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Long-term global longitudinal strain abnormalities in paediatric patients after multisystem inflammatory syndrome in children correlate with cardiac troponin T: a single-centre cohort study

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Abstract

Background: Multisystem inflammatory syndrome in children is an inflammatory syndrome related to severe acute respiratory syndrome coronavirus 2 with a high risk of cardiovascular complications (vasoplegia, cardiac shock). We investigated the cardiac outcomes in multisystem inflammatory syndrome in children, focusing on the identification of predictors for late cardiac function impairment. *Methods:* Clinical characteristics, conventional echocardiography (left ventricle ejection fraction, fractional shortening), 4-chamber left ventricular global longitudinal strain, and cardiac MRI of multisystem inflammatory syndrome in children patients (n = 48) were collected during admission, 6 weeks, 6 months, >12–≤18 months, and >18–≤24 months post-onset. Paired over-time patterns were assessed and multivariable regression analyses were performed to identify predictors for late global longitudinal strain impairment. *Results:* In total, 81.3% of patients had acute cardiac dysfunction (left ventricle ejection fraction <50% and/or fractional shortening <28%). The left ventricle ejection fraction and fractional shortening reached a plateau level ≤6 weeks, while the global longitudinal strain continued to decrease in the first 6 months post-onset (median −17.3%, $P < 0.001$ [versus acute]). At 6 months, 35.7% of the patients still had an abnormal global longitudinal strain, which persisted in 5/9 patients that underwent echocardiography >12–≤18 months post-onset and in 3/3 patients >18–≤24 months post-onset. In a multivariable analysis, soluble troponin T (>62.0 ng/L [median]) was associated with reduced global longitudinal strain at 6 months. Our cardiac MRI findings indicated acute myocardial involvement (increased T1/T2 value) in 77.8% (7/9), which recovered quickly without signs of fibrosis on convalescent cardiac MRIs. *Conclusions:* Late global longitudinal strain impairment is seen in some multisystem inflammatory syndrome in children patients up to one-year post-onset. Careful cardiac follow-up in patients with elevated troponin in the acute phase and patients with persistent abnormal global longitudinal strain is warranted until resolution of the global longitudinal strain since the long-term implications of such abnormalities are still unclear.

Introduction

Multisystem inflammatory syndrome in children is a severe acute respiratory syndrome coronavirus 2-related inflammatory syndrome in the paediatric population with a high risk of cardiovascular complications. Patients often present with symptoms closely resembling Kawasaki disease and have a high risk of severe multi-organ inflammation and dysfunction, including cardiovascular complications, with vasoplegia and cardiac shock in about half of the cases.[1,2] Coronary artery aneurysms, which are the most notorious complication of Kawasaki disease, have been described in multisystem inflammatory syndrome in children in about a quarter of the cases in the acute phase, with a majority normalising within six months.[3]

Cardiac dysfunction is generally assessed by echocardiography and defined as a left ventricle ejection fraction below 50% and/or a fractional shortening below 28%.[4] A vast number of studies have been published in a short time frame investigating the value of echocardiographic strain to investigate subclinical cardiac damage in multisystem inflammatory syndrome in children

Box 1. Previous studies that investigated speckle-tracking parameters in multisystem inflammatory syndrome in children

RESEARCH IN CONTEXT

Background

Multisystem inflammatory syndrome in children is a severe inflammatory syndrome with a high risk of cardiovascular complications, including cardiac dysfunction in about half of the cases. A vast number of studies have been published in a short time frame investigating the value of speckle tracking to follow-up subclinical cardiac damage in patients with multisystem inflammatory syndrome in children, particularly when conventional parameters (left ventricle ejection fraction, fractional shortening) remain normal.

Evidence before this study

We performed a systematic search in PubMed (December 1st, 2022) using the search terms "MIS-C" and "speckle tracking" (including related synonyms) to evaluate the value of speckle tracking as a marker for subclinical cardiac damage in multisystem inflammatory syndrome in children. Sixteen studies were identified: 2 cross-sectional/case-control, 10 retrospective cohort, and 4 case-control studies. Definitions for a decreased speckle-tracking values varied and patient populations were limited. A majority of the studies reported a delayed recovery of speckle-tracking parameters when compared to conventional parameters (left ventricle ejection fraction, fractional shortening). With the exception of two studies, which investigated speckle-tracking outcomes up to six months post-onset, follow-up periods were limited to a maximum of 4.4 months. Furthermore, none of the studies performed multivariable analyses to investigate the correlation of cardiac biomarkers with a prolonged abnormal global longitudinal strain.

Added value of the current study

In the current study, we investigate the short- and long-term cardiac outcomes up to one year post-onset in patients with multisystem inflammatory syndrome in children. Our study offers insight into the longitudinal patterns of laboratory outcomes, conventional echocardiography, global longitudinal strain, and cardiac MRI over the longest observational period as of yet. Remarkably, we found long-term subclinical myocardial impairment (based on global longitudinal strain) in several patients up to two years post-onset. Additionally, we identified cardiac troponin T as a useful marker for delayed global longitudinal strain recovery in multivariable analyses for the first time.

