ORIGINAL ARTICLE

Longitudinal Assessment of Global and Regional Left Ventricular Strain in Patients with Multisystem Inflammatory Syndrome in Children (MIS-C)

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) is one of the most significant sequela of coronavirus disease 2019 (COVID-19) in children. Emerging literature has described myocardial dysfunction in MIS-C patients using traditional and two-dimensional speckle tracking echocardiography in the acute phase. However, data regarding persistence of subclinical myocardial injury after recovery is limited. We aimed to detect these changes with deformation imaging, hypothesizing that left ventricular global longitudinal (GLS) and circumferential strain (GCS) would remain impaired in the chronic phase despite normalization of ventricular function parameters assessed by two-dimensional echocardiography. A retrospective, single-institution review of 22 patients with MIS-C was performed. Fractional shortening, GLS, and GCS, along with regional longitudinal (RLS) and circumferential strain (RCS) were compared across the acute, subacute, and chronic timepoints (presentation, 14–42, and > 42 days, respectively). Mean GLS improved from − 18.4% in the acute phase to − 20.1% in the chronic phase ($p = 0.4$). Mean GCS improved from − 19.4% in the acute phase to − 23.5% in the chronic phase ($p = 0.03$). RCS and RLS were impaired in the acute phase and showed a trend towards recovery by the chronic phase, with the exception of the basal anterolateral segment. In our longitudinal study of MIS-C patients, GLS and GCS were lower in the acute phase, corroborating with left ventricular dysfunction by traditional measures. Additionally, as function globally recovers, GLS and GCS also normalize. However, some regional segments continue to have decreased strain values which may be an important subclinical marker for future adverse events.

Keywords Coronavirus disease 2019 (COVID-19) · Multisystem inflammatory syndrome in children (MIS-C) · Two-dimensional speckle tracking echocardiography (2D-STE) · Longitudinal strain · Circumferential strain

Abbreviations

MIS-C	Multisystem inflammatory syndrome in children
COVID-19	Coronavirus disease 2019
2D-STE	Two-dimensional speckle tracking echocardiography
GLS	Global longitudinal strain
GCS	Global circumferential strain
RLS	Regional longitudinal strain
RCS	Regional circumferential strain
FS	Fractional shortening
KD	Kawasaki disease
PICU	Pediatric intensive care unit

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Introduction

The pediatric population has been relatively spared from the significant manifesations of acute coronavirus disease of 2019 (COVID-19) when compared to their adult counterparts. However, one significant contrast in this younger

cohort has been an exaggerated severe inflammatory disease, a newly described syndrome defined as multisystem inflammatory syndrome in children (MIS-C). Though rare, with the most recent United States incidence reported as 2.1 per 100,000 individuals under the age of 21, MIS-C has led to serious and life threatening complications in otherwise healthy children [1–4].

Although the understanding of the pathophysiology behind MIS-C is still evolving, there have been several clinical cardiac phenotypes [5]. The first described cases had a presentation similar to Kawasaki disease (KD) with coronary artery dilation and occasionally carditis, whereas later cases presented similarly to toxic shock syndrome secondary to an overwhelming immunological response. This included myocarditis, multisystem organ failure, a combination of cardiogenic and/or vasodilatory shock, and varying degrees of coronary artery involvement [3, 5]. MIS-C does not occur during the acute infection but rather is a delayed post-infectious response, consistently presenting 4–6 weeks after COVID-19 infection or exposure [5, 6]. There has been ample evidence of left ventricular (LV) dysfunction in the acute phase with severe cases presenting as cardiogenic shock, though many patients demonstrate rapid improvement in ventricular function after treatment [5, 6]. However, to our knowledge, there is limited data on the persistence of subclinical myocardial injury after clinical recovery. We aimed to assess for this using deformation imaging by 2-dimensional speckle tracking echocardiography (2D-STE) at different time points in the clinical course. We hypothesized that LV global longitudinal (GLS) and circumferential strain (GCS) would be impaired in the acute phase and remain diminished in the chronic phase in spite of normalization of ventricular function as assessed by traditional echocardiography.

Methods

This is a retrospective, single center review of patients who were admitted to the Yale New Haven Children's Hospital. We identified 38 patients between April 2020 and May 2021 with the discharge diagnosis of MIS-C as defined by the United States Centers for Disease Control and Prevention (CDC) criteria [7]. To be included, the patients must have had 2D echocardiographic views of the apical 4-chamber and parasternal short axis at the papillary muscle level suitable for strain analysis at all three time points—acute, sub-acute and chronic phases, defined as at presentation, 14–42 days after, and > 42 days, respectively. A total of 16 patients were excluded from our study, 10 due to inadequate followup, and 6 who did not have optimal image acquisition to allow for strain analysis. Thus,

a total of 22 patients were included in the final analysis. Of the 16 excluded patients, 3 were critically ill requiring vasopressor support, and the remaining 13 did not. Additional subgroup analysis was performed on 8 critically ill patients, defined as admission to the pediatric intensive care unit (PICU) for use of inotropes, vasopressors, or mechanical ventilation. This group is referred to as the PICU group hereon, with the remainder of the 14 patients classified into non-PICU group. Demographic, laboratory, and patient clinical management data was collected through retrospective review of electronic medical record.

