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Speckle-tracking and conventional echocardiography in MIS-C: tracking cardiac involvement and recovery

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Abstract

Background Multisystem inflammatory syndrome in children (MIS-C), a complication of COVID-19, is frequently associated with cardiac involvement. Although most affected children recover, the extent and duration of myocardial abnormalities remain uncertain. This study evaluates mid-term cardiac function in MIS-C patients, with and without cardiac involvement, using transthoracic echocardiography (TTE) and speckle-tracking echocardiography (STE).

Methods This case–control study (2022–2023) included 90 children: 30 with MIS-C and cardiac involvement, 30 with MIS-C without cardiac involvement, and 30 healthy controls. TTE and STE were used to assess left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) at diagnosis and at three months, comparing outcomes across groups.

Results The cardiac involvement group exhibited significantly elevated ferritin and C-reactive protein levels ($P=0.006$ and $P=0.017$, respectively) and a higher prevalence of troponin positivity (56.67% vs. 20%, $P=0.009$). At baseline, these patients had markedly reduced LVEF (56.5 ± 4.3) and GLS (-21.6 ± 3.21) compared to healthy controls (LVEF: 68.2 ± 5.21; GLS: -24.8 ± 1.48; both $P<0.001$). Notably, the basal segment showed significant longitudinal strain reduction (-18.75 ± 3.89 vs. -23.58 ± 0.27, $P=0.027$), while differences in the apical and mid segments were not significant. By three months, LVEF (69 ± 4.21, $P=0.53$) and GLS (-24.13 ± 2.39, $P=0.17$) normalized. Heart failure and coronary artery brightness resolved in all affected patients, and most structural abnormalities improved; only two cases exhibited persistent mild left ventricular dilation. Regional strain analysis at follow-up revealed values comparable to those of healthy controls across all segments.

Conclusion Cardiac dysfunction in MIS-C largely resolves within three months, with LVEF and GLS returning to normal. However, persistent myocardial abnormalities in a few cases highlight the need for long-term cardiac monitoring to detect and manage potential sequelae.

Keywords Multisystem Inflammatory Syndrome in Children (MIS-C), Cardiac dysfunction, Myocardial recovery, Speckle-tracking echocardiography (STE), Transthoracic echocardiography (TTE), Global longitudinal strain (GLS), COVID-19 in children

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) has emerged as a serious post-infectious complication of SARS-CoV-2, posing unique challenges in pediatric care and underscoring its public health significance [1, 2]. MIS-C is characterized by a hyperinflammatory response that can result in cardiovascular complications, including myocarditis, acute cardiac dysfunction, and coronary artery abnormalities [3, 4]. Although the exact pathophysiology remains unclear, growing evidence suggests an immune-mediated, post-viral mechanism resembling myocarditis [5].

As the coronavirus disease 2019 (COVID-19) pandemic progressed, it became clear that understanding the long-term cardiac implications of MIS-C is critical, particularly since many affected children exhibit transient cardiac abnormalities during the acute phase [6, 7]. Although many affected children regain normal cardiac function within months, some exhibit persistent or delayed-onset cardiac sequelae, raising concerns about potential long-term implications [8]. This underscores the necessity of continued cardiac monitoring and structured follow-up to mitigate adverse outcomes.

Speckle-tracking echocardiography (STE) is increasingly recognized as a valuable tool for evaluating myocardial mechanics in MIS-C. Unlike conventional echocardiography, which primarily assesses ejection fraction and chamber dimensions, STE provides a sensitive and detailed analysis of myocardial deformation and strain, allowing for the detection of subclinical cardiac dysfunction [9, 10]. Its application in MIS-C could enhance the identification of early myocardial impairment and guide timely interventions [10].

Despite its significance, limited research has investigated cardiac involvement in MIS-C, and no study has directly compared cardiac outcomes between patients with and without cardiac involvement. The lack of adequate data on mid- and long-term cardiac sequelae highlights the need for targeted investigations to refine clinical management and prevent complications.

This case–control study aims to bridge this gap by assessing mid-term cardiac function in pediatric MIS-C patients. Using transthoracic echocardiography (TTE) and STE, the study evaluates myocardial strain and function at diagnosis and three months post-diagnosis. By delineating the trajectory of cardiac recovery, the findings may inform clinical strategies for optimizing management and long-term outcomes in MIS-C patients.

Methods

This cross-sectional case–control study was conducted at Namazi Hospital, Shiraz, Iran, from September 2022 to June 2023. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (Ethics code: IR.SUMS.MED.REC.1401.323). Ethical considerations included obtaining informed consent from participants' guardians, providing free echocardiographic evaluations, and adhering to the principles outlined by the Ethics Committee and the Declaration of Helsinki.

Participants and sampling

A total of 90 children were included in the study, categorized into three groups: 30 children with multisystem inflammatory syndrome in children (MIS-C) and cardiac involvement, 30 children with MIS-C without cardiac involvement, and 30 healthy controls. MIS-C patients were younger than 18 years old and met the diagnostic criteria established in previous studies [11]. Healthy controls were children with no underlying medical conditions and confirmed absence of COVID-19.

Given the rarity of MIS-C, patient selection was based on convenience sampling from clinical diagnoses and paramedical findings, whereas the healthy controls were randomly selected from the hospital registry. Participants were age-matched within a tolerance of ± 1 year to ensure demographic comparability across groups. The sex distribution in the healthy control group was balanced (15 males [50%] and 15 females [50%]).

Eligibility criteria

Inclusion criteria for the MIS-C groups were a confirmed diagnosis of MIS-C according to established guidelines [11] and availability of echocardiographic and laboratory data. Exclusion criteria for all groups were:

- History of congenital heart disease.
- Presence of concurrent underlying diseases affecting cardiac function.
- Current cancer diagnosis or ongoing chemotherapy.

