RESEARCH

Clinical Predictors of Subacute Myocardial Dysfunction in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

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Abstract

Multisystem Inflammatory Syndrome in Children (MIS-C) often involves a post-viral myocarditis and associated left ventricular dysfunction. We aimed to assess myocardial function by strain echocardiography after hospital discharge and to identify risk factors for subacute myocardial dysfunction. We conducted a retrospective single-center study of MIS-C patients admitted between 03/2020 and 03/2021. Global longitudinal strain (GLS), 4-chamber longitudinal strain (4C-LS), mid-ventricular circumferential strain (CS), and left atrial strain (LAS) were measured on echocardiograms performed 3–10 weeks after discharge and compared with controls. Among 60 MIS-C patients, hypotension (65%), ICU admission (57%), and vasopressor support (45%) were common, with no mortality. LVEF was abnormal ($< 55\%$) in 29% during hospitalization but only 4% at follow-up. Follow-up strain abnormalities were prevalent (GLS abnormal in 13%, 4C-LS in 18%, CS in 16%, LAS in 5%). Hypotension, ICU admission, ICU and hospital length of stay, and any LVEF $< 55\%$ during hospitalization were factors associated with lower strain at follow-up. Higher peak C-reactive protein (CRP) was associated with hypotension, ICU admission, total ICU days, and with lower follow-up GLS ($r = -0.55$; $p = 0.01$) and CS ($r = 0.41$; $p = 0.02$). Peak CRP < 18 mg/dL had negative predictive values of 100% and 88% for normal follow-up GLS and CS, respectively. A subset of MIS-C patients demonstrate subclinical systolic and diastolic function abnormalities at subacute follow-up. Peak CRP during hospitalization may be a useful marker for outpatient cardiac risk stratification. MIS-C patients with hypotension, ICU admission, any LVEF $< 55\%$ during hospitalization, or a peak CRP > 18 mg/dL may warrant closer monitoring than those without these risk factors.

Abbreviations

MIS-C	Multisystem Inflammatory Syndrome in Children
GLS	Global longitudinal strain
4C-LS	4-Chamber longitudinal strain
CS	Circumferential strain
LAS	Left atrial strain
LVEF	Left ventricular ejection fraction

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Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C) associated with Coronavirus Disease 2019 (COVID-19) is a hyper-inflammatory syndrome defined for individuals < 21 years of age with fever, laboratory evidence of inflammation, evidence of clinically severe illness requiring hospitalization, multisystem (2+) organ involvement, no alternative plausible diagnosis, and positivity for current or recent SARS-CoV-2 infection or exposure to a COVID-19 case within 4 weeks prior to symptom onset [1]. The incidence of MIS-C in children infected with SARS-CoV-2 has been reported to be 0.03% to 0.6%, with over 8,600 MIS-C cases and 70 MIS-C deaths reported in the United States alone as of 6/27/2022, with some studies reporting nearly three-quarters of MIS-C patients requiring intensive care support [2–5]. MIS-C often involves a post-viral myocarditis and has been shown to cause shock, left ventricular (LV) systolic and diastolic dysfunction, atrioventricular valve regurgitation, pericardial effusions, and rarely coronary artery aneurysms [2, 6–13].

There are a limited number of studies on the cardiac effects of MIS-C beyond hospital discharge. Early studies have shown that LV ejection fraction (LVEF) almost always normalizes in the days to weeks following the acute illness [2, 7, 8, 11, 12, 14, 15]. Two-dimensional speckle tracking strain echocardiography is an imaging technique used to assess global and regional cardiac function via myocardial tissue deformation [16]. Left ventricular longitudinal and circumferential strain are markers of systolic function, and left atrial strain is a measure of left ventricular diastolic function. Despite typical improvement in LVEF, strain has been shown to be abnormal in MIS-C patients at short-term follow-up from acute illness [2, 6–8, 17, 18] with reported normalization at 3–4 month follow-up [11]. We do not have a clear understanding of which MIS-C patients are at greater risk for subacute cardiac complications such as persistent subclinical ventricular dysfunction. Identifying clinical factors during acute illness that can better risk stratify MIS-C patients is important for patient and family counseling, and for outpatient management of this patient population.

As strain and LVEF have been well-documented to be abnormal in many MIS-C patients during initial hospitalization in the literature, we aimed to (1) assess ventricular function of MIS-C patients via strain echocardiography at subacute follow-up after hospital discharge, and (2) identify markers of clinical severity during the hospitalization that may be associated with presence of strain abnormalities at follow-up.

Methods

Study Design and Population

We conducted a retrospective case–control and cohort study of all patients admitted with MIS-C at a single center from March 2020 to March 2021. IRB approval was obtained, and the study was HIPAA compliant. Informed consent was waived. All patients were diagnosed by the Infectious Disease service based on the criteria defined by the Center for Disease Control and Prevention (CDC). Age and gender-matched controls with normal echocardiograms, performed for indications of chest pain, murmur, or family history of congenital heart disease, were included for comparison.