(Box 1).[5–21] Global longitudinal strain, which measures deformation in the longitudinal axis, is the strain parameter that correlates best with subclinical left ventricle dysfunction.[22] Abnormal global longitudinal strain is a predictor for cardiac dysfunction in various diseases, including anthracycline (cancer treatment)-related cardiotoxicity, end-stage renal disease, myocarditis, and myocardial infarction.[23–26]

Despite quick normalisation of conventional systolic parameters, changes in the strain parameters are often seen in patients with multisystem inflammatory syndrome in children and normalisation takes longer compared to conventional measures.[5–20] It has therefore been postulated these parameters may be of importance in the clinical follow-up of multisystem inflammatory syndrome in children patients to identify subclinical cardiac dysfunction with delayed cardiac recovery and better map cardiac recovery. However, patient groups were usually small and lacked late convalescent echocardiography measurements due to the novelty of the disease. In-depth analyses including extensive patient populations with long-term follow-up and multivariable correlations with soluble are lacking. Creating better risk stratifications for children at risk for persisting subclinical cardiac dysfunction is important for patient counselling and deducting clinical follow-up recommendations in multisystem inflammatory syndrome in children. Therefore, in the current study, we aimed to investigate the short- and long-term cardiac outcomes of multisystem inflammatory syndrome in children based on laboratory outcomes, conventional echocardiography, apical 4-chamber left ventricular global longitudinal strain, and cardiac MRI in an observational cohort study.

Material and methods

A cohort study was conducted including children diagnosed with multisystem inflammatory syndrome in children between 2020 and 2022 for whom acute and convalescent cardiac imaging was performed to assess cardiac function. Data concerning cardiac imaging and clinical parameters were extracted to investigate short- and long-term cardiac outcomes in multisystem inflammatory syndrome in children.

Study population

Patients with multisystem inflammatory syndrome in children based on the criteria of the Centre for Disease Control and Prevention[27] and World Health Organization[28] were recruited at the Amsterdam University Medical Centre, location Academic Medical Centre and participating hospitals in the broad Amsterdam region, as part of our long-term observational Kawasaki disease study as approved by the Medical Ethical Board of the Academic Medical Centre (no. NL41023.018.12). Multisystem inflammatory syndrome in children patients were recruited between April 2020 and April 2022 (Fig. 1). Patients were only included if echocardiography and echocardiography-based speckle-tracking data were available during the acute disease phase (primary admission).

Clinical outcomes

Clinical (sex, age at onset, clinical presentation, treatment, complications, and recovery) and laboratory information (nadir laboratory value within first 2 weeks post-onset) was collected using electronic health records processed in a combined database (Castor).

Study outcomes

Primarily, our study focused on left ventricle dysfunction based on a left ventricle ejection fraction <50%, a fractional shortening <28%[4] or a global longitudinal strain above −17%.[29] Importantly, while our global longitudinal strain cut-off was based on the lower limit reported in children between 0 and 1 year old, it should be noted that this cut-off is quite lenient since the mean global longitudinal strain in children of all age groups is −20.2% (95% confidence interval between −20.8% and −19.6%).[29]

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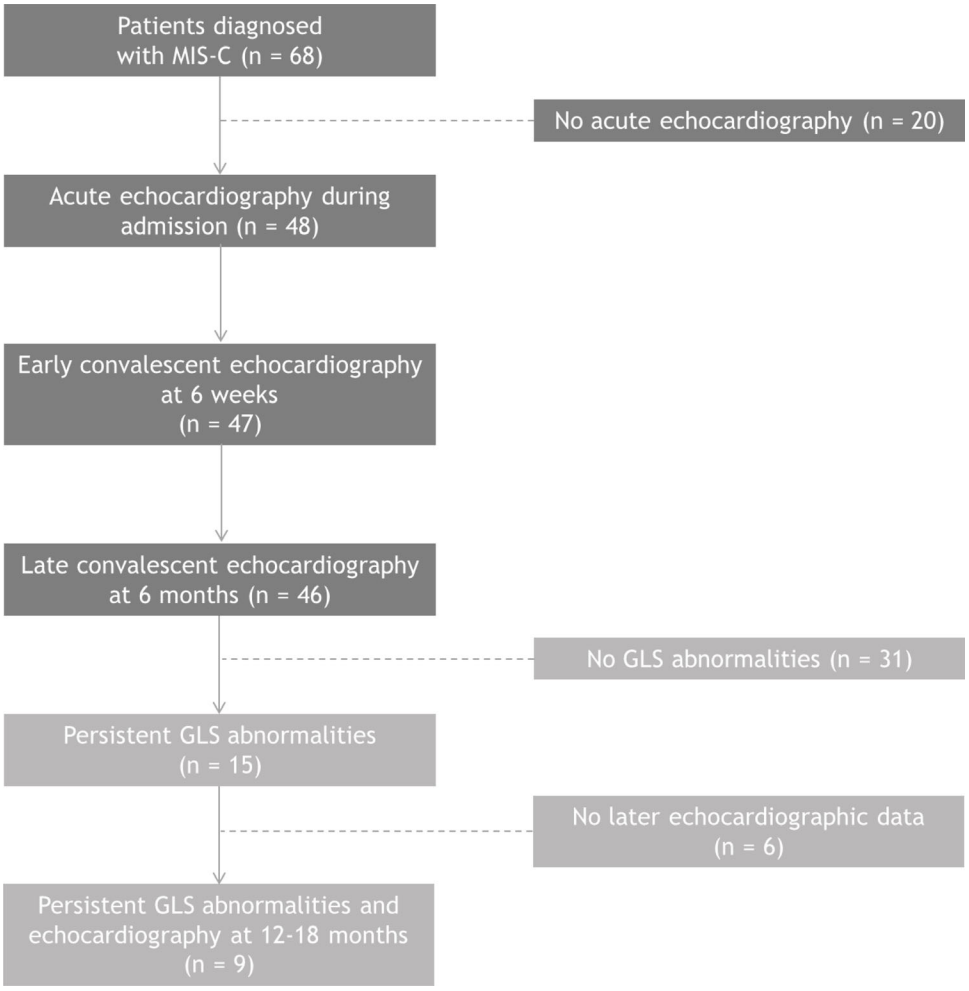

Figure 1. Patient inclusion in cohort study. Abbreviations: GLS = global longitudinal strain.

