Three-Dimensional Echocardiography and Global Longitudinal Strain in Follow-Up After Multisystem Inflammatory Syndrome in Children

Six-Month, Single-Center, Prospective Study

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Objective To assess the potential long-term cardiac effects after multisystem inflammatory syndrome in children (MIS-C) with cardiovascular involvement in the acute phase.

Study design Our prospective study involved children consecutively diagnosed with MIS-C between October 2020 and February 2022 and followed 6 weeks and 6 months after the disease. In patients with severe cardiac involvement during the acute phase, an additional check-up after 3 months was scheduled. In all patients at all check-ups, 3-dimensional echocardiography and global longitudinal strain (GLS) were used to assess ventricular function.

Results The study enrolled 172 children aged 1-17 years (median, 8 years). The means of ejection fraction (EF) and GLS for both ventricles were within normal limits after 6 weeks with no relationship with initial severity: left ventricular EF (LVEF) 60% (59%-63%), LV GLS –21.08% (−18.63% to −23.2%), right ventricular (RV) EF 64% (62%-67%), and RV GLS –22.8% (−20.5% to −24.5%). Further, statistically significant improvement of LV function was observed after 6 months—LVEF 63% (62%-65%) and LV GLS –22.55% (−21.05% to −24.25%; $P < .05$); however, RV function remained unchanged. The group with severe cardiac involvement showed LV function recovery pattern with no significant improvement between 6 weeks and 3 months after MIS-C, while still improving between 3 and 6 months after discharge.

Conclusions LV and RV function is within normal limits 6 weeks after MIS-C regardless of severity of cardiovascular involvement; LV function improves further between 6 weeks and 6 months after the disease. The long-term prognosis is optimistic with full recovery of cardiac function. *(J Pediatr 2023;260:113516)*.

Multisystem inflammatory syndrome in children (MIS-C) or pediatric multisystem inflammatory syndrome temporally associated with severe acute respiratory syndrome coronavirus 2/coronavirus disease 2019 is a new disease brought to worldwide attention by the severe acute respiratory syndrome coronavirus 2 pandemic.[1,2] This acute illness affects children exposed to the virus and presents with fever, elevated inflammatory markers, and a broad spectrum of symptoms from multiple organs, almost always involving the cardiovascular system, including severe systolic dysfunction of the left ventricle in some patients. Cardiovascular involvement seems to be temporary, especially if effective treatment is administered; however, the potential long-term effects of the disease are still unknown.[3-16]

The aim of the study was to assess the nature and duration of cardiovascular involvement in children after MIS-C for optimization of their recovery guidelines. Additionally, the efficacy of global longitudinal strain (GLS) and 3-dimensional echocardiography (3D-ECHO) in follow-up was tested according to its potential standardized and widespread use.

Methods

A prospective study evaluating changes in the cardiovascular system in children after MIS-C was conducted in the Department of Pediatric Cardiology at the Medical University of Warsaw between October 2020 and February 2022. The study enrolled consecutive patients diagnosed with MIS-C (according to World Health Organization clinical and laboratory criteria) evalu-

3D-ECHO	3-dimensional echocardiography
EF	Ejection fraction
GLS	Global longitudinal strain
MIS-C	Multisystem inflammatory syndrome in children
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
LV	Left ventricular
RV	Right ventricular
PICU	Pediatric intensive care unit

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ated 6 weeks and 6 months after the diagnosis. In children with severe cardiac involvement during the acute phase, an additional check-up after 3 months was arranged. The adapted criteria for severe cardiac involvement classification were left ventricular ejection fraction (LVEF) in echocardiography of <55%, serum concentration of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) of >5000 pg/mL (normal limit, <126 pg/mL), and serum concentration of troponin I of >500 ng/L (reference, <20 ng/L).

In all patients at each control point, 3D-ECHO and average GLS were used to assess LV and right ventricular (RV) function (Philips, Best, the Netherlands; CVx 3D). Additionally, in all cases laboratory blood tests and electrocardiography were performed.