During the early pandemic, similar to other institutions, we implemented a handheld echocardiogram protocol using Philips Lumify (Amsterdam, Netherlands) in order to reduce sonographer exposure and allow for easy decontamination [8]. Images obtained included apical 4-chamber and parasternal short axis views in 2-D and M-Mode. Due to the use of Lumify, which allows M-Mode but is unable to measure ejection fraction by Simpson's or 5/6 area-length methods, left ventricular fractional shortening (FS), measured by conventional M-mode, was used for consistency. All Lumify studies were performed by the same experienced sonographer, so the values of FS were thought to have less inter-observer variability. Followup images were obtained using traditional Philips EPIQ CVx. Images obtained were of adequate quality to be evaluated by post-processing strain software. Deformation imaging was performed using vendor-independent TOMTEC software version 1.4.0.64 (Munich, Germany) [9]. GLS from apical 4 chamber view and GCS from LV short axis at the papillary muscle level were compared across time points (Fig. 1). FS was unable to be performed on 4 patients due to missing M-mode evaluation. Though no consensus reference ranges for strain have been established, we defined strain values as abnormal if they were less than − 20%, in keeping with the cutoffs established by others [10, 11].

Pilot data was used for sample size power calculations, and timepoints were compared using one-way analysis of variance (ANOVA) with Tukey's multiple comparisons tests. When comparing the PICU versus the non-PICU subgroups, student's t-test was used. Statistical analysis was performed via GraphPad Prism version 9.1.2 (San Diego, CA). For demographic, treatment, and laboratory values, categorical data is presented as frequency (percent), and continuous variables as median (interquartile range [IQR]). Echocardiographic data was assumed to be normally distributed within the population in accordance with other studies, but graphical examination was also performed and demonstrated a normal distribution. As such, echocardiographic data is presented as mean (standard deviation [SD]). Left ventricular wall segments are as defined by American Heart Association
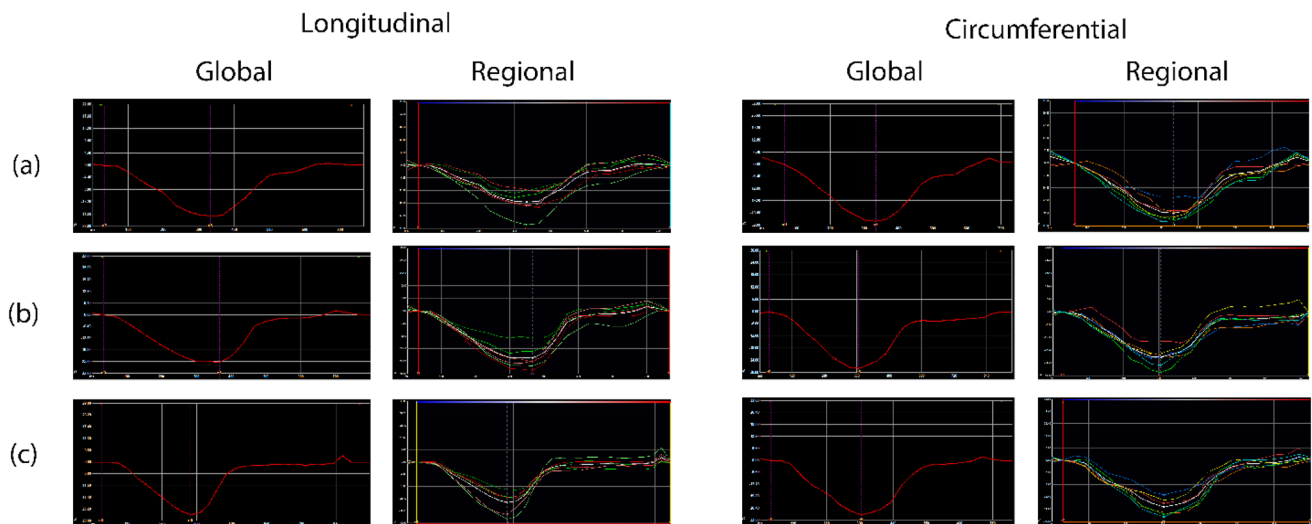
Fig. 1 Longitudinal and circumferential strain tracings in a critically ill patient in the **a** acute, **b** subacute, and **c** chronic phase

(AHA) nomenclature [12]. This study was approved by the Yale University institutional review board.

Results

Demographics and Clinical Presentation

A total of 22 patients were evaluated. All data is represented as the median (IQR) unless otherwise stated. The cohort age was 7.5 years (5–14) with 13 (59%) being male (Table 1). All patients presented with gastrointestinal symptoms and cardiac involvement, as determined by elevation in troponin-T and/or N-terminus pro-brain natriuretic peptide (BNP) levels [7].

The most common treatments in the acute phase included aspirin in 21 (96%), intravenous immunoglobulin in 18 (82%), pulsed steroids in 17 (77%), and anakinra in 7 (32%). Eight patients (36%) required PICU admission, with 7 of these requiring vasopressor or inotrope support and 2 requiring mechanical ventilation (Table 1). There was no mortality noted in our study.

