%)	13 (22)		
Intravenous immunoglobulin, n (%)	54 (90)		
Systemic steroids, n (%)	55 (92)		
Laboratory characteristics, n/total (%)			
SARS-CoV-2 PCR (+)	26/58 (45)		
SARS-CoV-2 IgG (+)	52/53 (98)		
Organ dysfunction, median (IQR)			
Troponin-I (ng/mL)	0.24 (0.03–0.91)		
BNP, pg/mL	795 (428–1270)		
eGFR, mL/min per 1.73 m^2	91 (65–110)		
Acute phase reactants, median (IQR)			
CRP, mg/dL	19.9 (15.8–25.8)		
D-dimer, mg/dL	4.9 (2.4–7.8)		
Ferritin, ng/mL	738 (447–1131)		
Hematologic abnormalities, median (IQR)			
Hemoglobin, g/dL	9.0 (7.9–10.0)		
Platelet count, 10^3/μL	153 (118–193)		
Absolute lymphocyte count, /μL	495 (300–895)		
Lactate dehydrogenase, U/L	686 (539–896)		
Clinical outcome, n/total (%)			
New York Heart Association classification at the last clinical visit	I: 51/51 (100)		
	II: 0		
	III: 0		
	IV: 0		

BMI indicates body mass index; BNP, brain-type natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; and PCR, nasopharyngeal reverse transcriptase polymerase chain reaction test. Race was self-reported upon registration.

at 1-month follow-up, adjusted for heart rate and body mass index percentile (Table 3). Further adjustment for race or ethnicity did not significantly change the results and therefore was not included in the final models. By 3-month follow-up, only GLS remained statistically significantly lower among subjects with MIS-C compared with controls; however, this statistical difference in GLS was small and not clinically relevant, because it was within the range of normal published values.[16] There was no difference in the GLS/GCS ratio between acute MIS-C and control conditions, indicating proportionally decreased longitudinal and circumferential contractile patterns without compensatory changes in circumferential strain. LV segmental longitudinal strains demonstrated similar impairments across basal, mid, and apical segments (Table 2 and Figure S1), suggesting global rather than segmental dysfunction.

In the survival curve analysis, the median time to normalization of both GLS and LAS was 6 days (95% CI, 3–9 days) (Figure S2). Median time to normalization
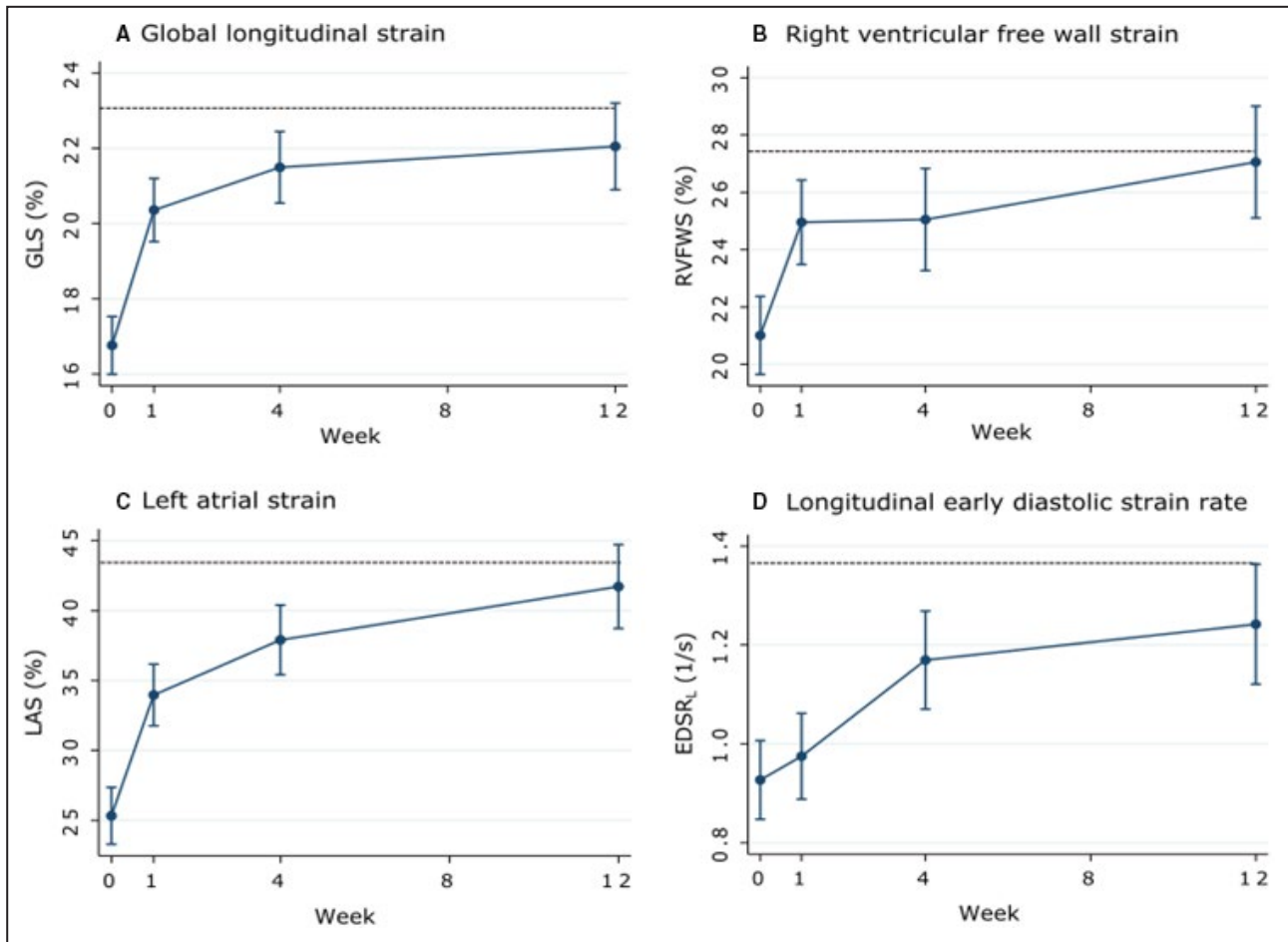
Figure 2. **Mean strain values over time, estimated from mixed effects models.**
Global longitudinal strain (GLS) (**A**), right ventricular free wall strain (RVFWS) (**B**), and peak left atrial strain (LAS) (**C**) improved dramatically within the first week, then continued to improve gradually over 3-month follow-up. **D**, Longitudinal early diastolic strain rate (EDSR$_L$) showed delayed improvement. Week=0 represents the day of first echocardiogram. Dotted lines represent mean values from our control groups. Error bars represent 95% CIs for the mean predictions, calculated using the Δ method of SEs.

