


Evolution of echocardiographic and cardiac magnetic resonance imaging abnormalities during follow-up in patients with multisystem inflammatory syndrome in children

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Aims

Multisystem inflammatory syndrome in children (MIS-C) with cardiovascular manifestations are frequent. However, there is lacking evidence regarding cardiological follow-up of this cohort of patients. The aim of our study was to describe the early and mid-term cardiac abnormalities assessed by standard and speckle-tracking echocardiography (STE), and cardiac MRI (CMR).

Methods and results

We enrolled 32 patients (21 male, 11 female), mean age 8.25 ± 4 years, with diagnosis of MIS-C. During admission, all children underwent TTE, STE with analysis of left ventricle global longitudinal strain (GLS) and CMR. Patients underwent cardiological evaluation at 2 (T1) and 6 months (T2) after discharge. Cardiac MRI was repeated at 6 months after discharge. Mean left ventricular ejection fraction (LVEF) at baseline was $58.8 \pm 10\%$ with 10 patients (31%) below 55%. Speckle-tracking echocardiography showed reduced mean LV GLS ($-17.4 \pm 4\%$). On CMR, late gadolinium enhancement (LGE) with non-ischaemic pattern was evident in 8 of 23 patients (35%). Follow-up data showed rapid improvement of LVEF at T1 (62.5 ± 7.5 vs. $58.8 \pm 10.6\%$, P -value 0.044) with only three patients (10%) below $\leq 55\%$ at T1. Left ventricular (LV) GLS remained impaired at T1 (-17.2 ± 2.7 vs. -17.4 ± 4 , P -value 0.71) and significantly improved at T2 ($-19 \pm 2.6\%$ vs. $-17.4 \pm 4\%$, P -value 0.009). LV GLS was impaired ($> -18\%$) in 53% of patients at baseline and T1, whereas only 13% showed persistent LV GLS reduction at T2. Follow-up CMR showed LGE persistence in 33.4% of cases.

Conclusion

Early cardiac involvement significantly improves during follow-up of MIS-C patients. However, subclinical myocardial dysfunction seems to be still detectable after 6 months of follow-up in a not negligible proportion of them.

Keywords

multisystem inflammatory syndrome in children • COVID-19 • speckle-tracking echocardiography • longitudinal strain • cardiac magnetic resonance • myocardial injury

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Introduction

During the early phase of the COVID-19 pandemic, children were considered relatively spared from severe manifestations of SARS-CoV-2 infection compared with adults.^{1–3} However, starting from mid-April 2020, multisystem inflammatory syndrome in children (MIS-C) has emerged as a major cause of morbidity in the paediatric population, previously exposed to SARS-CoV2 2–6 weeks earlier.^{4,5}

The characteristic features of the disease are fever, gastrointestinal symptoms, muco-cutaneous inflammation signs, myocardial and coronary artery involvement. Interestingly, this multisystemic illness shares features with other paediatric inflammatory conditions, such as Kawasaki disease (KD), bacterial sepsis, toxic shock syndrome and macrophage activation syndrome.⁶ However, haemodynamic shock, myocardial dysfunction, and gastrointestinal involvement are peculiar findings of this unique syndrome.^{7,8}

Cardiovascular manifestations in MIS-C are common, occurring in 34–82% of cases.⁹ They include myocardial dysfunction, coronary artery dilatation or aneurysms, conduction abnormalities, arrhythmias, pericarditis, and valvulitis. Severe cases can present with distributive or cardiogenic shock requiring fluid resuscitation and inotropic support.^{10,11} Among the others, left ventricular (LV) systolic dysfunction is the most frequent cardiac abnormal finding. Recent evidence support a rapid improvement of myocardial dysfunction after the acute event and that it may not be detected on cardiac MRI few weeks after symptoms onset. These data suggest an immune-mediated pathogenesis of MIS-C.^{12,13}

Multimodality and specific cardiac imaging techniques have highlighted subclinical myocardial dysfunction in a significant proportion of MIS-C patients.^{14,15} However, there is lacking evidence regarding mid-term cardiological follow-up of this cohort of patients. This issue is pivotal to establish the reversibility of such alterations and even more in view of providing advice for sports participation after recovery.

Therefore, the aims of our study were as follows: (i) to evaluate early cardiac involvement in a cohort of patients in the acute phase of MIS-C with two advanced cardiovascular imaging techniques, speckle-tracking echocardiography (STE), and cardiac MRI. (ii) To assess the evolution of cardiac function and myocardial dysfunction at 3 and 6 months after diagnosis.

Methods

Study design and population

This is a retrospective, cohort and single-center study performed at the Department of Women's and Children's Health of Padua University Hospital, Italy.

We enrolled patients with MIS-C diagnosis from 26 April 2020 to 2 October 2021. The diagnosis of MIS-C was made according to WHO criteria.⁴ On admission, clinical, laboratory, and microbiological data were measured. All subjects were tested for SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction (RT-PCR) on nasopharyngeal swab on admission. Serological assay included IgG detection, targeting a recombinant nucleocapsid (N)-spike (S) protein of SARS-CoV-2 (IgG cut-off 1.1 AU/mL).