Peak laboratory values were most notable for elevated BNP of 5566 pg/mL (2083–13,521). Inflammatory markers were also elevated with c-reactive protein and ferritin measured at 199 mg/L (76–300) and 422 ng/mL (230–602), respectively. In our overall cohort, troponin-T was 0.00 ng/mL (0.00–0.13), however when stratifying by PICU versus non-PICU cohorts, we noted a significant difference. Within the PICU cohort, peak troponin-T was 0.14 ng/mL (0.01–0.26), whereas the non-PICU cohort level was 0.00 ng/mL (0.00–0.27) [$p = 0.02$]. Similarly, median BNP within the PICU cohort was 16,739 pg/mL (9287–31,491)

Table 1 Demographic data, clinical presentation, and inpatient interventions

	$n = 22$
Age	7.5 (5–13.5)
Male	13 (59%)
Female	9 (41%)
Organ system involvement	
Cardiovascular	22 (100%)
Respiratory	7 (32%)
Renal	4 (18%)
Neurologic	8 (36%)
Hematologic	13 (59%)
Gastrointestinal	22 (100%)
Dermatologic	12 (55%)
Pediatric intensive care unit admission	8 (36%)
Mechanical ventilation	2 (9%)
Vasopressors	5 (23%)
Milrinone	3 (14%)
Anakinra	7 (32%)
IVIG	18 (82%)
Corticosteroids	17 (77%)
Remdisivir	1 (4%)
Aspirin	22 (96%)
Enoxaparin	9 (41%)

Data is presented as median (IQR) or *n* (%)

IVIG intravenous immune globulin

and in the non-PICU group 2736 pg/mL (1331–5566) [$p = 0.002$]. Institutional reference ranges for troponin and BNP were < 0.01 ng/mL and < 125 pg/mL, respectively. These data are outlined in Table 2.

Table 2 Peak laboratory values during admission broken down by subgroup

	n = 22 All patients	n = 16 Non-PICU	n = 8 PICU	p value
Troponin T (ng/mL)	0.00 (0.00–0.13)	0.00 (0.00–0.27)	0.14 (0.01–0.26)	0.02
BNP (pg/mL)*	5566 (2083–13,521)	2736 (1331–5566)	16,739 (9287–31,491)	< 0.01
CRP (mg/L)†	199 (76–300)	112 (56–300)	256 (187–295)	0.09
Ferritin (ng/mL)	422 (230–602)	294 (220–462)	688 (545–4769)	0.08
Creatinine (mg/dL)	0.49 (0.39–0.85)	0.44 (0.38–0.54)	1.07 (0.54–2.76)	0.06

Data are median (IQR)

BNP N-terminus pro-brain natriuretic peptide, *CRP* C-reactive protein

*Maximum value measured for BNP was 70,000 pg/mL

†Maximum value measured for CRP was 300 mg/L

2D Transthoracic Echocardiography Parameters

Echocardiographic data including FS and global and regional strain were normally distributed and are presented as mean and standard deviation (Table 3). For our overall study population, mean FS (SD) in the acute, subacute, and chronic phases was 32.2 (7.8), 37.8 (4.4), and 36.0 (6.0) respectively (Table 3). FS showed improvement from the acute to subacute phases ($p = 0.03$) and then remained stable [$p = 0.16$].

Within the PICU cohort, mean FS in the acute, subacute, and chronic phases was 28.7 (8.3), 38.0 (4.0), and 32.5 (5.3), respectively (Table 4). For the non-PICU cohort, FS at the same timepoints were 33.9 (7.3), 37.6 (4.7), and 37.8 (5.7). Though not statistically different, the FS for patients in the PICU subgroup trended lower than those in the non-PICU subgroup during the acute timepoint (Fig. 4).

Coronary artery dilation was seen in 2 (9%) of patients, one of whom had left main and right coronary artery dilation which resolved by the subacute phase. The second had dilation of the right, left main, left anterior descending, and left circumflex arteries during all phases of follow up. No patients demonstrated giant coronary artery aneurysms.