These parameters were investigated in the acute phase (during admission (median timing echocardiography at day 1 of admission [interquartile range 0–2])), at the outpatient clinic visit closest to 6 weeks post-onset (day 50 [interquartile range 44–57]), and at the outpatient clinic visit closest to 6 months post-onset (day 235 [interquartile range 178–273]). Of patients with persisting cardiac abnormalities, we also collected echocardiographic data ≥1-year post-onset, if available (day 455 [interquartile range 384–537]).

Over-time changes were visualised and associated with clinical characteristics (age, sex, and ICU admission) and serum laboratory measurements (C-reactive protein, leukocytes, thrombocytes, haemoglobin, albumin, aspartate aminotransferase, alanine transaminase, N-terminal pro b-type natriuretic peptide, troponin T, urea, creatinine, sodium, potassium, neutrophil count, lymphocyte count, triglyceride, D-dimer, fibrinogen, and ferritin) in the acute phase. Furthermore, the (over time) presence of coronary artery aneurysms on echocardiography and/or cardiac MRI was explored, defined as a Z score ≥2.5. T1/T2 signal intensities and fibrosis were examined by cardiac MRI.

Echocardiographic measurements

Data on 2D echocardiography (left ventricle ejection fraction), longitudinal strain parameters (global longitudinal strain) derived from speckle-tracking echocardiography, and M-mode (fractional shortening) were collected by Vivid E95 cardiac ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway) using EchoPAC software version 206 (revision 66.0). Although the left ventricle ejection fraction and fractional shortening had been calculated prospectively for the patients during admission, we recalculated these values for the purposes of this study, as well as the global longitudinal strain retrospectively, to minimise the risk of inter- and intra-observer variability. For the same reason, all measurements were performed by a single observer, an experienced paediatric cardiologist specialised in Kawasaki disease.

The left ventricle ejection fraction was measured from the two-chamber and four-chamber views using the biplane Simpson's method. Speckle-tracking measurements were performed from the four-chamber view by tracing the endocardial border to acquire longitudinal ε curves from the six segments (basal septum, mid septum, apical septum, apical lateral, mid lateral, and basal lateral) and averaging them. Although the global longitudinal strain is typically derived from the three standard apical views and averaged,[30] we used the global longitudinal strain measured in 4-chamber view, which is strongly correlated[31,32] and more time-efficient than the multimodal global longitudinal strain, as a proxy. M-mode echocardiography was performed from the parasternal long-axis views.

Cardiac MRI

A subgroup of patients underwent cardiac cardiac MRI. The patients that underwent acute cardiac MRI were a subgroup of

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patients with cardiac dysfunction related to multisystem inflammatory syndrome in children in December 2020, January 2021, and February 2021. At the time, little was known about the cardiac complications related to multisystem inflammatory syndrome in children and it was postulated to be a post-viral myocarditis.[33] Hence, acute cardiac MRI was performed in these cases for T1/T2 mapping during the acute phase (median timing at 10 days [range 5–13 days]). Part of these, as well as some additional patients with cardiac dysfunction during early convalescence (median 2.8 months) and late convalescence (median 7.4 months), underwent cardiac MRI in the convalescent phase to evaluate cardiac recovery and check for signs of fibrosis. Since all patients recovered quickly and none of the later scans showed signs of fibrosis, we stopped performing cardiac MRIs for the multisystem inflammatory syndrome in children patients from 2022 onwards.

Scans were performed using a 1.5-T whole-body MRI scanner with cardiac software (Siemens, Magnetom, Avanto; Siemens, Erlangen, and Germany). Cardiac MRI included the evaluation of ventricular function (end-diastolic volume, end-systolic volume, and ejection fraction), presence of oedema (T2 weighed imaging/mapping), hyperaemia and capillary leakage (T1 mapping), necrosis and fibrosis (late gadolinium enhancement), and evaluation of the pericardium. To investigate fibrosis as evaluated by late gadolinium enhancement, contrast agent (0.1 mmol/kg) was administered intravenously. Late gadolinium enhancement imaging in short axis and four-chamber geometries was performed using single-shot phase sensitive inversion recovery imaging using a look-locker sequence to determine the inversion time. Acute myocarditis was defined as guided by modified Lake Louise Criteria.[34]

Statistical analysis

Characteristics of the study population were summarised (frequencies [proportions], median [interquartile range]). We assessed over-time patterns of the serial measurements with a paired Friedman test.

We compared patient characteristics and biomarker levels between the multisystem inflammatory syndrome in children patients with and without cardiac dysfunction in the different timeframes (chi-square, Mann–Whitney U). Four variables that significantly differed between the groups in these analyses and of which the combination explained model explained the variance in abnormal global longitudinal strain best (based on Nagelkerke R^2) were included in a multivariable logistic regression to ascertain their effect on the likelihood that patients still had an abnormal global longitudinal strain (>[−17]%) after 6 months (excluding patients that had an abnormal global longitudinal strain before 6 months, but did not undergo later echocardiography). These covariates included age at onset (continuous, in months), elevated troponin T (>62.0 ng/L, exceeding the median value measured [normal range 0–14 ng/L]), elevated C-reactive protein (>187.9 mg/L, exceeding the median value measured [normal range 0–5 mg/L]), and cardiac dysfunction based on fractional shortening (<28%). We also performed a Cox regression analysis to investigate which of these factors were associated with the time to global longitudinal strain recovery.

Associations between left ventricle ejection fraction, fractional shortening, and global longitudinal strain were investigated using a non-linear Spearman rank correlation, as were correlations between these parameters with various blood markers (C-reactive protein, sedimentation, leukocytes, thrombocytes, haemoglobin, albumin, aspartate aminotransferase, alanine transaminase, N-terminal pro b-type natriuretic peptide, troponin T, urea, creatinine, sodium, potassium, neutrophil count, lymphocyte count, triglyceride, D-dimer, fibrinogen, and ferritin).