All patients underwent routinely blood tests including blood cell counts, biochemical profile, and markers of systemic inflammation (C-reactive protein—CRP, erythrocyte sedimentation rate—ESR, procalcitonin, ferritin, D-dimer, fibrinogen, LDH). Troponin I (TnI, normal value <34 ng/L) and brain natriuretic peptide (BNP, normal value <100 ng/L) were measured on admission and serially during hospital stay.

Admission to the paediatric intensive care unit was assessed according to the patient's haemodynamic status at the time of presentation in the emergency department. Pharmacologic treatment was established following the American College of Rheumatology guidelines for paediatric patients with MIS-C.¹⁶ All patients received a course of intravenous immunoglobulin (IVIg), intravenous corticosteroids (methylprednisolone), and antiplatelet therapy (aspirin). The use of biologic agents, such as Anakinra, an interleukin-1 receptor inhibitor, was reserved for patients with severe/critical disease refractory to standard therapy. One patient, with giant coronary aneurysms, coronary thrombosis, and myocardial ischaemia, also required thrombolytic therapy with Alteplase (t-PA), anticoagulant therapy, and dual antiplatelet therapy.

All patients underwent regular follow-up at 2 and 6 months after discharge in the paediatric cardiology outpatient clinic department, Padua University Hospital, Italy. During the follow-up evaluation, patients underwent repeated clinical evaluation, electrocardiogram (ECG), standard and STE. Cardiac MRI (CMR) was performed only at 6-month time (Figure 1). Moreover, depending on patient's clinical status and blood tests, immunologic and antiplatelet therapy was modified accordingly and the need for further investigations was assessed.

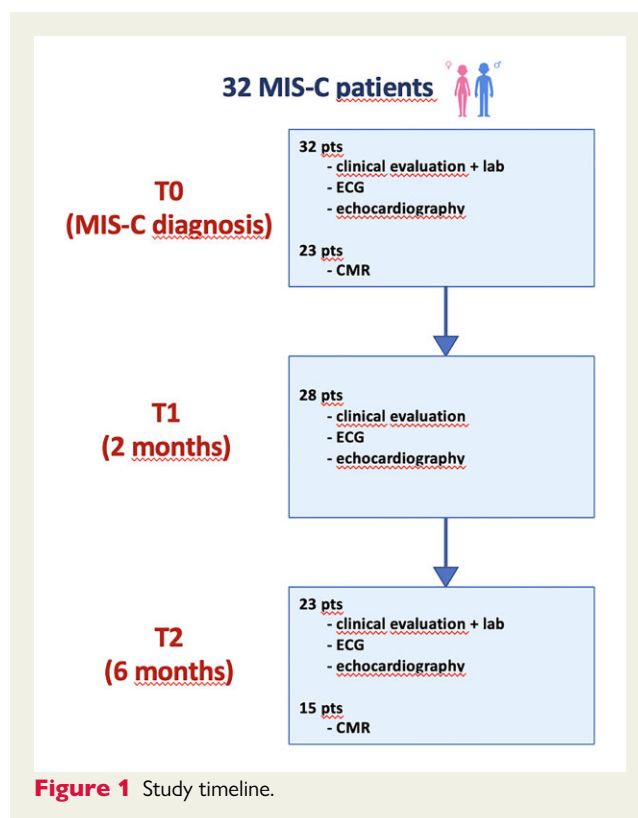


Figure 1 Study timeline.

Echocardiography

During the first day of hospitalization, all children underwent full cardiac evaluation, including ECG and transthoracic echocardiogram (TTE). During follow-up, cardiological evaluation with ECG and transthoracic echocardiography was performed 2 and 6 months after MIS-C diagnosis.

Standard 2D echocardiography was made by experienced paediatric echocardiographers using GE Vivid E9 (GE Healthcare, Chicago—IL, USA) and EpiQ 5 (Philips Medical Systems, Bothell—WA, USA) devices, following the recommendations for cardiovascular imaging during pandemic COVID-19.^{17,18} Standard echocardiographic parameters analyzed included: left ventricular ejection fraction (LVEF) by Simpson biplane method, early and late peak mitral inflow velocity by Power Doppler (E/A), right ventricular function estimation by Fractional Area Change (RV FAC), tricuspid annular plane systolic excursion (TAPSE) by M-mode, and early mitral annular lateral and septal diastolic peak velocity by TDI (E/e' lateral and medial). Coronary arteries were also evaluated following the American Heart Association (AHA) guidelines for KD.¹⁹

Longitudinal strain (LS) analysis of the left ventricle, by STE, was performed offline using GE EchoPac Software (GE Healthcare, USA).²⁰ Specifically, the best apical four-chamber, two-chamber, and three-chamber projections were selected for visualization of all segments of the left ventricle. Subsequently, by identifying 3 points (2 annular and 1 apical), the software is allowed to semi-automatically plot the myocardial profile during the cardiac cycle. The region of interest is adjusted by careful inspection of the endocardial boundary, and manual correction was performed when necessary. Finally, the automatic algorithm allows calculation of global longitudinal strain (GLS). Left ventricular longitudinal strain, calculated by speckle-tracking, is defined as the mean peak-negative value on the strain curve during systole (end of T wave on the ECG) of all segments studied.^{21,22} The peak-negative value of systolic strain for each regional segment of the left ventricle was also analyzed. Normal mean LV GLS values were considered as more negative than -18% according to recent meta-analysis by Levy et al.²³ on paediatric population. This is in agreement with our experience on normal healthy children. Analysis of the standard TTE and STE was performed by two experienced sonographers blinded to the clinical data.