Demographics and Clinical Data

Demographic, laboratory, and clinical data were obtained via retrospective electronic medical record chart review. Demographic variables included age, sex, race/ethnicity, body mass index (BMI), and BMI percentile. In the MIS-C patients, their hospitalization was reviewed and any history of hypotension, need for vasopressor or inotropic support, intubation/mechanical ventilation, MIS-C therapies received, total hospital length of stay, intensive care unit (ICU) admission, total ICU days, extracorporeal membrane oxygenation (ECMO) requirement, and mortality was documented. Hypotension was defined by established age-based thresholds (less than fifth percentile for age, or less than 90/50 for children 10 years or older) via review of available vitals documented in patient notes, or if "hypotension" was documented in patient notes. Not all vital signs were available for direct retrospective review. Laboratory values obtained during the acute illness included peak C-reactive protein (CRP), peak erythrocyte sedimentation rate (ESR), peak troponin, peak N-terminal pro-B-type natriuretic peptide (NT-proBNP), peak ferritin, peak procalcitonin, COVID-19 PCR result, and presence of COVID-19 antibody. Our hospital assay for COVID-19 antibody tested for antibody against the nucleocapsid proteins of the SARS-CoV-2 virus, as opposed to the spike protein; therefore, it identifies patients with evidence of prior infection but does not detect those that have antibody reflective of vaccination. Due to a lack of clinical guidelines regarding MIS-C follow-up, an institutional follow-up protocol was established in 2020, involving infectious disease follow-up at 2 weeks post-hospital discharge, and cardiology follow-up at 6 weeks post-discharge. Echocardiograms were performed at both encounters.

Echocardiographic Data

We reviewed the echocardiographic reports on studies performed during hospitalization and at subacute (3–10 week) follow-up. Cardiology clinic follow-up with an echocardiogram was recommended at 6 weeks post-discharge, though return timing varied from 3 to 10 weeks, which determined why we chose this follow-up time range. All echocardiograms were performed with Phillips Epiq CVx or GE Vivid

E95 scanners. LVEF was calculated using standard modified Simpson method (biplane method of disks). Left ventricular dilation was defined as a left ventricular internal diameter in diastole z-score of +2.0 or greater. This was measured from the standard echocardiographic parasternal short axis mid-papillary level view. Strain data was obtained by post-processing of 2D echocardiographic images via TomTec Cardiac Performance Analysis (Version TTA2.30.02-428126) on MIS-C follow-up echocardiograms and on age
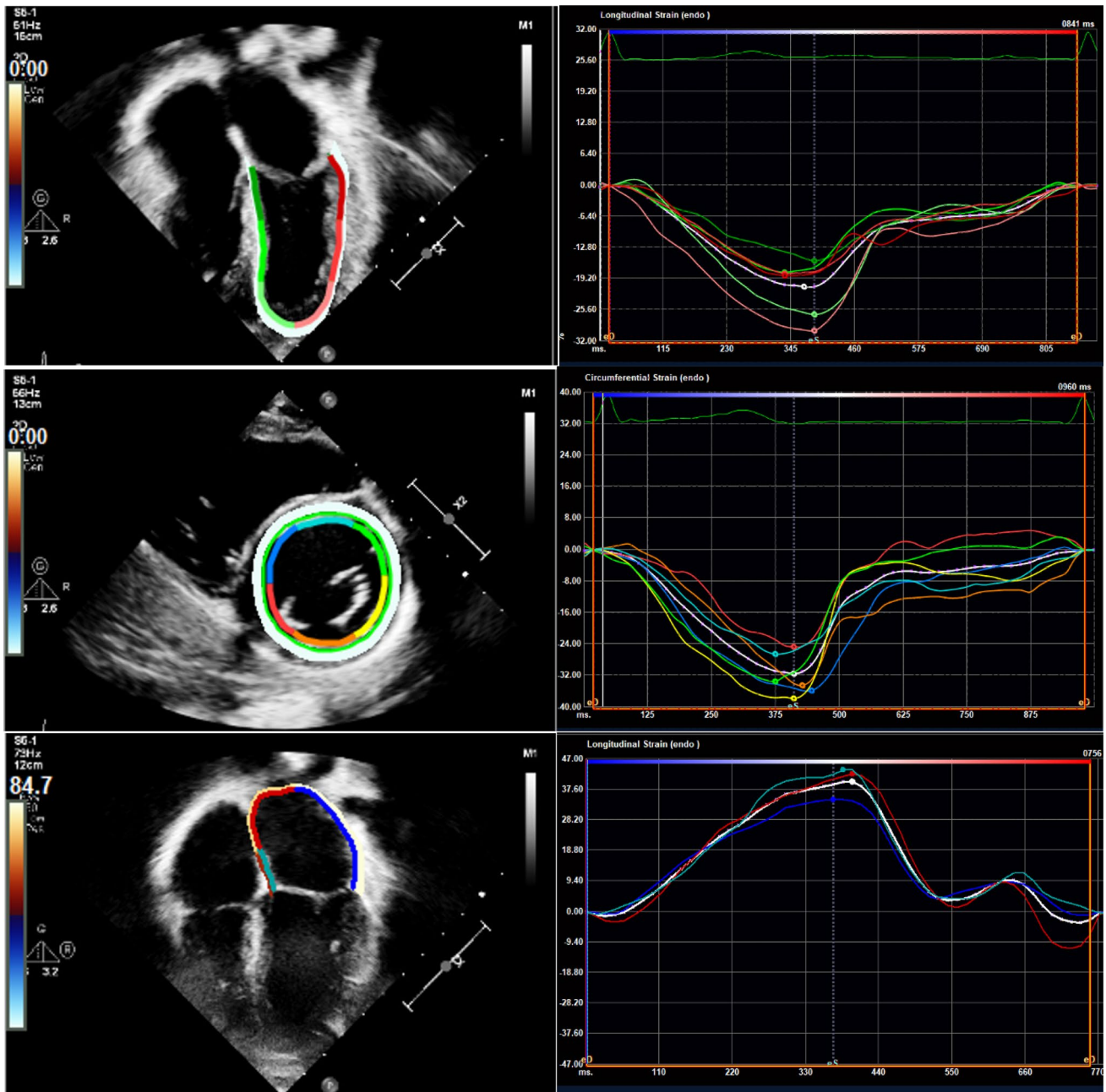

