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# Cardiovascular manifestations and cardiac magnetic resonance follow-up of multisystem inflammatory syndrome in children (MIS-C)

Selen Karagözlü[1], Mehmet G. Ramoğlu[1], Özlem Bayram[1], Jeyhun Bakhtiyarzada[1], Alperen Aydın[1], Mehmet Mustafa Yılmaz[1], Begüm Murt[1], Ersin Özkan[2], Hatice Belkıs İnceli[3], Anar Gurbanov[4], Yılmaz Şükriye[5], Berrin Demir[5], Halil Özdemir[3], Ergin Çiftçi[3], Tanıl Kendirli[4], Tayfun Uçar[1], Ömer Suat Fitoz[5] and Ercan Tutar[1]

[1]Ankara University, School of Medicine, Department of Pediatric Cardiology, Ankara, Turkey; [2]Ankara University, School of Medicine, Department of Pediatrics, Ankara, Turkey; [3]Ankara University, School of Medicine, Department of Pediatric Infectious Diseases, Ankara, Turkey; [4]Ankara University, School of Medicine, Department of Pediatric Intensive Care, Ankara, Turkey and [5]Ankara University, School of Medicine, Department of Pediatric Radiology, Ankara, Turkey

## Original Article

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**Corresponding author:**
Ercan Tutar; Email: ercantutar@gmail.com

## Abstract

*Objective:* This study aimed to evaluate the cardiovascular manifestations and surveillance of multisystem inflammatory syndrome in children (MIS-C) and to determine the correlation of echocardiographic findings with cardiac magnetic resonance imaging findings. *Methods:* Forty-four children diagnosed as MIS-C with cardiac involvement were enrolled in this observational descriptive study. The diagnosis of MIS-C was made according to the criteria of Centers for Disease Control and Prevention. Clinical findings, laboratory parameters, and electrocardiographic and echocardiographic findings at the time of diagnosis and during follow-up were evaluated. Cardiac magnetic resonance was performed on 28 (64%) cases. The 1-year follow-up imaging was performed in all cases with abnormal initial cardiac magnetic resonance findings. *Results:* Forty-four patients (56.8% male) with a mean age of 8.5 ± 4.8 years were enrolled in this study. There was a significant positive correlation between high-sensitivity cardiac troponin T (mean: 162 ± 444.4 pg/ml) and N-terminal pro b-type natriuretic peptide (mean: 10,054 ± 11,604 pg/ml) ($p < 0.01$). Number of cases with an electrocardiographic and echocardiographic abnormality was 34 (77%) and 31 (70%), respectively. Twelve cases (45%) had left ventricular systolic dysfunction and 14 (32%) cases had pericardial effusion on admission. Three cases (11%) had cardiac magnetic resonance findings that may be attributed to the presence of myocardial inflammation, and pericardial effusion was present in seven (25%) cases. Follow-up cardiac magnetic resonances of all cases were normal. Cardiac abnormalities were completely resolved in all except two cases. *Conclusions:* Myocardial involvement can be seen during acute disease, but MIS-C generally does not lead to prominent damage during a year of surveillance. Cardiac magnetic resonance is a valuable tool to evaluate the degree of myocardial involvement in cases with MIS-C.

Coronavirus disease-2019 has caused a global pandemic with high morbidity and mortality.[1] In April 2020, the physicians in the United Kingdom observed that children admitted to the paediatric intensive care unit with a hyperinflammatory condition characterised by fever, cardiovascular shock, and suspected severe acute respiratory syndrome coronavirus 2 infection.[2,3] The Royal College of Pediatrics and Child Health named this condition as paediatric multisystem inflammatory syndrome temporally related to coronavirus disease-2019.[4] The Centers for Disease Control and Prevention released a notice on this condition in May 2020, entitled "multisystem inflammatory syndrome in children" (MIS-C).[4]

Multisystem inflammatory syndrome in children is a severe systemic hyperinflammation syndrome that develops in children who have been exposed to severe acute respiratory syndrome coronavirus 2 in the previous 2–6 weeks.[5] Fever, increased inflammatory markers, and signs and symptoms of organ damage in the cardiovascular, respiratory, gastrointestinal, renal, neurological, haematologic, and dermatologic systems are the clinical manifestations. Cardiovascular symptoms are observed in 34–82% of children with MIS-C.[6,7] Cardiovascular system involvement may appear as hypotensive shock, myocardial dysfunction, and more rarely as coronary artery dilation or aneurysms. Children with MIS-C have variable degrees of abnormalities in cardiac enzymes, electrocardiogram, echocardiogram, and cardiac magnetic resonance imaging. Elevated N-terminal pro-B-type natriuretic peptide and troponin levels,

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sinus tachycardia, non-specific ST and T wave abnormalities, electrical conduction disorders, left ventricular systolic dysfunction, pericardial effusion, and cardiogenic shock are the most common cardiac abnormalities in children with MIS-C.[8–10]

In this study, we aimed to document the cardiovascular manifestations and follow-up of patients with MIS-C and to determine the correlation of echocardiographic findings with cardiac magnetic resonance imaging findings.