Cardiac MRI

Twenty-three patients underwent cardiac magnetic resonance imaging (CMR) during the acute phase of the disease. During the follow-up, 15 (65%) of these patients were referred for repeated CMR at ~6 months after MIS-C diagnosis.

The scan was performed with a 1.5-Tesla scanner (Philips Achieva, Philips Healthcare, Best, The Netherlands). Sedation with intravenous midazolam or ketamine was required for patients younger than 6 years old. Cardiac MRI included cine SSFP and T2-weighted images with fat suppression. First-pass perfusion with intravenous administration of contrast agent (0,1 mmol/kg body weight gadoterate meglumine) was realized in all patients. Late gadolinium enhancement (LGE) sequences, in short axis and four-chambers planes, were acquired 10 min after contrast administration using a

Table 1 Clinical characteristics of the patients

	MIS-C n = 32
Age at onset (years)	8.25 ± 4
Male	21 (65.6)
Comorbidity	3 (9.4)
Associated CHD	1 <i>bicuspid aortic valve</i>
positive NF SARS-CoV-2 swab	4 (12.5)
positive SARS-CoV-2 IgG title	27 (84.4)
<i>Clinical manifestations</i>	
Fever	32 (100)
GI	27 (84.4)
Muco-cutaneous	22 (68.8)
Neurological	7 (22)
Hypotension	9 (28.1)
Sinus Bradycardia	9 (28.1)
KD-like	13 (40.6)
ICU admission	5 (15.6)
<i>Laboratory</i>	
Tnl ≤ 34 ng/L	12 (37.5)
Tnl >34 ng/L	20 (62.5)
BNP (pg/mL)	612 ± 859
CRP (mg/L)	162 ± 91.4
PCT (ng/mL)	12.3 ± 86
ESR (mm/h)	54.5 ± 36.5
Ferritin (mcg/L)	922 ± 837
D-dimer (mcg/mL)	2069.4 ± 2484
LDH (U/L)	385 ± 255
<i>Treatment</i>	
IV steroids	32 (100)
IGIV	32 (100)
Aspirin	31 (97)
Anakinra	3 (9.4)
Other	4 (12.5)

Values are numbers (%) or mean ± standard deviation.

CHD, congenital heart disease; BNP, brain natriuretic peptide; CRP, C-reactive protein; ERS, erythrocyte sedimentation rate; GI, gastrointestinal symptoms; ICU, intensive care unit; IV, intravenous; IGIV, intravenous immunoglobulins; KD, Kawasaki disease; LDH, lactic dehydrogenase; PCT, procalcitonin; NP swab, naso-pharyngeal swab; Tnl, troponin I; WBC, white blood count.

standard 2-dimensional breath-hold phase-sensitive inversion recovery sequence with the inversion time selected to null the myocardial signal. In all patients, LV and RV end-diastolic volume, end-systolic volume, and ejection fraction were measured. The CMR images were analyzed for detecting the presence of myocardial oedema and fibrosis using standard LV 17-segment model and specifying the pattern (transmural, subendocardial, subepicardial). To rule out coronary dilatation or aneurysm, 3D SSFP isovolumetric MRA ECG and navigator gating was performed. Other findings, such as pericardial or pleural effusion and the presence of coronary thrombosis, were reported. All the CMR studied were performed by the same experienced physician (E.R.).

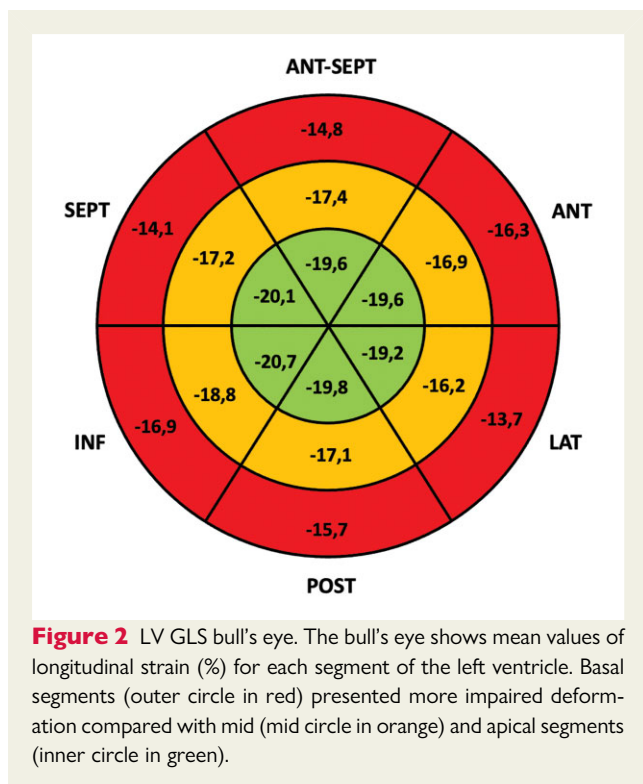


Figure 2 LV GLS bull's eye. The bull's eye shows mean values of longitudinal strain (%) for each segment of the left ventricle. Basal segments (outer circle in red) presented more impaired deformation compared with mid (mid circle in orange) and apical segments (inner circle in green).