A $P < 0.05$ was considered statistically significant. Statistical analyses were performed in IBM SPSS Statistics 25 and R studio. Graphs were made in GraphPad Prism 8.4.2.

Results

Inclusion

Of the 68 patients that presented with multisystem inflammatory syndrome in children, 20 patients were excluded due to the lack of echocardiographic imaging in the acute phase to enable retrospective speckle-tracking measurements. Therefore, 48, 47, and 46 patients were included in our acute, early convalescence (6 weeks), and late convalescence (6 months) analyses, respectively. Of the 15 patients with persistent global longitudinal strain abnormalities at 6 months, echocardiographic imaging was available for 9/15 at >12−≤18 months post-onset (Fig. 1). Of the five patients with persisting global longitudinal strain abnormalities at >12−≤18 months, echocardiographic imaging was available for 3/5 at >18−≤24 months post-onset.

Clinical outcomes

Our cohort consisted of 48 patients (median age 11.9 [interquartile range 6.9−14.5] years old, 58.3% male). A total of 66.7% of the cases presented with symptoms that fit the criteria of a complete Kawasaki disease presentation as well. Nearly all (91.7%) children presented with abdominal symptoms (vomiting, diarrhoea, and abdominal pain). Neurological symptoms were seen in 56.3%, mostly consisting of headaches (29.2%) and an altered mental state (29.2%), which also included hallucinations (8.3%), dizziness (8.3%), and fainting (6.3%). Circulatory shock defined as the need for inotropic support or fluid resuscitation >20 mL/kg was the most frequent complication (58.3%). Overall, inflammatory markers (C-reactive protein, leukocytes, sedimentation), cardiac-specific markers (N-terminal pro b-type natriuretic peptide, troponin T), haemostatic components (D-dimer, fibrinogen), and ferritin were elevated in the acute phase of multisystem inflammatory syndrome in children. In addition, hypoalbuminemia and hyponatremia were seen in the acute phase of our patients. All patients recovered quickly after treatment and were discharged without heart failure treatment. A detailed overview of the patient characteristics and clinical presentation can be seen in Table S1.

Echocardiography

Acute echocardiography findings

There were 48 patients with a four-chamber view available in the acute phase for speckle-tracking analysis. In the acute phase, 81.3% (n = 39) of patients presented with a decreased left ventricle ejection fraction and/or fractional shortening (Table 1, Fig. 2). Four (8.5%) patients had an abnormal global longitudinal strain (>[−17]%), despite a preserved left ventricle ejection fraction and fractional shortening (example shown in Figure S1). Two of these had hypotension, of which one required inotropic support and also had acute kidney injury; in the other IVIG infusion was halted prematurely. The third patient had respiratory insufficiency requiring nasal high-flow therapy (consolidations on chest radiograph) and the last did not have any complications.

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Table 1. Over-time proportion of patients with left ventricle ejection fraction, fractional shortening, and GLS below cut-off

Parameter below cut-off*	Acute	6 weeks post-onset	6 months post-onset
Left ventricle ejection fraction <50%	36 (76.6%)	11 (24.4%)	4 (9.1%)
Fractional shortening <28%	24 (53.3%)	1 (2.2%)	0 (0%)
Cardiac dysfunction*	39 (81.3%)	12 (26.7%)	4 (9.1%)
GLS >[−17]%	40 (85.1%)	30 (66.7%)	15 (35.7%)

*Based on left ventricle ejection fraction <50% and/or fractional shortening <28%(4).
Abbreviations: GLS = global longitudinal strain.

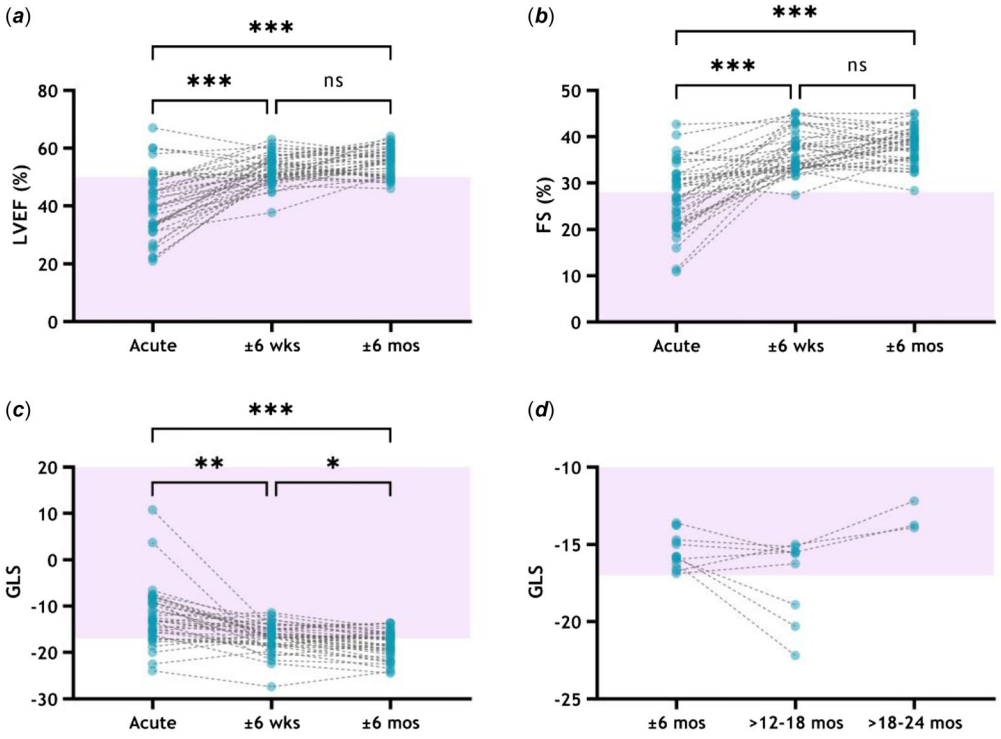

Figure 2. Left ventricle ejection fraction (A), fractional shortening (B), and GLS (C) over in first six months post-onset of disease with the pink range representing abnormal values; available GLS values in patients with abnormal GLS level at 6 months (D). Abbreviations: LVEF = left ventricle ejection fraction, FS = fractional shortening, GLS = global longitudinal strain.