of LVEF and RVFWS was 8 days (95% CI, 4–13 days) and 9 days (95% CI, 4–18 days), respectively.

ECGs were available in 54 of 60 (90%) in the acute stage, of which 10 (19%) showed inverted T waves in lateral/inferior leads. In these 10 patients, ECG changes normalized during follow-up (4 within subacute phase, other 5 within 1 month, and the last within 3 months). There was no evidence of high-grade atrioventricular block (ie, second-degree atrioventricular block–Mobitz type II or complete atrioventricular block).

Impact of Myocardial Injury on Short-Term Outcomes

All deformation parameters in the acute phase were worse in patients with biochemical evidence of myocardial injury than in those without (Figure 4). However, GLS and LAS also improved more rapidly between the acute and subacute phases among those with myocardial injury (P values for interaction with time of

0.015 and 0.017, respectively), such that no differences remained between injury (+) and injury (–) patients by 1-month follow-up. On average, over the follow-up period, there was also no statistically significant effect of myocardial injury on RVFWS or EDSR$_L$.

Missing Data

White race and Hispanic ethnicity were associated with a higher likelihood of missing subacute phase echocardiographic data, but not 1- or 3-month follow-up echocardiograms. The dominant reason for the missing data was attributable to the lack of follow-up. The severity of systolic dysfunction in the acute stage was not associated with missingness at any subsequent time point.

Serial Coronary Artery Assessment

Four subjects (4/60, 7%) had small coronary aneurysms involving the right coronary or left anterior descending artery in the acute phase, all of whom

Table 2. Strain Parameters at Each Stage in Follow-Up Study in Patients With MIS-C

| Variables	Acute (n=60)	Subacute (n=50)	1-mo follow-up (n=39)	3-mo follow-up (n=25)	Control (n=60)
GLS, %	−16.8±3.9	−20.2±2.8	−21.4±1.9	−21.8±1.8	−23.2±2.0
Segmental analysis, %					
Base	−15.9±4.1	−19.6±3.5	−21.3±2.2	−21.8±2.6	−22.8±2.9
Mid	−17.1±4.0	−20.4±3.1	−21.9±2.7	−22.2±2.9	−23.7±2.2
Apex	−17.2±4.5	−20.9±3.5	−20.9±2.8	−21.2±2.7	−23.0±2.6
GLSR, 1/s	−0.87±0.2	−0.98±0.2	−1.05±0.2	−1.04±0.2	−1.13±0.1
GCS, %	−18.4±5.3	−23.5±4.1	−25.4±2.9	−26.7±3.4	−26.0±3.2
GCSR, 1/s	−0.99±0.4	−1.21±0.3	−1.39±0.2	−1.33±0.2	−1.41±0.3
GLS/GCS ratio	0.91 (0.81–1.04)	0.86 (0.78–0.97)	0.86 (0.76–0.93)	0.81 (0.75–0.90)	0.90 (0.81–0.99)
$EDSR_L$, 1/s	0.93±0.3	0.98±0.3	1.17±0.3	1.24±0.3	1.37±0.4
$EDSR_C$, 1/s	1.06±0.4	1.17±0.3	1.44±0.4	1.43±0.3	1.61±0.4
LAS, %	25.3±8.8	33.8±8.3	37.6±4.8	41.7±7.9	43.2±7.7
RVFWS, %	−21.1±6.1	−24.8±4.4	−25.1±3.8	−26.7±4.7	−27.5±4.5

Values are expressed as median (interquartile range) or mean±SD. For statistical results on these parameters, please see Table 3 and Table S2. $EDSR_C$ indicates circumferential early diastolic strain rate; $EDSR_L$, longitudinal early diastolic strain rate; GCS, global circumferential strain; GCSR, GCS rate; GLS, global longitudinal strain; GLSR, GLS rate; LAS, left atrial strain; MIS-C, multisystem inflammatory syndrome in children; and RVFWS, right ventricular free wall longitudinal strain.

received intravenous immunoglobulin. All 4 had resolution of coronary aneurysms during follow-up (1 during subacute stage, 2 within 1 month, and the last within 2 months). No newly progressive coronary lesions were detected over the 3-month observation period.