For 3D-ECHO full-volume data from 2 consecutive heartbeats were recorded, and for the longitudinal strain 4-, 3-, and 2-chamber apical views were obtained for the left ventricle and a single 4-chamber apical view for the right ventricle. For both methods, an analysis of the recorded data was performed automatically on 1 echocardiographic station; in 3D-ECHO, the LVEF was assessed using a Philips Dynamic Heart Model, and RVEF using 3D Auto RV TomTec algorithm. The average GLS for both ventricles was calculated by TomTec software.

The study protocol was consistent with the standards of Helsinki Declaration and approved by University Bioethical Committee (KB/13/2021). All the legal guardians and patients >16 years of age signed informed consent for participation.

Continuous data were expressed as mean ± SD or median (IQR) in the case of non-normal distribution. Normal distribution was assessed with the Shapiro-Wilk test. Differences in means between groups were assessed with the unpaired *t* test for normal distribution or Mann-Whitney *U* test (other distribution). Repeated measure over time was performed with the Friedman test (multiple time points) and Wilcoxon signed-rank test (2 time points) for the entire sample and in selected subgroups. Categorical data were expressed as percentages. Differences in proportions were compared by means of χ^2 analysis (Pearson, with Yates correction when necessary). A 2-sided *P* value of <.05 was considered significant for all tests. Analyses were performed using the statistical package Statistica v. 13.1 software (Dell Inc., Tulsa, OK).

Results

The study enrolled 172 children diagnosed with MIS-C; no children with preexisting cardiovascular pathologies were included. The characteristics of the sample during the acute phase of the disease are presented in **Table I**.

More than one-third of the patients were classified as having severe cardiovascular involvement owing to low LV function on echocardiography or a high blood concentration of cardiovascular markers. The characteristics of this subgroup during the acute phase of the disease are presented in **Table I**. Ten children required treatment in the pediatric intensive care unit (PICU) owing to severe deterioration of LV function or cardiogenic shock. All patients underwent treatment according to the latest guidelines, with no mortality and no need for mechanical cardiac support.

At the time of discharge all patients were asymptomatic, had ventricular systolic function (LVEF and RVEF) within normal limits, normal serum concentration of inflammatory markers and troponin, and either normal or significantly improved concentration of NT-pro-BNP. At follow-up, 130 patients were evaluated after 6 weeks, 30 had an added check-up after 3 months, and 88 after 6 months. During follow-up, all patients remained asymptomatic and the means of LVEF, RVEF, and average GLS for both ventricles were within normal limits at the time of all check-up points for the whole studied group. However, although the means of RVEF and RV strain remained unchanged between 6 weeks and 6 months after discharge, the LVEF and average GLS for the left ventricle improved significantly. The detailed results are presented in **Table II** and in the **Figure**.

The differences between subgroups with originally mild and severe cardiovascular involvement at the common times of follow-up after 6 weeks and 6 months are presented in **Table III** and the **Figure**. The comparison between subgroups with mild and severe cardiovascular involvement during the acute phase of the disease showed no statistically significant difference regarding the means of LVEF, LV average GLS values, RVEF, and RV GLS at the time of check-up point 6 weeks after discharge.

Six months after discharge there was also no significant difference between the subgroups with mild and severe cardiovascular involvement regarding the means of all the assessed echocardiographic measures.

The subgroup of patients with severe cardiovascular involvement showed no significant improvement of LV function measured by LVEF and average GLS between check-up points after 6 weeks and 3 months ($P = .53$ for LVEF and 00.42 for LV GLS), while still improving the means of both results during the subsequent 3 months (at the check-up point 6 months after discharge, $P = .003$ for LVEF and 00.01 for LV GLS). In this subgroup, the means of RV GLS did not improve significantly between each control point, although the difference between results obtained after 6 weeks and 6 months was statistically significant ($P = .048$).