## Materials and methods

This observational descriptive study was conducted between April 2020 and December 2021 in Ankara University Faculty of Medicine, Department of Pediatric Cardiology. All children diagnosed as MIS-C with cardiovascular involvement were enrolled in this study. MIS-C-diagnosed children with no cardiovascular involvement were excluded from the study. The local ethics committee approved the study.

The diagnosis of MIS-C was done in accordance with the Centers for Disease Control and Prevention guidelines for MIS-C.[3,4] The cases were classified as mild, moderate, or severe according to the vasoactive inotropic score, degree of respiratory support, and degree of organ injury.[11]

### *Laboratory parameters*

The severe acute respiratory syndrome coronavirus 2 exposure was confirmed by serum IgG or total Ig antibody positivity in all cases. Laboratory parameters included C-reactive protein, erythrocyte sedimentation rate, procalcitonin, fibrinogen, D-dimer, ferritin, lactate, lactate dehydrogenase, complete blood count, albumin, creatinine, aspartate aminotransferase, and alanine aminotransferase. N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T were used as cardiac markers. Standard microbiological screening was performed for excluding other viral and bacteriological aetiologies.

### *Cardiac evaluation*

Cardiovascular involvement was defined in the presence of preshock/shock, left ventricular systolic dysfunction, coronary artery abnormality/aneurysm, increased troponin or N-terminal pro-B-type natriuretic peptide levels, arrhythmia, pericarditis/pericardial effusion, and/or valvulitis. All cases had detailed electrocardiographic and echocardiographic evaluations on admission, during hospitalisation, and follow-up. The N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T levels were measured on admission and during follow-ups.

Routine echocardiography was performed on admission, day 3, week 1, and, months 1, 3, 6, and 12. Additional echocardiography was performed in some cases if needed and the frequency was decided according to the severity of the disease. Echocardiography was performed by experienced paediatric cardiologists using Vivid 7 Pro (GE Medical Systems®) or Vivid 9N portable ultrasound machine (GE Medical Systems®). Standard echocardiographic measurements were obtained according to the American Society of Echocardiography guidelines.[12] Echocardiographic measurements included M-mode left ventricular fractional shortening, Simpson's biplane left ventricular ejection fraction, ratio of peak early diastolic filling velocity (E) over early diastolic mitral annular velocity (e′) (E/e′), tricuspid annular plane systolic excursion, mitral annular plane systolic excursion, and mitral-septal-tricuspid tissue Doppler index (E', A',S'(cm/sec)). Presence of pericardial effusion, valvular insufficiency, and coronary artery abnormalities was evaluated per the guidelines.[13–16] Coronary artery *z*-scores were classified as follows: normal <2; dilation >2 to <2.5; and aneurysm ≥2.5. Z-scores of all echocardiographic parameters were calculated using the published reference data.[16–19]

### *Cardiac magnetic resonance imaging*

Cardiac magnetic resonance was performed at a median duration of 2.3 months (min–max: 1–11 months) after MIS-C hospitalisation to evaluate the myocardial involvement and development of fibrosis and to assess ventricular function. Sixteen cases did not undergo cardiac magnetic resonance either because they had no echocardiographic abnormality or they did not want to take part in the procedure due to claustrophobia or risk of sedation. As a result, cardiac magnetic resonance imaging was performed in 28 cases. Control imaging was performed in cases with abnormal cardiac magnetic resonance findings in the first year of follow-up. Only in one case, cardiac magnetic resonance was performed on the 18$^{th}$ month of the follow-up, because the initial cardiac magnetic resonance could not be performed. Thus, no statistical analysis related to the cardiac magnetic resonance of this patient was performed.