Table 3 LV Strain by 2D-STE in each timepoint for entire cohort

	Acute	Subacute	Chronic	p value		
				Acute vs. subacute	Subacute vs. chronic	Acute vs. chronic
Fractional shortening	32.2 (7.8)	37.8 (4.4)	36.0 (6.0)	0.03	0.69	0.16
Longitudinal strain						
Global	− 18.4 (4.6)	− 21.4 (3.4)	− 20.1 (4.8)	0.06	0.57	0.40
Basal inferoseptal	− 17.2 (5.4)	− 21.3 (5.3)	− 22.3 (5.2)	0.03	0.79	0.01
Mid inferoseptal	− 19.6 (6.0)	− 23.4 (4.3)	− 21.6 (5.8)	0.05	0.50	0.44
Apical septal	− 21.1 (7.0)	− 23.3 (7.3)	− 20.1 (8.2)	0.60	0.33	0.88
Apical lateral	− 21.4 (7.6)	− 26.2 (5.3)	− 24.0 (6.5)	0.049	0.51	0.40
Mid anterolateral	− 18.4 (4.9)	− 21.6 (3.8)	− 20.8 (4.6)	0.06	0.83	0.19
Basal anterolateral	− 15.5 (5.3)	− 17.5 (3.9)	− 17.0 (4.5)	0.31	0.93	0.51
Circumferential strain						
Global	− 19.4 (6.4)	− 23.6 (4.5)	− 23.5 (4.2)	0.02	0.99	0.03
Mid anterior	− 21.9 (10.2)	− 26.6 (6.4)	− 26.7 (7.0)	0.14	0.99	0.14
Mid anterolateral	− 22.1 (8.5)	− 25.4 (8.6)	− 24.6 (6.7)	0.37	0.95	0.55
Mid inferolateral	− 19.6 (11.1)	− 24.3 (6.8)	− 25.4 (6.5)	0.16	0.89	0.06
Mid inferior	− 19.6 (7.5)	− 23.9 (7.2)	− 23.0 (7.79)	0.15	0.92	0.30
Mid inferoseptal	− 18.3 (6.8)	− 21.6 (7.2)	− 24.5 (6.7)	0.25	0.36	0.01
Mid anteroseptal	− 22.0 (6.7)	− 27.9 (7.7)	− 25.8 (6.9)	0.02	0.61	0.19

Fractional shortening, peak longitudinal and circumferential strain at the acute, subacute, and chronic timepoints. Global and segmental measurements are provided. Data presented as mean (SD). Fractional shortening was not able to be performed on 4/22 subjects due to missing M-mode evaluation

Table 4 LV Strain by 2D-STE and FS in each timepoint for the PICU and non-PICU subgroups

	Acute	Subacute	Chronic	p value		
				Acute vs. subacute	Subacute vs. chronic	Acute vs. chronic
PICU						
Fractional shortening	28.7 (8.3)	38.0 (4.0)	32.5 (5.3)	0.04	0.29	0.54
Global longitudinal strain	− 17.2 (6.2)	− 20.7 (4.0)	− 17.0 (4.0)	0.35	0.31	0.99
Global circumferential strain	− 18.4 (6.1)	− 24.5 (4.4)	− 22.2 (5.1)	0.08	0.68	0.33
Non-PICU						
Fractional shortening	33.9 (7.3)	37.6 (4.7)	37.8 (5.7)	0.30	0.99	0.26
Global longitudinal strain	− 19.0 (3.5)	− 21.8 (3.1)	− 21.8 (4.5)	0.14	0.99	0.13
Global circumferential strain	− 19.9 (6.7)	− 23.0 (4.6)	− 24.1 (3.6)	0.25	0.84	0.09

Fractional shortening, peak longitudinal and circumferential strain in the PICU and non-PICU patients at the acute, subacute, and chronic timepoints. Global and segmental measurements are provided. Data presented as mean (SD). Fractional shortening was not able to be performed on 2/8 subjects in the PICU subgroup and 2/14 in the non-PICU subgroup due to missing M-mode evaluation.

Global Circumferential and Longitudinal Strain

The mean GLS (SD) values in the acute, subacute, and chronic phase were − 18.4 (4.6), − 21.4 (3.4), and − 20.1 (4.8) respectively. GLS did not meet any statistical change in improvement from the acute to subacute [p = 0.06], subacute to chronic [p = 0.57], or acute to chronic [p = 0.4] timepoints, though there was a trend towards improvement (Table 3). The mean GCS (SD) values in acute, subacute, and chronic phase were − 19.4 (6.4), − 23.6 (4.5), and to − 23.5 (4.2), respectively (Fig. 2). GCS showed statistical improvement in both the acute to subacute [p = 0.02] and acute to chronic [p = 0.03] timepoints. The mean values for GLS and GCS were decreased in the acute phase but normalized by subacute and chronic phases when compared to previously published age-based normative data [10].

Regional Circumferential and Longitudinal Strain

In the acute phase, longitudinal strain was depressed in the basal inferoseptal (− 17.2 ± 5.4), mid inferoseptal (− 19.6 ± 6.0), mid anterolateral (− 18.4 ± 4.9), and basal anterolateral segments (− 15.5 ± 5.3). Similarly, circumferential strain at this timepoint was depressed in the mid inferolateral (− 19.6 ± 11.1), mid inferior (− 19.6 ± 7.5), and mid inferoseptal regions (− 18.3 ± 6.8) (Fig. 3). All regions except for the basal anterolateral segments showed a trend towards recovery by the subacute and chronic phases (Table 3).

Strain Within the PICU Subgroup and Non-PICU Subgroup

Within the PICU subgroup, GLS was depressed during the acute phase − 17.2 (6.2) and showed no improvement to the chronic phase − 17.0 (4.0) [p = 0.99]. GCS was similarly depressed in the acute phase at − 18.4 (6.1) but showed a trend towards recovery by the chronic phase to − 22.2 (5.1) [p = 0.33] (Table 4).

The GLS in the non-PICU group was also depressed in the acute phase at − 19.0 (3.5) and trended towards improvement by the chronic phase to − 21.8 (4.5), though not statistically significant [p = 0.13]. GCS in the acute phase was low at − 19.9 (6.7) and showed a trend towards normalization by the chronic phase was − 24.1 (3.6) [p = 0.09].