The healthy controls were children free of any known disease or recent COVID-19 exposure.

Data collection

Data collection for the MIS-C groups was conducted during hospitalization and included transthoracic

echocardiography (TTE) and speckle-tracking echocardiography (STE) assessments. Echocardiographic evaluations were conducted using a Vivid GE S6 ultrasound scanner with a 4 MHz transducer. Two-dimensional cine loops were acquired from three apical views (four-chamber, three-chamber, and two-chamber) and digitally stored for further analysis.

- For healthy controls, a single echocardiographic evaluation was performed without follow-up, whereas MIS-C patients underwent TTE and STE at diagnosis and three months post-diagnosis to assess myocardial strain and left ventricular function.
- The Simpson method was used to calculate left ventricular volumes and ejection fraction (LVEF), a standard approach in pediatric cardiology.
- Myocardial deformation and strain were analyzed using STE. Acoustic markers (speckles) were automatically tracked across the cardiac cycle using TomTec Image Arena software, a vendor-independent platform.

During the study period (September 2022–June 2023), the Omicron variant of SARS-CoV-2 was the predominant strain nationally and institutionally, as reported by local and national health agencies.

Definitions

MIS-C with Cardiac Involvement: Defined by echocardiographic findings, including LVEF < 57%, coronary artery involvement, valvular abnormalities, pericardial effusion, arrhythmias, and/or clinical signs of heart dysfunction.
Heart Failure: Defined as LVEF < 57%, determined through TTE assessments, in accordance with widely accepted pediatric cardiology guidelines.
Laboratory Tests: All laboratory tests were performed at the time of hospital admission.
Troponin Positivity: Defined as a troponin level > 20 ng/L, based on institutional laboratory standards for pediatric patients.

Bias reduction strategies

To mitigate potential bias:

- Two control groups were included: healthy children and MIS-C patients without cardiac involvement, to allow for comprehensive comparisons.
- Echocardiographic studies were conducted independently by two blinded pediatric cardiologists who were unaware of participant categorization. Discrepancies in interpretation were resolved by consensus.
- Random sampling was used for healthy controls, and age- and sex-matching were applied across groups.

Outcome measures

Primary outcomes included cardiac function and myocardial strain parameters assessed using STE and TTE. MIS-C patients' outcomes at diagnosis and follow-up were compared to evaluate cardiac recovery. Healthy controls served as a baseline reference for cardiac function.

Statistical analysis

Data were analyzed using SPSS (version 26). Continuous variables were expressed as means ± standard deviations and compared using Student's t-test. Categorical variables were presented as counts and percentages, analyzed using Chi-square tests. Echocardiographic parameters of MIS-C patients (both cardiac and non-cardiac involvement groups) were compared independently with those of healthy controls. A p-value < 0.05 was considered statistically significant.

Result

Demographic and clinical characteristics

Table 1 summarizes the demographic and laboratory characteristics of MIS-C patients. The two MIS-C groups showed no significant differences in age (7.72 ± 4.03 vs. 7.97 ± 3.59 years, $P = 0.08$) or gender distribution ($P = 0.44$). Healthy controls were matched by age within a ± 1 year tolerance and had a 1:1 sex ratio. Patients with cardiac involvement had longer hospital stays (6.7 ± 3.53 vs. 4.87 ± 1.47 days, $P = 0.011$) and required longer intensive care unit (ICU) stays (2.43 ± 2.31 days vs. 1.03 ± 0.93 days, $P = 0.003$), indicating a more severe clinical course.

Inflammatory markers

Inflammatory markers were significantly elevated in the cardiac involvement group, with higher C-reactive protein (CRP) (110.25 ± 56.99 vs. 72.03 ± 61.53 mg/L, $P = 0.017$) and ferritin levels (1417.42 ± 1447.11 vs. 510.97 ± 656.71 ng/dL, $P = 0.006$). Troponin positivity, defined as levels >20 ng/L, was more prevalent in the cardiac group (56.67% vs. 20%, $P = 0.009$), indicating greater myocardial injury. Although erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) were elevated in both groups, these differences did not reach statistical significance ($P = 0.47$ and $P = 0.51$, respectively).

Table 1 Demographic and Laboratory Characteristics of MIS-C Patients with and without Cardiac Involvement

Variables	Categories	MIS-C Non-Cardiac Group (n = 30)	MIS-C Cardiac Group (n = 30)	*P*-values
Age (years)		7.72 ± 4.03	7.97 ± 3.59	0.08
Gender	Female	15(50%)	12(40%)	0.44
	Male	15(50%)	18(60%)	
Admission Duration (days)		4.87 ± 1.47	6.7 ± 3.53	0.011
ICU Duration (days)		1.033 ± 0.93	2.43 ± 2.31	0.003
CRP (mg/L)		72.03 ± 61.53	110.25 ± 56.99	0.017
ESR (mm/hour)		51.17 ± 35.93	58 ± 33.73	0.47
WBC (cell/microliter)		8.86 ± 4.028	9.55 ± 4.05	0.51
Fibrinogen (mg/dL)		512.63 ± 198.03	489.2 ± 146.11	0.73
Ferritin (ng/dL)		510.97 ± 656.71	1417.42 ± 1447.11	0.006
Positive troponin (n, %)		6 (20%)	17 (56.67%)	0.009
Troponin (ng/mL)		19.28 ± 25.51	193.38 ± 490.95	0.057

CRP C-reactive protein, *ESR* Erythrocyte Sedimentation Rate, *WBC* White Blood Cell

Table 2 Distribution of cardiac complications in MIS-C patients with cardiac involvement over three months

