Cardiac Assessment in Children with MIS-C: Late Magnetic Resonance Imaging Features

Sema Yıldırım Arslan · Zumrut Sahbudak Bal · Selen Bayraktaroglu · Gizem Güner Ozenen · Nimet Melis Bilen · Erturk Levent · Oğuzhan Ay · Pınar Yazıcı Ozkaya · Ferda Ozkınyay · Candan Cicek · Akin Cinkooglu · Güzide Aksu · Gunes Ak · Zafer Kurugol

Received: 18 May 2022 / Accepted: 13 July 2022 / Published online: 2 August 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract
Multisystem Inflammatory Syndrome (MIS-C) is a new entity that emerges 2–4 weeks after the SARS-CoV-2 infection in children. MIS-C can affect all systems, the most severe of which is cardiac involvement. The duration of the cardiac symptoms is still uncertain and may be persistent or prolonged. The American College of Rheumatology Clinical Guidelines recommends cardiac magnetic resonance imaging (MRI) 2–6 months after the diagnosis of MIS-C in patients presenting with significant transient left ventricular (LV) dysfunction in the acute phase of illness (LV ejection fraction 50%) or persistent LV dysfunction. There are a few studies investigating cardiac MRI findings in MIS-C patients. In this study, we aimed to evaluate cardiac MRI findings, at the earliest 3 months after diagnosis, and compare these findings with the echocardiograms in children with MIS-C. A retrospective study including 34 MIS-C patients was conducted at a tertiary-level University Hospital between June 2020 and July 2021. Centers for Disease Control and Prevention criteria were used in the diagnosis of MIS-C. Cardiac MRI was performed at least 3 months after MIS-C diagnosis. The study included 17 (50%) boys and 17 (50%) girls with a mean age of 9.31 ± 4.72 years. Initial echocardiographic evaluation revealed cardiac abnormality in 13 (38.2) patients; 4 (11.8%) pericardial effusion, 4 (11.8%) left ventricular ejection fraction (LVEF) < 55%, and 5 (14.7%) coronary artery dilatation. Echocardiography showed normal LV systolic function in all patients during follow-up; coronary dilatation persisted in 2 of 5 (40%) patients at the 6th-month visit. Cardiac MRI was performed in 31 (91.2%) patients, and myocardial hyperemia was not detected in any patients (T1 relaxation time was < 1044 ms in all children). However, 9 (29%) patients’ MRI showed isolated elevated T2 levels, and 19 (61.3%) revealed at least one of the following findings: pericardial effusion, right ventricular dysfunction, or LVEF abnormality. In patients with MIS-C, a high rate of cardiac involvement, particularly pericardial effusion was determined by cardiac MRI performed at the earliest 2–6 months after diagnosis. Even if echocardiography does not reveal any abnormality in the initial phase, cardiac MRI should be suggested in MIS-C patients in the late period. This is the first study reporting cardiac MRI findings in the late period of MIS-C patients.

Keywords
MIS-C · Cardiac MRI · Echocardiography

Introduction
Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affected more than 332 million people as of January 2022 [1]. Children infected with SARS-CoV-2 appear less affected and show milder symptoms than adults [2]. However, pediatricians were faced with a new clinical syndrome, “Multisystem inflammatory syndrome in children (MIS-C),” which is similar to toxic shock and Kawasaki disease [3–5]. The post-infectious mechanisms and hyperinflammation play a role in MIS-C pathogenesis and MIS-C typically occurs 2–4 weeks after COVID-19 infection [1, 6–8]. It is unclear why only 1% of SARS-CoV-2 infected children developed MIS-C. Several studies reported a number of risk factors including overweight, asthma, ethnic origin, black or Asian, and defects in the SOCS1, XIAP, or CYBB genes for MIS-C [9, 10]. MIS-C may affect all systems; however, the most severe manifestation is cardiac involvement. At least one of the cardiac symptoms...
manifestations such as left ventricular dysfunction (LVD), shock, coronary artery dilatation (CAD) or aneurysms, valvulitis, pericardial effusion, arrhythmia, and conduction abnormalities occurs in approximately 80% of children with MIS-C [3, 5, 11–20].

Few studies demonstrated MIS-C-related ventricular dysfunction or CAD using standardized assessments. There are only five studies showing cardiac MRI findings in the early phase of MIS-C, and no studies on cardiac MRI findings in the late phase [21–25].

In this study, we aimed to determine long-term cardiac outcomes of MIS-C by cardiac MRI and compare MRI findings with echocardiographic findings.

Materials and Methods

A single-center retrospective study was conducted at a tertiary-level university hospital between June 11, 2020 and July 30, 2021. The MIS-C group consisted of 34 children. The diagnosis of MIS-C was established according to the criteria defined by the Centers for Disease Control and Prevention (CDC) in May 2020 [3, 26].

The Research Ethics Committee of Ege University Faculty of Medicine and the Ministry of Health approved the study (Ethical decision No 21-5.1 T/51).

We used a standardized form to collect the epidemiological data, clinical symptoms, and laboratory findings. Laboratory findings included whole blood count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin (Hb), platelet count (PLT), monocytes, and biochemical parameters including C-reactive protein (CRP), procalcitonin, D-dimer, fibrinogen, troponin-T, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Troponin-T levels were measured through a one-step enzyme immunoassay with a Dimension VistaVR system (Siemens, Munich, Germany). Reference ranges for conventional cardiac markers, Troponin-T and NT-proBNP, were accepted as < 14 ng/l and < 125 pg/ml, respectively. Combined nasopharyngeal and oropharyngeal swab specimens were collected in a viral transport medium, including VNat (Bioeks, Turkey). All samples were analyzed by using the Bio-spyee@ SARS CoV-2 Double Gene RT-qPCR (Bioeks, Turkey) at our Molecular Virology Laboratory. This assay amplifies and detects two targets (ORF1ab and N) of the virus with a limit of detection of 200 genomes per ml. The human gene target RNase P (RP) was measured in each sample for use in internal control. Reverse transcription-polymerase chain reaction (RT-PCR) was performed using the Rotor-Gene (Qiagen, Luxemburg). Results were considered positive if the signal was detected (Ct < 35) for RP, ORF1ab, and N genes.

