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Echocardiographic Indicators Associated with Adverse Clinical Course and Cardiac Sequelae in Multisystem Inflammatory Syndrome in Children with Coronavirus Disease 2019

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Background: Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 causes significant cardiovascular involvement, which can be a determinant of clinical course and outcome. The aim of this study was to investigate whether echocardiographic measures of ventricular function were independently associated with adverse clinical course and cardiac sequelae in patients with MIS-C.

Methods: In a longitudinal observational study of 54 patients with MIS-C (mean age, 6.8 ± 4.4 years; 46% male; 56% African American), measures of ventricular function and morphometry at initial presentation, predischarge, and at a median of 3- and 10-week follow-up were retrospectively analyzed and were compared with those in 108 age- and gender-matched normal control subjects. The magnitude of strain is expressed as an absolute value. Risk stratification for adverse clinical course and outcomes were analyzed among the tertiles of clinical and echocardiographic data using analysis of variance and univariate and multivariate regression.

Results: Median left ventricular apical four-chamber peak longitudinal strain (LVA4LS) and left ventricular global longitudinal strain (LVGLS) at initial presentation were significantly decreased in patients with MIS-C compared with the normal cohort (16.2% and 15.1% vs 22.3% and 22.0%, respectively, $P < .01$). Patients in the lowest LVA4LS tertile (<13%) had significantly higher C-reactive protein and high-sensitivity troponin, need for intensive care, and need for mechanical life support as well as longer hospital length of stay compared with those in the highest tertile (>18.5%; $P < .01$). Initial LVA4LS and LVGLS were normal in 13 of 54 and 10 of 39 patients, respectively. There was no mortality. In multivariate regression, only LVA4LS was associated with both the need for intensive care and length of stay. At median 10-week follow-up to date, seven of 36 patients (19%) and six of 25 patients (24%) had abnormal LVA4LS and LVGLS, respectively. Initial LVA4LS < 16.2% indicated abnormal LVA4LS at follow-up with 100% sensitivity.

Conclusion: Impaired LVGLS and LVA4LS at initial presentation independently indicate a higher risk for adverse acute clinical course and persistent subclinical left ventricular dysfunction at 10-week follow-up, suggesting that they could be applied to identify higher risk children with MIS-C. (J Am Soc Echocardiogr 2021;34:862-76.)

Keywords: MIS-C, COVID-19, Cardiac function, Ventricular strain

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Abbreviations

2D = Two-dimensional

COVID-19 = Coronavirus disease 2019

ECMO = Extracorporeal membrane oxygenation

ICU = Intensive care unit

LOS = Length of stay

LV = Left ventricular

LVA4LS = Left ventricular apical four-chamber peak longitudinal strain

LVCS = Left ventricular peak circumferential strain

LVEF = Left ventricular ejection fraction

LVGLS = Left ventricular global longitudinal strain

MIS-C = Multisystem inflammatory syndrome in children

MRI = Magnetic resonance imaging

ROC = Receiver operating characteristic

RV = Right ventricular

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2

STE = Speckle-tracking echocardiography

VA = Venoarterial

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has led to widespread morbidity and mortality in the United States and worldwide. Contrary to the initial medical and lay public perception that children with coronavirus disease 2019 (COVID-19) were asymptomatic or minimally symptomatic compared with adult patients, a small subset of these children went on to present with serious multiorgan inflammatory disease.[1-4] The Centers for Disease Control and Prevention has defined this severe presentation as multisystem inflammatory syndrome in children (MIS-C).[5] Patients with MIS-C manifest with persistent fever, signs of widespread inflammation, and multisystem organ involvement.[5] The majority of patients diagnosed with MIS-C have been reported to require intensive care therapy, with many experiencing prolonged hospitalization and requiring adjunctive therapies including vasopressors, intubation, and venoarterial (VA) extracorporeal membrane oxygenation (ECMO).[6,7]

Cardiovascular involvement is common in patients with MIS-C, with complications including cardiac dysfunction, shock, and myocarditis, which may have implications for clinical course and outcome.[6-8] Patients who required intensive care therapy were noted to have higher levels of inflammatory biomarkers and cardiac enzymes.[9] The majority of patients affected by MIS-C recover without apparent clinical sequelae. A comprehensive review of cardiac manifestations in patients affected by MIS-C indicated that 6% to 14% of patients had persistent myocardial dysfunction when evaluated at the time of discharge from the hospital.[10] To date, there are no studies assessing if cardiac sequelae persist beyond the acute phase when significant myocardial injury has occurred.

In adult patients with COVID-19, changes in both left ventricular (LV) and right ventricular (RV) function have been shown to be important indicators of clinical course and outcomes.[11,12] Compared with conventional echocardiographic parameters, LV and RV longitudinal systolic strain measured by two-dimensional (2D) speckle-tracking echocardiography (STE) evaluate myocardial function accurately and can discern subtle and early changes in ventricular function.[13] Additionally, 2D STE–measured LV apical four-chamber peak longitudinal strain (LVA4LS) has been applied to investigate LV function in different clinical settings for risk stratification and to prognosticate outcomes.[14] However, it has not been used in patients with MIS-C in this role.

In this retrospective, longitudinal, observational cohort study of children with MIS-C, we aimed to evaluate echocardiographic measures of ventricular function for risk stratification for adverse clinical course and cardiac sequelae.

METHODS

Study Design

This was an observational cohort study of 54 children admitted to Children's Hospital of Michigan who met the Centers for Disease Control and Prevention case definition of MIS-C between March 2020 and January 2021 (Supplemental Table 1).[5] Institutional review board approval with waiver of consent for local data collection was obtained through the Wayne State University institutional review board.

Clinical Data

A multidisciplinary team developed the protocol for the management of MIS-C and the longitudinal cardiovascular evaluation (Supplemental Table 2). Demographic and clinical data were collected, including history of contact with confirmed or suspected cases of COVID-19. The clinical data included anthropometrics, medical histories, hemodynamics, comorbidities, complications, treatments including intensive care unit (ICU) stay, duration of mechanical ventilation, requirement and duration of vasopressors, VA ECMO support, hospital length of stay (LOS), therapeutic intervention, and outcomes. Laboratory data included inflammatory markers, such as C-reactive protein and cardiac enzymes, including high-sensitivity troponin I, measured by immunoassay for the detection of cardiac injury.

Diagnosis of Confirmed Cases

Patients with positive nasopharyngeal swab testing for SARS-CoV-2 nucleic acid using reverse transcriptase quantitative polymerase chain reaction assay and/or positive qualitative detection of SARS-CoV-2 immunoglobulin G antibodies or an epidemiologic link to a person with COVID-19 were considered confirmed cases of SARS-CoV-2 infection.[5] Investigations to rule out infectious etiologies were negative for other viral and bacterial alternative plausible diagnoses.

Cardiovascular Evaluation

Considering the cardiovascular involvement in MIS-C, initial echocardiography was performed at a median of 9 hours (interquartile range, 3–20 hours) after admission. Patients underwent follow-up echocardiography if they had clinical deterioration during hospitalization and before discharge if indicated. Longitudinal echocardiographic examinations were performed during subsequent outpatient follow-up to date at a median of 3 and 10 weeks after diagnosis.