Statistical analysis

Categorical variables were presented as percentage (%), and continuous variables as mean \pm standard deviation. Shapiro–Wilk test and histogram were used to test normality for each variable. Student's *t*-test was performed for normally distributed continuous variables and Mann–Whitney U test for non-parametric continuous variables. χ^2 test or Fisher's exact test were performed for categorical variables to examine if there were significant differences between the groups. Wilcoxon's test was used to compare continuous variables of two non-independent samples from the same population. Linear mixed model analysis with random effects was used to evaluate changes in variables measured multiple times over time. Statistical analysis was performed using SPSS 21.0 (IBM, NY, USA).

Results

Thirty-two patients (11 females and 21 males) with confirmed MIS-C diagnosis were enrolled (Table 1). Mean age at diagnosis was 8.25 ± 4 years, mean BSA $1.08 \pm 0.37\text{m}^2$. The majority was of Caucasian origin (75%), the remaining had African (18.8%) or Asian (6.2%) ethnicity. Twenty-seven patients (84.4%) had serologic confirmation of previous SARS-CoV-2 infection, and most had no documented underlying disease. Thirteen children (40.6%) shared KD-like symptoms.

All patients (100%) presented with fever. The most involved organs were the gastrointestinal system (84.4%) and the mucocutaneous system (68.8%). Multisystem involvement, treatment, and laboratory findings are summarized in Table 1. In five cases (15.6%), ICU admission was needed, and four of them required inotropic support. Regarding cardiovascular symptoms, nine patients (28.1%) presented hypotension and nine (28.1%) sinus bradycardia.

Table 2 Early abnormal cardiac finding in MIS-C

	MIS-C (n = 32)
<i>ECG</i>	
ECG abnormalities	16 (50)
Ripolarization abnormalities	10 (31.2)
Sinus bradycardia	9 (28.1)
AV block	3 (9.4)
<i>Echocardiography</i>	
LVEF (%)	58.8 ± 10.6
GLS (%)	-17.4 ± 4
E/A ratio	1.9 ± 0.6
Deceleration time (msec)	151 ± 39
Average E/e' ratio	7.8 ± 1.9
TAPSE (mm)	19 ± 4.8
RV FAC (%)	43 ± 7
coronary dilatation	9 (28.1)
coronary thrombosis	1 (3)
pericardial effusion	9 (28.1)
<i>Cardiac MRI (n = 23/32)</i>	
LVEF	60 ± 9.8
LV oedema	3 (13)
LV LGE	8 (35)
RVEF	62 ± 6

Values are numbers (%) or mean \pm standard deviation.

AV block, atrioventricular block; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LV LGE, left ventricular late gadolinium enhancement; MIS-C, multisystem inflammatory syndrome in children; RV FAC, right ventricular fractional area change; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion.

In-hospital survival was 100%. All patients showed a hyperinflammatory state characterized by elevation of PCR, ESR, and D-Dimer. Troponin I was abnormal (>34 ng/L) in 20 children (62.5%). Brain natriuretic peptide was significantly elevated in 28 (87.5%) patients (mean value 612 ± 859 pg/mL).

ECG abnormalities were reported in 50% of cases, of which 10 patients with abnormalities of the repolarization phase showing negative T waves in eight patients, mostly in the lateral and inferior leads, and ST segment depression in two patients in the lateral leads. Nine patients (28.1%) presented sinus bradycardia, whereas three (9.4%) showed atrioventricular block (first-degree block in two cases and second degree Mobitz 1 in the other).

All patients underwent echocardiographic evaluation with a median time of 7 days since fever onset and 1 day since hospital admission. Mean left ventricular ejection fraction (LVEF) was $58.8 \pm 10.6\%$, and 10 patients (31%) presented an LVEF below 55%. Mean right ventricular FAC and TAPSE were $43 \pm 7\%$ and 19 ± 4.8 mm, respectively. Coronary dilatation (Z-score >2) was detected in nine patients (28.1%), of which eight had mild-to-moderate dilatation ($2 < \text{Z-score} < 4$). One 4-year-old child showed severe left descending artery dilation (z-score $+20$) with giant aneurysm and coronary thrombosis leading to acute anterior and lateral myocardial infarction and acute heart failure necessitating thrombolysis with