Anti-Spike immunoglobulin G (IgG) and IgM antibodies were measured in serum samples using rapid lateral flow immunoassay (LFIA) (Colloidal Gold-Hotgen, Germany).

Echocardiographic data were recorded from clinical notes and electronic record systems. All patients underwent 2-dimensional mode and 2-dimensional M-mode echocardiography using a Vivid E9 system with a 3–7 MHz transducer. All transthoracic echocardiography was reviewed and performed by the same pediatric cardiologist. M-mode measurements were carried out with standard techniques following the recommendation of the American Society of Echocardiography [27]. The dimensions of the coronary arteries were expressed as Z scores by the published reference standard [28]. Coronary artery dilatation was defined as having a maximum internal diameter of ≥ 3 mm in the absolute diameter classification and a Z score of ≥ 2 in the affected segment [28]. Left ventricular (LV) dysfunction was defined as an LV ejection fraction (EF) of < 55%.

The timing of echocardiography from the onset of MIS-C disease was as follows: (1) on admission; (2) at 1 month; (3) at 2–3 months; and (4) at 4–6 months.

Cardiac MRI studies were performed with a 1.5 Tesla scanner (Amira®, Siemens Healthineers, Erlangen, Germany). Patients were scanned with the electrocardiogram (ECG)-triggered using a 16-channel surface phased array of body coils. Short and long-axis images were acquired with steady-state free precession sequence (SSFP) to assess myocardial function. Short axis STIR (short Tau inversion recovery) and T1 and T2 and postcontrast T1-weighted images were obtained. Native T1 maps were acquired using a modified Look-Locker inversion recovery sequence (MOLLI). Ten minutes after injection of 0.2 mmol/kg gadolinium contrast agent, long and short axis late gadolinium enhancement (LGE) images were acquired using phase-sensitive inversion recovery sequence (PSIR).

Image analysis was performed by two radiologists (S.B. 12 years, A.C. 4 years of experience) experienced in cardiac imaging.

Cardiac volume–function data, and myocardial T1 and T2 levels were analyzed using the software; Medis medical imaging systems-Medis Suite 2.1 (Leiden, Netherlands). Native T1 maps were evaluated on basal and midventricular slices. A region of interest was drawn on septal, anterior, inferior, and lateral walls on T1- and T2-weighted images. The average of T1 and T2 levels of these segments was used to assess the mean native global T1 and T2 levels. The mean signal intensity with the highest level from any myocardial segment was determined as the segmental maximum level. T1 relaxation time levels greater than 2044 ms were considered abnormal T1 according to Pagano et al. [29]. Myocardial edema was defined as T2 relaxation time greater than 50 ms or signal intensity ratio of the myocardium to skeletal muscle equal to or greater than 2 on T2-weighted images.
A small dose (25 mg/kg/dose) of chloral hydrate was used for children with some MIS-C requiring sedation, while deep sedation or anesthesia was not required in any patients. Cardiac MRI was performed 3 or 6 months after MIS-C diagnosis. MRI was not performed during the initial hospitalization period in any patient.

**Statistical Analysis**

Statistical analysis was performed using SPSS statistical package (Version 25 for Windows). Data were expressed as means ± SD or medians (interquartile range) for continuous variables or percentages for categorical variables. Comparisons were made using the Student’s t test for normally distributed data and the χ² test for categorical data. The Mann–Whitney U test was used to compare differences in nonparametric data. Repeated measures analyses of variance were performed to evaluate changes of all echocardiographic parameters and laboratory data assessed on admission, during hospitalization, discharge, and follow-up 1, 3, 6 month. Repeated measures analysis of variance (RM ANOVA) was performed to evaluate changes in all echocardiographic parameters and laboratory data assessed on admission, first month, third, and sixth month. Statistical significance of differences and correlations were defined p value of < 0.05.

**Results**

Seventeen (50%) boys and 17 (50%) girls, with a median age of 9.31 ± 4.72 years, were included in this study. Demographic data are shown in Table 1. MIS-C was defined according to CDC criteria in all patients. None of the patients have been vaccinated.

Seventeen patients (50%) were admitted to the intensive care unit, while 11 (32.4%) patients required respiratory support. Thirteen (38.2%) PICU admitted patients required inotropes/vasopressors; 1 (2.9%) patient required hemodi-filtration for renal failure. Mortality did not occur. Length of hospital stay ranged from 3 to 29 days. Echocardiography revealed an abnormality in 18 (52.9%) patients: mild pericardial effusion, mild mitral regurgitation, 2 (5.9%) had mild tricuspid regurgitation, 2 (5.9%) had moderate tricuspid regurgitation, and 2 (5.9%) had bilateral CAD. None of the patients developed persistent heart failure.

At the 6th month of admission, none of the patients showed mitral regurgitation or tricuspid regurgitation. Serial echocardiography findings are listed in Table 2. The right coronary artery Z score progressed from 3.34 to 5.96 and the left coronary artery from 4.97 to 5.61 in the first patient. The second patient’s left coronary artery Z score progressed from 2.81 to 3.53.