Fig. 1 Strain analysis. Strain curve analyses ath lower CS at 3–10 week follow- strain analysis in the top panel from apical 4-chamber image, LV circumferential strain analysis in the middle panel from mid-papillary parasternal short-axis image, and left atrial strain analysis in the bottom panel from apical 4-chamber image

and gender-matched controls (Fig. 1). Global longitudinal strain (GLS), 4-chamber longitudinal strain (4C-LS), mid-ventricular circumferential strain (CS), and left atrial conduit strain (LAS) were measured from echocardiograms performed 3–10 weeks after hospital discharge. For MIS-C patients with pre-existing diagnoses that could impact strain values, such as congenital heart disease, cardiomyopathy, end stage renal disease, chronic hypertension, left ventricular hypertrophy, or malignancy, strain analysis was not performed. MIS-C patient echocardiograms were also excluded if they did not have an echocardiogram performed at our institution within the studied timeframe, or if image quality precluded strain assessment. The most optimal standard apical four-chamber, apical three-chamber, and apical two-chamber views were analyzed to measure left ventricular GLS. Mid-ventricular CS measurements utilized standard parasternal short axis imaging at the mid-papillary level, and left atrial strain was measured from standard apical four-chamber view. Regions of interest were manually traced and adjusted as needed to accurately track the endocardial border throughout a complete cardiac cycle. The automated TomTec CPA algorithm then allowed strain values to be calculated. GLS and CS are reported as negative percentages and left atrial conduit strain as a positive percentage per standard practice. We also measured strain in age and gender-matched controls using the same methods. All strain analyses were performed by a single observer (D.M.) with verification of accuracy by two cardiologists (A.H. and N.H.) with over 10 years of experience in performing and interpreting strain. In addition, author N.H. later performed a blinded strain analysis on a subset of the cohort ($n = 9$) to assess interobserver variability. There was very strong interobserver correlation, with interclass correlation coefficients of 0.91 for GLS, 0.89 for CS, 0.96 for LAS, and 0.89 for 4C-LS.

Statistical Analysis

Patient demographic characteristics and clinical findings were summarized using frequencies and percentages for categorical variables, means and standard deviations for normally distributed continuous measures, and medians and interquartile ranges for non-normally distributed continuous measures. Association of patient characteristics with hypotension, ICU admission, total hospital days, and total ICU days were examined using Pearson's chi-squared test, Mann–Whitney U test, and Kruskal–Wallis test. Two-sample t-test and one-way ANOVA were conducted to compare the means of CS, GLS, LAS, and 4C-LS across categorical variables with two groups (sex, ICU admission, hypotension, presence of LVEF < 55% during hospitalization, and cases vs. controls) and three groups (race/ethnicity), respectively. Spearman rank correlations were used to assess the

relationships between continuous measures, such as peak CRP and total ICU days. All reported p values were adjusted using the Benjamini–Hochberg procedure to control the false discovery rate (adjusted $p < 0.05$ for statistical significance). All data were analyzed using R (version 4.1.0) within RStudio (version 1.4.1717).

Results

Patient Characteristics

There were 60 patients admitted with MIS-C from March 2020-March 2021. The median age was 10 years (range 1–17 years, IQR 4.8–12.0 years), and 35/60 (58%) were male (Table 1). BMI was 85th percentile or greater in 48%, and 95th percentile or greater in 28%. Race/ethnicity was reported as 39% Hispanic, 29% African American, 27% White, and 5% Other (Table 1). Of the 60 MIS-C patients, 48 (80%) presented for cardiology follow-up within 3–10 weeks after hospital discharge (median 6 weeks, IQR 38–47 days). Of the patients who did not present for subacute follow-up, 7/12 (58%) had been admitted to the ICU. Similarly, 27/48 (56%) of those who followed up had been admitted to the ICU.

Clinical and Laboratory Findings During Hospitalization

Among the 60 MIS-C patients, hypotension (65%), ICU admission (57%), and need for vasopressor or inotropic support (45%) were common, while intubation/mechanical ventilation was uncommon (7%) (Table 1). No patients required ECMO and there were no deaths. The median length of hospital stay (LOS) was 7 days (range 4–16 days, IQR 6–9 days).

Of the 59 patients with a COVID-19 antibody test, 97% ($n = 58$) were positive, with a single presumed seronegative MIS-C presentation, and 26% were COVID-19 PCR positive at the time of diagnosis (Table 1). Peak inflammatory markers were elevated during hospitalization with a median CRP of 16.9 mg/dL (IQR 11.8–22.4, normal reference range 0–0.8 mg/dL), a median ESR of 71 mm/hr (IQR 44.8–101.8, normal reference range 0–20 mm/hr), and a median ferritin of 480 ng/mL (IQR 298–1054, normal reference range 24–354 ng/mL) (Table 1). Troponin I level (ref range < 0.48 ng/mL) was elevated in 17% of our cohort at some point during the acute illness. Peak NT-proBNP was abnormal in all MIS-C patients (median 5322 pg/mL [IQR 1712–17,425]), with 99th percentile reported as up to 216 pg/mL in healthy pediatric patients 1–19 years old (19).