When comparing these two subgroups, GLS in the chronic phase was noted to have remained depressed in the PICU subgroup but was improved in the non-PICU subgroup [p = 0.02] (Fig. 4).

Discussion

Fractional Shortening

Although not statistically different, patients who required intensive care due to MIS-C had decreased fractional shortening compared to those with milder disease. BNP levels were eight-fold higher on average than those who were not critically ill. There was also a statistically signficant difference in peak troponin-T levels between the two groups, though on average had lower levels than others have presented [6]. This may be due to institutional variations in troponin isoform measured and severity of presentation to our center. However, similar to the work by Matsubara et. al who separated subjects by an elevation in troponin levels, we found similar differences in fractional shortening and ejection fraction [13]. Few patients required mechanical ventilation or vasopressors (9% and 23%,
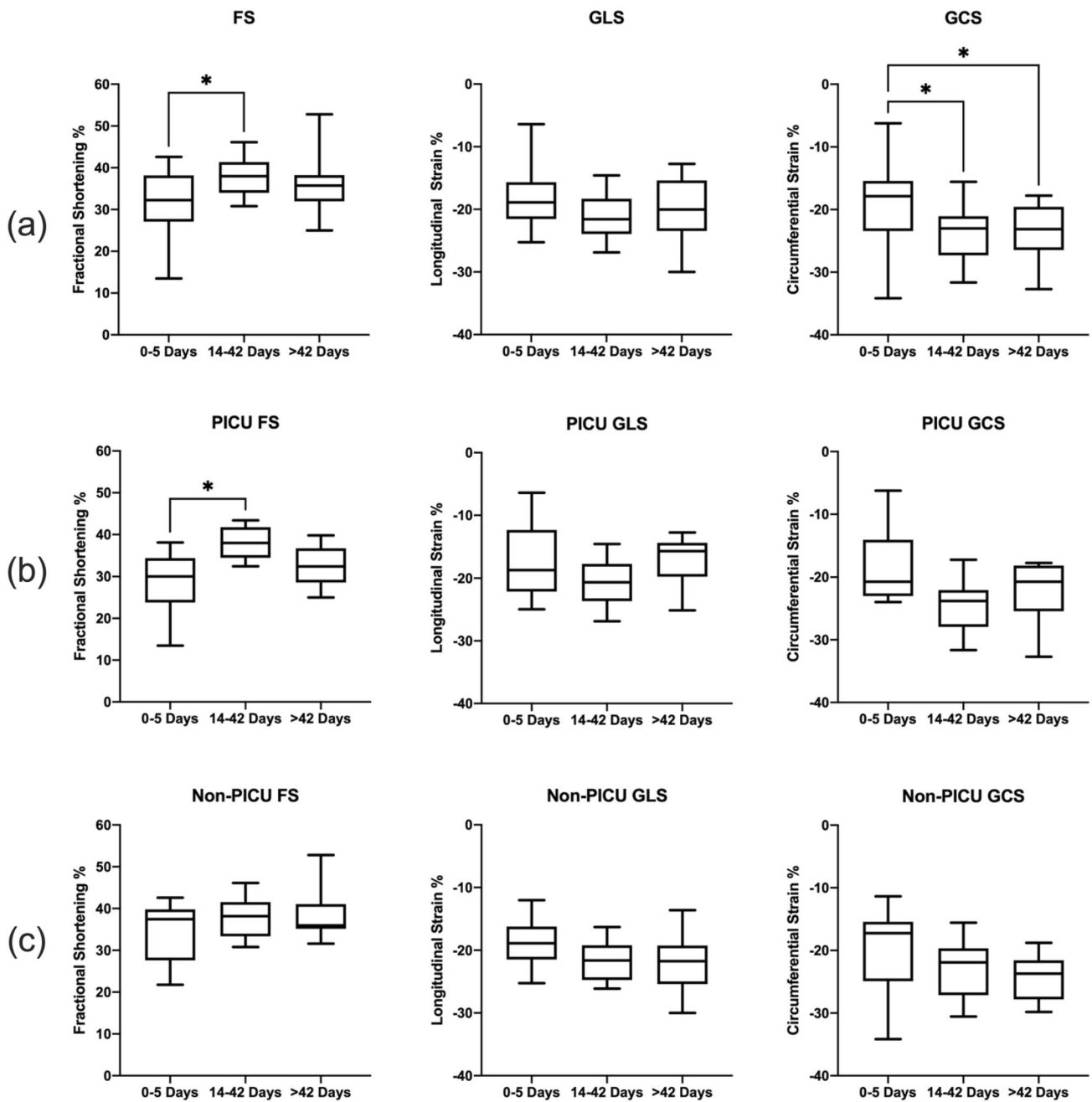
Fig. 2 Changes in LV strain by time point. Fractional shortening (FS), global longitudinal strain (GLS), and global circumferential strain (GVS) in **a** all patients, **b** critically ill patients (PICU), and **c** non-critically ill patients (Non-PICU). *Difference between groups was statistically significant ($p < 0.05$)

respectively). Overall, there was a statistically and clinically significant improvement in fractional shortening across the cohort from the acute to subacute phases.