Transthoracic Echocardiography. Echocardiograms (Philips iE33; Philips Medical Systems, Andover, MA) were obtained by experienced sonographers according to American Society of Echocardiography guidelines.[15] All echocardiographic data, including LV strain, LV ejection fraction (LVEF), tricuspid annular plane systolic excursion, coronary artery measurements, RV function, and valvular

HIGHLIGHTS

- Children with MIS-C can develop significantly impaired LV function.
- Initial impaired LV strain can be associated with adverse clinical course.
- Initial impaired strain may indicate subclinical LV dysfunction at 10 wks follow-up.
- This study supports the use of LV strain to identify higher risk children with MIS-C.

regurgitation, were retrospectively analyzed. LVEF was measured using the 5/6 area-length method because of the lowest inter- and intraobserver percentage error reported by this method.[16] RV systolic function was assessed by both visual inspection and by tricuspid annular plane systolic excursion.[17] Coronary artery morphometry were measured per previously reported guidelines.[18]

Speckle-Tracking Echocardiography. Deformational measures of the left ventricle for cardiac mechanics were obtained using 2D STE according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[19,20] To reduce exposure and contamination, STE was assessed offline using vendor-independent 2D Cardiac Performance Analysis software (TomTec Imaging Systems, Munich, Germany). LV peak longitudinal systolic strain was measured in apical four-chamber view (LVA4LS) and LV peak circumferential strain (LVCS) in the parasternal short-axis view at the level of the mitral valve papillary muscle at the peak of T wave of the electrocardiogram just before closure of the aortic valve. LV global longitudinal strain (LVGLS) was obtained from two-, three-, and four-chamber apical views at the peak of T wave of the electrocardiogram just before closure of the aortic valve.

LVA4LS was obtained in all 54 patients at initial presentation and in all 36 patients who presented for the follow-up to date (Figure 1). LVGLS was available in only 39 of 54 patients at the initial presentation because apical two- and three-chamber views could not be obtained during early stages of the pandemic, when reduced availability of personal protective equipment and critical condition of patients resulted in challenges in detailed image acquisition. Of the initial 39 patients with available LVGLS, we were able to obtain LVGLS measurements in all 25 who presented for follow-up to date at a median of 10 weeks.

For assessment of ventricular synchrony, we measured mechanical dispersion, the time difference between segments from opposite walls with the shortest and the longest times to peak systolic strain in the apical four-chamber view, which was defined as maximum opposing wall motion delay.

Strain parameters were compared with those of age- and sex-matched normal control subjects who presented to our echocardiography laboratory for murmur and chest pain evaluation (Supplemental Table 3) and had normal cardiac findings. To achieve a 2:1 ratio of control subjects to patients, 108 normal control subjects were included.

Coronary artery *Z* score was calculated on the basis of the formula used by McCrindle *et al.*[21] *Z* scores of volumetric and dimensional parameters, including those of coronary arteries >2.0, were considered abnormal.[18] Abnormal findings such as pericardial effusion and valvulitis were additionally recorded. Cardiac magnetic resonance imaging (MRI) was not performed during hospitalization because of unstable clinical condition and risk for contamination of the MRI area.

Inter- and Intraobserver Variability and Reproducibility

Reproducibility of the strain measurements was assessed using inter- and intraobserver reliability measures on 20 imaging studies from the MIS-C cohort. Each observer performed offline analysis using the same measurement protocol. Intraobserver variability was assessed by one investigator (Y.S.), who repeated the analysis (blinded to the initial results) on the same cardiac cycles 1 month apart to reduce recall bias. Interobserver variability was tested for all analyses by a second observer (A.M.) blinded to the results of the first observer.

Statistical Analysis

Categorical variables are reported as numbers and percentages. The normality of continuous variables was tested using the Shapiro-

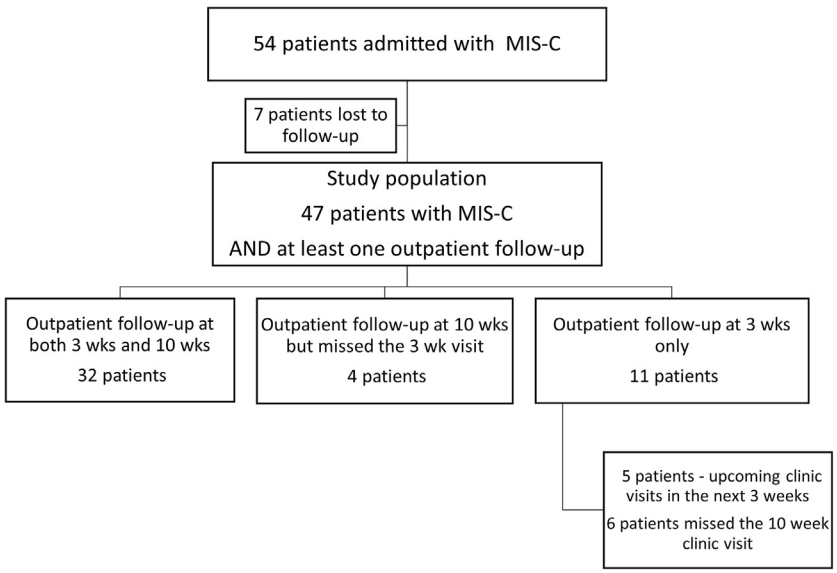

Figure 1 Flow diagram describing the study cohort and outpatient follow-up.

Table 1 Comparison of patient characteristics, presentation, and course according to the LVA4LS tertiles

	Total cohort	Lowest tertile: LVA4LS < 13.0%	Middle tertile: 13% < LVA4LS < 18.5%	Highest tertile: LVA4LS > 18.5%	*P*
Parameter	(*N* = 54)	(*n* = 18)	(*n* = 18)	(*n* = 18)	
Age, y	6.8 ± 4.4	10.5 ± 3.8	5.3 ± 3.2	4.2 ± 3.6	<.001
Gender, male	25 (46.0)	10 (56.0)	7 (39.0)	8 (44.0)	.594
Ethnicity					.683
African American	30 (56.0)	13 (72.0)	9 (50.0)	8 (44.0)	
Caucasian	6 (11.0)	2 (11.0)	2 (11.0)	2 (11.0)	
Middle Eastern	8 (15.0)	1 (6.0)	3 (17.0)	4 (22.0)	
Other/unknown	10 (18.0)	2 (11.0)	4 (22.0)	4 (19.0)	
Height, cm	118 ± 33	147 ± 21	105 ± 26	101 ± 29	<.001
Weight, kg	27 (17–36)	35 (30–80)	24 (15–28)	18 (9–27)	<.001
BMI, kg/m^2	18.4 (15.7–21.5)	18.8 (16.2–29.5)	18.4 (15.6–19.4)	16.8 (14.7–21.2)	.255
Overweight or obese	20 (37.0)	9 (50.0)	7 (39.0)	4 (22.0)	.221
SARS-CoV-2 testing results					
Nasopharyngeal PCR positive	24 (44.0)	9 (50.0)	8 (44.0)	7 (39.0)	.858
IgG antibody positive	36 (67.0)	15 (83.0)	13 (72.0)	8 (44.0)	.146
Comorbidities*	16 (30.0)	9 (50.0)	5 (28.0)	2 (11.0)	.02
Clinical presentation					
Classic Kawasaki criteria	8 (15.0)	1 (6.0)	4 (22.0)	3 (17.0)	.358
Fever	53 (98.0)	17 (94.0)	18 (100.0)	18 (100.0)	.361
Rash	26 (48.0)	9 (50.0)	9 (50.0)	8 (44.0)	.929
Lymphadenopathy	13 (24.0)	5 (28.0)	4 (22.0)	4 (22.0)	.904
Gastrointestinal symptoms	40 (74.0)	15 (83.0)	15 (83.0)	10 (56.0)	.090
Respiratory distress	15 (28.0)	8 (44.0)	5 (28.0)	2 (11.0)	.083
Chest pain	3 (6.0)	3 (17.0)	0 (0.0)	0 (0.0)	.042
Hypotension	28 (52.0)	16 (89.0)	9 (50.0)	3 (17.0)	<.001
C-reactive protein, mg/L (normal, <5 mg/L)					
Initial	129 (72–194)	160 (113–238)	145 (99–191)	47 (33–110)	.004
Peak	164 (84–269)	291 (177–333)	162 (108–265)	82 (44–164)	.001
Discharge	27 (10–47)	18 (9–37)	37 (10–67)	27 (15–55)	.407
hs-Tn, ng/L (normal, <50 ng/L†)					
Initial	40 (9–125)	114 (17–406)	60 (15–119)	7 (4–11)	<.001
Initial > 50 ng/L	24 (47.0)	12 (71.0)	9 (50.0)	3 (17.0)	.008
Peak	104 (19–224)	406 (117–908)	100 (43–168)	14 (9–79)	<.001
Peak > 50 ng/L	35 (66.0)	17 (100.0)	12 (67.0)	6 (33.0)	<.001
DC	16 (6–41)	23 (16–57)	16 (10–40)	6 (4–9)	.001
DC > 50 ng/L	9 (18.0)	5 (31.0)	2 (12.0)	2 (12.0)	.268
Medications administered					
IVIG	43 (78.0)	17 (94.0)	14 (78.0)	12 (67.0)	.114
Aspirin	42 (78.0)	16 (89.0)	14 (78.0)	12 (67.0)	.276
Remdesivir	7 (13.0)	6 (33.0)	1 (6.0)	0 (0.0)	.006
Infliximab	13 (24.0)	8 (44.0)	1 (6.0)	4 (22.0)	.024
Steroids	12 (22.0)	7 (39.0)	5 (28.0)	0 (0.0)	.015
Enoxaparin	5 (9.0)	4 (22.0)	1 (6.0)	0 (0.0)	.057
Antibiotics	42 (78.0)	18 (100.0)	16 (89.0)	8 (44.0)	<.001