Table 1 Patient characteristics and laboratory values

MIS-C patient and clinical characteristics	
Age (years)*	10.0 (4.8–12.0)
Sex	
Female	25 (41.7%)
Male	35 (58.3%)
Race/ethnicity	
African-American	17 (28.8%)
Hispanic	23 (38.0%)
Other*	19 (32.2%)
Not available	1
Presence of hypotension	
No	21 (35.0%)
Yes	39 (65.0%)
ICU admission	
No	26 (43.3%)
Yes	34 (56.7%)
Received vasopressor or inotropic support	
No	33 (55.0%)
Yes	27 (45.0%)
Intubated/mechanically ventilated	
No	56 (93.3%)
Yes	4 (6.7%)
Length of stay (total hospital days)*	7.0 (6.0, 9.0)
Total ICU days*	1.0 (0.0–4.0)
MIS-C patient laboratory values	
Peak ESR (mm/hr)*	71.0 (44.8–101.8)
Peak CRP (mg/dL)**	17.5 (7.9)
Peak troponin (ng/mL)*	0.0 (0.0–0.3)
Peak NT-proBNP (pg/mL)*	5,322 (1,712–17,425)
Peak procalcitonin (ng/mL)*	4.2 (1.5–10.8)
Peak ferritin (ng/mL)*	480 (298–1.054)
COVID-19 PCR	
Negative	43 (74.1%)
Positive	15 (25.9%)
Not performed	2
COVID-19 antibody	
Positive	58 (96.67%)
Negative	1 (1.67%)
Not performed	1 (1.67%)

Other racial/ethnic group includes Asian, White, and other

*Median (interquartile range)

**Mean (standard deviation)

MIS-C therapies administered included corticosteroids in 59/60 (98%) and intravenous immune globulin (IVIG) in 58/60 (97%). In cases of refractory disease despite corticosteroids and IVIG, 7/60 (12%) were treated with Anakinra and 2/60 (3%) were treated with Infliximab.

Table 2 Ventricular function in MIS-C patients

Lowest LVEF during hospitalization	$n = 58$
Median (IQR)	57.0% (52.0–61.0)
Presence of any LVEF < 55% during hospitalization	$n = 58$
No	41 (70.7%)
Yes	17 (29.3%)
LVEF at 3–10 week follow-up	$n = 45$
Median (IQR)	65.0% (61.0–67.0)
Presence of any LVEF < 55% at 3–10 week follow-up	$n = 45$
No	43 (95.6%)
Yes	2 (4.4%)

IQR Interquartile range

Additionally, 49/60 (82%) received Aspirin, and 32/60 (53%) were anticoagulated with Enoxaparin.

Echocardiographic Data

Left Ventricular Ejection Fraction

LVEF was abnormal (defined as < 55%) in 17/58 (29%) of MIS-C patients at some point during their hospitalization, with lowest LVEF 50–54% in 8/58 (14%), LVEF 40–49% in 5/58 (8%), and LVEF 30–39% in 4/58 (7%). No patients had an LVEF below 30%. Median LVEF in the MIS-C cohort was 57% (IQR 52–61). Follow-up echocardiograms at 3–10 weeks post-discharge showed that median LVEF improved to 65% (IQR 61–67) (Table 2). LVEF was abnormal in only 2/45 (4%) at 3–10 week follow-up (one with an LVEF 53% and one LVEF 54%). Both patients had hypotension during the acute illness requiring inotropic/vasopressor support and ICU admission. Both patients had normalization of LVEF on their subsequent echocardiogram when assessed 3–4 months later.

Strain

Of the 60 MIS-C patients, 45 had echocardiograms during the subacute follow-up timeframe that met inclusion criteria for strain analysis. Twelve patients did not have an echocardiogram in the subacute period, one followed up elsewhere, one had poor image quality precluding strain analysis, and one was excluded due to pre-existing left ventricular hypertrophy. Of these, 30/45 (67%) had adequate 4, 3, and 2 chamber apical images to obtain GLS, 45/45 (100%) had adequate 4 chamber apical images to obtain 4C-LS, 44/45 (98%) had adequate parasternal short axis mid-chamber imaging for assessment of CS, and 43/45 (96%) had adequate left atrial imaging from apical 4 chamber view for LAS analysis.

Table 3 Strain in MIS-C at 3–10 week follow-up versus age and gender-matched controls

Strain	MIS-C patients ($n = 45$) versus controls ($n = 45$)	p-value*
CS**		<0.001
Mean (SD)	− 26.0 (3.0) vs − 29.2 (3.3)	
LAS**		0.007
Mean (SD)	34.5 (10.7) vs 43.2 (12.5)	
GLS**		0.020
Mean (SD)	− 20.4 (2.8) vs − 22.0 (1.9)	
4C-LS		0.003
Mean (SD)	− 20.6 (3.1) vs − 22.9 (2.5)	

SD standard deviation

*Two sample *t*-test; Benjamini–Hochberg adjusted *p*-value

**Inadequate image quality precluded inclusion of these variables in some patients such that $n = 44$ for CS, $n = 43$ for LAS, and $n = 30$ for GLS.