Cardiac Magnetic Resonance Imaging

CMR was available in 15 of 60 (25%) cases, of which 1 patient was excluded because of the incidental finding of anomalous origin of the left coronary artery from the right sinus of Valsalva. Of the evaluable cohort of 14

patients, 12 (86%) had biochemical evidence of myocardial injury at presentation. Five patients underwent CMR during the subacute phase (median, 8 days [interquartile range, 6–10 days]), all of whom had biochemical evidence of myocardial injury, and 9 underwent CMR during follow-up period (median, 162 days [interquartile range, 104–265 days]) (Table 4). Two patients in the subacute phase who had evidence of myocardial edema (1 focal, 1 global) also showed discrete and diffuse fibrosis at the same time, despite normal LV systolic function by strain, conventional echocardiography, and CMR. Only one patient who underwent CMR during follow-up
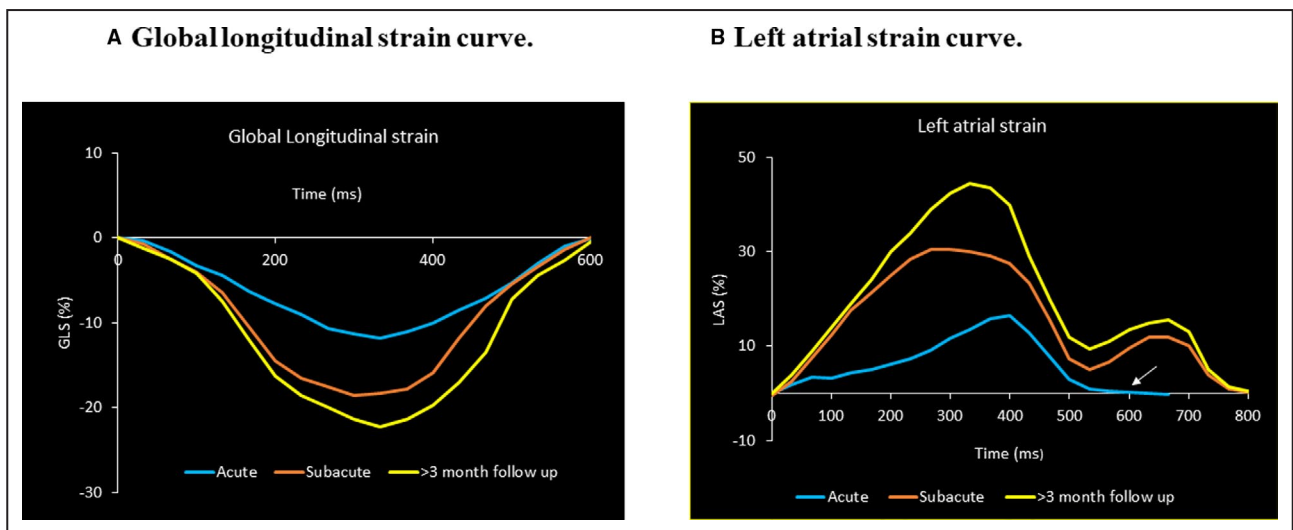
Figure 3. Global longitudinal strain (GLS) curves (A) and left atrial strain (LAS) curves (B) in the same subject with multisystem inflammatory syndrome in children over acute, subacute, and 3-month follow-up study.
Of note, there was a rapid initial improvement in both GLS and LAS within the first week, followed by continued gradual improvement through 3-month follow-up. Moreover, left atrial active contraction phase is lost in the acute phase in this patient (white arrow).

Table 3. Pairwise Comparisons Between MIS-C and Controls at 1- and 3-Month Follow-Up Study (Linear Regression Adjusted for BMI Percentile and Heart Rate)

| Variables	1-mo follow-up (n=39 MIS-C)			3-mo follow-up (n=25 MIS-C)		
	Conditional mean difference*	95% CI	P value	Conditional mean difference*	95% CI	P value
GLS, %	−1.62	−2.5 to −0.7	<0.001†	−1.15	−2.1 to −0.2	0.020†
EDSR$_L$, 1/s	−0.23	−0.4 to −0.1	0.006†	−0.12	−0.3 to 0.1	0.202
LAS, %	−5.48	−8.6 to −2.4	0.001†	−0.73	−3 to 1.5	0.707
RVFWS, %	−2.13	−4.1 to −0.1	0.038	−0.79	−0.1 to 0	0.487

BMI indicates body mass index; EDSR$_L$, longitudinal early diastolic strain rate; GLS, global longitudinal strain; LAS, left atrial strain; MIS-C, multisystem inflammatory syndrome in children; and RVFWS, right ventricular free wall longitudinal strain.

*Mean difference between MIS-C cases at each time point and 60 controls, adjusted for BMI percentile for age and sex and heart rate.

†P values indicate statistical significance based on the Benjamini-Hochberg critical value for each strain parameter. P values without dagger do not meet the threshold for statistical significance when corrected for multiple comparisons.