Problem	Admission (n = 30)	3-month F/U (n = 28)
HF	14 (46.6%)	0 (0%)
MR	9 (30%)	3 (10.7%)
TR	21 (70%)	3 (10.7%)
PI	12 (40%)	3 (10.7%)
AI	2 (6.6%)	0 (0%)
Pericardial effusion	4 (13.3%)	0 (0%)
Arrhythmia	2 (6.6%)	0 (0%)
Coronary artery brightness	3 (10%)	0 (0%)
LAD and LCA aneurysm	1 (3.3%)	1 (3.6%)
RCA Dilation	1 (3.3%)	0 (0%)
Coronary artery lack of tapering	1 (3.3%)	0 (0%)
Mild LV dilation	5 (16.6%)	2 (7.1%)

Abbreviations: *HF* heart failure, *MR* mitral regurgitation, *TR* tricuspid regurgitation, *PI* Pulmonic insufficiency, *AI* Aortic insufficiency, *LAD* Left Anterior Descending artery, *LCA* Left Coronary Artery, *RCA* Right Coronary Artery, *LV* left ventricular

Cardiac outcomes

Mid-term cardiac outcomes were assessed during a three-month follow-up. Of the initial cohort, three patients in the cardiac group (one death, two lost to follow-up) and two in the non-cardiac group (both lost to follow-up) were excluded from follow-up analyses.

At admission, 14 patients with cardiac involvement exhibited heart failure, which had completely resolved in all surviving patients by the three-month follow-up (Table 2). Arrhythmias occurred in two patients: one case of fatal ventricular tachycardia and one case of transient sinus bradycardia, which resolved within 48 h and did not recur.

Coronary artery abnormalities were noted in one patient with aneurysms in the left anterior descending (LAD) and left main coronary artery (LMCA), exhibiting a Z-score of 5–10, indicating significant dilation. These abnormalities remained stable over three months with no functional impairments. Structural abnormalities, including mitral regurgitation (MR), tricuspid regurgitation (TR), and pulmonic insufficiency (PI), were prevalent at admission but showed significant improvement by follow-up, with only three cases of each persisting. Aortic insufficiency and pericardial effusion, initially observed in two and four patients, respectively, resolved completely by follow-up.

Coronary artery brightness, initially noted in three patients, resolved entirely during follow-up. Mild left ventricular (LV) dilation was observed in five patients, persisting in only two cases at follow-up. Two patients showed mild LV dilation with subclinical myocardial dysfunction, indicating persistent myocardial changes associated with structural LV abnormalities.

Comparative analysis of echocardiographic parameters at baseline

Baseline echocardiography revealed significantly reduced left ventricular ejection fraction (LVEF) in the cardiac group (56.5 ± 4.3) compared to healthy controls (68.2 ± 5.21) and the non-cardiac MIS-C group (70.5 ± 4.10) ($P < 0.001$ for both comparisons). Global longitudinal strain (GLS) was also significantly impaired (-21.6 ± 3.21 vs. -24.8 ± 1.48 in healthy controls, $P < 0.001$). Similar differences were noted across 4CGLS, 3CGLS, and 2CGLS ($P < 0.001$ for each),

Table 3 Baseline and Follow-up 2D Conventional and Speckle-Tracking Echocardiographic Parameters in MIS-C Patients and Healthy Controls

Variables	Categories	Healthy Controls (HC)	MIS-C Non-Cardiac Group	MIS-C Cardiac Group	*P*-values
LVEF	Baseline	68.2 ± 5.21	70.5 ± 4.10	56.5 ± 4.3	0.14* **< 0.001**$
	F/U		71.2 ± 4.18	69 ± 4.21	0.12* 0.53$
GLS	Baseline	-24.8 ± 1.48	-24.1 ± 2.51	-21.6 ± 3.21	0.19* **< 0.001**$
	F/U		-24.2 ± 2.39	-24.13 ± 2.39	0.19* 0.17$
4CGLS	Baseline	-24.3 ± 1.75	-23.91 ± 2.50	-20.89 ± 2.67	0.48* **< 0.001**$
	F/U		-24.8 ± 2.11	-24.91 ± 2.1	0.14* 0.12$
3CGLS	Baseline	-24.05 ± 1.27	-24.32 ± 1.62	-22.01 ± 2.51	0.22* **< 0.001**$
	F/U		-24.56 ± 1.85	-24.61 ± 2.31	0.28* 0.35$
2CGLS	Baseline	-24.38 ± 1.64	-25.12 ± 2.10	-21.67 ± 3.41	0.13* **< 0.001**$
	F/U		-23.98 ± 2.5	-23.98 ± 2.02	0.46* 0.31$
Apex Region	Baseline	-24.36 ± 0.56	-24.47 ± 0.57	-22.40 ± 2.64	0.37* **0.08$**
	F/U		-24.37 ± 0.83	24.13 ± 0.83	0.21* 0.15$
Mid Region	Baseline	-24.11 ± 0.46	-24.10 ± 1.03	-21.99 ± 2.91	0.88* 0.15$
	F/U		-24.11 ± 0.50	-24.35 ± 0.63	0.63* 0.28$
Base Region	Baseline	-23.58 ± 0.27	-23.97 ± 0.42	-18.75 ± 3.89	0.15* **0.027$**
	F/U		-23.92 ± 0.66	-23.59 ± 0.51	0.37* 0.83$

Abbreviations: *LVEF* left ventricular ejection fraction, *GLS* global longitudinal strain, *4CGLS* four chamber global longitudinal strain, *3CGLS* Global Longitudinal Strain of three chamber view, *2CGLS* two chamber global longitudinal strain

* MISC without cardiac involvement vs. healthy controls

$ MISC with cardiac involvement vs. healthy controls

emphasizing substantial myocardial strain reduction in patients with cardiac complications (Table 3). At baseline, longitudinal strain (LS) in the apex (-22.40 ± 2.64) and mid (-21.99 ± 2.91) regions was slightly lower in the MIS-C cardiac group compared to healthy controls (-24.36 ± 0.56 and -24.11 ± 0.46, respectively), though these differences were not statistically significant ($P > 0.05$). In contrast, the base region exhibited a significant LS reduction in the MIS-C cardiac group at baseline (-18.75 ± 3.89 vs. -23.58 ± 0.27, $P = 0.027$), suggesting a greater susceptibility to myocardial dysfunction.