Table 3 Cardiac findings in patient with or without myocardial injury

	Tnl+(n = 20)	Tnl-(n = 12)	P-value
BNP (pc/mL)	891 ± 988	146 ± 120	0.03*
PCR (mg/L)	188 ± 100	118 ± 53	0.016*
PCT (ng/mL)	48.8 ± 103	19.8 ± 36	0.22
VES (mm/h)	56 ± 35	51 ± 40	0.73
D-dimer (mcg/mL)	1827 ± 2717	2473 ± 2085	0.19
SARS-CoV-2 Ig title (kAU/L)	11.5 ± 28.1	10.3 ± 8.6	0.12
LVEF echo (%)	55 ± 10	64 ± 8	0.032*
GLS (%)	-16.3 ± 4.2	-19.3 ± 3.2	0.02*
E/A	2 ± 0.66	1.7 ± 0.57	0.14
E/e' average	8.1 ± 1.7	7.5 ± 2.2	0.42
TAPSE (mm)	19.5 ± 5.3	18.1 ± 4	0.44
RV FAC (%)	44.8 ± 7.7	40.3 ± 6	0.15
Coronary dilatation	6 (30)	3 (25)	0.76 (X ² 0.09, p 1 FET)
Pericardial effusion	4 (20)	5 (42)	0.18 (X ² 1.7)
CMR (n = 23)	Tnl+(n = 17)	Tnl-(n = 6)	P-value
CMR LVEF (%)	59.4 ± 11.4	64 ± 1.3	0.38
CMR LV LGE	5 (30)	3 (50)	0.36 (X ² 0.82, p 0.62 FET)

Values are numbers (%) or mean ± standard deviation.

BNP, brain natriuretic peptide; CRP, C-reactive protein; ERS, erythrocyte sedimentation rate; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LV LGE, left ventricular late gadolinium enhancement; MIS-C, multisystem inflammatory syndrome in children; PCT, procalcitonin; RV FAC, right ventricular fractional area change; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; Tnl, troponin I. * = $P < 0.05$.

t-PA, anticoagulant therapy, and adjunctive antiplatelet drug. Pericardial effusion was described in nine patients (28.1%).

Speckle-tracking echocardiography analysis showed impaired LV GLS higher than -18% in 53% of patients with a mean LV GLS in all the cohort of $-17.4 \pm 4\%$. Basal and mid LV segments were the most affected (Figure 2).

Median time to CMR was 18 days from fever onset and 11 days from hospital admission. Left ventricular ejection fraction on CMR was $60 \pm 9.8\%$ and four patients showed $LVEF \leq 55\%$. Late gadolinium enhancement with non-ischaemic pattern was detected in 8 of 23 (35%), and all of them had the imaging performed within 19 days from the symptom's onset. Pericardial effusion was observed in five patients (21.7%). Myocardial oedema was detected in three patients (13%): mild oedema in two cases, who underwent examination in the first 13 days of disease, whereas in the patient with acute myocardial infarction secondary to coronary thrombosis, the oedema involved the middle anterior wall, septum, and apex. The acute cardiac involvement data in MIS-C are summarized in Table 2.

Patients with elevated Tnl levels (>34 ng/L) showed significantly higher levels of circulating BNP compared with patients with normal Tnl levels (891 ± 988 vs. 146 ± 120 , P -value 0.03). Patients with higher Tnl did not show significant differences in SARS-CoV-2 IgG titles, nor in inflammatory markers (ESR, D-Dimer, Ferritin), except for CRP (188 ± 100 vs. 118 ± 53 , $P = 0.016$) and white blood cell count (10332 ± 4079 vs. 7471 ± 2503 , P -value 0.02). On echocardiography, patients with higher levels of Tnl showed significantly lower LVEF (55 ± 10 vs. $64 \pm 8\%$, P -value 0.032) and impaired LV GLS

(-16.3 ± 4.2 vs. $-19.3 \pm 3.2\%$, P -value 0.02), whereas there was no difference in right ventricular systolic functional parameters (TAPSE: 19.5 ± 5.3 vs. 18.1 ± 4 mm, P -value 0.44; RV FAC: 44.8 ± 7.7 vs. $40.3 \pm 6\%$, P -value 0.15), or the presence of coronary dilatation ($X^2 = 0.09$; $P = 0.76$). In addition, the two groups showed comparable LGE on CMR ($X^2 = 0.82$; $P = 0.36$) (Table 3, Figure 3).

Follow-up study

Twenty-eight patients underwent T1 follow-up 2 months after diagnosis with median time of 48.5 ± 17 days. Two patients (7%) were still taking cardiovascular therapy, antiarrhythmic (beta-blocker) in one case, and heart failure therapy (ACE inhibitor, beta-blocker, spironolactone) in the other. Electrocardiogram abnormalities were reported in five patients (18%); only one patient (3.5%) presented first-degree atrioventricular block. Standard echocardiography showed mean LVEF of $62.5 \pm 7.5\%$ with three patients (10%) below 55%. TAPSE was 19.7 ± 3.2 mm and mean right ventricular FAC $42 \pm 5.5\%$. Coronary dilatation persisted in only 2 of the 28 patients (7.2%), in one case of mild degree (Z -score +2.2). None presented pericardial effusion.

Overall, on T1 assessment our cohort of patients showed mean left ventricular GLS values of $-17.2 \pm 2.7\%$, persistently reduced compared with basal assessment. Fifty-three percent of patients presented an abnormal LV GLS value higher than -18%. Consistently with baseline evaluation, basal segments of left ventricle were more affected by GLS impairment.