In this study, LV EF was shown to be correlated with serum NT-ProBNP levels ($r = -0.473$, $p = 0.05$), RCA size with CRP ($r = 0.997$, $p = 0.003$), and LCA size with CRP ($r = 0.971$, $p = 0.006$), and ferritin levels ($r = 0.893$.}

**Table 1** Demographic and clinical characteristics of MIS-C patients

| Patients (n:34) | Gender | | Age, years (mean ± SD) | BMI, Z score (mean ± SD) | COVID-19 IgM and/or IgG antibodies (n, %) | History of previous COVID-19 disease | Family history of COVID-19 | The age distribution, n (%) | Underlying diseases, n (%) | Signs and symptoms, n (%) |
|----------------|-------|---|--------------------|--------------------------|-------------------------------------|-------------------------------|--------------------------|---------------------------|------------------------|---------------|
|                | Female (n, %) | 17 (50) | 9.31 ± 4.72 | 0.29 ± 1.36 | 34 (100) | 3 (8.8) | 12 (35.3) | 8 (23.5) | 21 (61.8) | 5 (14.7) | - | 34 (100) | 19 (55.9) | 17 (50) | 14 (41.2) | 11 (32.2) | 24 (70.6) | 22 (64.7) | 21 (61.8) | 6 (17.6) | 4 (11.8) | 11.6 ± 5.3 | 3.6 ± 2.4 | 33 (97.1) | 27 (79.4) | 3 (8.8) | 11 (32.4) | 17 (50) |

SD standard deviation, BMI body mass index, Ig immunoglobulin, IVIG intravenous immunoglobulin, PICU pediatric intensive care unit left coronary artery dilatation in 1 (5.9%) patient.
Cardiac MRI could be performed in 31 (91.2%) patients. It could not be performed in 3 patients because they were living in other cities and did not want to come to the hospital. Cardiac MRI was performed in the 3rd month in 12 (38.7%) patients and in the 6th month in 19 (61.3%) patients. Cardiac MRI parameters are shown in Table 3. Late gadolinium enhancement was not detected in any of the patients. We did not detect myocardial hyperemia, whereas 9 (29%) patients showed abnormal T2 levels. Abnormal T2 levels were not associated with WBC, ANC, ALC, PLT, monocyte, CRP, procalcitonin, ESR, D-dimer, NT-proBNP, and Troponin-T on admission ($p > 0.05$). The mean level of native T2 was correlated with NT-proBNP levels ($p = 0.049$, $r = 0.457$) at the 6-month visit. The group with abnormal T2 did not show any statistical differences in system involvement, the inflammatory state in the acute phase, length of hospital stay, length of PICU stay, steroids usage, or other treatments such as inotropes and oxygen support. Cardiac MRI revealed pericardial effusion in 14 (45.2%) patients and LVD in 5 (16.1%) patients, while echocardiography did not show any abnormalities in these patients. Coronary artery dilatation was determined in 2 patients via echocardiography, whereas cardiac MRI was normal in these patients.

**Table 2** Echocardiographic features of MIS-C patients on admission and at 6 months of diagnosis

|                        | Admission ($n = 34$) | 6th-month visit ($n = 17$) |
|------------------------|---------------------|---------------------------|
| Coronary artery dilatation (n, %) | 5 (14.7) | 2 (11.8) |
| Right                  | 0 (0)              | 0 (0)                     |
| Left                   | 3 (8.8)            | 1 (5.9)                   |
| Bilateral              | 2 (5.9)            | 1 (5.9)                   |
| Pericardial effusion (n, %) | 4 (11.8) | 0 (0) |
| Abnormal EF (n, %)     | 4 (11.8)           | 0 (0)                     |
| MY (n, %)              | 12 (35.3)          | 0 (0)                     |
| Mild                   | 12 (35.3)          | 0 (0)                     |
| Moderate               | 0 (0)              | 0 (0)                     |
| Severe                 | 0 (0)              | 0 (0)                     |
| TY (n, %)              | 4 (11.8)           | 0 (0)                     |
| Mild                   | 2 (5.9)            | 0 (0)                     |
| Moderate               | 2 (5.9)            | 0 (0)                     |
| Severe                 | 0 (0)              | 0 (0)                     |
| LVEF (mean±SD, %)      | 59.6±8.2           | 66.5±6.3                  |
| LVFS (mean±SD, %)      | 35.2±3             | 40.6±14.3                 |

*EF* ejection fraction, *FS* fractional shortening, *MIS-C* multisystemic inflammatory syndrome in children *MY* mitral regurgitation, *TY* tricuspid regurgitation, *LVEF* left ventricular ejection fraction, *LVFS* left ventricular fractional shortening, *RVEF* right ventricular ejection fraction, *RCA* right coronary artery, *LCA* left coronary artery

$ p = 0.041 $) with the total length of hospital stay ($r = 0.906$, $p = 0.034$).

Cardiac MRI could be performed in 31 (91.2%) patients. It could not be performed in 3 patients because they were living in other cities and did not want to come to the hospital. Cardiac MRI was performed in the 3rd month in 12 (38.7%) patients and in the 6th month in 19 (61.3%) patients. Cardiac MRI parameters are shown in Table 3. Late gadolinium enhancement was not detected in any of the patients. We did not detect myocardial hyperemia, whereas 9 (29%) patients showed abnormal T2 levels. Abnormal T2 levels were not associated with WBC, ANC, ALC, PLT, monocyte, CRP, procalcitonin, ESR, D-dimer, NT-proBNP, and Troponin-T on admission ($p > 0.05$). The mean level of native T2 was correlated with NT-proBNP levels ($p = 0.049$, $r = 0.457$) at the 6-month visit. The group with abnormal T2 did not show any statistical differences in system involvement, the inflammatory state in the acute phase, length of hospital stay, length of PICU stay, steroids usage, or other treatments such as inotropes and oxygen support. Cardiac MRI revealed pericardial effusion in 14 (45.2%) patients and LVD in 5 (16.1%) patients, while echocardiography did not show any abnormalities in these patients. Coronary artery dilatation was determined in 2 patients via echocardiography, whereas cardiac MRI was normal in these patients.