period had residual edema. However, this patient had no fibrosis and showed normal systolic function by echocardiography. No patients had CMR studies both in the subacute stage as well as in the follow-up stage. There were no associated regional wall motion abnormalities by the eye-ball method in CMR of the affected regions, in patients with focal changes. One patient with abnormal findings in CMR in the follow-up stage (No. 8 in Table 4) showed reduced strains in the affected regions. No patients showed evidence of CAAs by CMR.
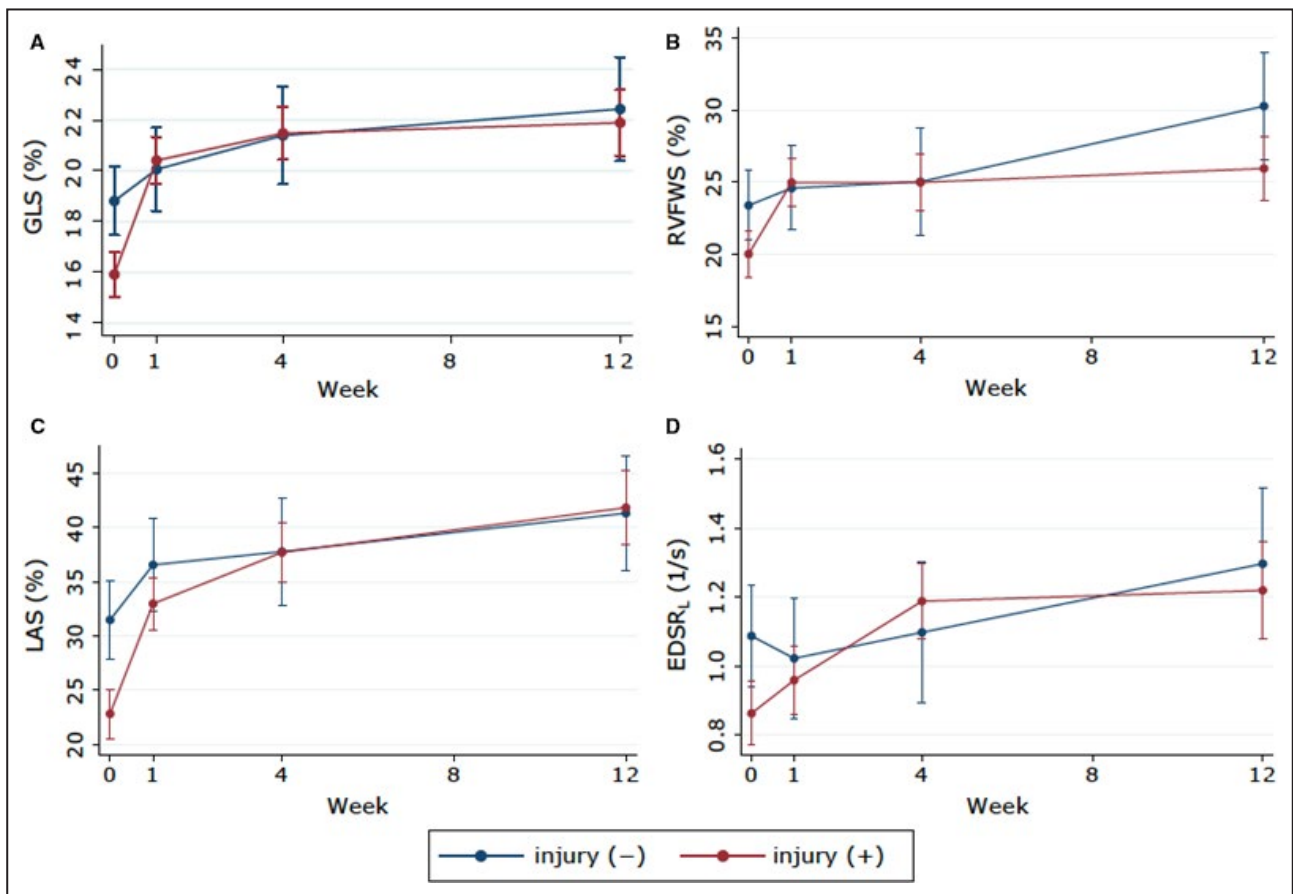
Figure 4. Mean strain values over time for patients with myocardial injury (+) and those without injury (–), estimated from mixed effects models.
Global longitudinal strain (GLS) (**A**) and peak left atrial strain (LAS) (**C**) were significantly decreased in patients with myocardial injury at baseline. However, neither GLS nor LAS differed between myocardial injury (+) and (–) groups at follow-up because of a greater slope of improvement in the myocardial injury (+) group (P values for interaction between myocardial injury and time were 0.015 and 0.017, respectively). Error bars represent 95% CIs for the mean predictions, calculated using the Δ method of SEs. EDSR$_L$ (**D**) indicates longitudinal early diastolic strain rate; and RVFWS, (**B**) right ventricular free wall strain.

Table 4. Cardiac MRI Findings in Patients With MIS-C in Subacute and Follow-Up Stages

Patient no.	Days	Edema	Fibrosis		LVEF/GLS by echocardiography (at closest time point to CMR), %	Biochemical evidence of myocardial injury at presentation
			Discrete	Diffuse		
Subacute phase						
1	5	–	–	–	72	+
					–20.8	
2	6	Global	+	+	69	+
		a thin midmyocardial layer at the mid short axis (subepicardium)			–18.8	
3	8	–	–	–	55	+
					–18.7	
4	10	Focal	+	+	61	+
		midlateral FW of the LV (subepicardium)			–23.8	
5	18	–	–	–	62	+
					–21.5	
Follow-up phase						
6	81	–	–	–	64	+
					–21.2	
7	84	–	–	–	65	+
					–21.5	
8	104	–	–	–	66	–
					–19.9	
9	127	NA	–	–	66	+
					–22.1	
10	162	–	–	–	67	+
					–20.4	
11	204	Focal	–	–	56	+
		Anterior septum anterior/anterolateral wall			–18.9	
12	265	–	–	–	66	–
					–24.6	
13	278	–	–	–	60	+
					–22.4	
14	285	–	–	–	69	+
					–24.2	

CMR indicates cardiac magnetic resonance imaging; FW, free wall; GLS, global longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; MIS-C, multisystem inflammatory syndrome in children; MRI, magnetic resonance imaging; and NA, not available. "+" indicates present, whereas, "–" indicates absent

Reproducibility

Intraclass correlation coefficients for interobserver reliability for GLS, $EDSR_L$, and LAS were 0.90, 0.92, and 0.92, respectively. Intraclass correlation coefficients for intraobserver reliability for GLS, $EDSR_L$, and LAS were 0.88, 0.94, and 0.97, respectively.

DISCUSSION

Our study provides a detailed characterization of the evolution of cardiac manifestations of MIS-C several months after onset of illness. We demonstrate that (1) all deformation parameters improved quickly within the first week, followed by continued gradual improvement and complete normalization by 3 to 4 months; (2) biochemical evidence of myocardial injury at presentation did not affect short-term echocardiographic outcomes; and (3) coronary arteries were spared during follow-up.