Discussion

From our studied cohort of 172 patients, a relatively small subsample represented the most severe clinical phenotype in the acute phase of the disease; only 10 children (17%) needed escalated treatment in the PICU owing to severely impaired cardiac function or symptoms of shock. None required mechanical cardiovascular support. Because MIS-C is a heterogenous disease, the literature shows significant variability. A recent analysis published by Rao et al classifies approximately one-half of almost 1200 children hospitalized with MIS-C in the US centers participating in PEDSnet as a

Table I. Baseline demographic and clinical characteristics of the whole cohort

Characteristics	Value
Entire cohort	
Demographic characteristics	
Patients, n	172
Age at presentation, years	8 (4-11)
Age at presentation range, years	1-17
Male sex, n	115 (67)
Clinical characteristics	
Weight status categories, n	
Underweight (<5th percentile)	15 (8.7)
Normal weight (5th to 85th percentile)	116 (67.4)
Overweight (85th to 95th percentile)	17 (9.9)
Obese (≥95th percentile)	24 (14)
Hospitalization	
PICU admission, n	10 (5.8)
Discharged, n	172 (100)
Laboratory results	
NT-pro-BNP on admission (reference <126), pg/mL	2925 (681-7400)
NT-pro-BNP after 6 weeks (reference <126), pg/mL	50 (32-73)
NT-pro-BNP after 6 months (reference <126), pg/mL	48.5 (32-94)
Troponin I on admission (reference <20), ng/L	27.7 (7.9-92.8)
Troponin I after 6 weeks (reference <20), ng/L	1 (1-2.9)
Troponin I after 6 months (reference <20), ng/L	1 (0.5-1)
Echocardiographic findings on admission	
LVEF, %	63 (54-68)
LVEF range, %	10-78
Coronary dilatation, n	3 (1.74)
Coronary aneurysm, n	2 (1.16)
Pharmacological treatment in acute phase	
Intravenous immunoglobulin	156 (90.7)
Methylprednisolone intravenously	79 (45.9)
Biological therapy, n	1 (0.58)
Severe cardiac involvement in MIS-C group	
Demographic characteristics	
Patients, n	65
Age at presentation, years	9 (4-13)
Age at presentation range, years	1-17
Male sex, n	44 (68)
Clinical characteristics	
Weight status categories, n	
Underweight (<5th percentile)	1 (2)
Normal weight (5th to 85th percentile)	46 (71)
Overweight (85th to 95th percentile)	9 (14)
Obese (≥95th percentile)	9 (14)
Hospitalization	
PICU admission, n	10 (15)
Intubation, n	4 (40)
Inotropic support, n	9 (90)
Days in the PICU range, n	7 (4-31)
Discharged, n	65 (100)
Laboratory results	
NT-pro-BNP on admission (reference <126), pg/mL	9399 (5768-21 259)
NT-pro-BNP after 6 weeks (reference <126), pg/mL	45 (31-63)
NT-pro-BNP after 6 months (reference <126), pg/mL	50 (34-85)
Troponin I on admission (reference <20), ng/L	97 (39-264)
Troponin I after 6 weeks (reference <20), ng/L	1 (1-4)
Troponin I after 6 months (reference <20), ng/L	1 (0.5-1)
Echocardiographic findings on admission	
LVEF, %	51 (46-58)
LVEF range, %	10-67
Coronary dilatation, n	2 (3)
Coronary aneurysm, n	0
Pharmacological treatment in acute phase	
Intravenous immunoglobulin, n	61 (94)
Methylprednisolone intravenously, n	41 (63)
Biological therapy, n	0

Values are median (IQR) or number (%).

severe clinical phenotype, with 72.5% requiring PICU treatment owing to hypotension or shock.[9] In contrast, the most recent meta-analysis published by Jlang et al analyzed 123 studies from around the world, with a population of 4475 children, and notes a 37% prevalence of shock symptoms on admission.[3]

The laboratory findings concerning cardiovascular involvement in our cohort are similar to those reported in literature. The majority of children had elevated NT-pro-BNP and troponin I serum concentrations; however, our data suggest that NT-pro-BNP concentrations is more specific than troponins in the affected group (the mean results exceeding the normal range of >23-fold for the whole group and 74-fold in the subgroup with severe cardiovascular involvement, whereas the concentrations of troponin I were, respectively, 1.35- and 4.6-fold higher than the normal limit). The meta-analysis by Jlang et al notes elevated troponin in 62% and NT-pro-BNP in 54% of children with MIS-C; however, no comment is made on the actual values of their concentrations and how they exceed normal ranges.[3]