Table 4 presents the comparison of mean longitudinal strain across various cardiac segments among the study groups. At baseline, significant reductions in longitudinal strain were observed in the MIS-C cardiac involvement group compared to healthy controls, particularly in specific myocardial segments. Segmental strain analysis of MIS-C cardiac patients identified pronounced impairments in the anterior and lateral walls of the apex ($P = 0.002$), the mid anterior wall ($P < 0.001$), and the mid lateral wall ($P = 0.003$). The basal segments, including the anterior ($P = 0.001$), lateral ($P < 0.001$), inferolateral ($P < 0.001$), and anteroseptal walls ($P < 0.001$), showed marked impairments, reflecting a global impact on myocardial contractility in patients with cardiac involvement. In particular, the basal walls may serve as critical regions for focused clinical assessment.

Table 4 Comparison of the mean longitudinal strain of different heart segments/regions across the study groups

Cardiac segments	Categories	Healthy Controls (HC)	MIS-C Non-Cardiac Group	MIS-C Cardiac Group	*P*-values
anterior wall of apex	Baseline	-24.62 ± 3.08	-24.73 ± 2.96	-19.70 ± 7.63	0.88* **0.002**$
	F/U		-25.01 ± 2.74	-23.97 ± 2.69	0.76* 0.18$
lateral wall of apex	Baseline	-24.24 ± 2.58	-25.14 ± 3.10	-18.40 ± 9.51	0.22* **0.002**$
	F/U		-23.68 ± 1.98	-22.68 ± 6.21	0.19* 0.21$
inferolateral wall of apex	Baseline	-24.92 ± 2.9	-23.89 ± 3.01	-23.51 ± 4.54	0.11* 0.15$
	F/U		-24.42 ± 4.05	-23.96 ± 3.87	0.41* 0.36$
Inferior wall of apex	Baseline	-24.97 ± 4.15	-23.66 ± 4.61	-24.21 ± 3.96	0.2* 0.40$
	F/U		-23.86 ± 3.99	-25.01 ± 2.87	0.18* 0.41$
septal wall of apex	Baseline	-24.76 ± 3.32	-24.76 ± 3.32	-24.59 ± 4.25	0.43* 0.86$
	F/U		-24.21 ± 3.65	-24.38 ± 4.17	0.51* 0.85$
anteroseptal wall of apex	Baseline	-24.78 ± 3.42	-24.65 ± 2.96	-23.98 ± 3.85	0.78* 0.39$
	F/U		-25.02 ± 2.89	-24.78 ± 2.82	0.24* 0.69$
mid anterior wall	Baseline	-24.95 ± 3.16	-25.36 ± 2.46	-18.21 ± 8.2	0.58* **< 0.001**$
	F/U		-24.65 ± 2.98	-24.71 ± 3.41	0.17* 0.86$
mid lateral wall	Baseline	-24.16 ± 2.75	-23.2 ± 1.05	-18.5 ± 9.81	0.07* **0.003**$
	F/U		-23.84 ± 2.01	-25.02 ± 2.81	0.09* 0.37$
Mid inferolateral wall	Baseline	-23.84 ± 2.75	-24.51 ± 3.12	-22.98 ± 3.15	0.38* 0.26$
	F/U		-23.95 ± 3.41	-23.82 ± 1.91	0.32* 0.62$
Mid inferior wall	Baseline	-24.11 ± 3.03	-25.12 ± 4.03	-25.21 ± 3.81	0.27* 0.22$
	F/U		-24.68 ± 2.75	-24.98 ± 2.91	0.32* 0.37$
Mid septal wall	Baseline	-23.86 ± 2.10	-23.46 ± 2.31	-23.51 ± 3.01	0.48* 0.6$
	F/U		-24.03 ± 1.99	-23.64 ± 2.57	0.37* 0.55$
Mid anteroseptal wall	Baseline	-23.27 ± 2.02	-22.97 ± 1.85	-23.53 ± 3.81	0.55* 0.74$
	F/U		-23.54 ± 1.96	-23.91 ± 2.69	0.49* 0.89$
anterior wall of basal	Baseline	-23.68 ± 2.42	-23.52 ± 1.23	-16.25 ± 7.54	0.74* **0.001**$
	F/U		-24.13 ± 2.54	-22.78 ± 5.04	0.38* 0.17$
lateral wall of basal	Baseline	-24.05 ± 3.16	-24.03 ± 2.76	-12.57 ± 14.08	0.97* **< 0.001**$
	F/U		-24.24 ± 4.01	-23.67 ± 2.41	0.33* 0.21$

Table 4 (continued)

Cardiac segments	Categories	Healthy Controls (HC)	MIS-C Non-Cardiac Group	MIS-C Cardiac Group	*P*-values
inferolateral wall of basal	Baseline	-23.68 ± 2.50	-24.22 ± 2.63	-18.23 ± 6.43	0.41* **< 0.001**[$]
	F/U		-23.97 ± 2.47	-23.45 ± 3.16	0.67* 0.75[$]
inferior wall of basal	Baseline	-23.38 ± 1.74	-23.84 ± 2.03	-23.22 ± 4.35	0.34* 0.85[$]
	F/U		-22.75 ± 2.15	-24.18 ± 2.03	0.21* 0.31[$]
septal wall of basal	Baseline	-23.3 ± 2.11	-23.56 ± 3.11	-21.21 ± 3.12	0.70* **0.004**[$]
	F/U		-23.71 ± 2.46	-23.40 ± 3.04	0.64* 0.71[$]
anteroseptal wall of basal	Baseline	-23.75 ± 2.26	-24.65 ± 2.34	-21.05 ± 3.59	0.13* **< 0.001**[$]
	F/U		-24.71 ± 2.24	-24.05 ± 2.14	0.09* 0.32[$]

[*] MISC without cardiac involvement vs. healthy controls

[$] MISC with cardiac involvement vs. healthy controls

In contrast, MIS-C patients without cardiac involvement exhibited strain values more comparable to controls, with only minor, non-significant differences in segments such as the mid lateral wall ($P=0.07$) and inferolateral wall of apex ($P=0.11$).