(*Continued*)

Table 1 (*Continued*)

	Total cohort	Lowest tertile: LVA4LS < 13.0%	Middle tertile: 13% < LVA4LS < 18.5%	Highest tertile: LVA4LS > 18.5%	*P*
Hospital course					
ICU admission	35 (65.0)	18 (100.0)	12 (75.0)	5 (28.0)	<.001
Mechanical ventilator support	11 (20.0)	8 (44.0)	3 (17.0)	0 (0.0)	.004
Ventilator duration, d‡	5 (4–9)	5.5 (5– 9)	5 (4–5)	0 (0.0)	.163
Inotropic support	23 (43.0)	14 (78.0)	8 (44.0)	1 (6.0)	<.001
ECMO support	4 (7.0)	4 (22.0)	0 (0.0)	0 (0.0)	.013
ECMO length, d‡	4.5 (3–6)	4.5 (3–6)	0 (0–0)	0 (0–0)	NA
LOS, d					
ICU	2 (0–7)	7 (4–10)	2 (0–3)	0 (0–2)	<.001
Total hospital course	5 (3–9)	10 (7–14)	4 (3–6)	4 (3–5)	<.001

Data are expressed as mean ± SD, number (percentage), or median (interquartile range) except as indicated.
BMI, Body mass index; *DC*, discharge; *hs-Tn*, high-sensitivity troponin; *IgG*, immunoglobulin G; *IVIG*, intravenous immunoglobulin; *NA*, not applicable; *PCR*, polymerase chain reaction.
*Of 16 patients with comorbidities, 12 had asthma, one had type 1 diabetes, one had propionic academia, one had proximal renal tubular acidosis with normal kidney function, and one had recently repaired pyloric stenosis.
†Acute myocardial injury, per the Beckman Coulter high-sensitivity cardiac troponin I assay, is defined as a value of >50 ng/L.
‡Median (range).

Wilk test. Nominal variables were evaluated using the χ^2 test. For normally distributed data, analysis of variance was used to determine statistical significance; for nonparametric data, the Kruskal-Wallis test was used. For clinical parameters that were not normally distributed, median and interquartile ranges were generally reported.

The cohort data were divided into three groups of tertiles on the basis of LVA4LS. Similarly, analysis was also performed by dividing cohort into tertiles on the basis of LVEF and LVGLS. Differences in demographic parameters, laboratory values, clinical course, and outcomes among the tertiles were compared for significant differences. The tertiles were used for descriptive purposes for the entire cohort. For receiver operating characteristic (ROC) curve and regression analyses, LVEF, LVA4LS, and LVGLS were used as continuous variables for correlation.

Univariate linear and logistic regressions, as well as multivariate linear and logistic regressions, were used to determine independent predictors of adverse clinical course and cardiac sequelae. Echocardiographic and laboratory parameters that were found to be correlated in univariate analysis were used in the multivariate models. Given the significant correlation between LVA4LS and LVGLS, LVA4LS was used in the multivariate regression analysis for need for ICU and LOS.

To determine the optimal cutoff value of prognostic LV functional parameters for detecting increased requirement of intensive care during admission and cardiac sequelae at a median of 10 weeks, ROC curves were used. Reproducibility was assessed using intraclass correlation coefficient analysis and coefficients of variation for inter- and intraobserver reliability. SPSS version 26 (IBM, Armonk, NY) was used to perform the statistical analyses, and graphs were created using Stata version 15.1 (StataCorp, College Station, TX). *P* values of $< .05$ were considered to indicate statistical significance.

RESULTS

Patient Characteristics

Table 1 details the demographic, laboratory, and clinical characteristics of our cohort. The cohort consisted of 54 patients with a mean age of 6.8 ± 4.4 years, of whom 46% ($n = 25$) were male and 56% ($n = 30$) were African American. Of 54 patients, 46 had positive serologic or polymerase chain reaction results for SARS-CoV-2, with eight patients having epidemiologic links to COVID-19 cases.

Clinical Presentation and Course

Presenting symptoms included persistent fever (>38.5°C) of acute onset and variable duration accompanied with generalized weakness in 53 of 54 patients. Eight patients (15%) had skin rash, cheilitis, conjunctivitis, cervical adenopathy, and erythema of hands and/or feet, meeting the criteria for typical Kawasaki disease.[18]

Significant hypotension (systolic blood pressure ≤ fifth percentile for age, gender, and height) with depressed LV systolic function, persistent tachycardia, and signs of low cardiac output was present on admission or developed early during the admission in 28 patients (52%).[22] Three patients had normal LVEF and hypotension due to distributive shock. Twenty-three patients required intravenous inotropic support, with 11 needing mechanical ventilation. Acute LV dysfunction with "myocardial stunning" and fulminant heart failure developed in four patients, requiring VA ECMO support. Indications for initiation of ECMO were cardiogenic shock ($n = 2$), cardiac arrest ($n = 1$), or life-threatening arrhythmia refractory to medical management ($n = 1$).

Mild to moderate mitral regurgitation was present in 30% and mild tricuspid regurgitation in 30% of patients early in clinical course (Table 2). Mitral regurgitation resolved by 10-week follow-up. Mild tricuspid regurgitation was persistent in two patients at 10-week follow-up. The available tricuspid regurgitation gradient was normal in these patients. Small pericardial effusions were present in 14 patients (25%) on admission or early in the clinical course and none at 10-week follow-up.

Six patients (11.0%) had abnormal coronary artery measurements of one or more segments (*Z* score = 2.07–4.2) on initial inpatient echocardiography. Two of those patients fulfilled the clinical criteria for typical Kawasaki disease. Coronary artery dilation was diffuse and did not have an aneurysmal appearance. At the 3- and 10-

Table 2 Comparison of echocardiographic data among the three LVA4LS tertile groups