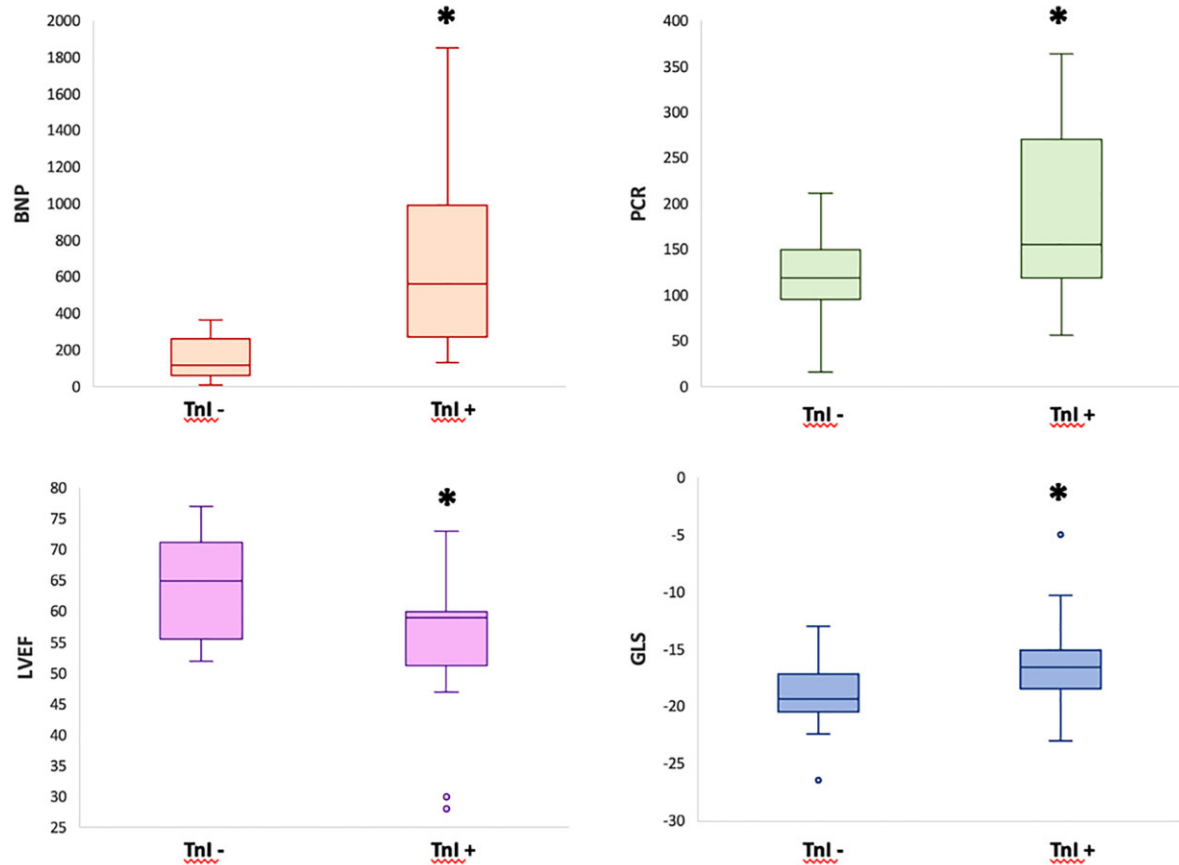


Figure 3 MIS-C and myocardial involvement. Patients with elevated Tnl levels (>34 ng/L) showed higher levels of BNP and CRP, reduced LVEF, and higher LV GLS compared with patients with normal values of Tnl. * = $P < 0.05$.

Subsequent cardiological follow-up (T2) was performed in 23 patients with a median time of 207 days from MIS-C diagnosis. Five patients (21.7%) had ECG abnormalities: three cases showed abnormal ventricular repolarization, two cases showed interventricular conduction delays, and in one case the first-grade atrioventricular block was confirmed. Standard echocardiography showed a mean LVEF of $65.7 \pm 8.2\%$, with one patient (4%) below 55%, and a mean TAPSE of 21.1 ± 3.6 mm. No patient presented pericardial effusion, whereas coronary dilatation persisted in two patients. The analysis of STE images displayed normalization of mean GLS of the left ventricle in most of the cohort (87%). The mean LV GLS value of our cohort at 6 months was in the normal range, $-19 \pm 2.6\%$. Follow-up echocardiographic data are summarized in Table 4.

T2 follow-up data showed a statistically significant improvement in left ventricular systolic function parameters compared to disease onset (LVEF 65.7 ± 8.2 vs. $58.8 \pm 10.6\%$, P -value < 0.001 and LV GLS -19 ± 2.6 vs. $-17.4 \pm 4\%$, P -value 0.009) (Figure 4). Furthermore, on mixed effect analysis LVEF and LV GLS improved significantly during follow-up ($P < 0.001$ and $P = 0.048$, respectively) with an estimated increase at each evaluation of 3.39% for EF and an estimated decrease of -0.81% regarding GLS. There was no correlation between the absolute improvement of LV systolic function and the basal levels of Tnl or BNP. In particular, LVEF improved during the first 2 months of follow-up (58.8 ± 10.6 vs. $62.5 \pm 7.5\%$,

P -value 0.044), whereas LV GLS showed a significant improvement between 2 and 6 months after MIS-C onset (-17.2 ± 2.7 vs. $-19 \pm 2.6\%$, P -value 0.007). Particularly, at baseline and T1, 53% of patients (17/32 and 15/28, respectively) showed reduced LV GLS, whereas only 3 of 23 patients (13%) had impaired LV GLS at T2. There was no significant difference in right ventricular systolic functional parameters over time (Table 5).