In the MIS-C cohort, the mean GLS was − 20.4% (SD 2.8%), mean 4C-LS was − 20.6% (SD 3.1%), mean CS was − 26.0% (SD 3.0%), and mean LAS was 34.5% (SD 10.7%) (Table 3). The mean values for GLS, 4C-LS, CS, and LAS were all statistically significantly lower in the MIS-C cohort at 3–10 week follow-up compared to the control cohort (Table 3). Since age-specific cut-offs for strain are not widely established, we used a cut-off of two standard deviations below the mean of our control group to establish abnormal values. Using this method, our threshold for abnormal GLS and 4C-LS was < − 18%, for CS was − 22.6%, and for LAS was 18%. With these cut-offs, GLS was abnormal in 13% (4/30) of MIS-C patients, 4C-LS was abnormal in 18% (8/45), CS was abnormal in 16% (7/44), and LAS was abnormal in 5% (2/43) of MIS-C patients at 3–10 week follow-up.

Left-Ventricular Dilation

Three MIS-C patients (3/60, 5%) had evidence of mild LV dilation at presentation. One patient had persistence of mild LV dilation through 8 month follow-up (with normal ejection fraction and fractional shortening at that time), with normalization of LV size when next assessed at 14 month follow-up. This patient did not have an echocardiogram in the subacute follow-up timeframe so strain was not available for assessment. Of note, this was the only MIS-C patient in our cohort to have not received corticosteroids or IVIG. This was due to a favored diagnosis of culture negative sepsis at the time of admission, which was just prior to the description of MIS-C as an illness entity, and was later retrospectively diagnosed with MIS-C. No other MIS-C patients had LV dilation at follow-up. Both MIS-C patients with mild LV dilation at initial presentation who received MIS-C therapies

Table 4 Correlations between clinical markers during hospitalization and 3–10 week follow up strain

	GLS		CS	
	ρ (rho)*	p-value**	ρ (rho)*	p-value**
Peak CRP	− 0.55	**0.011**	− 0.41	**0.024**
Peak Troponin	− 0.33	0.165	− 0.32	0.091
Peak NT-proBNP	− 0.28	0.281	− 0.12	0.581
Length of stay (total hospital days)	− 0.29	0.249	− 0.40	**0.027**
Total ICU days	− 0.32	0.186	− 0.41	**0.024**

Statistically significant values ($p < 0.05$) are given in bold

*Spearman rank correlation coefficient, ρ (rho)

** Benjamini–Hochberg adjusted p-value

(corticosteroids and IVIG) had normalization of LV size during the hospitalization.

Associations Between Markers of Clinical Severity and Follow-Up Strain

Demographics and Hospital Course

Race/ethnicity and sex were not associated with any clinical markers of severity or with follow-up strain values. ICU admission was associated with lower follow-up CS ($p = 0.03$). Total hospital length of stay ($r = − 0.4$, $p = 0.03$) and total ICU days ($r = − 0.41$, $p = 0.02$) correlated with lower CS at 3–10-week follow-up, though not with GLS (Table 4, Fig. 2). Hypotension during acute illness was associated with lower GLS at 3–10 week follow-up ($p = 0.048$) (Table 5).

Cardiac Biomarkers

Higher peak NT-proBNP was associated with presence of hypotension ($p = 0.02$), ICU admission ($p = 0.009$), and correlated with total ICU days ($r = 0.51$, $p = 0.001$). Peak NT-proBNP was not associated with strain abnormalities at 3–10 week follow-up (Table 4). Peak troponin was not associated with hypotension, ICU admission, or strain abnormalities at 3–10 week follow-up (Table 4). Nine patients with an abnormal troponin during acute illness had an echocardiogram with strain analysis in the subacute follow-up period. Three of these nine patients (33%) had an abnormal GLS and CS at subacute follow-up.