Because MIS-C is a newly described disease, there is a paucity of follow-up data about the appropriate frequency and duration of cardiac monitoring. Because of the lack of standardization, presently follow-up care of these patients is highly variable and has led to confusion among both the care team and patients' families. Because we have described cardiac strain patterns in

the acute and subacute phases of MIS-C in detail in our previous study,[5] the primary emphasis of the present study was to describe evolution of cardiac findings in MIS-C during short-term, longitudinal follow-up.

Functional Cardiac Outcomes During Short-Term Follow-Up

The rapid recovery in systolic function in our cohort is consistent with recent studies. One large multicenter study (n=539) in the United States by Feldstein et al reported median time to normalization of LVEF of 4 days (interquartile range, 3–8 days). Of those with follow-up data available, 91.0% had a normal LVEF by 30 days, and 99.4% by 90 days.[3] The other most recent single-center study (n=46) in the United Kingdom by Penner et al showed normalization of LVEF in all patients by 6 months.[19] In these studies, however, only LVEF was used as an index of systolic function, and strain parameters were not evaluated. Myocardial strain is more sensitive for ventricular dysfunction in both children and adults, even when conventional parameters, such as LVEF, are normal, and is not influenced by demographic and clinical cofounders, such as age or body surface area.[16,20] In the acute and subacute phases of MIS-C, subclinical dysfunction can be detected using strain parameters despite preserved LVEF.[5,21] In addition, strain parameters can detect the segmental pattern of cardiac dysfunction, such that our MIS-C cohort showed proportional decrease in segmental strains across basal/mid/apical segments, suggesting global rather than segmental impairment (Figure S1). In our series, there was lack of any increase in GCS to compensate for the decrease in GLS characterized by unchanged GLS/GCS ratio (Table 2). Using strain indexes of systolic function, another recent single-center study by Sanil et al demonstrated that 24% (6/25) of patients with MIS-C had abnormal LV GLS (<–19%) at median 10-week follow-up study, which is not consistent with our present findings. This difference may be attributed to our use of a more conservative outcome definition (GLS <–17%) and our inclusion criteria. Sanil et al used a higher cutoff value for GLS <–19%, which may have resulted in inclusion of more patients in the LV dysfunction group during the follow-up stages.[22] Moreover, their study included 4 patients who developed myocardial stunning requiring venoarterial extracorporeal membrane oxygenation during the acute phase, whereas in our cohort patients requiring extracorporeal membrane oxygenation support were excluded. Overall, the acuity level of our cohort with respect to intensive care unit admission, need for invasive ventilation, and use of vasopressors was highly comparable to that of a larger multicenter surveillance cohort published by the "Overcoming COVID-19 Investigators"[3] and, therefore, we believe our findings to be generalizable.

To date, indexes of LV diastolic function and RV systolic function during the follow-up period have not been evaluated previously in MIS-C. Our findings demonstrate that LV diastolic and RV systolic function also improve rapidly within the first week, followed by continued gradual improvement. All deformation parameters reached normal levels by 3 to 4 months.

This rapid functional recovery of LV diastolic function is a distinctive feature of MIS-C. Many other causes of acute heart failure in children result in more delayed recovery of diastolic function over several months or years. In Kawasaki disease shock syndrome, diastolic dysfunction assessed by conventional echocardiography persists for up to 1 year.[23] In biopsy-proven viral (non–COVID-19) myocarditis in children with normal ejection fraction (n=13), diastolic dysfunction (lateral e′ and $EDSR_L$) also persists over 1 year, despite recovery of systolic function.[11] In our cohort with MIS-C, all indexes of diastolic function normalized at the last follow-up visit. This finding has important implications for resumption of vigorous and competitive physical activities and provides direct evidence to support current "consensus-based" recommendations.

Diastolic Function in MIS-C

Our study was unique in that we used 2 deformation parameters, LAS and $EDSR_L$, to assess LV diastolic function. Noninvasive assessment of diastolic dysfunction has not been well established in children. Conventional parameters, such as E/e′, used in adult diagnostic algorithms incorrectly classify up to 30% of patients with overt and often severe pediatric cardiomyopathy as having normal diastolic function.[24]

Recent studies have proposed LA strain as a surrogate measure of LV diastolic function in adults, reinforced by strong correlation between peak LA strain and LV filling pressures in adults referred for left heart catheterization.[25] This finding was also confirmed in our previous study in children with dilated LAs.[26] In addition, our previous MIS-C study demonstrated that LAS was the single strain parameter most strongly associated with troponin-I levels.[5] Because of its role in atrioventricular coupling, recently there has been a concerted call for incorporating LA strain into the adult American Society of Echocardiography diastolic function guidelines.[12] This may have utility in children as well, including those with global myocardial dysfunction attributable to MIS-C.

$EDSR_L$ has been used to assess diastolic function in LV in various diseases in both adults and children.[11,27] Because of the lack of normative pediatric reference data for $EDSR_L$, we used the distribution in our controls to define abnormal cutoff values (<2 SDs below normal). In our cohort with MIS-C, $EDSR_L$ showed a more gradual recovery pattern compared with LAS, but still normalized within 3 months.