Longitudinal echocardiography patterns

Next, we evaluated the longitudinal patterns of the left ventricle ejection fraction, fractional shortening, and global longitudinal strain. The left ventricle ejection fraction and fractional shortening resolved quickly post-treatment in a majority of the patients and none of the patients required treatment for heart failure after discharge. The left ventricle ejection fraction and fractional shortening reached a plateau level within the first 6 weeks of follow-up (Fig. 2), while the global longitudinal strain continued to remain significantly decreased from the acute phase to 6 weeks ($P = 0.007$ [vs. acute]) until 6 months ($P < 0.001$ [vs. acute]) (Fig. 2, Table S2).

Although in most patients the left ventricle ejection fraction and fractional shortening had normalised at 6 months, there were four patients that still had a decreased left ventricle ejection fraction (values between 46 and 49%). In total, 35.7% (n = 15) had a persistently abnormal global longitudinal strain value at 6 months, including the four patients that also had a decreased left ventricle ejection fraction. Echocardiography between >12 and ≤18 months post-onset was available for nine patients with an abnormal global longitudinal strain at 6 months (Fig. 2D). The left ventricle ejection fraction had normalised in all, but global longitudinal strain was still abnormal in five of these patients (55.6%) with values between −15.5% and −16.3%. Of 3/5 of these patients, an additional echocardiogram was available between >18 and ≤24 months post-onset. All three of these showed an abnormal global longitudinal strain between −12.2% and −13.9% and one of the patients also had an abnormal left ventricle ejection fraction (48%).

Clinical symptoms in patients with persisting global longitudinal strain abnormalities

Two of the patients with a persisting abnormal global longitudinal strain at 6 months had clinical symptoms. The first was a 16-year-old girl admitted to the ICU due to multisystem inflammatory syndrome in children with circulatory insufficiency, who recovered quickly after treatment (intravenous immunoglobulins, methylprednisolone pulse, noradrenaline, and milrinone). Noticeably, the patient had premature ventricular contractions (solitary, uniform, maximum of 544/hour) and described a worsened exercise intolerance.

The second patient was a 12-year-old boy with multisystem inflammatory syndrome in children and circulatory insufficiency, with rapid recovery after treatment with IVIG and methylprednisolone. Coincidently, an atrial septal defect (type II) was detected,

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Table 2. Associated blood parameters in patients with decreased LVEF, FS, or GLS per timeframe

Timeframe	Decreased parameter	More often worse in patients with decreased parameter[a]
Acute	LVEF <50%, $n = 36$	C-reactive protein ($P = 0.03$), N-terminal pro b-type natriuretic peptide ($P = 0.005$), ferritin ($P = 0.03$)
	FS <28%, $n = 24$	Age ($P = 0.05$), NT-pro-BNP ($P = 0.02$), urea ($P = 0.02$), creatinine ($P = 0.02$), fibrinogen ($P = 0.01$)
	GLS >[−17]%, $n = 40$	Creatinine ($P = 0.04$)
6 weeks post-onset	LVEF <50%, $n = 9$	N-terminal pro b-type natriuretic peptide ($P = 0.01$)
	FS <28%, $n = 1$	None
	GLS >[−17]%, $n = 30$	Troponin T ($P<0.001$), N-terminal pro b-type natriuretic peptide ($P = 0.02$)
6 months post-onset	LVEF <50%, $n = 4$	Troponin T ($P = 0.02$), creatinine ($P = 0.02$)
	FS <28%, $n = 0$	N/A
	GLS >[−17]%, $n = 17$	C-reactive protein ($P = 0.01$), Troponin T ($P = 0.02$), creatinine ($P = 0.003$)

[a]Significance (p value) based on Mann–Whitney *U* test.
Abbreviations: LVEF = left ventricle ejection fraction, FS = fractional shortening, GLS = global longitudinal strain.

which was closed without complications. The patient is currently asymptomatic but has ventricular extra systoles (uniform, no ventricular tachycardia). The other patients with persistent abnormal global longitudinal strain did not have clinical complaints during late convalescence (fatigue, dyspnoea, and exercise intolerance).

Echocardiographic parameter correlations

Detailed information on the longitudinal changes of the left ventricle ejection fraction, fractional shortening, and global longitudinal strain are depicted in Table 1 and Table S2. The left ventricle ejection fraction values were significantly correlated with fractional shortening values (r = 0.8 [95% CI 0.7–0.8), $P < 0.001$) and global longitudinal strain values (r = −0.6 [95% CI [−0.7]–[−0.5]], $P < 0.001$). Fractional shortening values were also significantly correlated with global longitudinal strain values (r = −0.5 [95% CI [−0.6]–[−0.3], $P < 0.001$) (Figure S2).

Coronary artery aneurysms

Transient coronary artery aneurysms were seen in five (10.4%) patients. All normalised within a median of 8 (range 2–193) days post-onset of disease (Table S1).

Cardiac MRI

Cardiac MRI was performed in 27 patients (56.3% of the study population). Cardiac MRI was performed in the acute phase (n = 9), at 6 weeks post-onset (n = 4) and at the outpatient visit closest to 6 months (n = 17) post-onset.