Inflammatory Markers

Higher peak in-hospital CRP was associated with presence of hypotension (13.8 mg/dL $\pm$ 7.4 vs 19.5 mg/dL $\pm$ 7.5;
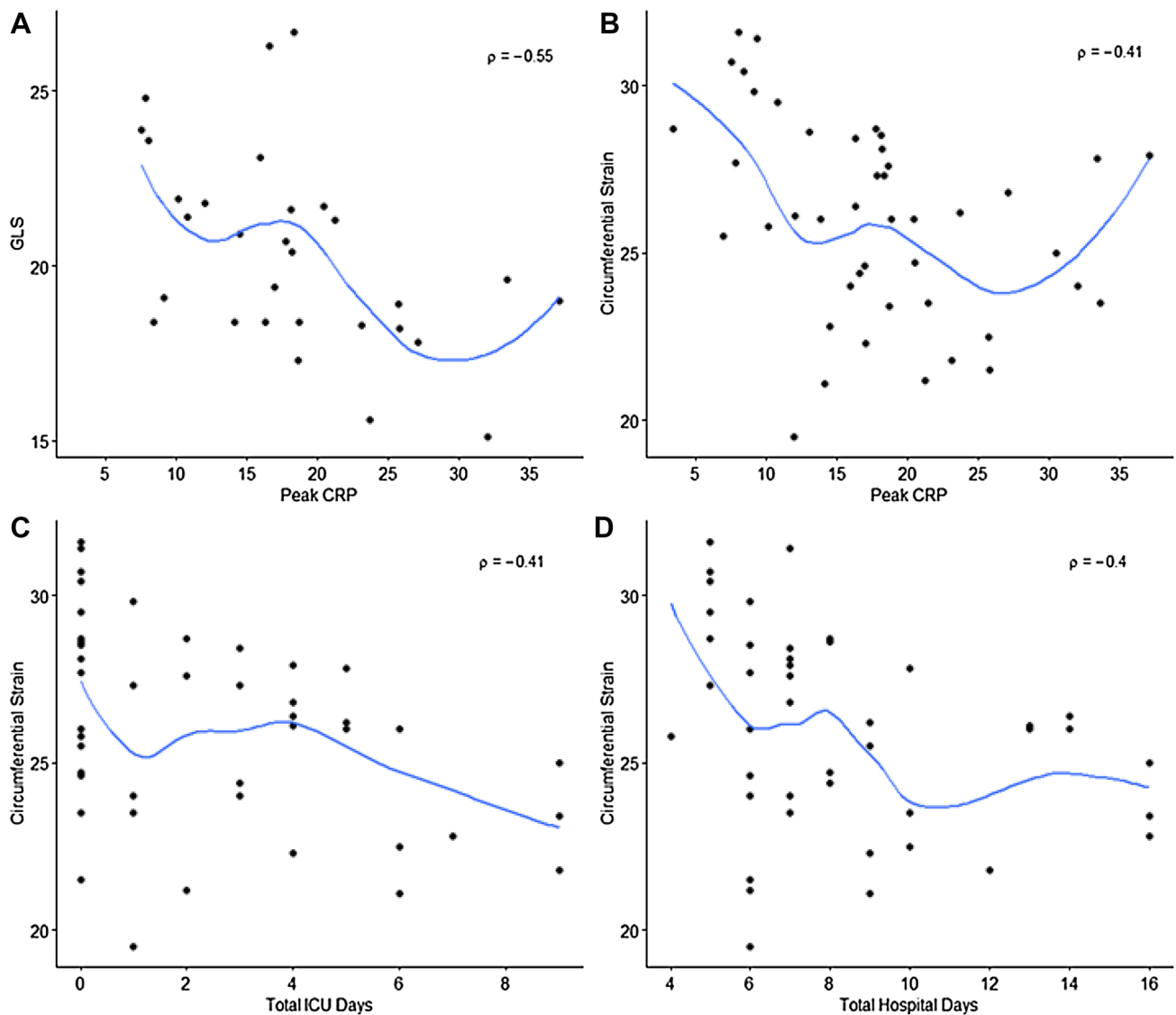
Fig. 2 Correlations with 3–10 week follow-up strain values. **A** Correlation plot demonstrating higher peak CRP during acute MIS-C illness was significantly associated with lower GLS at 3–10 week follow-up ($r = -0.55$, $p = 0.01$). **B** Correlation plot demonstrating higher peak CRP during acute MIS-C illness was significantly associated with lower CS at 3–10 week follow-up ($r = -0.41$, $p = 0.02$). **C** Correlation plot demonstrating greater number of total ICU days was significantly associated with lower CS at 3–10 week follow-up ($r = -0.41$, $p = 0.02$). **D** Correlation plot demonstrating greater number of total hospital days was significantly associated with lower CS at 3–10 week follow-up ($r = -0.4$, $p = 0.03$). Loess smoothing curve represented in blue. Strain values are reported as absolute values (%) for ease of figure interpretation

$p = 0.03$), ICU admission (13.9 mg/dL $\pm$ 7.5 vs 20.2 mg/dL $\pm$ 7.2; $p = 0.01$), and total ICU days ($r = 0.36$, $p = 0.02$). Of the 4 out of 30 (13%) MIS-C patients with an abnormal GLS (< 18%) at 3–10 week follow-up, all four (100%) had been admitted to the ICU, and the mean peak CRP of these 4 patients was 25.4 mg/dL (range 18.6–32 mg/dL). A peak CRP > 18 mg/dL had a positive predictive value of 27% (4/15) for abnormal follow-up GLS and a positive predictive value of 20% (4/20) for abnormal follow-up CS. A peak CRP < 18 mg/dL had a negative predictive value of 100% (15/15) for normal GLS and 88% (21/24) for normal CS at

follow-up. Higher peak CRP was significantly associated with lower GLS ($r = -0.55$; $p = 0.01$) and lower CS ($r = -0.41$; $p = 0.02$) at 3–10 week follow-up (Table 4, Fig. 2).

Ventricular Function

The presence of any LVEF < 55% during hospitalization was associated with hypotension ($p = 0.02$), ICU admission ($p = 0.01$), and total ICU days ($p = 0.04$). The presence of any LVEF < 55% during acute illness was associated with lower

Table 5 Associations between clinical markers during hospitalization and 3–10 week follow up strain values

	GLS		CS	
	Mean (SD)	*p*-value*	Mean (SD)	*p*-value*
Hypotension		**0.048**		0.535
No	− 22.1 (3.1)		− 26.6 (2.8)	
Yes	− 19.5 (2.3)		− 25.7 (3.1)	
Presence of any LVEF < 55% during hospitalization		0.290		**0.046**
No	− 20.8 (2.9)		− 26.7 (2.7)	
Yes	− 19.0 (2.0)		− 24.2 (3.1)	

Statistically significant values ($p < 0.05$) are given in bold

SD standard deviation

*Two sample *t*-test; Benjamini–Hochberg adjusted *p*-value

CS ($p = 0.046$) and lower 4C-LS ($p = 0.04$) at 3–10 weeks (Table 5). Mean CS was − 26.7% in the LVEF ≥ 55% group versus − 24.2% in the LVEF < 55% group ($p = 0.046$). Mean 4C-LS was − 21.2% in the LVEF ≥ 55% group versus − 19.1% in the LVEF < 55% group ($p = 0.04$).