Myocardial Injury and Cardiac Outcomes

We defined the biochemical evidence of myocardial injury by elevated troponin-I (≥0.09 ng/mL) or BNP (>800 pg/mL) because many other studies have demonstrated a significant increase in these parameters in patients with MIS-C and used them as cardiac biomarkers. The median troponin-I level in our cohort with MIS-C was 8-fold higher than the upper limit of normal at our institution. Despite the high incidence of myocardial involvement described in most cohorts with MIS-C,[2] mortality was low in most studies and functional recovery was excellent. As of May 3, 2021, the Centers for Disease Control and Prevention reported 35 deaths of 3742 total MIS-C cases in the United States.[28] In our cohort, patients with myocardial injury had worse deformation parameters at presentation; however, this did not predict worse short-term echocardiographic outcomes. This is consistent with a recent multicenter study on MIS-C (n=539) that showed similar likelihood and temporal trajectory of recovery of ejection fraction, regardless of initial severity of dysfunction.[3]

In contrast, elevated troponin level in adult patients with COVID-19 is a robust prognostic marker.[29] Even a small increase in troponin I (0.03–0.09 ng/mL) in adults with COVID-19 (n=2736) was significantly associated with higher in-hospital mortality, as well as increased LV and RV dysfunction.[13,30] Higher troponin concentrations were also associated with increased short-term mortality among children (n=65) with acute, fulminant myocarditis from the pre–COVID-19 era.[31] The clinical implications of troponin-I in MIS-C remain unclear; however, our findings suggest that although elevated troponin levels are associated with worse cardiac function at disease onset, they do not appear to have similar prognostic implications in children with MIS-C as they do in adults with COVID-19 or in children with fulminant viral myocarditis. Although we previously demonstrated that increased troponin-I was strongly associated with RVFWS in the acute phase,[5] our current study shows that irrespective of troponin elevations, RV systolic function recovers quickly during the follow-up phase.

CMR Findings

In the subacute stage of our study, a subset of consecutive patients who underwent clinically indicated CMR had evidence of edema, as well as discrete and diffuse fibrosis in the setting of normal function by echocardiography. This is consistent with a report by Theocharis et al from the United Kingdom, which showed myocardial edema in 50% and fibrosis in 20% of MIS-C cases (n=20) at a median of 20 days after disease onset, regardless of cardiac function and timing of presentation.[32] The distribution patterns of edema and fibrosis were both global and focal in our MIS-C cohort, and 2 met criteria for myocarditis in the subacute phase.

To date, only one case series from France showed CMR findings in a single patient with MIS-C during the convalescent phase (28 days after the disease onset) who had myocardial edema without fibrosis.[33] Our CMR follow-up cohort is also small (n=9); however, it represents a number that is higher than currently available studies in children during the follow-up stage. One patient in our cohort who presented with LV dysfunction (LVEF=43%) along with elevated troponin of 3.9 ng/mL in the acute phase had evidence of residual focal edema in the follow-up stage as late as 204 days after disease onset. However, echocardiographic function had normalized by then. The implications of edema so late after acute illness are perplexing and are different from conventional myocarditis, where CMR markers of myocardial inflammation resolve earlier.[15] In adult patients with COVID-19 who had recovered from their disease, there have been reports of ongoing myocardial inflammation with edema,[34,35] and the same may be the case in patients with MIS-C. In adults, after recovery from COVID-19 (with or without hospitalization), LVEF and RV ejection fraction were lower than those in controls (LVEF: 57% versus 62%; RV ejection fraction: 54% versus 59%; both $P<0.01$). In addition, 78 of 100 adult patients had abnormal CMR findings, including myocardial edema or fibrosis at a median of 71 days after acute infection.[34] Another recent CMR study (n=26) on adults with cardiac symptoms after recovery from COVID-19 reported abnormal myocardial tissue characterization in 58%, including myocardial edema, fibrosis, and impaired RV function.[35] These studies in adults did not control for preexisting conditions, which existed in some of the subjects. Reassuringly, there was no fibrosis in the few children who underwent follow-up CMR. The need for a repeated CMR is based on the echocardiographic evidence of the severe cardiac dysfunction detected by echocardiography. Further studies are needed to determine whether there may be any long-term damage, including possible evolvement of fibrosis and edema.