Global Strain

In our cohort of MIS-C patients, we found a decrease in both GLS and GCS in the acute phase compared to published normative reference ranges [11]. This impairment is consistent with the clinical presentation of MIS-C that includes evidence of cardiac dysfunction, myocardial injury, elevation of cardiac biomarkers, and occasionally, cardiogenic shock. These findings of abnormal strain have also been described in various other reports [13–16]. Our results showed significant normalization in the GCS from the acute to chronic phase. GLS did not statistically
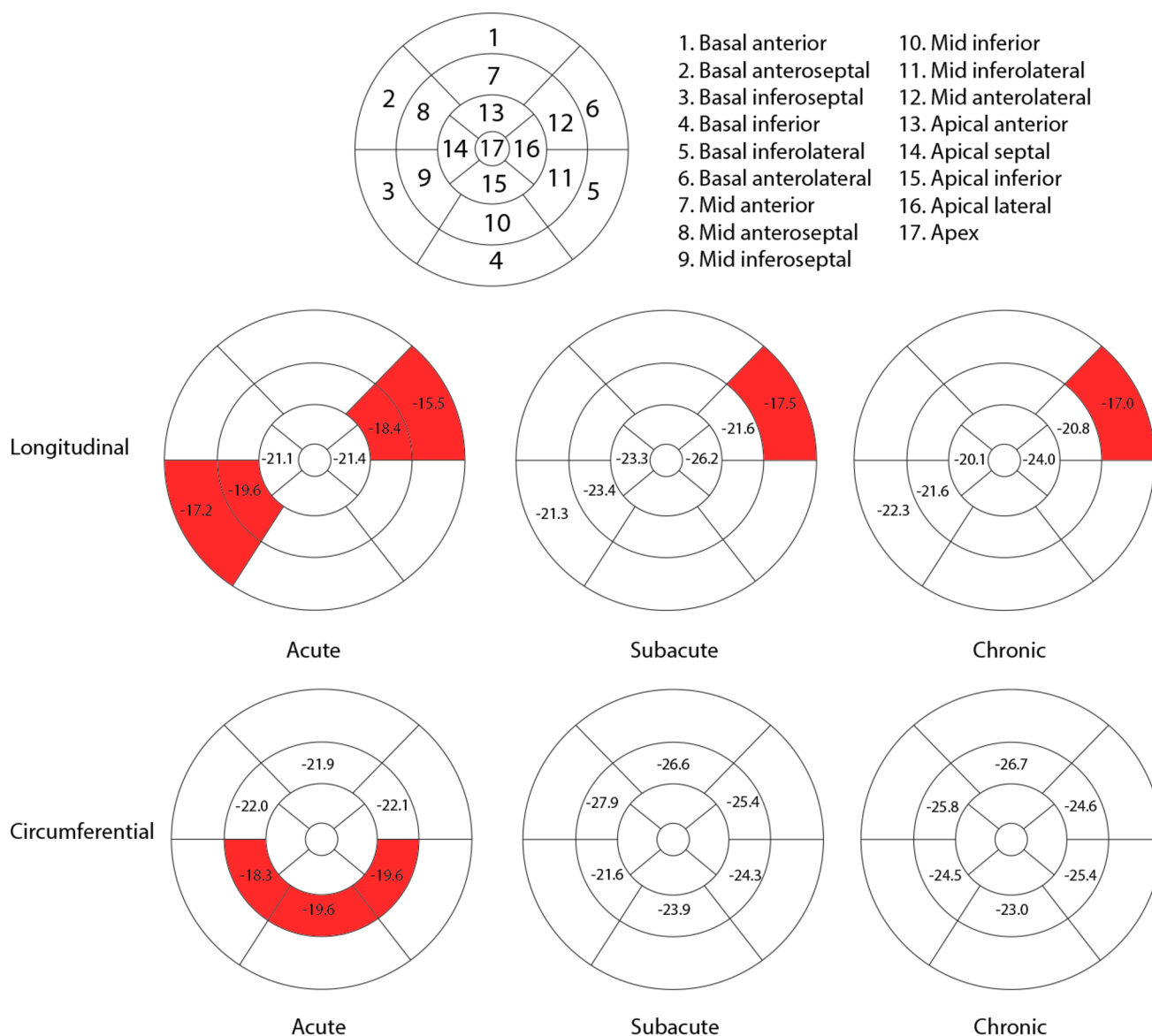
Fig. 3 LV regional strain by timepoint. Visualization of the average regional longitudinal strain (RLS) and regional circumferential strain (RCS) in the cohort across the acute, subacute, and chronic phases

change, but on average was considered normal (− 20% or greater) by the chronic phase [10]. This difference in recovery between GCS and GLS was also noted by Gaitonde et. al [14]. Conversely, another study by Theocharis et. al. showed a statistical improvement in GLS from admission to discharge [14, 16].

In the PICU subgroup, GLS was more significantly impaired and persisted to be abnormal in the chronic phase despite improvement in the fractional shortening. These results are similar to publications who reported that patients with MIS-C in the lowest tertile for GLS at presentation had persistent depression in GLS at a 10 week follow up [17].