Parameter	Total cohort	Lowest tertile: LVA4LS < 13.0%	Middle tertile 13.0% < LVA4LS < 18.5%	Highest tertile: LVA4LS > 18.5%	*P*
Patients in group					
Initial	54	18	18	18	NA
Predischarge*	31	17	11	3	NA
3-wk follow-up	43	16	14	13	NA
10-wk follow-up	36	14	11	11	NA
Days from admission to initial echocardiography	0 (0–2)	1 (0–2)	0 (0–2)	0 (0–1)	NA
Days from admission to predischarge echocardiography	5 (3–8)	7 (4–9)	4 (2–6)	5 (4–5)	NA
Days from admission to 3-wk follow-up echocardiography	22 (19–26)	25 (21–27)	23 (20–27)	19 (17–21)	NA
Days from admission to 10-week follow-up echocardiography	64 (54–75)	65 (58–73)	62 (50–81)	64 (55–65)	NA
LVA4LS, %					
Initial	16.2 (11.2–19.4)	10.1 (8.0–11.2)	16.2 (15.0–16.6)	20.3 (19.4–22.0)	<.001
Predischarge	17.1 (15.2–20.0)	15.8 (12.6–19.9)	19.4 (16.8–19.8)	18.6 (17.7–21.2)	.09
3-wk follow-up	19.9 (18.9–22.1)	17.7 (17.0–19.5)	20.1 (19.7–20.7)	21.3 (20.1–23.9)	.002
10-wk follow-up	20.5 (19.7–22.0)	18.5 (16.4–20.0)	21.3 (20.5–22.2)	20.9 (20.6–22.4)	.013
LVA4LS < 19%					
Initial	41	18	18	5	<.001
Predischarge	20	12	6	2	.685
3-wk follow-up	18	12	3	3	.003
10-wk follow-up	7	7	0	0	<.001
LVCS, %					
Initial	16.3 (13.5–21.6)	13.6 (8.2–15.6)	16.3 (13.5–19.2)	22.8 (20.9–25.1)	.023
Predischarge	21.3 (18.6–23.7)	19.1 (16.9–22.0)	22.9 (21.3–26.3)	22.1 (20.3–22.9)	.136
3-wk follow-up	21.6 (20.7–23.4)	21.2 (19.8–23.6)	21.9 (21.0–22.5)	22.4 (20.6–24.8)	.580
10-wk follow-up	23.3 (21.1–26.3)	21.7 (20.1–25.1)	23.4 (22.7–24.8)	23.9 (21.7–27.2)	.130
LVEF, %					
Initial	54.2 ± 14.1%	43.9 ± 14.5%	52.5 ± 11.1%	66.2 ± 4.4%	<.001
Predischarge	62.2 ± 8.0%	61.6 ± 8.2%	61.0 ± 6.4%	69.0 ± 12.1%	.316
3-wk follow-up	63.7 ± 5.8%	62.7 ± 6.7%	63.6 ± 5.2%	64.9 ± 5.3%	.605
10-wk follow-up	63.6 ± 4.6%	62.6 ± 4.6%	65.3 ± 3.9%	63.3 ± 5.3%	.343
LVEF < 55%					
Initial	23	13	10	0	<.001
Predischarge	6	2	2	0	.631
3-wk follow-up	2	2	0	0	.170
10-wk follow-up	1	1	0	0	.446
TAPSE, mm					
Initial	1.7 (1.4–1.9)	1.7 (1.5–1.9)	1.6 (1.4–1.9)	1.9 (1.6–2.0)	.459
Predischarge	2.0 (1.9–2.0)	2 (1.9–2.1)	2 (2.0–2.0)	1.7 (1.4–1.9)	.174
3-wk follow-up	2.0 (1.9–2.1)	2.1 (1.9–2.2)	2.0 (1.9–2.1)	1.9 (1.7–2.1)	.139
10-wk follow-up	2.0 (1.9–2.1)	2.1 (2–2.2)	2.0 (1.9–2.0)	2.0 (1.9–2.1)	.099
Abnormal RV function					

(*Continued*)

Table 2 (*Continued*)

Parameter	Total cohort	Lowest tertile: LVA4LS < 13.0%	Middle tertile 13.0% < LVA4LS < 18.5%	Highest tertile: LVA4LS > 18.5%	*P*
Initial	10	9	1	0	<.001
Predischarge	0	0	0	0	NA
3-wk follow-up	0	0	0	0	NA
10-wk follow-up	0	0	0	0	NA
Coronary dilation					
Initial	6	4	1	1	.224
Predischarge	5	2	3	0	.401
3-wk follow-up	1	1	0	0	.472
10-wk follow-up	1	1	0	0	.446
Mitral valve regurgitation					
Initial	16	8	7	1	.022
Predischarge	8	5	3	0	.557
3-wk follow-up	0	0	0	0	NA
10-wk follow-up	0	0	0	0	NA
Tricuspid valve regurgitation					
Initial	16	10	4	2	.010
Predischarge	11	7	4	0	.388
3-wk follow-up	3	2	1	0	.422
10-wk follow-up	2	1	1	0	.614
Pericardial effusion					
Initial	14	5	6	3	.509
Predischarge	13	10	3	0	.077
3-wk follow-up	1	1	0	0	.422
10-wk follow-up	0	0	0	0	NA

Data are expressed as number, median (interquartile range), or mean ± SD.
TAPSE, Tricuspid annular plane systolic excursion.
*Predischarge echocardiography was performed if previous echocardiograms showed reduced cardiac function or if there was a clinical concern requiring echocardiography.

week follow-up visits, only one patient had abnormal coronary artery measurement (*Z* score = 2.36).

Laboratory Data

All patients had elevated C-reaction protein (Table 1). Significantly elevated high-sensitivity troponin I (>50 ng/L) as evidence of myocardial inflammation with myocardial injury was present in 35 of 54 patients (64%).

Treatment

The majority of patients received first-line treatment with intravenous immunoglobulin (78%) and aspirin (78%). On the basis of associated comorbidities, high-risk patients received remdesivir (13%). Those with persistent severe inflammatory state received infliximab (24%) and corticosteroids (22%). A subset of patients (n = 7 [13%]) admitted to the general pediatric floor had decreased myocardial strain but did not have early institution of anti-inflammatory or immunomodulation (intravenous immunoglobulin) treatment. Their clinical course deteriorated, requiring intensive care management and later institution of immunomodulation (intravenous immunoglobulin) treatment. In the later days of the pandemic, patients with similarly affected myocardial strain received early anti-inflammatory and/or immunomodulation therapy, leading to favorable clinical courses.

Echocardiographic Characteristics of Clinical Course

LV Function: Deformational Measures. For clarity we report the absolute values of all strain measures in our study. The means of LVA4LS and LVGLS of age- and gender-matched normal control subjects were similar to values reported in a meta-analysis among children (Supplemental Table 3).[23]

On the basis of data from our normal cohort, LVGLS and LVA4LS of <19.0% and LVCS of <20% were defined as abnormal, which were lower than about 2 SDs from the mean strain value of the normal control subjects (Supplemental Table 3). Compared with normal control subjects, patients with MIS-C had overall a significantly decreased median LVGLS of 15.1%, LVA4LS of 16.2%, and LVCS of 16.3% ($P < .01$) at initial echocardiography (Table 2, Figures 2 and 3). Patients were divided into tertiles on the basis of LVA4LS, with the lowest tertile including patients with LVA4LS < 13%, the middle tertile including patients with LVA4LS between 13% and 18.5%, and the highest tertile including patients with LVA4LS > 18.5%.