Coronary Artery Outcomes

Variation in published rates of CAAs may be explained by differences in reporting (absolute lumen dimensions versus z score) and definitions adopted for CAAs (z score >2.0 versus z score >2.5). In our study, de novo measurements of coronary arteries were performed by 3 designated, experienced readers, similar to the concept of a core laboratory used in multicenter studies. Using this method, we found that coronary arteries were spared during the short-term follow-up. Only 4 patients (7%) had small CAAs in the acute phase, all of which normalized during follow-up. This finding was consistent with a recent large multicenter study by
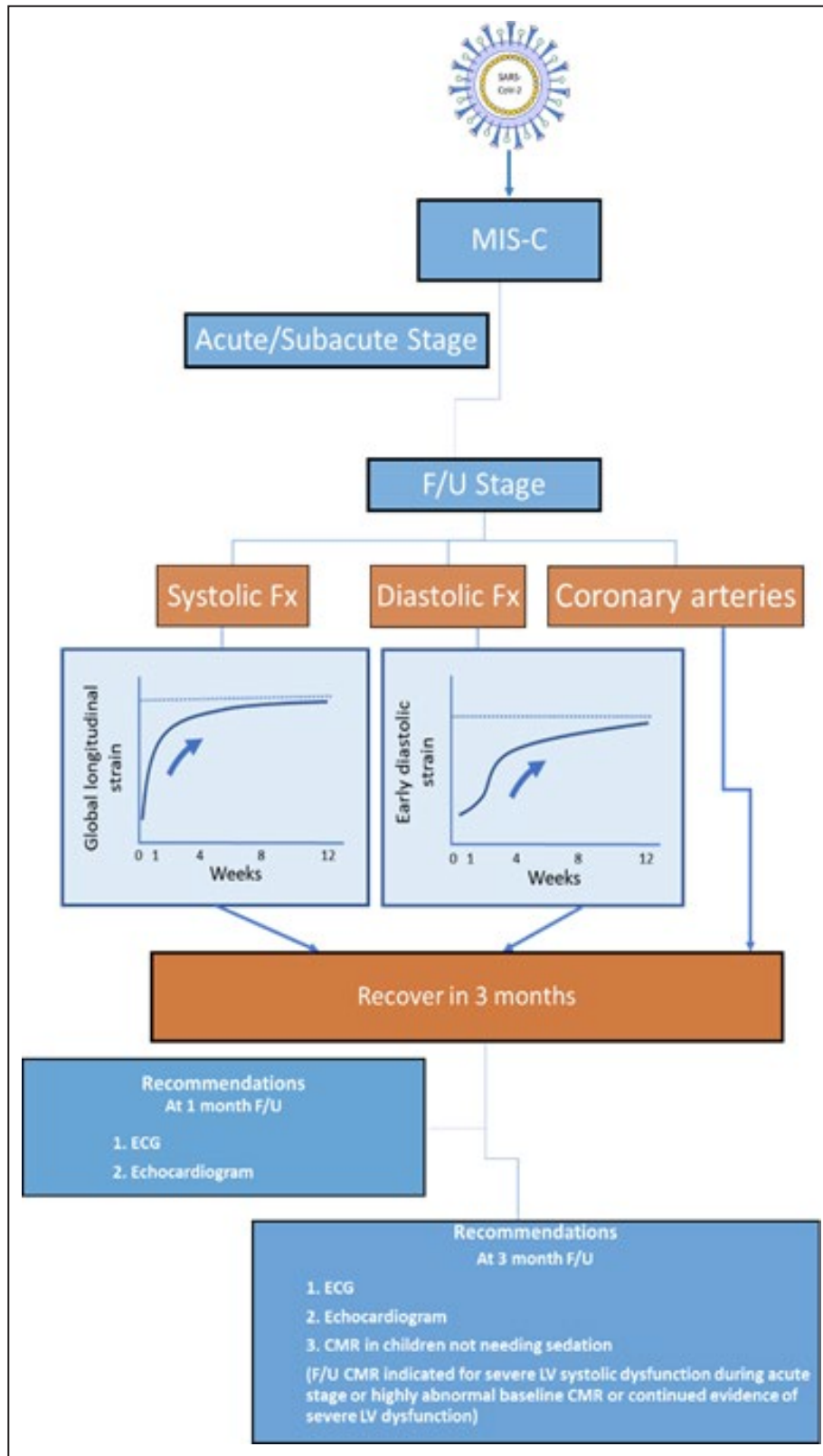
Figure 5. Outcome diagram showing good functional recovery and good coronary outcomes during a 3-month short-term follow-up (F/U) period.
CMR indicates cardiac magnetic resonance imaging; and MIS-C, multisystem inflammatory syndrome in children.

Feldstein et al, which reported mild to moderate aneurysms (13.4%), which regressed to normal dimension in 79.1% of patients by 30 days, and in 100% by 90 days.[3] However, a more recent study by Penner et al reported 2 cases with coronary aneurysms (maximum z scores of 9.2 and 2.9) who required antiplatelet therapy for up to 6 months.[19] Although most MIS-C cases, including those in our present cohort, have good coronary outcomes, longer-term studies are needed to reveal the natural history of this disease.

Researchers should also take into account the phenomenon of transient coronary dilatation in non–Kawasaki disease, febrile illnesses, where z scores may exceed 2 but virtually never >2.5.[36] Therefore, it is important that CAA is defined by a z score of >2.5. Transient coronary dilations in febrile illnesses may reflect a physiologic response to increased myocardial oxygen demand caused by fever, tachycardia, myocardial inflammation, circulating inflammatory mediators, or endothelial dysfunction.

Clinical Implications

MIS-C frequently affects the cardiovascular system at presentation. Nevertheless, functional recovery is excellent, and this has important implications for the management of this population, especially as related to physical activity and sports participation. Current recommendations about resumption of physical activity are consensus based; however, all consensus statements treat MIS-C as equivalent to myocarditis and recommend a similar gradual return to unrestricted physical activity over a period of at least 3 months.[37,38] The data from our current study would suggest that this approach is probably conservative and safe. The more rapid recovery of diastolic function in our current MIS-C population compared with viral myocarditis and the lack of late CMR findings consistent with myocarditis are both reassuring. Our numbers are obviously small, but support the current consensus algorithms for activities and sports in the pediatric population. This study may help provide data-derived consensus for discharging these patients from cardiology care, if their ECGs and echocardiograms are normal at a 3-month follow-up evaluation (Figure 5).

Limitations

Our current study provides a detailed characterization of short-term cardiac outcomes in patients with MIS-C, and longer-term outcomes are not available presently. However, a shorter time frame was chosen as it is important to provide guidelines about this newly emergent disease to frontline physicians who are faced with these patients in their daily practice. Long-term data will also need to be presented when they become available in the future. As this was a retrospective study, image acquisition was performed for clinical purposes and was not prospectively standardized for obtaining noncompressed images using digital imaging and communications in medicine technique. Nevertheless, frame rates of digital imaging and communications in medicine images were similar for both control patients and patients with MIS-C. We wish to acknowledge that BNP elevation can be caused by stretching of the myocardium; however, in this study, the cutoff value of BNP greatly exceeded the 97.5 percentile in children. Therefore, it was used as a marker of myocardial injury. We decided not to use the exercise tests as an additional clinical outcome because few were available, which would not allow meaningful statistical analysis. The group with MIS-C has significantly larger body statures and higher body mass index compared with normal controls. This is because obesity is a known risk factor of MIS-C. To address this, we adjusted for differences in body mass index. Last, we acknowledge that missing follow-up data are a major limitation of this study. Although baseline severity of cardiac dysfunction was not associated with missingness of follow-up data, there may be nonrandom missingness that could result in biased estimates.

CONCLUSIONS

Lack of knowledge about the short-term consequences of MIS-C has led to uncertainty among physicians in making recommendations about follow-up. Our detailed characterization of short-term cardiac outcomes provides evidence that functional recovery and coronary outcomes are good. Moreover, our use of more sensitive deformation parameters provides further reassurance that there is no persistent subclinical dysfunction. These findings may inform early guidelines for outpatient management strategies and recommendations for returning to competitive sports. The echocardiographic parameters described in this study may form the basis of future long-term follow-up studies.