Additionally, GCS in the same subgroup was depressed in the acute phase but trended towards improvement by the chronic phase. On the contrary, those in the non-PICU group, showed lesser degree of impairment at presentation in the GLS and GCS values and had a more robust improvement, which correlated with their overall clinical presenation.

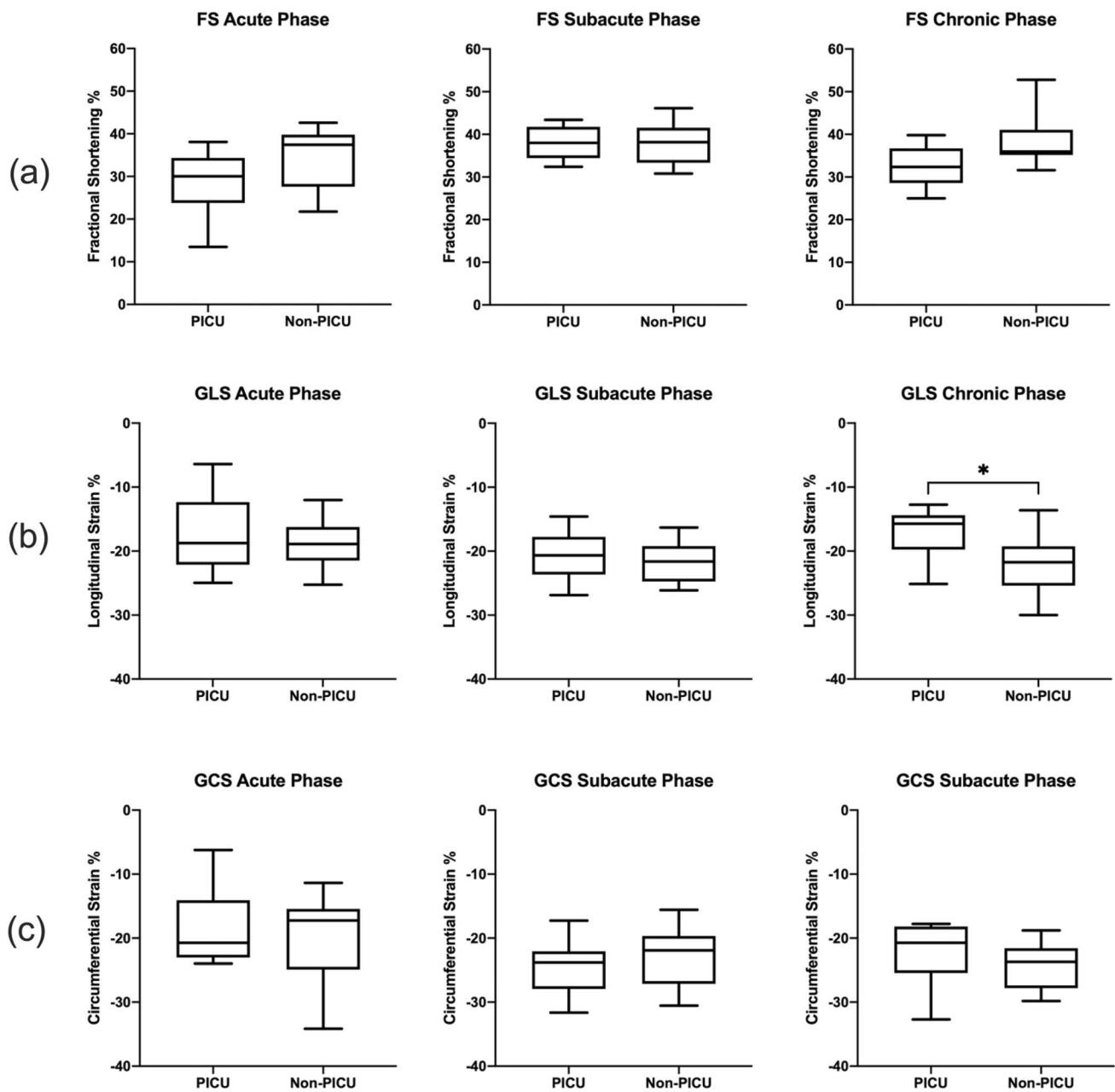Other publications have also demonstrated impaired GLS and GCS in MIS-C patients [13, 16]. Such findings

Fig. 4 Changes in LV strain by subgroup. Comparison of **a** fractional shortening (FS), **b** global longitudinal strain (GLS), and **c** global circumferential strain (GCS) between PICU and non-PICU patients within the acute, subacute, and chronic phases. *Difference between groups was statistically significant ($p < 0.05$)

are consistent with those in both the adult and pediatric literature which have routinely demonstrated the sensitivity of 2D-STE for subtle myocardial dysfunction across multiple disease processes such as sepsis and heart failure with preserved ejection fraction [18–21]. Our findings add to this growing evidence and further support the utilization of GLS and GCS as markers of subclinical myocardial injury in both the acute and longitudinal follow up phases of MIS-C.