**Table 3** Cardiac MRI features of 31 MIS-C patients

|                        | Mean±SD, month |
|------------------------|---------------|
| The length of duration after diagnosis               | 4.8±1.5       |
| LVEDV (mean±SD, ml)                           | 82.7±49.6     |
| LVESV (mean±SD, ml)                            | 33.4±18.6     |
| LVEF (mean±SD, %)                               | 58.5±6.1      |
| RVEF (mean±SD, %)                               | 59.5±8.8      |
| The diameter of pericardial effusion (mean±SD, mm) | 5.5±1.09      |
| The basal levels of native T1 (mean±SD, ms)       | 903±38.6      |
| The maximum basal levels of native T1 (mean±SD, ms)| 947.9±41.9    |
| The level of midventricular native T1 (mean±SD, ms)| 933.4±47      |
| The maximum level of midventricular Native T1 (mean±SD, ms) | 985.5±55.5 |
| The basal level of native T2 (mean±SD, ms)        | 47±5.13       |
| The maximum basal level of native T2 (mean±SD, ms)| 51.09±7.99    |
| Level of midventricular native T2 (mean±SD, ms)    | 48.4±5.17     |
| The maximum level of midventricular native T2 (mean±SD, ms) | 54.7±8.06    |
| LVEF abnormality (n, %)                          | 5 (16.7)      |
| Right ventricular dysfunction (n, %)              | 6 (19.4)      |
| Pericardial effusion (n, %)                      | 14 (45.2)     |

*MRI* magnetic resonance imaging, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction,

**Discussion**

MIS-C is a new entity that develops 2–4 weeks after COVID-19. Cardiovascular system manifestations have been reported in as high as 80% of MIS-C patients [31]. Echocardiography is the first-line imaging for the detection of cardiac dysfunction. Depressed left ventricular systolic function and decreased ejection fraction, CAD, aneurysm, and pericarditis have been reported [32, 33]. Capone et al. [34] evaluated 50 MIS-C patients of which 33 (66%)
presented with cardiac manifestations which were LVD in 26 (52%) patients, and CAD in 10 (20%) patients. Theoharis et al. [20] showed that out of 11 patients with cardiac involvement, 8 (40%) had LV systolic dysfunction, 2 (10%) had left anterior descending coronary artery dilatation, and 1 (5%) had right coronary artery dilatation on admission. We observed cardiovascular involvement in 13 (38.2%) patients on admission, which was lower than in the study by Capone et al. [34]. However, in our study, LVD was less frequently observed (12.9%) than in previous studies, with varying degrees of reduction in ejection fraction.

In previous studies, pericardial effusion has been shown in 9–72% of MIS-C patients [19, 35, 36]. Valverde et al. [19] reported 80 (27.9%) patients with pericardial effusion at admission, 66 (25%) of them being mild, 8 (3%) of them moderate. Pericardial effusion persisted in 20.6% of patients during hospitalization. We detected 4 (11.8%) patients with pericardial effusion on admission; all of them were mild. In the follow-up period, echocardiographic examination showed that pericardial effusion completely recovered in all patients.

A previous study determined 50% mitral regurgitation and 72% pericardial effusion via echocardiography among MIS-C patients on admission, while only 20% had small pericardial effusion and 18% had mild mitral regurgitation at discharge [36]. Valverde et al. [19] reported the rate of mitral regurgitation and tricuspid regurgitation in a large European MIS-C cohort as 42.5% and 5.9%, respectively. In this study, the initial echocardiographic evaluation showed mild mitral regurgitation in 12 (35.3%) patients and tricuspid regurgitation in 4 (11.8%) patients, and all those patients recovered within 6 months. Mitral regurgitation was less, and tricuspid regurgitation was more frequent in our cohort than in previous studies [19, 36].

The incidence of coronary artery abnormalities varies considerably across studies. Usually, mild or moderately sized coronary artery abnormalities have been reported in 9% to 26.7% of the MIS-C cases, and large/giant coronary artery aneurysms have been reported in several studies [11, 12, 14, 37, 38]. Valverde et al. [19] showed coronary artery abnormalities in 69 (24.1%) of the 286 patients and giant aneurysm in 1 (0.3%) patient. Coronary artery ectasia (Z score: 2.53 and 2.6 in the right coronary artery) was detected in only two patients (4%) in one of the previous studies and they recovered until discharge [36]. Similar to these studies, coronary artery abnormalities were detected in 14.7% of patients in our study.