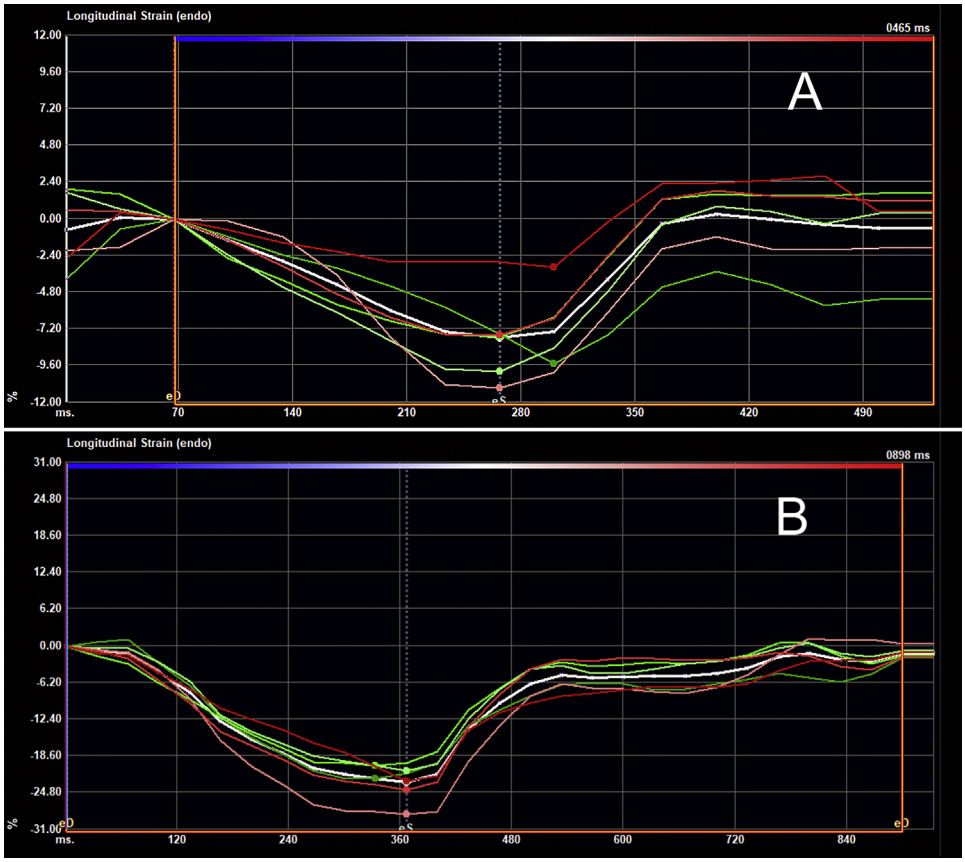

Figure 2 **(A)** Individual longitudinal strain parameters for a single patient with MIS-C with abnormal strain. **(B)** Longitudinal strain in a normal control subject. In both **(A)** and **(B)**, each *colored line* represents one LV segment. The *dots* represent the peak longitudinal ventricular strain for each segment. In **(A)**, the segments reach peak strain at different times, suggesting dyssynchrony. This patient, who belonged to the lowest tertile, had LV peak longitudinal strain of −9.0%, which is severely decreased in comparison with the normal control subject, whose strain was −23.0% **(B)**.

As seen in Table 1, compared with patients in the highest tertile, those in the lowest tertile were older and were more likely to have elevated initial and peak C-reactive protein and high-sensitivity troponin I (Figure 4; $P < .05$). The lowest tertile also had an increased percentage of hypotensive presentation and cardiogenic shock, increased need for and longer duration of invasive mechanical ventilation and inotropic support, increased need for ICU admission, and longer LOS ($P < .05$ for all parameters). All four VA ECMO patients were in the lowest tertile.

Overall findings of clinical course were similar when the patients were divided into tertiles on the basis of LVGLS (Supplemental Tables 4 and 5). Dyssynchrony (maximum opposing wall motion delay > 67 msec) was present in 11 patients (20%) at initial echocardiography. All patients with dyssynchrony required ICU management but had no hemodynamically significant arrhythmias.

LV Function: Conventional Measures. For the entire cohort, the median ± SD LVEF was 54.2 ± 14.1%. Abnormal LVEF, defined as <55%, was present in 23 patients (42%) at initial echocardiography.[24] Differences in clinical parameters and levels of biomarkers among the three tertiles were statistically significant (Supplemental Table 6).

RV Function. Table 2 demonstrates measurements of RV function. The average tricuspid annular plane systolic excursion was within the normal range for the entire cohort compared with age-matched published normative data,[25] with no statistically significant difference among the tertiles. RV function by visual estimation was abnormal in 10 patients (19%). These patients with abnormal RV function also had significant LV dysfunction secondary to myocardial injury from severe inflammatory response to COVID-19.

Echocardiographic Indicators of Clinical Course

Table 3 shows the results of the univariate binary logistic and linear regression analysis. LVA4LS, LVGLS, and LVEF at initial echocardiography and initial high-sensitivity troponin I correlated with the need for ICU admission, as well as ICU and hospital LOS. The *R* values were higher for LVA4LS than for the other independent variables.

Table 4 demonstrates the results of the multivariate binary logistic and linear regression. Initial LVA4LS was associated with the need for ICU admission, while LVEF and initial troponin were not. Initial LVA4LS correlated with both hospital and ICU LOS.

LVA4LS, LVGLS, LVEF, and initial troponin were entered into ROC analysis to estimate the probability of ICU admission (Figure 5). Each of these parameters was statistically significantly associated with ICU admission ($P < .05$); the ROC curves of LVA4LS and LVGLS had higher areas under the curves than troponin and LVEF curves.

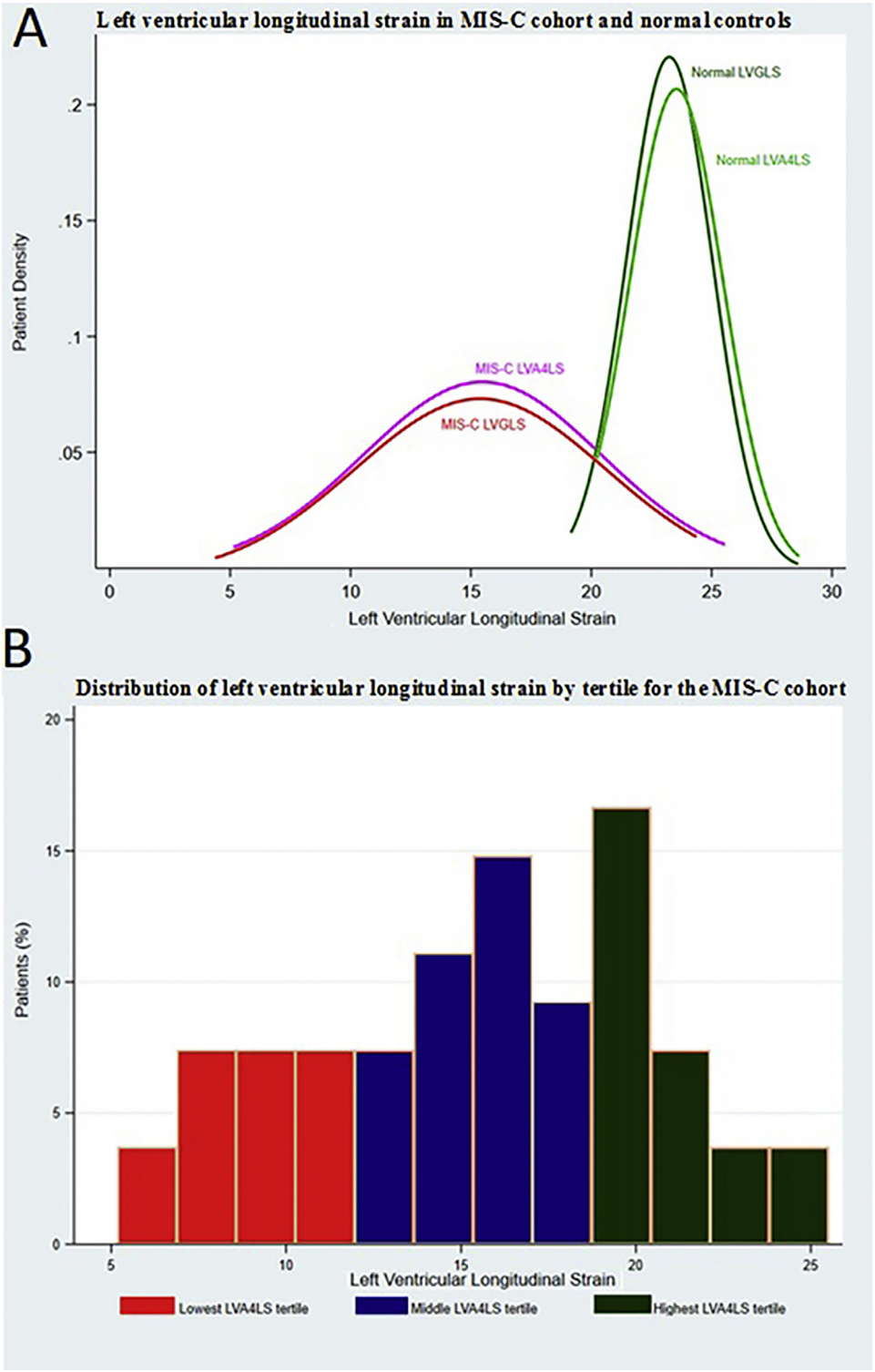

Figure 3 **(A)** Distribution of LVA4LS and LVGLS in patients with MIS-C (*pink* and *red lines*, respectively) compared with normal control subjects (*green lines*; $P < .01$). Overall, the normal cohort tended to have higher strain than the MIS-C cohort. LVA4LS and LVGLS were similar in the MIS-C cohort. **(B)** Distribution of LVA4LS tertile for the MIS-C cohort. *Red* represents the lowest tertile, *blue* represents the middle tertile, and *green* represents the highest tertile.