The nine patients that underwent acute cardiac MRI were a subgroup of patients with cardiac dysfunction related to multi-system inflammatory syndrome in children in December 2020, January 2021, and February 2021. Two of these patients showed no signs of myocarditis, pericardial effusion, or fibrosis on cardiac MRI. In contrast, increased T1 and/or T2 values were seen in 77.8% (7/9) of the patients, criteria suggestive of acute myocarditis with signs of slight pericardial effusion in three.

Of the patients with abnormalities on the acute cardiac MRI, three underwent another cardiac MRI 6 months post-onset and had normalised. The others were not repeated, since there were no clinical signs of cardiac dysfunction, and all echocardiographic parameters had normalised. Additionally, none of the cardiac MRIs at 6 weeks (n = 4) or 6 months (n = 17) had shown signs of increased T1/T2 values or fibrosis on the late gadolinium enhancement-cardiac MRIs.

No additional coronary artery aneurysms were identified by cardiac MRI.

Associations of laboratory measurements with echocardiography and cardiac MRI in the acute phase

Table 2 shows a detailed description of the acute blood parameter values that were significantly worse in patients with a decreased left ventricle ejection fraction, fractional shortening, and global longitudinal strain than those with a normal cardiac function during follow-up. Patients with a decreased left ventricle ejection fraction or fractional shortening had higher acute N-terminal pro b-type natriuretic peptide values than patients with a normal left ventricle ejection fraction or fractional shortening in the acute phase, while higher cardiac troponin T values were not associated with decreased left ventricle ejection fraction and fractional shortening in the acute phase.

Due to the limited number of cardiac MRIs performed, we were not able to assess the association of clinical outcomes and laboratory measurements with the cardiac MRI data. However, all of the patients with T1/T2 abnormalities as per cardiac MRI also had cardiac dysfunction based on left ventricle ejection fraction, fractional shortening, and global longitudinal strain.

Associations of laboratory measurements with prolonged global longitudinal strain abnormalities

Noticeably, different peak values of soluble blood markers in the acute phase were associated with the acute cardiac outcomes than with the late cardiac outcomes. Troponin T ($P < 0.001$) and N-terminal pro b-type natriuretic peptide ($P = 0.02$) were both significantly associated with a global longitudinal strain >[−17]% at 6 weeks (Table 2). C-reactive protein ($P = 0.01$), troponin T ($P = 0.02$), and creatinine ($P = 0.003$) values were all significantly associated with a global longitudinal strain >[−17]% at 6 months (Table 2, Fig. 3). In a logistic regression analysis, patients with elevated troponin T (above median, >62.0 ng/L [normal range 0–14 ng/L]) were 9.3 (95% CI 1.3–67.6) times more likely to exhibit abnormal global longitudinal strain during late convalescence disease than patients with a troponin level lower than 62.0 ng/L. This effect was independent of age at onset (continuous, in

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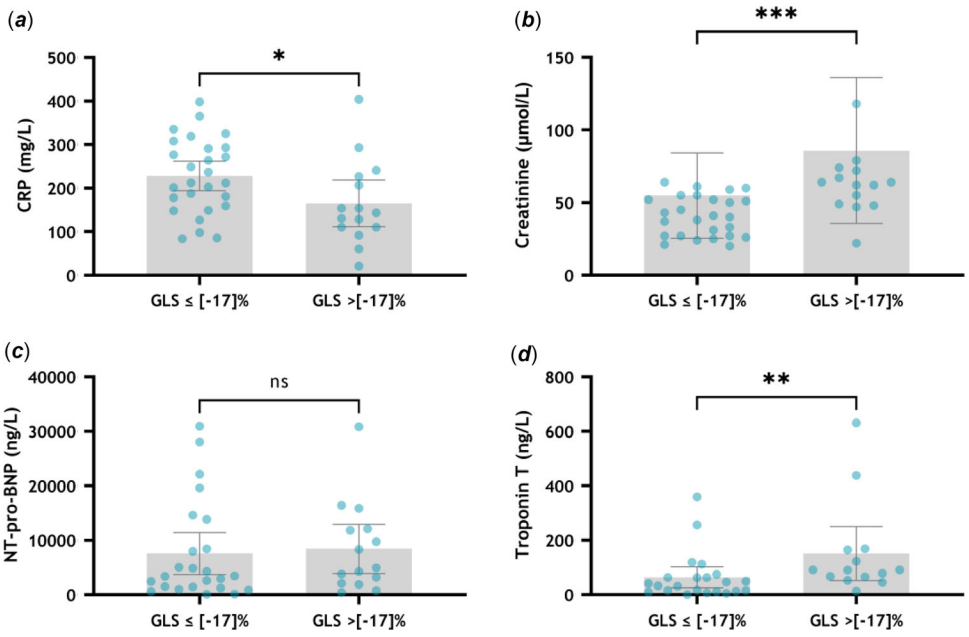

Figure 3. Acute levels of C-reactive protein (A), creatinine (B), N-terminal pro b-type natriuretic peptide (C), and troponin T (D) in patients with a normal (≤[−17]%) and abnormal (>[−17]%) GLS after 6 months. Abbreviations: GLS = global longitudinal strain, NT-pro-BNP = N-terminal pro b-type natriuretic peptide.

months), elevated C-reactive protein (above median, >187.9 mg/L [normal range 0–5 mg/L]), and decreased fractional shortening (<28%), which were not significantly associated with the prediction of a prolonged abnormal global longitudinal strain. The logistic regression model was statistically significant ($\chi^2(4) = 12.3$, $P = 0.02$) and explained 41.0% (Nagelkerke R^2) of the variance in abnormal global longitudinal strain and correctly classified 76.5% of cases. We validated these findings in a Cox Regression analysis and found that an elevated troponin T value was also significantly associated with the time to recovery of the global longitudinal strain with a hazard ratio of 0.4 ($P = 0.05$, confidence interval 0.1–1.0), while age at onset, elevated C-reactive protein, and decreased fractional shortening were not. Furthermore, the peak acute values of troponin significantly correlated with the global longitudinal strain during late convalescence ($r = 0.5$, $P = 0.002$).