Previous studies generally evaluated acute and early cardiac involvement of MIS-C cases [39–46]. Capone et al. [34] reported early midterm results of cardiac MRI performed in the convalescence phase 2–4 weeks after discharge in 11 of 50 MIS-C patients with initial LVD. They did not determine persistent edema or fibrosis at 8 weeks, despite higher troponin levels during hospitalization (median: 37, IQR: 9–109, reference < 14 ng/L) in these patients [34]. In two other studies, cardiac MRI was performed in MIS-C patients, usually within the first 1 month, and fibrosis was not reported in the acute phase [20, 47]. Bermejo et al. [40] performed cardiac MRI (between 12 and 72 days) in 20 of 44 MIS-C patients with a median age of 8 years. They detected small areas of LGE in 2 patients, abnormal mean T1 levels in 1 patient, and normal mean global T2 levels of basal, midventricular, and apical slices in all patients. Higher T2 levels in the apical lateral segment in 1 patient, and basal septal levels were abnormal in 1 patient. Blondiaux et al. [32] performed MRI 14 days after discharge in four children and found diffuse myocardial edema and hyperemia without evidence of focal myocardial necrosis/fibrosis. Dominguez et al. [21] performed cardiac MRI in 12 of 37 MIS-C patients with a median age of 8 years and detected myocardial edema in 7 patients, pericardial effusion in 5 patients, and decreased left ventricular function in 3 patients. Valverde et al. [19] reported T2 hyperintensity in 14 (33.3%) of 42 patients, pericardial effusion in 10 (23.8%), early gadolinium enhancement in 1 (2.4%) and 6 (14.3%) LGE. Studies of cardiac MRI in MIS-C patients are summarized in Table 4. However, cardiac MRI was generally performed in the acute phase, and the number of patients was, respectively, small in these studies [20, 32, 34, 39–46]. Theoharis et al. [20] detected myocardial edema in 10/20 (50%) patients. Matsubara et al. [24] reported the cardiac outcomes of 14 of 60 patients with MIS-C. Cardiac MRI was performed in five patients during the subacute phase and nine patients during the following period. Only one of nine patients had residual edema on cardiac MRI [24]. The recent study by Dove et al. [25] detected late gadolinium enhancement, T1 mapping abnormalities, and abnormal or borderline extracellular volume calculations suggesting myocardial fibrosis in two of 51 patients, and no patient had T2 mapping abnormalities corresponding with edema. In our study, echocardiography did not show any abnormality at the 6th month (except coronary dilatation), whereas cardiac MRI demonstrated cardiac involvement, particularly pericardial effusion. Sixty-one percentage of the patients still had at least one of the following findings: pericardial effusion (45.2%), right ventricular dysfunction (19.4%), and LVEF abnormality (16.7%).

Bermejo et al. [40] detected abnormal T2 levels correlated with elevated D-dimer on admission. We did not observe any correlations between T2 levels with WBC, ANC, ALC, PLT, monocyte, CRP, procalcitonin, ESR, D-dimer NT-proBNP, and troponin-T (p > 0.05).

Several studies have reported the short-term outcomes of cardiac complications in children with MIS-C. Cardiac complications persisted during firstly and second months at follow-up in two studies [48, 49]. Caro-Paton et al. [50] showed
Table 4  A literature review of published studies regarding cardiac MRI findings of MIS-C patients

| Article                  | Age                | Number of patients performed MR/number of total patients | MR findings                                                                 | The time of MRI                                      | Study design          | Hospital                                                                 |
|-------------------------|--------------------|--------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------|-----------------------|--------------------------------------------------------------------------|
| Bermejo et al.[40]      | Median age: 8 years | 20/44                                                  | 2 patients: Late gadolinium enhancement                                    | 27±14 days                                      | Royal Brompton Hospital Syria Street London, UK                         |
| Biko et al. [41]        | Mean ± SD: 9.7± 3.97| 1/10                                                   | No findings consistent with myocarditis, myocardial edema, and normal myocardial delayed enhancement and T1 mapping | Acute phase                                      | Retrospective          | Children’s Hospital of Philadelphia or an affiliated hospital          |
| Blondiaux et al. [32]   | Mean ± SD: 9 ± 3 years | 4/8                                                   | T1 mapping values and T2-STIR ratio suggesting myocardial hyperemia and edema | 3 patient: Acute phase, 1 patient: Recovery phase (14 days after discharge) | Retrospective          | Sorbonne Université, Paris, France                                      |
| Capone et al. [34]      | Median age: 8.5 years | 11/50                                                  | None of the patients: persistent edema or fibrosis                         | 2–4 weeks after discharge                       | Cohort study           | Cohen Children’s Medical Center, New York                                |
| Domínguez et al. [21]   | Median age: 8 years  | 12/37                                                  | 7 patients: Myocardial edema, 5 patients: Pericardial effusion and 3 patients: Decreased left ventricular function | Between 5 and 100 days after symptom onset     | Retrospective          | Hospital Universitario Virgen del Rocío, Seville, Spain                |
| Dove et al. [25]        | Median age: 11.3 years | 51/51                                                  | Two patients: Late gadolinium enhancement, 10 patients: Isolated elevated T1 values | The median time of 105 days after diagnosis     | Retrospective          | Emory University School of Medicine,                                     |
| Jain et al. [46]        | Mean ± SD: 8.7± 5.5 years | 1/3                                                   | Myocardial edema                                                            | On day 6                                         | Case series            | Maria Fareri Children’s Hospital at Westchester Medical Center, New York |
| Matsubara et al. [24]   | Mean ± SD: 10± 4.3 years | 15/60                                                  | Two patients in the subacute phase who had evidence of myocardial edema (1 focal, 1 global) | Five patients: During the subacute phase (median, 8 days), 9 patients: During follow-up period (median, 162 days) | Retrospective          | Institutional Review Boards of Children’s Hospital of Philadelphia, and St. Peter’s University Hospital |
| Minocha et al. [42]     | Median age: 2.8 years | 1/33                                                   | 1 patient: Myocarditis                                                     | Acute phase                                      | Retrospective          | Hassenfeld Children’s Hospital at NYU Langone and Bellevue Hospital Center |
| Palabiyik et al. [39]   | Median age: 7.68 years | 1/45                                                   | 1 patient: Decrease in the pericardial effusion and systolic functions and an increase in cardiac dimensions | Acute phase                                      | Retrospective          | Bakirkoy Dr. Sadi Konuk Training and Research Hospital                  |
| Prieto et al. [43]      | Median age: 7 years  | 5/5                                                    | No myocardial edema or enhancement abnormalities                           | Median day after admission:16 day, [9–17]      | Case series            | Hospital Universitario 12 de Octubre, Madrid, Spain                    |
| Article             | Age                          | Number of patients performed MR/number of total patients | MR findings                                                                 | The time of MRI | Study design          | Hospital                                                |
|--------------------|------------------------------|---------------------------------------------------------|------------------------------------------------------------------------------|-----------------|-----------------------|---------------------------------------------------------|
| Sirico et al. [44] | Mean ± SD: 8.1 ± 4 years     | 17/23                                                    | 1 patient: LV edema, 6 patients: Left ventricle late gadolinium enhancement, 2 patients: Pericardial effusion | Within 19 days  | Retrospective          | Women’s and Children’s Health (W&CHD) of Padua University Hospital, Italy |
| Tannoury et al. [22]| Mean ± SD: 11 ± 5.5 years    | 1/4                                                      | Minimal myocarditis area in the mid inferior septum and mid inferior wall | 3.5 months      | A case series          | American University of Beirut Medical Center           |
| Theocharis et al. [20]| Mean ± SD: 10.6 ± 3.8 years | 20/20                                                    | 13 patients: EF normal, 3 patients: Borderline EF, 4 patients: EF < 50%, 10 patients: Myocardial edema | Median day 20 [11–29 days] | Retrospective          | Evelina London Children’s Hospital                    |
| Webster et al. [23] | Mean ± SD 13.8 ± 2.2         | 6/6                                                      | Biventricular size and function were normal                                  | 61 days         | Prospective            | Lurie Children’s Hospital of Chicago                   |
| Valverde et al. [19]| Median age: 8.4 years        | 42/286                                                   | 14 patients (33.3%): T2 hyperintensity, 10 patients (23.8%): pericardial effusion, 6 patients (14.3%): Late gadolinium enhancement | During hospitalization | 55 participating European hospitals                   |
cardiac complications in 3 (25%) patients. Pouletty et al. [51] demonstrated mild LV dysfunction persisted in only two of 7 patients admitted to the intensive care unit. A study focused on follow-up of patients with MIS-C determined only one patient with a medium CA aneurysm (Z score 9.8) was stable at the 6th month of initial diagnosis [52]. These reports highlighted that the majority of the cardiac manifestations resolved during the short-term follow-up period. In our study, CAD persisted in 2 (40%) of 5 patients with CAD detected by echocardiography which was higher than the literature.