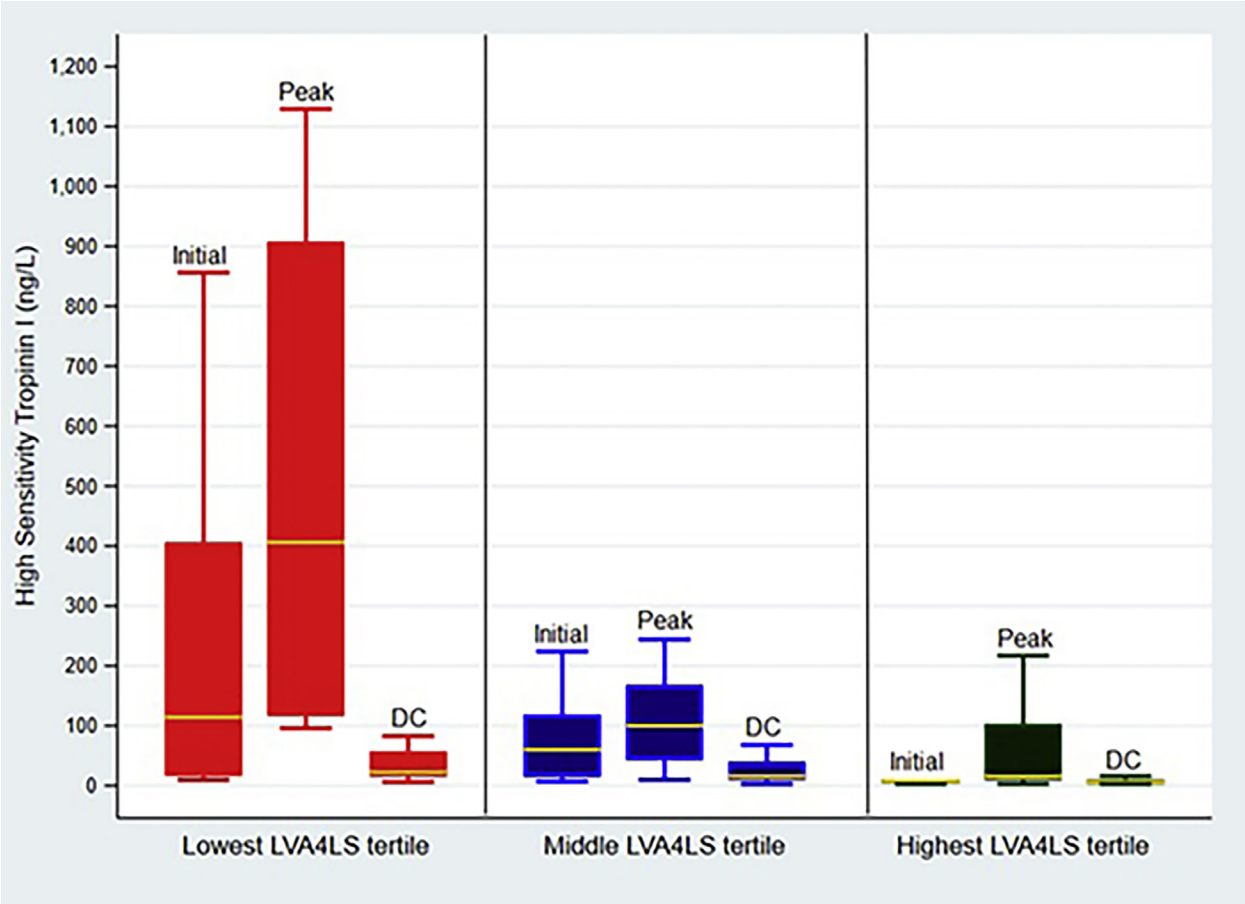

Figure 4 Box-and-whisker plots for each of the tertiles, with the median value signified by the *yellow line*. Initial and peak troponin levels were higher for the lowest tertile, with median troponin levels normalizing (<50 ng/L) at discharge (DC) for all tertiles.

Initial LVA4LS of <16.2% (median value of the MIS-C cohort) indicated the need for ICU admission with 74% sensitivity, 95% specificity, and 96% positive predictive value. Initial LVGLS < 15.2% (median value of the MIS-C cohort) indicated the need for ICU admission with 73% sensitivity, 100% specificity, and 100% positive predictive value.

Echocardiographic Indicators of Cardiac Outcomes

The median hospital LOS was 5 days for the entire cohort. VA ECMO was successfully weaned and removed in all four patients in a median of 4.5 days. There was no mortality in our cohort, and all patients were discharged from the hospital. The median high-sensitivity troponin level normalized before discharge in all tertiles (Figure 4). Of 54 patients, 43 (79%) were seen for follow-up at a median of 3 weeks and 36 (66%) at a median of 10 weeks after diagnosis to date. All patients were asymptomatic with normal clinical examination at follow-up. All patients underwent echocardiography at follow-up.

LVEF normalized at 10-week follow-up in all but one patient, who had an LVEF of 54% (Supplemental Table 7). Although LVEF normalized at outpatient follow-up, seven of 36 patients who presented for follow-up to date (19%) continued to have abnormal LVA4LS (Table 2, Supplemental Figure 1). The patients with abnormal LVA4LS at 10-week follow-up were all in the lowest tertile at initial presentation.

Of the 39 patients who had available LVGLS at initial presentation, 25 presented for 10-week follow-up to date, of whom six (24%) had abnormal LVGLS (Supplemental Table 5). Three of these patients had additional follow-up of median 6 months, two of whom continue to have subclinical decreased LVA4LS (11.3% and 15.9%) and LVGLS (12.3% and 17.0%).

LVA4LS ≤ 16.2% at initial echocardiography was associated with abnormal LVA4LS at 10-week follow-up, with sensitivity of 100% and specificity of 66% ($P < .01$). LVGLS ≤ 15.2% at initial echocardiography also had sensitivity of 100%, specificity of 74% ($P < .01$), and negative predictive value of 100% with regard to abnormal LVGLS at 10-week follow-up. Conversely, all children with normal LVGLS and LVA4LS at initial echocardiography continued to have normal LV systolic function at median 10-week follow-up.

Initial LVA4LS and initial troponin were associated with LVA4LS at 10-week follow-up (Table 4). Similarly, LVGLS at initial echocardiography and initial troponin were associated with LVGLS at 10-week follow-up. Initial LVEF did not predict LVEF at 10-week median follow-up.

Synchrony improved over time, but four patients (7%) still exhibited persistent dyssynchrony at 10-week follow-up. The overall number was too small to formally analyze for adverse outcomes. Similarly, LVCS improved over time but remained abnormal in two patients at 10-week follow-up. RV systolic function was normal at discharge for all patients and continued to be normal at median 10-week follow-up (Table 2).