Follow-up CMR was performed in 15 patients at 6 months from MIS-C diagnosis. LVEF was $58.8 \pm 8.8\%$ comparable with baseline, and RVEF was $60.8 \pm 5\%$. Of the eight patients presenting LGE on baseline CMR, six underwent a follow-up scan and five of them showed persistence of LGE with non-ischaemic pattern. However, LGE extension was reduced at quantitative analysis compared with the acute phase. Oedema was detected only in the patient with previous myocardial infarction secondary to anterior descending thrombosis. Small pericardial effusion was detected in four patients (26.7%).

Discussion

To the best of our knowledge, this is the first study to analyze and correlate echocardiographic and CMR combined data during the initial acute phase of MIS-C and later during follow-up.

Table 4 Cardiac findings in MIS-C follow-up

T1 (n = 28)	
Median time (days)	48.5
ECG T1	
ECG abnormalities	5 (18)
Ripolarization abnormalities	3 (10.7)
AV block	1 (3.5)
Echocardiography T1	
VEF (%)	62.5 ± 7.5
GLS (%)	-17.2 ± 2.7
E/A ratio	1.8 ± 0.4
TAPSE (mm)	19.7 ± 3.2
RV FAC (%)	42 ± 5.5
coronary dilatation	2 (7.2)
pericardial effusion	0 (0)
T2 (n = 23)	
Median time (days)	207
ECG T2	
ECG abnormalities	5 (21.7)
Ripolarization abnormalities	3 (13)
AV block	1 (4.3)
Echocardiography T2	
LVEF (%)	65.7 ± 8.2
GLS (%)	-19 ± 2.6
TAPSE (mm)	1.9 ± 0.5
RV FAC (%)	21.1 ± 3.6
Coronary dilatation	2 (8.7)
Pericardial effusion	0 (0)

Values are numbers (%) or mean ± standard deviation.

AV block, atrioventricular block; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; MIS-C, multisystem inflammatory syndrome in children; RV FAC, right ventricular fractional area change; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion.

We demonstrated that myocardial abnormalities revert in a large proportion of the studied patients with a different time course over follow-up. However, LGE detected by CMR at baseline persists in a significant proportion of patients after 6 months from MIS-C diagnosis.

Early phase

This study confirms our preliminary data in 23 patients regarding early phase cardiac involvement in MIS-C patients.¹⁴ Myocardial injury based on troponin elevation is hereby confirmed to affect about two-thirds (65%) of our cohort, and subclinical left ventricle systolic dysfunction estimated by a decrease in mean GLS values was persistently evident in a substantial proportion (53%) of our MIS-C population. Moreover, CMR performed early after diagnosis showed non-ischemic pattern of LGE in a third (34.7%) of evaluated patients, in agreement to our previous data.

Follow-up

Follow-up data from our population show an excellent clinical response to treatment with an overall survival of 100% and almost all patients asymptomatic at two and 6 months after MIS-C diagnosis. Only two children were on cardiovascular therapy at T1. Electrocardiogram abnormalities, present in 50% of cases in the acute phase, showed a gradual improvement, accounting for 20% of cases at 2 and 6 months. Noteworthy, our data show almost complete resolution of bradyarrhythmias during follow-up.

Echocardiographic monitoring of our cohort of MIS-C patients showed a statistically significant improvement in left ventricular systolic function parameters, LVEF and LV GLS, 6 months after disease diagnosis. Particularly, LVEF increased significantly during the first 2 months of follow-up, in contrast to LV GLS, which improvement was mainly evident in the second part of our follow-up. In support of this finding, considering an abnormal value of mean LV GLS as higher than -18%, we identified 53% patients with impaired deformation at T0 and T1 and only 13% at T2.²³

The stable reduction in LV GLS values at T1 reflects the persistence of subclinical myocardial dysfunction that can only be detected by STE as demonstrated in different studies in children.^{24,25} On the other side, LVEF is less sensitive to subclinical myocardial injury.²⁶ Furthermore, LVEF is recognized to be more load dependent compared to GLS, possibly explaining the faster recovery after the resolution of the acute phase. The later improvement and disappearance of an apex-base gradient of GLS alteration support the normalization of left ventricular regional/segmental contractility at 6 months after disease diagnosis.

No statistically significant differences were detected regarding RV systolic function parameters (TAPSE and FAC), which were always within normal limits, highlighting left ventricle higher sensitivity to myocardial involvement in MIS-C. Furthermore, echocardiographic assessment has demonstrated a significant improvement of coronary arteries dilation during follow-up with a prevalence of 8.6% at T2 compared with 28% in the acute phase.