Disclosures
None.

Supplemental Material
Tables S1–S2
Figures S1–S2

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Supplemental Material

Table S1. Conventional echocardiographic parameters at each stage in follow-up study in MIS-C patients.

Variables	Acute (n=60)	Subacute (n=50)	1M f/u (n=39)	3M f/u (n=25)	Control (n=60)
Timing at echocardiogram, days	–	3 (2 - 6)	22 (20 - 29)	91 (65 - 131)	–
Frame rate, frames per second	54 ± 8	58 ± 11	58 ± 10	55 ± 7	54 ± 6
Heart rate, beats/min	117 ± 24	81 ± 23	85 ± 17	77 ± 12	76 ± 15
Systolic BP, mmHg	102 ± 14	109 ± 11	115 ± 12	116 ± 13	111 ± 11
Diastolic BP, mmHg	57 ± 9	60 ± 10	67 ± 7	65 ± 9	62 ± 8
LVEF, %	55 ± 10	61 ± 6	64 ± 4	64 ± 5	65 ± 4
LVFS, %	30.0 ± 8	35 ± 5	35 ± 3	35 ± 3	37 ± 4
Averaged E/e' ratio	8.2 ± 2.1	8.2 ± 1.6	7.3 ± 1.2	6.8 ± 1.1	6.5 ± 1.4
TAPSE, cm	1.8 ± 0.4	2.2 ± 0.5	2.0 ± 0.3	2.1 ± 0.3	2.2 ± 0.4

Values are expresses as median (interquartile range) or mean ± standard deviation (SD).

BP = blood pressure; f/u = follow up; LVEF = left ventricular ejection fraction; LVFS = left ventricular fractional shortening; M = month; MIS-C = multisystem inflammatory syndrome in children; TAPSE = tricuspid annular plane systolic excursion.

Table S2. Comparison of deformation parameters between acute and subacute phases in MIS-C patients estimated from linear mixed effects model.

| Variables	Difference between acute and subacute phases	95% CI	p-value
GLS, %	3.60	[2.6, 4.6]	<0.001
EDSR$_L$, 1/s	0.05	[-0.1, 0.2]	0.411
LAS, %	8.64	[6.0, 11.3]	<0.001
RVFWS, %	3.95	[2.2, 5.7]	<0.001

CI = confidence interval; EDSR$_L$ = longitudinal early diastolic strain rate; GLS = global longitudinal strain; LAS = peak left atrial strain; MIS-C = multisystem inflammatory syndrome in children; RVFWS = right ventricular free wall longitudinal strain.

Figure S1 Mean segmental strains in MISC cases compared.
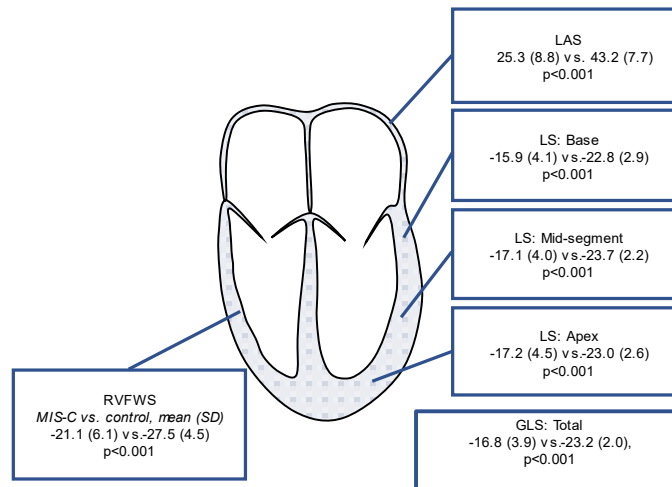
Similar impairments in mean segmental strain are observed across all LV segments. Data are expressed as means with standard deviations (SD) in parentheses for MIS-C vs. control comparisons. GLS = LV global longitudinal strain; GCS = LV global circumferential strain; RVFWS = RV free wall strain; LAS = left atrial strain; $EDSR_L$ = longitudinal early diastolic strain rate.

Figure S2 Kaplan Meier survival curves to estimate median time to recovery of normal function for MIS-C subjects with abnormal strain at baseline.
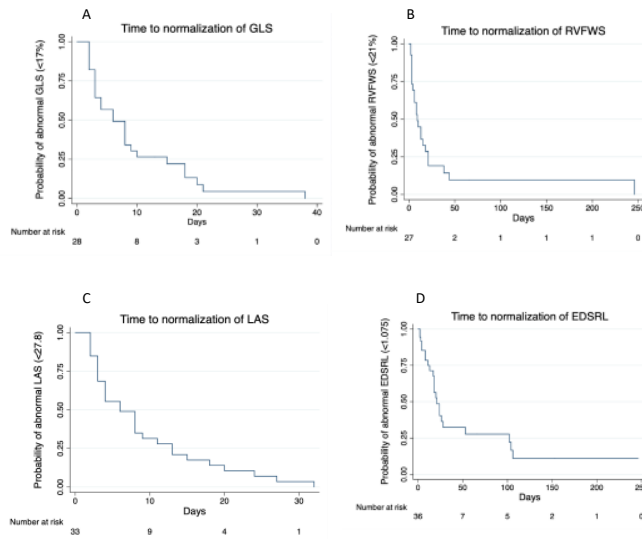
In the survival curve analysis, the median time to normalization of GLS (A), RVFWS (B) and LAS (C) was 6 days (95%CI [3 – 9]), 9 days (95%CI [4 – 18]) and 6 days (95%CI [3 – 9]), respectively.