Table 3 Univariate regression models

Dependent variable*	Independent variable†	Odds ratio/correlation coefficient (95% CI)	*P*	*R*
Univariate binary logistic regression				
ICU admission	LVA4LS from initial echocardiography	0.602 (0.454 to 0.797)	<.001	0.785
	LVGLS from initial echocardiography	0.658 (0.503 to 0.860)	.002	0.716
	LVEF from initial echocardiography	0.000003 (0.000001 to 0.005)	.001	0.646
	Initial high-sensitivity troponin	1.015 (1.003 to 1.028)	.018	0.559
Univariate linear regression				
ICU LOS	LVA4LS from initial echocardiography	−0.633 (−0.845 to −0.422)	<.001	0.641
	LVGLS from initial echocardiography	−0.605 (−0.869 to −0.341)	<.001	0.607
	LVEF from initial echocardiography	−0.160 (−0.246 to −0.074)	<.001	0.459
	Initial high-sensitivity troponin	0.002 (0.0001 to 0.003)	.036	0.288
Hospital LOS	LVA4LS from initial echocardiography	−0.634 (−0.873 to −0.396)	<.001	0.599
	LVGLS from initial echocardiography	−0.620 (−0.909 to −0.332)	<.001	0.588
	LVEF from initial echocardiography	−0.162 (−0.255 to −0.0.68)	.001	0.438
	Initial high-sensitivity troponin	0.002 (−0.0001 to 0.003)	.068	0.255
LVA4LS at 10-wk follow-up	LVA4LS from initial echocardiography	0.282 (0.103 to 0.462)	.003	0.481
	Initial high-sensitivity troponin	−0.002 (−0.003 to −0.001)	.001	0.530
LVGLS at 10-wk follow-up	LVGLS from initial echocardiography	0.346 (0.192 to 0.501)	<.001	0.695
	Initial high-sensitivity troponin	−0.002 (−0.002 to −0.001)	<.001	0.614
LVEF at 10-wk follow-up	LVEF from initial echocardiography	0.063 (−0.044 to 0.170)	.241	0.201
	Initial high-sensitivity troponin	−0.002 (−0.003 to −0.00027)	.023	0.378

*ICU admission was a categorical variable, while the other variables were continuous.
†All independent variables were continuous variables.

Reproducibility

The intraclass correlation coefficient for interobserver variability for LVA4LS was 0.979 (95% CI, 0.922–0.995; $f = 51.612$; $P < .001$) and for LVCS was 0.987 (95% CI, 0.931–0.997; $f = 102.930$; $P < .001$), indicating minimal interobserver variability. The intraclass correlation coefficient for intraobserver variability for LVA4LS was 0.994 (95% CI, 0.986–0.998; $f = 177$; $P < .001$), indicating minimal intraobserver variability. The coefficient of variation was similar between both observers (27% and 26%, respectively) and for repeated measurements for a single observer (26% and 28%).

DISCUSSION

In this longitudinal observational study with the largest cohort of children with MIS-C from a single center to date, we comprehensively evaluated the prognostic value of LV function using conventional echocardiography and 2D STE. Patients with the greatest degree of LV longitudinal strain impairment at the initial stage of MIS-C were more likely to have a higher incidence of hypotension, acute myocardial injury, inotropic requirement, cardiogenic shock, requirement for VA ECMO support, and longer hospital LOS. LVA4LS and LVGLS

Table 4 Multivariate regression models

Dependent variable*	Independent variables†	Odds ratio/correlation coefficient (95% CI)	*P*	*R*
Multivariate binary logistic regression				
ICU admission	LVA4LS from initial echocardiography	0.683 (0.477 to 0.980)	.038	0.785
	LVEF from initial echocardiography	0.056 (0.000 to 17,118)	.655	
	Initial hs-Tn	1.012 (0.994 to 1.023)	.233	
Multivariate linear regression				
ICU LOS	LVA4LS from initial echocardiography	−0.662 (−0.992 to −0.331)	.001	0.645
	LVEF from initial echocardiography	0.020 (−0.102 to 0.142)	.744	
	Initial hs-Tn	0.0003 (−0.001 to 0.002)	.720	
Hospital LOS	LVA4LS from initial echocardiography	−0.639 (−0.995 to −0.282)	.001	0.599
	LVEF from initial echocardiography	−0.002 (−0.122 to 0.126)	.972	
LVA4LS at 10-wk follow-up	LVA4LS from initial echocardiography	0.195 (0.001 to 0.388)	.040	0.598
	Initial hs-Tn	−0.0013 (−0.0022 to −0.0002)	.020	
LVGLS at 10-wk follow-up	LVGLS from initial echocardiography	0.240 (0.088 to 0.393)	.004	0.795
	Initial hs-Tn	−0.001 (−0.0019 to −0.0001)	.007	

hs-Tn, high-sensitivity troponin.
*ICU admission was a categorical variable, while the other variables were continuous.
†All independent variables were continuous variables.

were able to indicate the risk for subclinical LV dysfunction persistent up to 10-week follow-up after resolution of acute illness in a subset of patients with MIS-C, independently of other echocardiographic parameters and inflammatory biomarkers. Therefore, a comprehensive assessment of LV strain may be essential for risk stratification in patients with MIS-C at hospital admission for acute adverse clinical course; patients with initial abnormal LV strain may benefit from early institution of specific immunomodulatory and/or anti-inflammatory therapy to favorably influence their clinical courses and outcomes.

Echocardiographic Measures of LV Function as Indicators of Clinical Course in MIS-C

As noted in previous studies, cardiovascular involvement is prevalent in MIS-C.[6,7,9] Reports have characterized cardiovascular involvement in MIS-C during the inpatient phase, noting elevated troponin levels and decreased LVEF.[26,27] To date, there are no studies that have assessed ventricular strain beyond the acute inpatient phase in MIS-C.

In our cohort, the clinical presentation and course of MIS-C were similar to those reported from Western Europe and some regions of the United States, with difference in the acuity of clinical course and novel findings of postinfectious persistent subclinical LV dysfunction up to a median of 10 weeks in children with a relative paucity of preexisting cardiovascular conditions.[3,4,7,9] We observed acute heart failure with ventricular dysfunction in the majority of patients and cardiogenic shock in a subset of patients requiring VA ECMO support (9%) in the course of illness. Elevated high-sensitivity troponin I above the normal threshold (greater than the 99th percentile upper reference limit of 50 ng/L) and significant LV dysfunction by strain imaging were indicative of myocardial injury and adverse acute clinical course in a majority of children with MIS-C in our cohort. Detection of decreased myocardial strain at presentation influenced the early initiation of anti-inflammatory and immunomodulatory therapy in the later stages of the pandemic.

It is significant to recognize that patients with MIS-C are at higher risk for adverse clinical course and potential poor outcomes and might benefit from assessment of prognostic risk factors at the onset of illness to help institute vigilant monitoring and early therapeutic measures to avert such course. Our study revealed important prognostic value of significant LV longitudinal strain (LVA4LS and LVGLS) impairment at early stage of MIS-C in patients who are likely to have severe hemodynamic instability and clinical deterioration that was superior to conventional LV systolic functional index. Correlations of abnormal LVGLS and LVA4LS with cardiac inflammatory biomarkers, such as high-sensitivity troponin I in our and other studies, highlight the presence of myocarditis in patients with MIS-C and suggest the use of LVGLS and LVA4LS in risk stratification of clinical course.[10,26-28]

RV Function in MIS-C

A subset of our patients developed reduced RV function in the acute phase; however, unlike many adults with COVD-19, these patients had concomitant significantly decreased LV systolic function due to myocardial damage.[11] Each of these patients had complete recovery of RV function before discharge, with no persistent dysfunction at