Comparative analysis of echocardiographic parameters at follow-up

At three-month follow-up, significant improvements in cardiac function were observed. LVEF in the cardiac group increased to 69 ± 4.21, aligning with values in the non-cardiac group (71.2 ± 4.18) and showing no significant difference from healthy controls ($P=0.53$). Longitudinal strain analysis at follow-up revealed stabilization across all groups. GLS in the cardiac involvement group also improved to -24.13 ± 2.39, comparable to healthy controls (-24.8 ± 2.39, $P=0.17$) (Table 3). Other parameters, including 4CGLS and 2CGLS, also demonstrated recovery, with follow-up values closely paralleling those of the control and non-cardiac groups (*P*-values ranging from 0.12 to 0.46).

In the follow-up assessment of mean segmental strain in the apex, mid, and base regions, both MIS-C subgroups demonstrated values comparable to healthy controls. At follow-up, LS values remained stable in all regions, with no significant differences between groups ($P>0.05$), indicating a trend toward myocardial recovery over time. Recovery trends were also consistent across all specific segmental strain parameters, with no significant residual dysfunction. While follow-up strain values in MIS-C patients with cardiac involvement remained lower than those in healthy controls, strain recovery was observed in all segments and no significant differences were noted.

As illustrated in Fig. 1, the findings highlight region-specific reductions in myocardial strain at baseline in MIS-C patients with cardiac involvement, which improved significantly by follow-up. While follow-up strain values in MIS-C patients with cardiac involvement remained lower than those in healthy controls, strain recovery was observed in all segments and no significant differences were noted. However, the persistence of reduced GLS in two cases, aneurysms in the LAD and LCA (one case), and mild LV dilation (two cases) in a few cases (though not all) at three months underscore the importance of targeted echocardiographic monitoring to identify patients at higher risk of sustained myocardial dysfunction.

Treatment strategies

Treatment approaches were comparable between groups. Methylprednisolone pulse therapy was administered to 20% of patients with cardiac involvement versus 10% of the non-cardiac group, with no significant difference ($P=0.28$). Similarly, intravenous immunoglobulin (IVIg) therapy was utilized in 33.33% of patients in both groups ($P=1$), suggesting consistent therapeutic strategies across MIS-C cases, regardless of cardiac involvement.