Regional Strain

We noted significant changes in regional LV strain within this cohort. In the acute phase, there was abnormal longitudinal strain, particularly in the anterolateral and inferoseptal regions as outlined in Fig. 3. Evaluation of circumferential strain showed impairment in the three inferior regions (inferoseptal, inferior, and inferolateral). Interestingly, a similar pattern of abnormal regional strain has been reported in

both pediatric and adult cases of viral myocarditis which has correlated with regions of myocardial edema and fibrosis on cardiac magnetic resonance imaging [22–24]. This suggests that some of the patterns of myocardial injury with MIS-C may be similar to that of viral myocarditis, though this would require further investigation with cardiac magnetic resonance imaging or endomyocardial biopsy. There are ongoing MRI-based studies for MIS-C patients at this time, which may shed more light on this in the future.

Additionally, this distribution of abnormal regional LV strain roughly correlates to the vascular distributions of the right coronary artery and left circumflex arteries [12]. In comparison, one study of Kawasaki disease patients showed an impairment of strain in the inferolateral and anteroseptal regions, which in turn correlates to the distribution of the left anterior descending artery, which has been the most commonly involved site of aneurysmal change in KD [25, 26]. Though coronary artery changes were overall a rare finding in our cohort, it has been described in patients with MIS-C [6]. Future studies may better elucidate the relationship, if any, between regional wall abnormalities in MIS-C patients and the coronary dilational changes that have been observed.

Finally, the majority of the segments improved to normal values for longitudinal and circumferential strain into the chronic phase. However, the basal anterolateral region had persistently impaired longitudinal strain at − 17%. The clinical significance of this persistent regional impairment in strain is currently not known but does suggest that there may be scar tissue formation and fibrosis that persists despite clinical recovery and normalization of the measured ejection fraction by echocardiography. This may in turn serve as a nidus for development of cardiac arrhythmia, and the identification of this risk, if any, could serve as a future avenue for research.

Limitations

Our study is limited due to the nature of being a single-center retrospective study with a relatively small sample size. This is in part due to the rare occurrence of MIS-C and that even a smaller subset of those have severe disease.

Due to pandemic decontamination constraints and to limit sonographer exposure, at our center we adopted a protocol using the Lumify tablet-based system to capture initial echocardiographic data. The utilization of the Lumify device limited the initial views obtained to apical 4-chamber and parasternal short axis at the level of the papillary muscle, so our reported regional strain analysis may not be representative of all LV segments. When COVID-19 precautions were lifted or the patient was discharged, the subsequent echocardiograms were performed on a traditional machine with comprehensive evaluation. Though ideally a traditional machine would have been used at all timepoints, both the American Society of Echocardiography and the European Association of Cardiovascular Imaging have published statements supporting the use of portable ultrasound to quantify left ventricular function [27, 28]. Additionally, though to our knowledge there have been no head to head comparisons of strain values generated by tablet-based portable devices versus cart-based echocardiographic devices, TOMTEC's vendor-independent calculations have been shown to have minimal differences between devices [9]. By harnessing the power of machine learning and artificial intelligence, software such as TOMTEC may pave the way for more widespread use of tablet-based ultrasound, thereby reducing costs and increasing accuracy, as some have speculated [29]. Finally, within our echocardiography laboratory, we also did an internal quality review of the studies obtained on our tablet during the acute pandemic phase and established that no critical information was compromised [30]. Thus, we feel confident our images were adequate quality for analysis using TOMTEC.

Some of the initial echocardiograms were performed using this protocol and as a result FS data for 4 patients was unavailable and excluded from FS analysis. Similarly, to avoid selection bias, we selected the first echocardiogram obtained for each phase. Some subjects may have had deterioration in their cardiac function after the initial evaluation. Therefore, it is possible the GLS, GCS, and FS values could have been lower in the acute phase. Further, 5 of 8 of the PICU cohort required vasopressors on admission which may have also affected the results of the initial echocardiograms obtained. Finally, a significant proportion of the MIS-C patients seen in our institution were excluded from the study due to lack of adequate imaging (6) or loss to followup (10). The majority (13) of these were not critically ill, whereas the remainder 3 required PICU admission and vasopressor support. We believe these exclusions to be due to chance alone, though there may have been a self-selection bias in which less ill children may be less likely to adhere to regular followup, leading to an overestimation in the long term sequelae of MIS-C.

Evaluation of pediatric left ventricular strain is also limited due to its novelty and lack of guidelines and cutoff measurements for this evaluation. It has also been shown that there is high variability between software manufacturers and normal values have not been established or agreed upon amongst the medical community [10].

Conclusion

In our longitudinal study of MIS-C patients, we show that global and regional strain are abnormal during acute disease, which correlates with the LV dysfunction as measured

by FS. This dysfunction was more profound in those with more clinically severe disease. As myocardial and clinical recovery occurs, global and regional strain values also normalize. We also show continued regional abnormalities in the chronic phase which may represent an important marker of subclinical disease and possible increased risk of adverse events in the future. Thus far, there has not been a clear consensus on the optimal frequency and duration of follow-up for these patients with MIS-C. It is unclear what markers are important to determine complete cardiac clinical recovery. Despite clinical improvement in symptoms and fractional shortening, we do not fully understand the implications of anormal regional strain that may represent subclinical myocardial injury. For now, our data seems to emphasize the need for continued long-term follow-up of these patients.

Declarations

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