MIS-C seems to be a severe acute disease with minor complications on the midterm. If we are not going to start treatment for cardiac involvement, performing cardiac MRI in general in young children who need sedation for cardiac MRI data, and in patients with mild and asymptomatic pericardial effusions or ventricular dysfunction may be a topic of discussion. However, we showed abnormalities with cardiac MRI even in asymptomatic patients or without biochemical abnormality. Therefore, we suggest performing cardiac MRI on all MIS-C patients, even echocardiography does not reveal any abnormality.

**Conclusion**

Echocardiography and cardiac MRI are sensitive and specific tools to evaluate cardiac involvement in patients with MIS-C. However, this study demonstrated that cardiac MRI is more sensitive and specific in the late phase of MIS-C. Pericardial effusion was the most common finding in the late period. Cardiac MRI evaluation may be suggested for all MIS-C patients at the late phase; even echocardiography does not detect any abnormality. More extensive and prospective design studies are needed to determine cardiac residual long-term damages.

**Limitations**

The first limitation of our study is its retrospective nature. Second, it is a single-center study, and a limited number of patients could be evaluated.

**Acknowledgements** Thank you also to the research group at our University Medical Center for their contribution.

**Author contributions** SYA and ZSB, SB, and FFO conceived the paper and wrote the first draft of the manuscript. GGO, NMB, EL, OA, PYO, ZK, CC, AC, GA, and GA, contributed data and data analysis, as well as critical evaluation and editing of the text. All of the writers were involved in the patient’s care. The final manuscript was reviewed and approved by all writers.

**Funding** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Declarations**

**Conflict of interest** The authors have no conflicts of interest relevant to this article to disclose.

**References**

1. WHO health emergency dashboard. Available at https://www.covid19who.int/. Accessed 18 Jan 2022
2. Lu X, Zhang L, Du H et al (2020) Chinese pediatric novel coronavirus study team. SARS-CoV-2 infection in children. N Engl J Med 382:1663–1665. https://doi.org/10.1056/NEJMc2005073
3. CDC (2020) Health Advisory: Multi-system Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)
4. Verdoni L, Mazza A, Gervasoni A et al (2020) An outbreak of severe kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 395:1771–1778. https://doi.org/10.1016/S0140-6736(20)31103-X
5. Toubiana J, Poirault C, Corsia A et al (2020) Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 369:m2094. https://doi.org/10.1136/bmj.m2094
6. Consiglio CR, Cotugno N, Sardh F et al (2020) The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 183(968–981):e7. https://doi.org/10.1016/j.cell.2020.09.016
7. Vella L, Giles JR, Baxter AE et al (2021) Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. Sci Immunol. https://doi.org/10.1126/sciimmunol.abf7570
8. Gruber CN, Patel RS, Trachtman R et al (2020) Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 183(982–985):e14. https://doi.org/10.1016/j.cell.2020.09.034
9. Hoste L, Van Paemel R, Haerynck F (2021) Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr 180(7):2019–2034
10. Chou J, Platt CD, Habiballah S et al (2021) Mechanisms underlying genetic susceptibility to the multisystem inflammatory syndrome in children (MIS-C). J Allergy Clin Immunol 148(3):732–738.e1
11. Dufort EM, Kourmanis EH, Chow EJ et al (2020) Multisystem inflammatory syndrome in children in New York state. N Engl J Med 383:347–358. https://doi.org/10.1056/NEJMoa2021756
12. Feldstein LR, Rose EB, Horwitz SM et al (2020) Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 383:334–346. https://doi.org/10.1056/NEJMoa2021680
13. Riphagen S, Gomez X, Gonzalez-Martinez C et al (2020) Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet 395:1607–1608. https://doi.org/10.1016/S0140-6736(20)31094-1
14. Whitaker E, Bamford A, Kenny J et al (2020) Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated With SARS-CoV-2. JAMA 324(3):259–269. https://doi.org/10.1001/jama.2020.10369
15. Belhadjer Z, Ment M, Bajolle F et al (2020) Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.120.048360
16. Cheung EW, Zachariah P, Gorelik M et al (2020) Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents. JAMA. https://doi.org/10.1001/jama.2020.10374

