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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 morphology 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
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. The Centers for Disease Control and Prevention has defined this severe presentation as multisystem inflammatory syndrome in children (MIS-C). Patients with MIS-C manifest with persistent fever, signs of widespread inflammation, and multisystem organ involvement. 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). 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.

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. 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. 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. 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). 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. 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.

**Transesophageal Echocardiography.** Echocardiograms (Philips iE33; Philips Medical Systems, Andover, MA) were obtained by experienced sonographers according to American Society of Echocardiography guidelines. All echocardiographic data, including LV strain, LV ejection fraction (LVEF), tricuspid annular plane systolic excursion, coronary artery measurements, RV function, and valvular...
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-
Table 1  Comparison of patient characteristics, presentation, and course according to the LVA4LS tertiles

| Parameter                          | Total cohort (N = 54) | Lowest tertile: LVA4LS < 13.0% (n = 18) | Middle tertile: 13% < LVA4LS < 18.5% (n = 18) | Highest tertile: LVA4LS > 18.5% (n = 18) | P       |
|------------------------------------|-----------------------|------------------------------------------|---------------------------------------------|------------------------------------------|---------|
| 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/m²                         | 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)

| Hospital course | Total cohort | Lowest tertile: LVA4LS < 13.0% | Middle tertile: 13% < LVA4LS < 18.5% | Highest tertile: LVA4LS > 18.5% | P |
|-----------------|--------------|-------------------------------|-----------------------------------|-------------------------------|---|
| ICU admission   | 35 (65.0)    | 18 (100.0)                    | 12 (75.0)                         | 5 (28.0)                      | <.001 |
| Mechanical vent. | 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 I; 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).

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 ± 5.7%                         | 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  |

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

**Laboratory Data**

All patients had elevated C-reactive 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 [113%]) 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).

On the basis of data from our normal cohort, LVA4LS and LVGLS 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%.
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. 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, 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.
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 dysynchrony 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).
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 3 Univariate regression models |
|-------------------------------------|
| **Dependent variable**<sup>*</sup> | **Independent variable**<sup>†</sup> | **Odds ratio/correlation coefficient**<sup>(95% CI)</sup> | **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 −0.068) | .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 |

<sup>*ICU admission was a categorical variable, while the other variables were continuous.</sup>

<sup>†All independent variables were continuous variables.</sup>
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. Reports have characterized cardiovascular involvement in MIS-C during the inpatient phase, noting elevated troponin levels and decreased LVEF. 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. 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.

### Table 4: Multivariate regression models

| Dependent variable | Independent variables | Odds ratio/correlation coefficient (95% CI) | P  | R   |
|-------------------|-----------------------|--------------------------------------------|----|-----|
| 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 |     |
| 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 |     |
|                   | Initial hs-Tn                 | 0.0013 (−0.002 to −0.0002) | .020 |     |
| LVA4LS at 10-wk follow-up | LVA4LS from initial echocardiography | 0.195 (0.001 to 0.388) | .040 | 0.598 |
|                   | Initial hs-Tn                 | −0.001 (−0.0019 to −0.0001) | .007 |     |
| LVGLS at 10-wk follow-up | LVGLS from initial echocardiography | 0.240 (0.088 to 0.393) | .004 | 0.795 |

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

**RV Function in MIS-C**

A subset of our patients developed reduced RV function in the acute phase; however, unlike many adults with COVID-19, these patients had concomitantly significantly decreased LV systolic function due to myocardial damage. Each of these patients had complete recovery of RV function before discharge, with no persistent dysfunction at
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. In our cohort, the severity of LVA4LS and LVGLS impairment at initial presentation indicated the postillness 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 function, 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 LVGLS 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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**REFERENCES**

1. Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of COVID-19 in children in early January 2020 in Wuhan, China. N Engl J Med 2020;382:1370-1.
2. CDC COVID-19 Response Team. Coronavirus disease 2019 in children—United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422-6.
3. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334-46.
4. Kauhsik S, Aydim SL, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr 2020;224:24-9.
5. Centers for Disease Control and Prevention. Emergency preparedness and response: multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed May 13, 2021.
6. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19–associated multisystem inflammatory syndrome in children—United States, March–July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074-80.
7. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347-58.
8. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802-10.
9. Valverde I, Singh Y, Theocharis P, Chikermane A, Di Filippo S, Kucinska B, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation 2021;143:21-32.
10. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A, Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr 2021;180:307-22.
11. Li Y, Li H, Zhu S, Xie Y, Wang B, He L, et al. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. J Am Coll Cardiol Img 2020;13:2287-99.
12. Faridi KF, Hennessey KC, Shah N, Soufar A, Wang Y, Sugeng L, et al. Left ventricular systolic function and inpatient mortality in patients hospitalized with coronavirus disease 2019 (COVID-19). J Am Soc Echocardiogr 2020;33:1414-5.
13. Abou R, van der Bijl P, Bax JJ, Delgado V. Global longitudinal strain: clinical use and prognostic implications in contemporary practice. Heart 2020;106:1438-44.
14. Adamson GT, Arunamata A, Tacy TA, Silverman NH, Ma M, Maskatia SA, et al. Postoperative recovery of left ventricular function following repair of large ventricular septal defects in infants. J Am Soc Echocardiogr 2020;33:368-77.
15. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the pediatric Council of the American Society of echocardiography. J Am Soc Echocardiogr 2006;19:1413-30.
16. Margossian R, Chen S, Sleeper LA, Tani LY, Shirali G, Golding F, et al. The reproducibility and absolute values of echocardiographic measurements of left ventricular size and function in children are algorithm dependent. J Am Soc Echocardiogr 2015;28:549-58.e1.
17. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.

18. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927-99.

19. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr 2011;12:167-205.

20. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. J Am Soc Echocardiogr 2015;28:183-93.

21. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, et al. For the Pediatric Heart Network Investigators. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation 2007;116:1749.

22. Banker A, Bell C, Gupta-Malhotra M, Samuels J. Blood pressure percentile charts to identify high or low blood pressure in children. BMC Pediatr 2016;16:98.

23. Levy PT, Machefsky A, Sanchez AA, Patel MD, Rogal S, Fowler S, et al. Reference ranges of left ventricular strain measures by two-dimensional speckle-tracking echocardiography in children: a systematic review and meta-analysis. J Am Soc Echocardiogr 2016;29:209-25.

24. Margossian R, Schwartz ML, Prakash A, Wruck L, Colan SD, Atz AM, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging measurements of functional single ventricular volumes, mass, and ejection fraction (from the Pediatric Heart Network Fontan Cross-Sectional Study). Am J Cardiol 2009;104:419-28.

25. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heindl B, Gamillscheg A, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of Z score values. J Am Soc Echocardiogr 2009;22:715-9.

26. Alsaidi T, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation 2021;143:78-88.

27. Kelly MS, Valle CW, Fernandes ND, Cummings BM, Lahoud-Rahme M, Chiu JS. Multisystem inflammatory syndrome in children: cardiac biomarker profiles and echocardiographic findings in the acute and recovery phases. J Am Soc Echocardiogr 2020;33:1288-90.

28. Gaitonde M, Kelleman MS, Cox De, Border WL, Sachdeva S. COVID-19-related multisystem inflammatory syndrome in children affects left ventricular function and global strain compared with Kawasaki disease. J Am Soc Echocardiogr 2020;33:1285-7.

29. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol 2020;76:1947-61.

30. American Academy of Pediatrics. COVID-19 interim guidance: return to sports. Available at: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/covid-19-interim-guidance-return-to-sports/. Accessed May 13, 2021.