Conversely, CMR performed at 6 months after MIS-C diagnosis showed the persistence of LGE with non-ischaemic pattern in almost all patients with LGE detection during the acute phase. However, quantitative analysis showed a reduction of the LGE extension among the involved myocardial segments compared to the early phase. Overall LGE was detected in 5 of 15 patients (33.4%). The high percentage of persisting LGE abnormalities may also reflect a selection bias for CMR study. In fact, it is more likely that parents of patients with LGE at the baseline CMR study were more incline to accept a second CMR study, whereas some of the MIS-C patients (and parents) with normal CMR baseline study and a more benign clinical course were more reluctant to perform a follow-up CMR.

This finding demonstrated that CMR is a useful tool for the detection of subclinical myocardial damage in MIS-C. However, our findings support the hypothesis that to document the complete resolution of such injury, CMR should be procrastinated beyond 6 months.

Limitations

The single-center nature of our study may constitute a limitation. However, this increases the reproducibility and decrease the inter-observer variability of our measurements. Another possible limitation

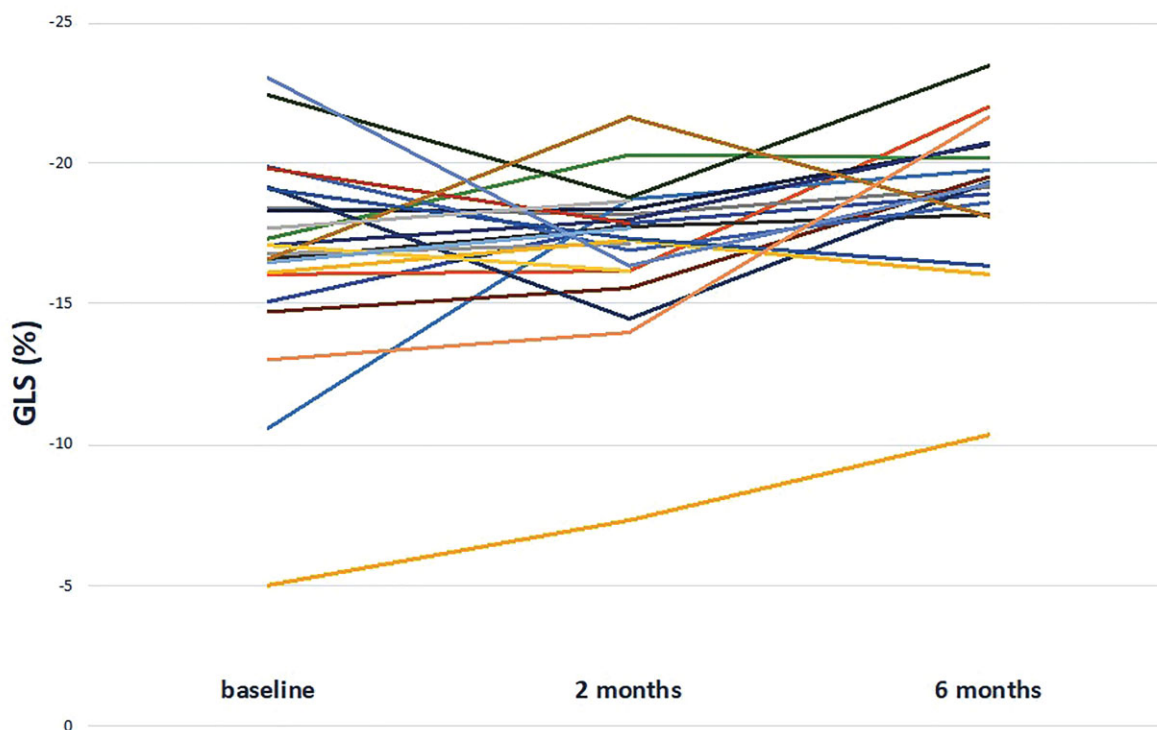


Figure 4 Distribution of GLS values during follow-up.

Table 5 Distribution of ventricular functional parameters at baseline and during follow-up

	Baseline	2 months	6 months	P*	P [†]	P [‡]
LVEF (%)	58.8 ± 10.6	62.5 ± 7.5	65.7 ± 8.2	0.044	0.72	<0.001
LV GLS (%)	-17.4 ± 4	-17.2 ± 2.7	-19 ± 2.6	0.71	0.007	0.009
TAPSE (mm)	19 ± 4.8	19.7 ± 3.2	21.1 ± 3.6	0.37	0.09	0.24

Values are numbers (%) or mean ± standard deviation. GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion. P* value between baseline and 2 months; P[†] value between 2 and 6 months; P[‡] value between baseline and 6 months.

may lie in the speckle-tracking analysis, which was limited to the assessment of the longitudinal deformation of the left ventricle. On this purpose, multiple studies demonstrated the strong prognostic value of longitudinal deformation, and, on the other side, the clinical value of circumferential and radial strain has to be proven yet.^{27–29}

Conclusions

Patients with MIS-C show an excellent clinical outcome in the short term. Standard and STE are useful tools in the diagnosis and follow-up. GLS improves significantly at 6 months after diagnosis, and its normalization might clear the patient from further follow-up.

Our data suggest to regularly follow-up MIS-C patients by performing echocardiography and speckle-tracking analysis, whereas

CMR, including LGE, could be limited to patients with a more severe acute clinical picture or in patients who do not normalize LV GLS within 6 months after the onset of the disease.

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Conflict of interest: None declared.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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