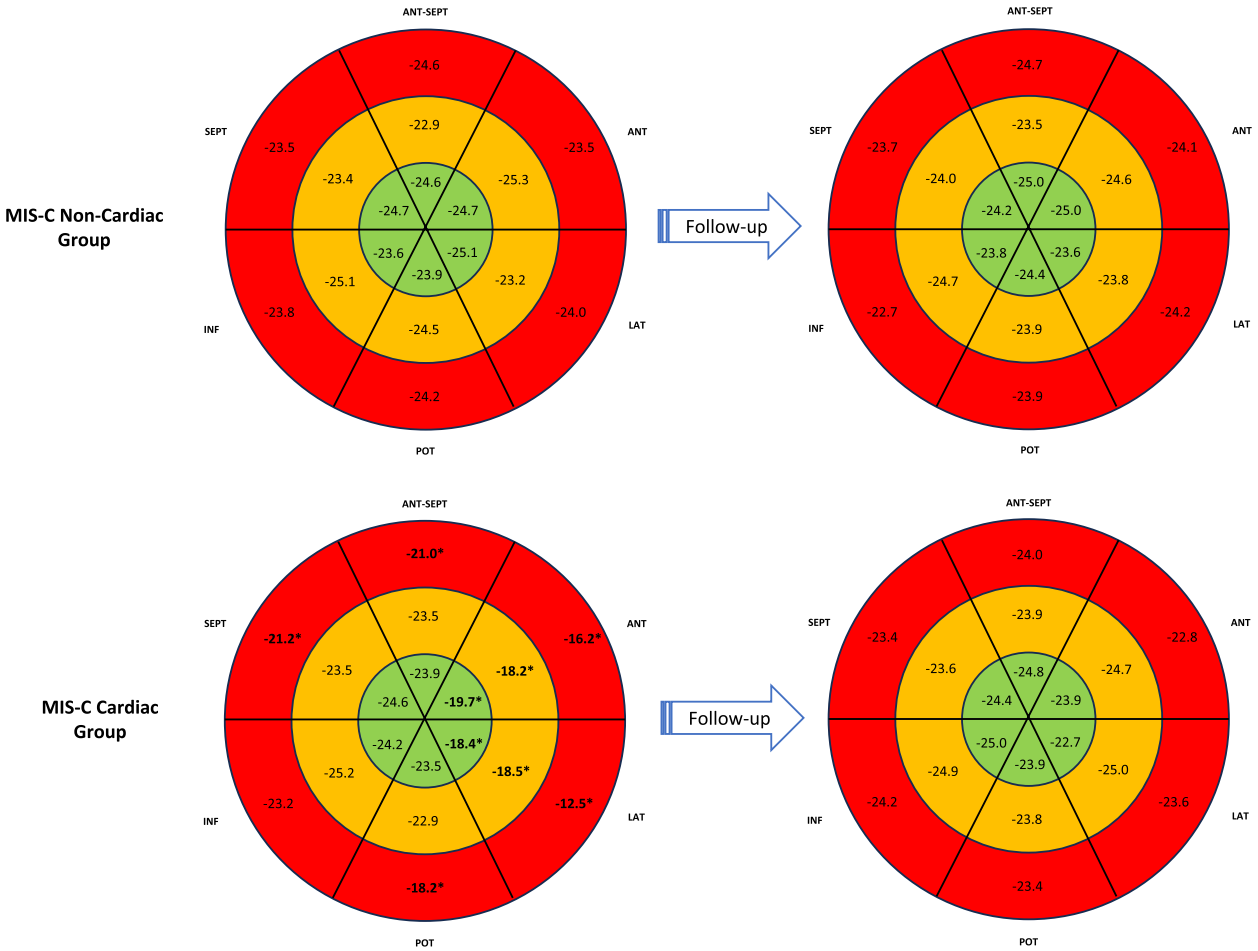

Fig. 1 Left ventricle GLS Bull's Eye. Bull's Eye representation of the mean longitudinal strain values (%) for each segment of the left ventricle. Basal segments (red) exhibited the most impaired deformation compared to mid-wall (orange) and apical (green) segments. Segments with a significant difference compared to the healthy control group are marked with an asterisk (*)

Discussion

This study highlights the clinical and cardiac implications of multisystem inflammatory syndrome in children (MIS-C), particularly myocardial dysfunction and its mid-term recovery. Patients with cardiac involvement experienced more severe clinical courses, as indicated by prolonged hospital stays and elevated inflammatory and cardiac biomarkers. Initial echocardiographic assessments revealed significant myocardial impairment, with substantial recovery observed within three months. Segmental strain analysis further demonstrated regional myocardial vulnerability, particularly in basal myocardial segments.

Inflammatory and cardiac biomarkers

Elevated inflammatory markers upon admission, including CRP and ferritin, reflect the systemic inflammatory burden in MIS-C patients with cardiac involvement. Our cohort's mean CRP level of 110.25 mg/L is consistent with findings by Whittaker et al. [12], who reported a median of 229 mg/L in MIS-C, notably higher than in other Kawasaki-like conditions. Similarly, elevated ferritin levels (mean: 1417.42 ng/dL) have been associated with cardiac complications, including coronary artery dilation and shock, as noted by Valverde et al. [13].

Troponin positivity was markedly higher (56.67%) in patients with cardiac involvement, supporting findings from Sirico et al. [5], who reported elevated troponin levels in 65% of MIS-C patients with cardiac involvement. Despite a non-significant mean difference in troponin levels ($P=0.057$), its prognostic value for myocardial injury remains critical, as emphasized by Zimmerman et al. [14]. Although our study did not measure B-type natriuretic peptide (BNP), previous research by Kostik et al. [15] and Sirico et al. [5] has linked elevated troponin and BNP levels to systemic inflammation and myocardial dysfunction in severe MIS-C cases. Establishing standardized diagnostic criteria and biomarker thresholds

is crucial for enhancing risk stratification in MIS-C patients.

Echocardiographic parameters

Baseline echocardiography revealed significantly reduced left ventricular ejection fraction (LVEF) in the cardiac involvement group (56.5 ± 4.3) compared to healthy controls and MIS-C patients without cardiac involvement ($P < 0.001$). This finding is consistent with Sirico et al. [5], who reported a mean LVEF of 59 ± 10% during the acute phase of MIS-C, and Garbin et al. [16], who noted that 39% of their MIS-C cohort had reduced LVEF (< 55%) at diagnosis. These results validate LVEF as a critical indicator of myocardial dysfunction in MIS-C.

Global longitudinal strain (GLS) was similarly impaired (-21.6 ± 3.21 vs. -24.8 ± 1.48 in controls, $P < 0.001$). This aligns with Sirico et al. [5], who documented a mean GLS of -17 ± 4.3%, and Kabayash et al. [17], who observed significantly lower GLS values in MIS-C patients compared to healthy controls. Both studies emphasize the diagnostic value of speckle-tracking echocardiography (STE) in detecting subclinical myocardial injury [5, 17]. Our study extends this evidence by documenting significant impairments across GLS subparameters, including 4CGLS, 3CGLS, and 2CGLS.

At three months, the LVEF improved to 69 ± 4.21, within the normal range, consistent with findings by Garbin et al. [16] and Wolf et al. [8], who observed normalization within 6–12 months. However, while GLS showed near-complete recovery (-24.13 ± 2.39, $P = 0.17$ vs. controls), Wolf et al. [8] reported persistent abnormalities in 35% of their cohort, suggesting heterogeneity in recovery trajectories influenced by disease severity, management protocols, and follow-up durations. Regional strain analysis demonstrated significant reductions in basal-level myocardial segments, aligning with Sirico et al. [5], who reported greater impairment in basal segments (53%) compared to mid (41%) and apical segments (18%). These regional vulnerabilities may reflect immune-mediated injury, microvascular dysfunction, and cytokine-driven inflammation [18]. Similar heterogeneity in myocardial involvement has been observed in other conditions; for instance, Mohammadi et al. [19] identified more pronounced basal strain abnormalities associated with cardiotoxicity in pediatric cancer survivors, suggesting a systemic rather than focal pattern of injury.

Strain recovery was noted at follow-up, with residual abnormalities persisting in only a few cases, mirroring observations in post-viral myocarditis and adult post-COVID syndromes [20]. Incomplete recovery may be attributed to unresolved inflammation, delayed myocardial remodeling, or fibrosis [20]. Pezel et al. [21] highlighted that myocardial fiber orientation and segment-specific mechanics likely contribute to the differential responses of various myocardial regions to systemic stressors.