In our study we emphasize impaired systolic function of the left ventricle as the most important echocardiographic finding during the acute stage of MIS-C; the other changes described in literature, including pericardial effusion, coronary involvement, and significant mitral regurgitation, were observed rarely in our cohort. Only in 5 patients were coronary anomalies observed, and all of them resolved fully during early follow-up. The echocardiographic results described in different studies are heterogenous; however, impaired LV

Table II. Echocardiographic parameters of the whole group on follow-up

Parameters	6 Weeks after MIS-C	6 Months after MIS-C
LVEF 3D, %	60 (59-63)	63 (62-65)
LV GLS	−21.08 (−18.63 to −23.2)	−22.55 (−21.05 to −24.25)
RVEF 3D, %	64 (62-67)	65 (63-67)
RV GLS	−22.8 (−20.5 to −24.5)	−23.7 (−21.9 to −26.7)
Coronary artery dilatation, n	3 (1.74)	0
Coronary artery aneurysm, n	2 (1.74)	0

Values are median (IQR) or number (%).

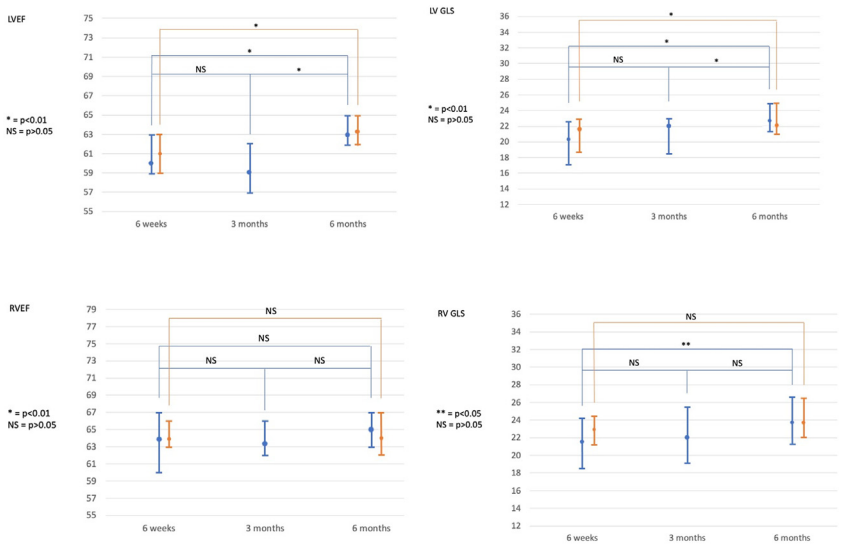

Figure. LVEF, LV GLS, RVEF, RV GLS changes in mild cardiac involvement group and severe cardiac involvement group in MIS-C on follow-up. In RED–Mild Cardiac Involvement Group, in BLUE–Severe Cardiac Involvement Group.

systolic function is universally accepted as the most relevant finding.[1,3,4,6,13,14,17-19]

In our cohort, RV function was affected rarely during the acute phase of the disease, and in all cases it was within normal limits. Furthermore, echocardiography showed no further improvement during follow-up, which remains in agreement with findings published by other investigators.[10,13]

An assessment of the recovery pace of cardiac muscle after MIS-C was among the main goals of our study. During follow-up, all of our patients were asymptomatic and with normal blood concentrations of cardiac biomarkers, which agrees with the data published so far.[10-12,20,21] For that reason, we focused on a detailed analysis of LV function using echocardiography to address our second main goal: the efficacy of 3D-ECHO and GLS in follow-up after MIS-C.