17. Dionne A, Mah DY, Son MFB et al (2020) Atrioventricular block in children with multisystem inflammatory syndrome. Pediatrics 146(5):e2020009704. https://doi.org/10.1542/peds.2020-009704

18. Matsubara D, Kauffman HL, Wang Y et al (2020) Echocardiographic findings in pediatric multisystem inflammatory syndrome associated With COVID-19 in the United States. J Am Coll Cardiol 76:1947–1961

19. Valverde I, Singh Y, Sanchez-de-Toledo J et al (2020) Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation 143(1):21–32

20. Theocharis P, Wong J, Pushparajah K et al (2020) Multimodality cardiac evaluation in children and young adults with multisystem inflammation associated with COVID-19. Eur Heart J Cardiovasc Imaging 22(8):896–903. https://doi.org/10.1093/ehjci/jeaa212

21. Caro-Dominguez P, Navallàs M, Riaza-Martin L et al (2021) Imaging findings of multisystem inflammatory syndrome in middle eastern children during the COVID-19 pandemic: a case series. Cardiol Young 17:1–4. https://doi.org/10.1017/S1047951121002614

22. Tannoury TE, Bulbul ZR, Bitar FF (2021) Cardiac manifestations and short-term outcomes of multisystem inflammatory syndrome in children. J Pediatr Cardiol 51(9):1608–1620. https://doi.org/10.1007/s00247-021-05065-0

23. Webster G, Patel AB, Carr MR et al (2021) Cardiovascular magnetic resonance imaging in children after recovery from symptomatic COVID-19 or MIS-C: a prospective study. J Cardiovasc Magn Reson 23(1):86. https://doi.org/10.1186/s12968-021-00786-5

24. Matsubara D, Chang J, Kauffman HL et al (2022) Longitudinal assessment of cardiac outcomes of multisystem inflammatory syndrome in children associated With COVID-19 infections. J Am Heart Assoc 11(3):e023251. https://doi.org/10.1161/JAHA.121.023251

25. Dove ML, Oster ME, Hashemi S, Slesnick TC (2022) Cardiac magnetic resonance findings after multisystem inflammatory syndrome in children. J Pediatr 200(22–23):3476–3477.e3476. https://doi.org/10.1016/j.jpeds.2022.02.049

26. WHO (2020) World Health Organization Multisystem inflammatory syndrome in children and adolescents with COVID-19. Published May 15, 2020. https://www.who.int/publication-summary/item

27. Sahn DJ, DeMaria A, Kisslo J et al (1978) Prolongation of a survey of echocardiographic measurements. Circulation 58:1072–1083

28. Dallaire F, Dahdah N (2011) New equations and a critical appraisal of coronary artery Z scores in healthy children. J Am Soc Echocardiogr 24:60–74

29. Pagano JJ, Yim D, Lam CZ et al (2020) Normative data for myocardial native T1 and extracellular volume fraction in children. Radiol Cardiothorac Imaging 2(4):e190234

30. Ferreira VM, Schulz-Menger J, Holmvang G et al (2018) Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol 72(24):3158–3176

31. Chiotos K, Bassiri H, Behrens EM et al (2020) Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatric Infect Dis Soc 9:393–398

32. Blondiaux E, Parisot P, Redheuil A et al (2020) Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. Radiology 297:E283–E288

33. Sporotto F, Friedman K, Son M et al (2021) Cardiac manifestations in SARS-CoV-2 associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr 180(2):307–322. https://doi.org/10.1007/s00431-020-03766-6

34. Capone CA, Misra N, Ganigara M et al (2021) Six month follow-up of patients with multi-system inflammatory syndrome in children. Pediatrics 148(4):e2021050973

35. DeBiasi RL, Harahsheh AS, Srinivasalu H et al (2021) Multisystem inflammatory syndrome of children: sub-phenotypes, risk factors, biomarkers, cytokine profiles, and viral sequencing. J Pediatr 237:125–135.e18

36. Kavuri AV, Bagrul D, Gül AEK et al (2021) Echocardiographic findings and correlation with laboratory values in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. Pediatr Cardiol 26:1–13. https://doi.org/10.1007/s00246-021-02738-3

37. Godfred-Cato S, Bryant B, Leung J et al (2020) COVID-19-associated multisystem inflammatory syndrome in children—United States. Morb Mortal Wkly Rep 2020(69):1074–1080