Discussion

In the current cohort study, we investigated the longitudinal cardiac outcomes in patients with multisystem inflammatory syndrome in children. Acute cardiac involvement was seen in a majority of the multisystem inflammatory syndrome in children patients, as well as a delayed recovery of the global longitudinal strain compared to conventional echocardiographic measures in several patients up to two years post-onset. Patients with an elevated troponin T value (>62.0 ng/L) during acute disease were 9.3 times more likely to exhibit abnormal global longitudinal strain during late convalescence disease than patients with a lower troponin. Additionally, the peak acute values of troponin significantly correlated with the global longitudinal strain during late convalescence.

Conventional echocardiography in multisystem inflammatory syndrome in children

Regarding acute cardiac outcomes in our multisystem inflammatory syndrome in children population, cardiac dysfunction based on a decreased left ventricle ejection fraction or fractional shortening was seen in 81.3% with vasoactive support needed in 50% of our patients. This indicates a skewed presentation of severe multisystem inflammatory syndrome in children cases in the Amsterdam UMC, a tertiary hospital and expertise centre for Kawasaki disease. Previous studies have reported left ventricle ejection fraction dysfunction in up to 67%[9] and cardiac shock in about half of multisystem inflammatory syndrome in children cases with rapid left ventricle ejection fraction recovery within several days post-treatment in most patients.[1,2] Similarly, in our study, left ventricle ejection fraction and fractional shortening had normalised in the majority of the patients during early and late convalescence.

Global longitudinal strain in multisystem inflammatory syndrome in children

Global longitudinal strain was decreased in 85.1% of the multisystem inflammatory syndrome in children patients in the acute phase. This is consistent with findings in other studies identified in our systematic search.[5–19] In these studies, up to 90% of patients had an abnormal global longitudinal strain during admission.[19]

Similar to the subset of studies that included speckle-tracking measurements during follow-up,[5,8,10–13,16,18] global longitudinal strain values improved significantly during follow-up, but showed delayed recovery when compared to conventional parameters (left ventricle ejection fraction, fractional shortening). Remarkably, 35.7% of the multisystem inflammatory syndrome in children patients had persistently abnormal global longitudinal strain after 6 months, a large proportion when compared to a previous study with a follow-up of six months, which reported a persistently impaired global longitudinal strain in 13% of the multisystem inflammatory syndrome in children patients ($n = 23$)[18] and another study that reported normal cardiac function in all multisystem inflammatory syndrome in children patients after six months ($n = 32$).[10] While global longitudinal strain is known to have a low inter- and intra-operator variability and a low inter-vendor variation,[22] these discrepancies may be due to the skewed presentation of severe multisystem inflammatory syndrome in children cases in the Amsterdam UMC, which was mentioned previously. Furthermore, as mentioned in the methods, we measured the

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global longitudinal strain in 4-chamber view, instead of deriving it from the averaged three standard apical views.[30] Although the two are strongly correlated[31,32] and we chose this approach to be able to include a larger patient population, it could have led to a slight overestimation of strain abnormalities, since an overall global longitudinal strain can be normal even if a single plane is abnormal. Contrastingly, our proportion of global longitudinal strain abnormalities could also have been underestimated, since our global longitudinal strain cut-off was based on the lower limit reported in children between 0 and 1 year old. It should be noted that this cut-off was quite lenient since the mean global longitudinal strain in children of all age groups is −20.2% (95% confidence interval between −20.8% and −19.6%).[29] The clinical implications of an abnormal global longitudinal strain in patients with a recovered left ventricle ejection fraction and fractional shortening are unclear. Only two of our patients had clinical complaints during late convalescence that may have been linked to the prior multisystem inflammatory syndrome in children episode. The latter patients had a persistently abnormal global longitudinal strain >1-year post-admission and had premature ventricular contractions that were first noticed during the acute disease episode. While these premature ventricular contractions could have been pre-existent, the female patient also had clinical complaints of exercise intolerance. Previous studies in adult heart failure patients with a recovered left ventricle ejection fraction suggest that an abnormal global longitudinal strain may predict future deterioration of left ventricular function.[35] In this population, global longitudinal strain >[−14]% is also associated with major adverse cardiac events (cardiovascular death, emergency heart transplantation, left ventricular assist device, or intra-aortic balloon pump implantation),[36] although extrapolation of data from adult heart failure patients to previously healthy children with acute ventricular dysfunction secondary to a hyperinflammatory disease is difficult.

Noticeably, the global longitudinal strain in three patients with an abnormal global longitudinal strain between >12 and ≤18 months had worsened at their consecutive check-ups between >18 and ≤24 months. Although no hard conclusions can be drawn, the lack of normalisation of global longitudinal strain is concerning. Even though the long-term implications of global longitudinal strain abnormalities are still unclear, we advocate that careful cardiac follow-up is warranted in patients with a persistent abnormal global longitudinal strain, since they may be at risk for cardiovascular events in the future.

Cardiac MRI in multisystem inflammatory syndrome in children

Our cardiac MRI findings indicated acute myocardial involvement in a majority of the patients in the acute phase (77.8% [7/9]). This is high compared to previous reports describing myocarditis in up to 73%,[33,37] possibly due to the limited subgroup investigated in our study (only 9/48 patients with a median left ventricle ejection fraction of 33.0% vs. 39.0% of the complete study population).