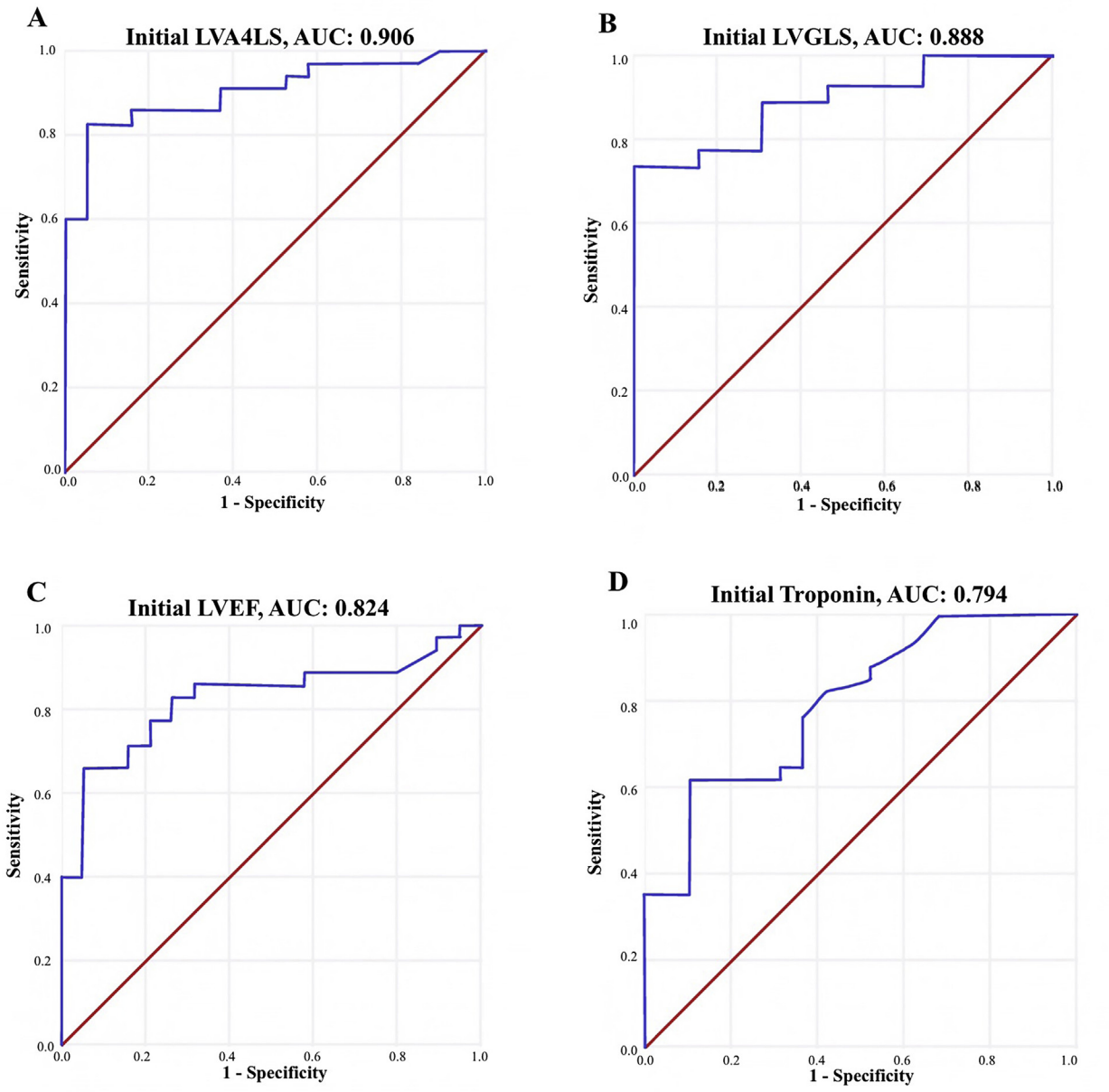

Figure 5 **(A)** LVA4LS at initial echocardiography, area under the curve (AUC) = 0.906. **(B)** LVGLS at initial echocardiography, AUC = 0.888. **(C)** LVEF at initial echocardiography, AUC = 0.824. **(D)** Initial troponin, AUC = 0.794. $P < .05$ for all panels.

most recent follow-up. We speculate that the right ventricle in our patient cohort did not have increased hemodynamic overload secondary to lung pathology such as acute respiratory distress syndrome or pneumonia, unlike those in adults with COVID-19.

Echocardiographic Measures of Cardiac Function as Indicators of Cardiac Sequelae in MIS-C

Our study is the first, to our knowledge, to report persistent subclinical cardiac dysfunction at 10-week median follow-up in ≥19% of patients who had MIS-C. A previous study in children with MIS-C showed that a myocarditis-like picture may remain subtle and subclinical even with normal LVEF in early convalescence but may have distinct dysfunction in systolic and diastolic deformational parameters up to 8 days after diagnosis.[29] In our cohort, the severity of LVA4LS and LVGLS impairment at initial presentation indicated the post-illness cardiac sequelae. MIS-C patients who had LVA4LS of >16.2% at initial echocardiography had normal LVA4LS at 10-week follow-up, with a negative predictive value of 100%. LVA4LS of ≤13.0% at initial presentation may indicate incomplete recovery of LV systolic function in the short term. Although clinically asymptomatic, persistence of subclinical cardiac dysfunction in a subset of patients at median 10-week follow-up, and persisting up to 6 months in a smaller subset of patients, in our cohort raises the concern for persistent myocardial injury, which warrants long-term follow-up.

Our follow-up data in these patients provides support for the recommendations by the American Academy of Pediatrics that if a

patient had a severe presentation of MIS-C, he or she should be referred for cardiac evaluation before returning to sports.[30]

Although performing 2D STE for all hospitalized patients with MIS-C may be challenging, our study suggests that specifically focused cardiac ultrasound with 2D STE for LV function assessments in these patients may help in risk stratification and treatment initiation. Additionally, LVA4LS was found to correlate well with LVGLS and by itself was found to be useful in predicting clinical course and cardiac outcome.

Limitations

A limitation of our study is that it was a single-center observational study with a relatively small number of patients, evaluating short-term outcomes, and therefore has limited generalizability. However, in the context of MIS-C, this sample size may be quite significant. The lack of prospective independent validation may be a limitation for the use of our sensitivity and specificity cutoff values for the general population.

Additionally, not all of our patients have yet followed up in the clinic for repeat echocardiography, which limited our analysis at outpatient follow-up. Although LVGLS is considered a standard marker for evaluation of cardiac function, because of challenging clinical conditions, not all patients had echocardiographic views obtained to perform LVGLS analysis at initial presentation. Similarly, we were not able to obtain all parameters of LV diastolic dysfunction, for the same reason. We were unable to assess differences in clinical management and their potential effects on clinical course and outcome.

Additionally, cardiac MRI was not performed during hospitalization because of unstable clinical condition and risk for contamination of the MRI area. We intend to use cardiac MRI in the future to evaluate cardiac function in patients with persistently abnormal LVLS to discern long-term cardiac well-being. For our regression analysis, we did not use brain natriuretic peptide or other markers such as D-dimer, as these were not routinely obtained in all of our patients.

CONCLUSION

Children with MIS-C due to COVID-19 can develop life-threatening cardiac decompensation. Our findings demonstrate that in children with MIS-C, impaired LVGLS and LVA4LS at initial presentation are independent indicators of a higher incidence of acute adverse clinical course and risk for persistent subclinical LV dysfunction at median 10-week follow-up. Consequently, LV longitudinal strain may be of prognostic value in risk stratification for need of intensive care therapy and for early therapeutic intervention.

Of our cohort, ≥19% continued to have abnormal LVA4LS and LVGLS at median 10-week follow-up, highlighting that these patients can continue to have subclinical myocardial dysfunction. Patients with significantly abnormal strain at presentation (LVA4LS < 13.0%) seemed to be at highest risk for having abnormal strain at 10-week follow-up. This group of patients, although clinically asymptomatic at follow-up, warrant continued monitoring to ensure that they have no long-term cardiac sequelae. This warrants further multicenter studies to assess if any of these subclinical changes may have long-term effects.

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