The clinical implications of these findings are significant. Advanced imaging techniques, such as cardiac MRI with late gadolinium enhancement, could improve the detection of subclinical dysfunction and guide tailored management strategies. Strain imaging should be incorporated into follow-up protocols for MIS-C patients with cardiac involvement, particularly focusing on basal-segment strain abnormalities.

Structural cardiac abnormalities and coronary artery involvement

Valvular regurgitation, coronary artery involvement, and pericardial effusion were notable findings, consistent with Karimi et al. [22]. However, higher rates of left ventricular (LV) dysfunction (46.66%) and tricuspid regurgitation (70%) in our study may reflect differences in imaging sensitivity and study design. Cantarutti et al. [6] identified coronary aneurysms in 35% of MIS-C patients, a finding potentially influenced by variations in imaging protocols, timing of assessments, or regional differences in MIS-C presentation.

Encouragingly, structural abnormalities showed significant improvement within three months, echoing trends reported in the literature [7, 8, 22]. Most cases of valvular regurgitation and coronary artery dilation resolved [8, 22]. Notably, all cases of heart failure in our cohort resolved within three months, corroborating findings from Mannarino et al. [23], who documented full recovery of cardiac function in MIS-C patients. However, Zimmerman et al. [14] cautioned that subclinical abnormalities might persist, underscoring the need for long-term monitoring. Emerging evidence suggests gender and age may influence specific cardiac outcomes [15, 24], warranting further investigation. Future randomized trials should explore early anti-inflammatory interventions to mitigate cardiac complications.

Treatment and recovery

Our study observed a rapid recovery of cardiac function, with global metrics normalizing within weeks, consistent with Matsubara et al. [7]. However, minor residual strain abnormalities persisted in some of our cases, and a few patients exhibited left anterior descending (LAD) and left coronary artery (LCA) aneurysms or mild LV dilation at follow-up. Similarly, Garbin et al. [16] reported normalization of LVEF within months but noted subtle strain abnormalities, paralleling our observations. Persistent abnormalities in cardiac magnetic resonance imaging (CMR) findings despite clinical improvement, as

documented by Zimmerman et al. [14] and Arslan et al. [25], underscore the critical role of advanced imaging in long-term monitoring.

The variability in recovery timelines across studies highlights the heterogeneity of MIS-C presentations, influenced by genetic predisposition, treatment protocols, and imaging techniques. Standardized imaging protocols and large-scale longitudinal studies are needed to better define the cardiac trajectory of MIS-C.

The national consensus management pathway for MIS-C associated with COVID-19 [26] recommends intravenous immunoglobulin (IVIg) as the first-line therapy for all MIS-C cases, with additional methylprednisolone or biologic agents tailored to disease severity or refractory symptoms [26]. Our findings demonstrate consistent adherence to these guidelines [26], with minimal variability in glucocorticoid regimens, reflecting clinical discretion in managing severe inflammation, such as significant pericardial effusion [19]. Our findings support the integration of strain echocardiography and CMR in follow-up protocols to detect subclinical dysfunction and guide management [6]. Future research should focus on the impact of specific therapeutic interventions on cardiac recovery in MIS-C.

Limitation

This study has several limitations. Echocardiographic assessments were conducted at two time points, limiting insights into recovery dynamics. The small sample size and single-center design may reduce statistical power and generalizability. The absence of cardiac magnetic resonance imaging (CMR) restricts assessment of myocardial fibrosis or edema. Additionally, lack of fever duration data prevents evaluation of its role as a disease severity marker. Despite these limitations, our study provides a comprehensive analysis of cardiac involvement in MIS-C, incorporating conventional and advanced echocardiographic parameters. Future studies should include larger cohorts and advanced imaging techniques.

Conclusion

This study demonstrates that LVEF and GLS are initially reduced in MIS-C patients with cardiac involvement but show significant recovery by three months, with most patients experiencing no lasting sequelae. While myocardial dysfunction in MIS-C resolves substantially over time, residual abnormalities in some patients highlight the need for ongoing monitoring and further research into potential long-term effects. Comprehensive cardiac assessment should remain integral to MIS-C management to optimize patient outcomes.

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Authors' contributions
N.M. and E.S. made contributions to the conception and design of the work; S.O., H.A., H.M., A.N., M.R.E., K.H., N.A., and M.H.M. contributed to the investigation and data collection; and H.H. contributed to interpretation of data, data visualization, manuscript writing, and revisions. All authors reviewed the manuscript.

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Data availability
The dataset supporting the findings of this study will be accessible to researchers affiliated with academic and scientific institutions upon reasonable request. Industry-affiliated individuals will not be granted access. Requests for data should be directed to the corresponding author via email (omidshorafa@gmail.com).

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the ethical standards of the Research Ethics Committee of Shiraz University of Medical Sciences (Approval ID: IR.SUMS.MED.REC.1401.323) and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants' guardians before enrollment in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771–8. https://doi.org/10.1016/s0140-6736(20)31103-x.
2. Portman MA, Cimaz R. Should coronavirus disease 2019–associated inflammatory syndromes in children affect social reintegration? JAMA Pediatr. 2020;174(9):827–8. https://doi.org/10.1001/jamapediatrics.2020.2810.
3. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142(5):429–36. https://doi.org/10.1161/circulationaha.120.048360.
4. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the