Thankfully, later cardiac MRIs did not show signs of myocardial involvement or fibrosis. Similar to previous reports[38,39] and in contrast to typical myocarditis,[40,41] none of the patients in our study required heart failure treatment after discharge and systolic function and troponin levels normalised promptly post-treatment. Other studies found late gadolinium enhancement in 20% (4/20)[19] and 35% (8/23)[18] of multisystem inflammatory syndrome in children patients during the acute phase of disease. One of the studies we identified in our systematic search found residual oedema in one out of nine patients after 204 days of disease onset.[14] The patient had presented with left ventricle dysfunction and elevated troponin in the acute phase, which had completely normalised during follow-up. However, no fibrosis was seen on the cardiac MRI of the patient. Other studies focused on cardiac MRI abnormalities two[38] to three[39] months post-diagnosis did not report any abnormalities either, concurrent with our own findings.

Prediction of prolonged global longitudinal strain abnormalities

In our multivariable analyses, for the first time, the highest acute value of cardiac troponin significantly predicted delayed global longitudinal strain recovery, suggesting subclinical myocardial involvement in part of the multisystem inflammatory syndrome in children patients. Cardiac biomarkers (N-terminal pro b-type natriuretic peptide, troponin) have previously been associated with disease severity (ICU admission[2,42]) and decreased cardiac function (based on left ventricle ejection fraction, fractional shortening, and/or global longitudinal strain) in multisystem inflammatory syndrome in children.[5,6,9–11,13,18,20] Two other studies investigated the potential of N-terminal pro b-type natriuretic peptide and troponin I to predict an abnormal global longitudinal strain.[14,16] One did not find an association between the cardiac biomarkers and global longitudinal strain abnormalities at 3−10 weeks post-onset, although 3/9 (33%) patients with an abnormal troponin I during acute illness had an abnormal global longitudinal strain and circumferential strain at subacute follow-up.[14] The other study found an association between the initial troponin I value and longitudinal strain value 10 weeks post-onset.[16] It should, however, be noted that the outcomes associated with troponin I may differ from those associated with troponin T, although both are associated with cardiovascular events.[43]

Elevated levels of troponin in patients receiving cardiotoxic chemotherapy have also been described to be a sensitive measurement for early detection of cardiotoxicity.[25] In line with our findings, N-terminal pro b-type natriuretic peptide levels have not been consistently described as predictor for cardiotoxicity.[22]

Future studies

In the future, we recommend in-depth analyses of the prognostic value of an integrated approach of imaging techniques and biomarkers in severe inflammatory disorders, such as multisystem inflammatory syndrome in children, similar to the approach used to predict cardiotoxicity related to cancer treatment.[4,22] Since the incidence of multisystem inflammatory syndrome in children seems to be diminishing, concurrent with the rise in paediatric SARS-CoV-2 vaccination status and possibly decreased abilities to induce a hyperinflammatory response of the currently ruling SARS-CoV-2 variant omicron,[44] such studies should also focus on other similar hyperinflammatory disorders, such as Kawasaki disease and toxic shock syndrome. Furthermore, mechanisms underlying persisting global longitudinal strain abnormalities should be further elucidated, for instance, by investigating if these findings may be linked to the mitochondrial dysfunction recently implicated in long coronavirus disease 19.[45] It would be interesting to evaluate if patients with mitochondrial dysfunction and long coronavirus disease 19 have persisting global longitudinal strain abnormalities, as has been suggested in studies with patients that have fully recovered from coronavirus disease 19.[46,47]

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Study limitations and strengths

Limitations of the current study include the limited number of subjects, due to the rarity of multisystem inflammatory syndrome in children, limiting the (multivariable) analyses that we could perform within the current patient population. Also, a single observer (experienced paediatric cardiologist specialised in Kawasaki disease) recalculated the echocardiographic (left ventricle ejection fraction, fractional shortening, and global longitudinal strain) values retrospectively in this study, which could introduce bias, but minimises the risk of inter- and intra-observer variability. Moreover, there may have been selection bias, since we could only include patients of whom echocardiographic data in the acute phase were available, likely representing a more severely affected subpopulation of multisystem inflammatory syndrome in children patients. Lastly, only 9 of the 15 patients with global longitudinal strain abnormalities at 6 months had echocardiography available between >12 and ≤18 months.

However, the maximum follow-up of previous studies did not exceed 4.4 months (due to the novelty of the disease),[5,8,10–13,16,18] with the exception of two studies that investigated cardiac outcomes in multisystem inflammatory syndrome in children up to 6 months.[10,18] This stresses another major strength of our current study, which adds insight into the dynamics during late convalescence, up to two years after the disease episode. Also, to our knowledge, this is the first study to perform a multivariable regression analysis to investigate the correlation of delayed cardiac recovery with cardiac biomarkers in multisystem inflammatory syndrome in children.

Conclusion

In conclusion, multisystem inflammatory syndrome in children is a severe inflammatory disorder with a high risk of cardiac complications and delayed recovery of speckle-tracking outcomes compared to conventional echocardiographic measures (left ventricle ejection fraction, fractional shortening). Although cardiac function generally recovers within several months, without signs of fibrosis on convalescent cardiac MRIs, a subgroup of children may retain long-term subclinical cardiac damage, which is associated with cardiac troponin T levels in the acute phase. In patients with elevated troponin in the acute phase and patients with persistent abnormal global longitudinal strain despite normalisation of left ventricle ejection fraction and fractional shortening, we advocate for careful, serial cardiac monitoring until resolution of the abnormal global longitudinal strain, as the long-term implications of such abnormalities are still unclear.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/S1047951124000465

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