38. Lee PY, Day-Lewis M, Henderson LA et al (2020) Distinct clinical and immunological features of SARS-CoV-2 induced multisystem inflammatory syndrome in children. J Clin Invest 130(1):5942–5950

39. Palabiyik F, Akçay N, Sevketoglu E et al (2021) Imaging of multisystem inflammatory disease in children (MIS-C) associated with COVID-19. Acad Radiol 28(9):1200–1208

40. Bermejo IA, Bautista-Rodriguez C, Fraisse A et al (2021) Short-term sequelae of multisystem inflammatory syndrome in children assessed by CMR. JACC Cardiovasc Imaging 14(8):1666–1667

41. Biko DM, Ramirez-Suarez KI, Barrera CA et al (2021) Imaging of children with COVID-19: experience from a tertiary children’s hospital in the United States. Pediatr Radiol 51(2):239–247. https://doi.org/10.1007/s00247-020-04830-x

42. Minocha PK, Phoon CKL, Verma S et al (2021) Cardiac findings in pediatric patients with multisystem inflammatory syndrome in children associated with COVID-19. Clin Pediatr 60(2):119–126. https://doi.org/10.1177/0009922820961771

43. Prieto LM, Toral B, LLorente A et al (2021) Cardiovascular magnetic resonance imaging in children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 and heart dysfunction. Clin Microbiol Infect 27(4):648–650. https://doi.org/10.1016/j.cmi.2020.10.005

44. Sirico D, Basso A, Refo E et al (2021) Early echocardiographic and cardiac MRI findings in multisystem inflammatory syndrome in children. J Clin Med 10(15):3360. https://doi.org/10.3390/jcm10153360

45. Williams ES, Kaplan JI, Thatcher F et al (1980) Prolongation of proton spin-lattice relaxation times in regionally ischemic tissue from dog hearts. J Nucl Med 21:449–450

46. Jain S, Nolan SM, Singh AR et al (2020) Myocarditis in multisystem inflammatory syndrome in children associated with coronavirus disease 2019. Pediatr Rev 28:308–310

47. Mavrogeni SI, Kolovou G, Tsirimpis V et al (2021) The importance of heart and brain imaging in children and adolescents with multisystem inflammatory syndrome in children (MIS-C). Rheumatol Int 41(6):1037–1044. https://doi.org/10.1007/s00296-021-04845-x

48. Cattalini M, Della Paolera S, Zunica F et al (2021) Defining Kawasaki disease and pediatric inflammatory multisystem syndrome temporally associated to SARS-CoV-2 infection during SARS-CoV-2 epidemic in Italy: results from a national, multicenter survey. Pediatr Rheumatol 19(1):29. https://doi.org/10.1186/s12969-021-00511-7

49. Harahsheh AS, Krishnan A, DeBiasi RL et al (2021) Cardiac echocardiogram findings of severe acute respiratory syndrome...
coronavirus-2-associated multisystem inflammatory syndrome in children. Cardiol Young 5:1–9. https://doi.org/10.1017/S1047951121003024

50. Caro-Paton GL, de Azagra-Garde AM, Garcia-Salido A et al (2021) Shock and myocardial injury in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection: what we know. Case series and review of the literature. J Intensive Care Med 36(4):392–403. https://doi.org/10.1177/0885066620969350

51. Pouletty M, Borocco C, Ouldali N et al (2020) Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis 79(8):999–1006. https://doi.org/10.1136/annrheumdis-2020-217960

52. Penner J, Abdel-Mannan O, Grant K et al (2021) 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. Lancet Child Adolesc Health 5(7):473–482. https://doi.org/10.1016/S2352-4642(21)00138-3

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

**Authors and Affiliations**

Sema Yildirim Arslan¹ · Zumrut Sahbudak Bal¹ · Selen Bayraktaroglu² · Gizem Guner ozenen¹ · Nimet Melis Bilen¹ · Erturk Levent³ · Oguzhan Ay³ · Pinar Yazici Ozkaya⁴ · Ferda Ozkinay¹ · Candan Cicek⁵ · Akin Cinkooglu² · Guzide Aksu⁶ · Gunes Ak⁷ · Zafer Kurugol¹

Sema Yildirim Arslan
semayildirimarslan@gmail.com

Selen Bayraktaroglu
selen.bayraktaroglu@ege.edu.tr

Gizem Guner Oznen
gzmguner86@gmail.com

Nimet Melis Bilen
nmelisaydin@hotmail.com

Erturk Levent
erturk.levent@ege.edu.tr

Oguzhan Ay
oguzhanay1@gmail.com

Pinar Yazici Ozkaya
dryazicipinar@gmail.com

Ferda Ozkinay
ferdabo@yahoo.com

Candan Cicek
candanc2001@yahoo.com

Akin Cinkooglu
acinko@gmail.com

Guzide Aksu
guzide.aksu@ege.edu.tr

Gunes Ak
gunes.ak@ege.edu.tr

Zafer Kurugol
zafer.kurugol@ege.edu.tr

¹ Division of Infectious Disease, Department of Pediatrics, Medical School of Ege University, Izmir, Turkey

² Department of Radiology, Medical School of Ege University, Izmir, Turkey

³ Division of Pediatric Cardiology, Department of Pediatrics, Medical School of Ege University, Izmir, Turkey

⁴ Division of Pediatric Intensive Care Unit, Department of Pediatrics, Medical School of Ege University, Izmir, Turkey

⁵ Department of Microbiology, Medical School of Ege University, Izmir, Turkey

⁶ Division of Immunology and Rheumatology, Department of Pediatrics, Medical School of Ege University, Izmir, Turkey

⁷ Department of Clinic Biochemistry, Medical School of Ege University, Izmir, Turkey