Discussion

In this single-center study, we sought to identify associations between markers of clinical severity in MIS-C during hospitalization and presence of echocardiographic strain abnormalities at follow-up. These findings may allow us to stratify which pediatric patients are at greatest risk for persistent myocardial dysfunction following MIS-C, with the goal of improving longitudinal care for this population. We found that (1) when compared to controls, MIS-C patients show significantly reduced LV global longitudinal, LV circumferential, and left atrial strain at subacute follow-up after hospital discharge despite typical improvement/normalization in LVEF; (2) hypotension, ICU admission, and the presence of any LVEF < 55% during the acute illness were risk factors for persistent strain abnormalities, and (3) higher peak CRP was associated with numerous markers of clinical severity as well as lower GLS and CS at follow-up. A peak CRP value < 18 mg/dL during the acute illness may suggest a lower risk of myocardial dysfunction at follow-up. Strain has been shown to be abnormal in subacute follow-up in MIS-C in single center cohort studies such as Sanil et al. and Matsubara et al., and our findings further support this conclusion in a slightly larger cohort [7, 11]. Additionally, we have identified clinical predictors during the acute illness for subacute myocardial dysfunction. We hope that these findings will be beneficial for providers in their longitudinal guidance, management, and counseling for patients and families affected by MIS-C.

Ventricular dysfunction is common in MIS-C, and conventional echocardiographic measures of LV systolic function, such as LVEF, may not adequately define the magnitude or frequency of cardiac involvement over the course of the disease process. LVEF normalized in the vast majority of our cohort, consistent with previously reported data [2], where 34% of MIS-C patients (172/503) had an LVEF < 55% at some point during acute illness, with LVEF normalizing in 91% within 30 days and 99.4% within 90 days. In our cohort, despite typical improvement of LVEF, there was a 13% incidence of abnormal GLS at 3–10 week follow up, validating findings in a larger MIS-C cohort of what has been similarly reported in prior studies [7, 8, 11, 15, 17]. Given typical LVEF improvement, abnormal strain findings in this period likely reflect subclinical myocardial dysfunction that is improving. GLS is a well-described marker of regional subclinical myocardial function and has been shown to be abnormal in various pediatric and adult inflammatory myocardial pathologies [20, 21]. While the presence of echocardiographic strain abnormalities in isolation are not diagnostic for, or indicative of the presence of myocarditis, it is very likely that these findings are the result of the post-viral myocardial inflammation commonly described in MIS-C [22, 23].

Circumferential strain is a measure that is less commonly used in clinical practice and is a less reproducible measure of myocardial deformation compared to GLS; however, changes in CS may also be an important component of cardiac function assessment in myocardial inflammatory pathologies [20, 24] and has been shown to be abnormal in MIS-C [11]. We found a 16% incidence of abnormal circumferential strain (CS) at follow-up. Markers of worse MIS-C disease severity (any in-hospital LVEF < 55%, longer hospital length of stay, longer ICU length of stay) correlated with CS but not with GLS, highlighting the importance of this measure when screening for the presence of myocardial dysfunction.

Left atrial strain (LAS) is a relatively new deformation metric which has been described as a measure of LV diastolic function. Decreased LAS values have been associated with worse LV diastolic function in adults with heart failure with reduced LVEF, as well as heart failure with preserved LVEF [25–27]. Cameli et al. found LAS to be a better predictor of LV end diastolic pressure (LVEDP) than the more commonly assessed tissue Doppler derived *E/e'* [28]. LAS is not commonly analyzed on standard pediatric echocardiography; however, it has been demonstrated to correlate with markers of LV diastolic function in healthy children, obese children, and children with cardiomyopathies [29, 30]. In a 28 patient MIS-C cohort, Matsubara et al. reported significantly decreased LAS during hospitalization when compared

to control subjects. This marker of diastolic dysfunction persisted at hospital discharge despite typical normalization of LVEF [6]. We expanded further on this and evaluated LAS in the subacute period and found that a small subset of MIS-C patients had suspected diastolic function abnormalities in the form of decreased LAS at follow-up. However, in the absence of robust normative LAS values in children, larger studies are needed for validating this as a measure of diastolic function in MIS-C.

The thresholds for abnormal strain in pediatrics are not well-defined. Measurements and normative values are vendor specific, and often only established in adult age ranges. Normative LV strain values are reported via 2-D TomTec CPA in healthy young adults in Mutluer et al., though normative pediatric strain values using TomTec CPA are only reported in smaller cohorts [31–33]. The lack of large pediatric datasets for strain using TomTec CPA specifically prompted our use of an age and gender matched control group to allow for the most accurate comparison, avoiding inter-vendor and inter-reader variability. We therefore used a cut-off of two standard deviations below the mean of our control group to establish abnormal values, similar to analysis performed in Sanil et al. [7]. Our values are similar to what has been reported in previous small studies using the same vendor [6, 32, 33].

Previous small studies on myocarditis have suggested a correlation between LV longitudinal strain abnormalities by echocardiography and late gadolinium enhancement on cardiac MRI; however, larger studies are needed to better correlate pediatric echocardiographic strain values with MRI findings in healthy controls and in those with myocardial inflammation and/or injury [20, 21, 23, 34]. Interestingly, the percentage of MIS-C patients with abnormal LV strain in our study is similar to the incidence of myocarditis reported by Aeschlimann et al., who demonstrated MRI evidence of myocarditis in 18% of 111 MIS-C patients in a multicenter international registry when MRI was performed a median of 28 days after onset of symptoms [9]. Abnormal myocardial function as evidenced by echocardiographic strain may be secondary to multiple potential pathophysiologic states. Myocardial inflammation, myocardial edema, or direct viral-mediated myocardial injury may all potentially contribute. The primary mechanism for ventricular dysfunction in MIS-C may differ from classic viral myocarditis, given that MIS-C appears to be a post-viral hyper-inflammatory mediated process [35]. Early cardiac MRI studies have shown that persistence of myocardial edema is seen in a subset of MIS-C patients, and there are rare reports of late gadolinium enhancement [35]. Larger cohort studies will be needed to further explore contributing factors to the commonly seen myocardial dysfunction in MIS-C.