The adapted techniques for follow-up proved both effective and fast, with no need for general anesthesia. A fully automatized protocol allowed for routine and repeatable functional testing, being most advantageous in comparison with protocols using other sensitive imaging modalities, including cardiac magnetic resonance, requiring general anesthesia in the smallest children, and offering similar results.[6,20,21]

In our group, ventricular function was within normal limits 6 weeks after discharge. A similar trend in all or almost all patients during the first 2 months of the disease was also observed in smaller cohorts in studies published Chakraborty et al, Farooqi et al, and Penner et al.[10-12] The use of GLS is advocated by Matsubara et al, Kobayashi et al, and Liu et al, but in the acute phase of MIS-C and not in follow-up.[14,17,19] Only a few studies applied GLS as the follow-up tool. Garbin et al obtained similar results to our study with normalization of LV GLS early in the 6-month follow-up.[13] In contrast, Das et al reported a small percentage (21%) of patients with GLS below normal limits 2 months after MIS-C, and Sirico et al presented a small population (13%) of patients with impaired GLS as long as 6 months after the disease.[15,22]

The use of both 3D-ECHO and average GLS in the assessment of LV function allowed us to observe further improvement in all the patients between 6 weeks and 6 months after discharge, and this tendency was present in both the mild and severe cardiovascular involvement subgroups. Furthermore, at the level of both mandatory check-up points, after 6 weeks and 6 months, no statistically significant difference was noted between measures of systolic left and RV function between the subgroups with different clinical courses, which remains in agreement with the results published by Garbin et al.[13] A similar pattern of cardiac recovery in all patients may be considered an optimistic prognostic factor.

Table III. Echocardiographic parameters in mild cardiac involvement group and severe cardiac involvement group in MIS-C on follow-up

	6 Weeks after MIS-C			6 Months after MIS-C		
Parameters	**Mild cardiac involvement group**	**Severe cardiac involvement group**	***P* value**	**Mild cardiac involvement group**	**Severe cardiac involvement group**	***P* value**
LVEF 3D, %	61 (59-63)	60 (58.9-63)	.32	63.5 (62-65)	63 (62-65)	.97
LV GLS	−21.4 (−18.8 to −23.5)	−20.5 (−18.6 to −22.8)	.25	−22.1 (−20.8 to −23.9)	−22.8 (−21.4 to −25.1)	.20
RVEF 3D, %	64 (63-66)	64 (60-67)	.35	64 (62-67)	65 (63-67)	.20
RV GLS	−23.4 (−21.3 to −24.6)	−21.5 (−18.6 to −24.3)	.14	−23.6 (−22.1 to −26.6)	−23.8 (−21.5 to −26.8)	.83

Values are median (IQR).

An interesting tendency was observed in the subgroup of patients with originally severe cardiovascular involvement qualified for an additional middle check-up point after 3 months: a significant improvement in LV function took place only between 3 months and 6 months after the disease. In our cohort, during that time the majority of patients returned to relatively normal life, although, especially in the first 12 months of our study with pandemic limitations affecting all aspects of public life, their activity was diminished. Further studies are needed to answer the question of whether this trend is unique to the severely affected group. Nevertheless, because the increasing activity of our patients seems to be aligned with a more effective ventricular function recovery trend, it may be beneficial to shorten their exercise limitations after full normalization of laboratory findings, echocardiogram, electrocardiograph, and exercise testing.

There were limitations to our study. Our sample was obtained in a single center and, being consistent, homogenous and with relatively small number of PICU admissions, may not represent trends corresponding with other regions of the world. Only a small portion of 3D-ECHO and GLS data are available from the acute phase of the disease, because most echocardiograms on admission were performed as an emergency and involved only routine assessment of cardiac function. The results of patients who rescheduled their check-up visits owing to infections or for other reasons, were not included into the analysis to maintain the straightforward approach. The algorithm of our follow-up was prospectively arranged as more rigorous for severely affected patients, and it would be interesting to observe if the pace of cardiac recovery is consistent in the mildly affected population.

These results of detailed assessment of ventricular function in children after MIS-C give us hope that their recovery may be fast and complete and their prognosis optimistic, with no dependence on original severity; however, as with any new disease, caution is still mandatory. The structured follow-up algorithm is an essential tool for further prognostic assessment. ■

Declaration of Competing Interest

The authors declare no conflicts of interest.

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