covid-19 pandemic in Paris, France: prospective observational study. BMJ. 2020;369:m2094. https://doi.org/10.1136/bmj.m2094.
5. Sirico D, Basso A, Reffo E, Cavaliere A, Castaldi B, Sabatino J, et al. Early echocardiographic and cardiac MRI findings in multisystem inflammatory syndrome in children. J Clin Med. 2021;10(15) https://doi.org/10.3390/jcm10153360
6. Cantarutti N, Battista V, Stagnaro N, Labate M E, Cicenia M, Campisi M, et al. Long-Term Cardiovascular Outcome in Children with MIS-C Linked to SARS-CoV-2 Infection—An Italian multicenter experience. Biology. 2022;11(10):1474 https://www.mdpi.com/2079-7737/11/10/1474
7. Matsubara D, Chang J, Kauffman HL, Wang Y, Nadaraj S, Patel C, et al. Longitudinal assessment of cardiac outcomes of multisystem inflammatory syndrome in children associated with COVID-19 infections. J Am Heart Assoc. 2022;11(3):e023251. https://doi.org/10.1161/JAHA.121.023251.
8. De Wolf R, Zaqout M, Tanaka K, Muiño-Mosquera L, van Berlaer G, Vandekerckhove K, et al. Evaluation of late cardiac effects after multisystem inflammatory syndrome in children. Front Pediatr. 2023;11:1253608. https://doi.org/10.3389/fped.2023.1253608.
9. He M, Leone DM, Frye R, Ferdman DJ, Shabanova V, Kosiv KA, et al. Longitudinal assessment of global and regional left ventricular strain in patients with Multisystem Inflammatory Syndrome in Children (MIS-C). Pediatr Cardiol. 2022;43(4):844–54. https://doi.org/10.1007/s00246-021-02796-7.
10. Sabri MR, Ahmadi A, Saviz M, Ghaderian M, Dehghan B, Mahdavi C, et al. Cardiac function in pediatric patients with MIS-C using speckle tracking and conventional echocardiography: a longitudinal single-center study. Pediatr Cardiol. 2024. https://doi.org/10.1007/s00246-024-03432-w.
11 Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. New England J Med. 2020;383(4):334–46. https://doi.org/10.1056/NEJMoa2021680.
12. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259–69. https://doi.org/10.1001/jama.2020.10369.
13. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation. 2021;143(1):21–32. https://doi.org/10.1161/circulationaha.120.050065.
14. Zimmerman D, Shwayder M, Souza A, Su JA, Votava-Smith J, Wagner-Lees S, et al. Cardiovascular follow-up of patients treated for MIS-C. Pediatrics. 2023;152(6). https://doi.org/10.1542/peds.2023-063002
15. Kostik MM, Bregel LV, Avrusin IS, Efremova OS, Belozerov KE, Dondurei EA, et al. Heart Involvement in multisystem inflammatory syndrome, associated with COVID-19 in children: the retrospective multicenter cohort data. Front Pediatr. 2022;10. https://doi.org/10.3389/fped.2022.829420
16. Garbin M, Raso I, Piersanti A, Gianolio L, De Silvestri A, Calcaterra V, et al. Advanced echocardiographic analysis in medium-term follow-up of children with previous multisystem inflammatory syndrome. Children (Basel). 2022;9(6). https://doi.org/10.3390/children9060917
17. Kobayashi R, Dionne A, Ferraro A, Harrild D, Newburger J, VanderPluym C, et al. Detailed assessment of left ventricular function in multisystem inflammatory syndrome in children using strain analysis. CJC Open. 2021;3(7):880–7. https://doi.org/10.1016/j.cjco.2021.02.012.
18. Stendahl JC, Parajuli N, Lu A, Boutagy NE, Guerrera N, Alkhalil I, et al. Regional myocardial strain analysis via 2D speckle tracking echocardiography: validation with sonomicrometry and correlation with regional blood flow in the presence of graded coronary stenoses and dobutamine stress. Cardiovasc Ultrasound. 2020;18(1):2. https://doi.org/10.1186/s12947-019-0183-x.
19. Mohammadi H, Hosseini H, Bordbar M, Mehdizadegan N, Amoozgar H, Edraki MR, et al. Permanent longitudinal strain damage of cardiotoxic drugs in childhood cancer: What is the safe level? Ann Pediatr Cardiol. 2024;17(1):36–44. https://doi.org/10.4103/apc.apc_146_23.
20. Yim J, Tsang MYC, Venkataraman A, Balthazaar S, Gin K, Jue J, et al. Cardiac phenotyping of SARS-CoV-2 in British Columbia: a prospective echo study with strain imaging. J Cardiovasc Imaging. 2023;31(3):125–32. https://doi.org/10.4250/jcvi.2022.0120.
21. Pezel T, Bluemke D A, Wu C O, Lima J A C, Ambale Venkatesh B. Regional strain score as prognostic marker of cardiovascular events from the Multi-Ethnic Study of Atherosclerosis (MESA). Front Cardiovasc Med. 2022;9. https://doi.org/10.3389/fcvm.2022.870942
22. Karimi A, Ghafouri P, Alilou S, Rezaei N, Ashraf Talesh S, Ashraf H. Echocardiographic findings in Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19: a systematic review. Iran J Pediatr. 2022;32(2):e119001. https://doi.org/10.5812/ijp.119001.
23. Mannarino S, Raso I, Garbin M, Ghidoni E, Corti C, Goletto S, et al. Cardiac dysfunction in Multisystem Inflammatory Syndrome in Children: an Italian single-center study. Ital J Pediatr. 2022;48(1):25. https://doi.org/10.1186/s13052-021-01189-z.
24. Davies NG, Klepac P, Liu Y, Prem K, Jit M, Eggo RM. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med. 2020;26(8):1205–11. https://doi.org/10.1038/s41591-020-0962-9.
25. Arslan SY, Bal ZS, Bayraktaroglu S, Ozenen GG, Bilen NM, Levent E, et al. Cardiac assessment in children with MIS-C: late magnetic resonance imaging features. Pediatr Cardiol. 2023;44(1):44–53. https://doi.org/10.1007/s00246-022-02977-y.
26. Harwood R, Allin B, Jones CE, Whittaker E, Ramnarayan P, Ramanan AV, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolescent Health. 2021;5(2):133–41. https://doi.org/10.1016/S2352-4642(20)30304-7.

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