The only MIS-C patient who did not receive corticosteroids or IVIG, due to presentation prior to the description of

MIS-C as a diagnostic entity, had LV dilation at presentation and was the only MIS-C patient in our cohort to have LV dilation at follow-up. This finding could be coincidental but potentially suggestive of the beneficial effects of typical MIS-C therapies and may be important to consider in patients who do not receive or have access to MIS-C therapies. LV end-diastolic dimension z-score at presentation has been shown to be predictive of incomplete recovery and mortality in pediatric acute myocarditis, and attention to LV size is important in MIS-C patients with myocarditis [36].

Typically, inflammatory markers are significantly elevated in MIS-C [37–39]. Zhao et al. reported an association with peak CRP and MIS-C severity [38]. Not surprisingly, mean peak CRP was higher in our patients admitted to the ICU; however, peak CRP during acute illness as a possible predictor of myocardial functional abnormalities beyond hospital discharge has not been previously reported. In our cohort, higher peak CRP was associated with lower GLS and CS at subacute follow-up (Fig. 1), and a peak CRP < 18 mg/dL had a high negative predictive value for normal GLS and CS at follow-up. We therefore suggest attention to this marker during clinical evaluation and management in follow-up. Our findings support further investigation in larger-scale studies to more clearly delineate inflammatory marker ranges/thresholds that could be predictive of cardiovascular outcomes in this hyper-inflammatory syndrome to assist in risk stratification and outpatient management.

Cardiac biomarkers are often abnormal in MIS-C as well [37, 40–42]. Troponin I was elevated in only 17% of our cohort, which contrasts with the findings reported in Sanil et al., in which high-sensitivity troponin I was elevated in 64% of their cohort [7]. This difference may be attributable to their use of a high-sensitivity troponin assay and our pediatric center's reliance on a non-high sensitivity troponin assay during the study period. They also reported an association between initial troponin value and 10-week follow-up LV apical 4 chamber longitudinal strain; however, in our cohort, cardiac biomarker peak values were not associated with follow-up strain. We may be under-powered to detect an association between the presence of any abnormal troponin and follow-up strain, given that a much smaller percentage of our cohort had an abnormal troponin. The association of peak NT-proBNP levels with hypotension and ICU admission could be in part due potential greater fluid resuscitation in patients presenting with hypotension. The degree of NT-proBNP level elevation may be confounded by the degree of volume resuscitation [43].

In general, children of Hispanic ethnicity and African American race have been disproportionately affected by MIS-C [3, 44]. Prior studies have concluded clear racial/ethnic disparities in MIS-C diagnosis, with 57% of MIS-C cases in the United States occurring in those identifying as

"Hispanic/Latino" or "Black/Non-Hispanic" as of 3/28/22 [3]. In our MIS-C cohort, we did not find any associations between race/ethnicity and clinical markers of severity, which is in line with the conclusions of Javalkar et al. [45]. We also did not find any associations with race/ethnicity and follow-up strain, although our study may be under-powered to detect this.

Limitations

This is a single center investigation with limitations inherent to a retrospective study design. The recommended cardiology follow-up time was 6 weeks post-hospital discharge, though time intervals were variable, from 3 to 10 weeks for subacute cardiology follow-up with an echocardiogram. Not all MIS-C patients returned for a follow-up echocardiogram. Strain analysis was therefore not available for these patients, though illness severity appeared similar based upon rates of ICU admission in the group that did not follow-up compared to those who did. Patients with poor echocardiographic imaging precluding accurate strain measurements were excluded from the strain analysis to maintain accuracy and reproducibility of the data. The clinical significance of echocardiographic strain abnormalities, especially in the presence of a normal LVEF, is not well known in the presence of a hyperinflammatory condition such as MIS-C. This is a needed area for future investigation. Analyzing strain during acute presentation, at subacute follow-up, and longitudinally in larger cohort MIS-C studies may allow us to better understand myocardial function trends and recovery in individual MIS-C patients over time, though measuring strain at multiple time points was not our primary aim and is beyond the scope of this study. Given the lack of large datasets establishing normative strain values in the pediatric population for TomTec Cardiac Performance Analysis speckle tracking echocardiography, we attempted to address this limitation with age and gender-matched control patients for comparison.

Conclusions

A subset of MIS-C patients demonstrate subclinical myocardial systolic and diastolic function abnormalities as evidenced by abnormal strain at subacute follow-up. We demonstrated that markers of greater MIS-C disease severity (presence of any LVEF < 55% during the acute illness, hypotension, ICU admission) are risk factors for persistent subacute cardiac dysfunction. Peak serum C-reactive protein during acute illness is associated with MIS-C severity, as well as with myocardial dysfunction at follow-up, and may

therefore be useful for outpatient cardiac risk stratification. This data will allow for improved guidance for providers and counseling for families affected by MIS-C. Further studies are required to assess long-term cardiac functional abnormalities and their clinical correlates to improve management of children with MIS-C.

Declarations

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