The cardiac magnetic resonance imaging was performed on a 1.5 T MR scanner (Philips Ingenia, Philips Healthcare, Best, Netherlands®). The software was IntelliSpace Portal image and information management software version 10.1. Axial turbo spin echo images with black blood technique were used to obtain information on the morphology of the right ventricle and left ventricle. Conventional balanced steady-state free precession (bSSFP) cine images were taken in the short and long axis planes of the ventricles to evaluate ventricular function. Myocardial oedema was defined as increased signal intensity on T2-weighted imaging. A segmented phase sensitive inversion recovery-spoiled gradient echo sequence was used for contrast dynamics. For evaluation of delayed enhancement, late contrast-enhanced imaging at 10 minutes after intravenous administration was obtained in short and long axes.

### *Statistical analysis*

Statistical analyses were performed by the SPSS 11.5 statistical package (IBM Corp., Armonk, NY, USA). Mean ± standard deviation, median (minimum-maximum), and percentage were used for descriptive analyses. Receiver operating characteristic analysis was performed, and Youden Index value was used to calculate the cut-off value for the quantitative variable. Univariate and multivariate logistic regression analyses were used to determine the risk factors affecting left ventricular ejection fraction. Single and multivariate linear regression analyses were used to determine the factors affecting the grade. The statistical significance level was set at 0.05.

## Results

Seventy-one children were diagnosed with MIS-C between April 2020 and December 2021, and 44 cases (100%) with cardiovascular involvement were enrolled in the study. Two of the cases had previous cardiac disease: hypertrophic cardiomyopathy and pulmonary hypertension with operated atrial septal defect. The mean age of the cases was 8.5 ± 4.8 years, and the male-to-female ratio was 25/19 (1.31). The most common symptoms on admission were fever (97%), rash (61.4%), nausea-vomiting (52.3%),

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**Table 1.** Demographic data, clinical characteristics, and laboratory findings of cases with MIS-C.

| Clinical characteristics | | n (%) |
|---|---|---|
| Inflammatory | Fever >38°C on admission | 43 (97) |
| Gastrointestinal | Nausea-vomiting | 23 (52.3) |
| | Abdominal pain | 26 (59.1) |
| | Diarrhoea | 22(50) |
| Mucocutaneous | Rash | 27 (61.4) |
| | Conjunctival injection | 17(38.6) |
| | Extremities hyperaemia/oedema/desquamation | 4(9.1) |
| | Oral mucosa hypaeremia | 8 (18.2) |
| Cardiovascular | Palpitation | 15 (34.1) |
| | Hypotension | 17 (38.6) |
| | Chest pain | 3 (6.8) |
| | Dyspnoea | 11 (25) |
| | Shock | 4 (9.1) |
| Neurologic | Headache | 10 (22.7) |
| | Meningismus | 2 (4.5) |
| | Convulsion | 2 (4.5) |
| | Changes in consciousness | 4 (9.1) |
| MIS-C grade | Mild | 23 (52.3) |
| | Moderate | 9 (20.5) |
| | Severe | 12 (27.3) |
| Survival | One-year follow-up | 43 (97) |
| **Laboratory parameters** | **Cut-off value; n (%)** | **Median (Min-Max)** |
| NT-ProBNP (pg/ml) | >125; 44 (100) | 5222 (127–35,000) |
| HS-Troponin-T (pg/ml) | >14; 28 (63.6) | 29,2(3–2098) |
| C-reactive protein (mg/L) | >5; 42 (95.4) | 125 (2,9-475) |
| Procalcitonin (ng/mL) | >0.5; 35 (85.3) | 2,94 (0–168) |
| Erythrocyte sedimentation rate (mm/h) | >20; 40 (93) | 41 (2–109) |
| Haemoglobin (g/dL) | <11,5; 37 (84) | 10 (4,3–13,9) |
| White blood cell (/mm$^3$) | <13,500; 40 (93) | 1550 (600–16,000) |
| Thrombocyte (/mm$^3$) | <15,0000; 20 (45) | 162 (46–492) *10$^3$ |
| Neutrophile (/mm$^3$) | >8000; 42 (95.4) | 16,305 (6470–49,130) |
| Lymphocyte (/mm$^3$) | <1500; 35 (79.5) | 1050 (280–4990) |
| Creatinine (mg/dL) | >0.9; 5 (11.3) | 0.56 (0,22–6,84) |
| Aspartate aminotransferase (U/L) | >35; 33 (75) | 48 (19–3734) |
| Alanine aminotransferase(U/L) | >35; 29 (65.9) | 43.5 (11–1832) |
| D-dimer (ng/mL) | >243; 43 (97.7) | 1235 (208–8687) |
| Ferritin (ng/mL) | >150; 33 (78.5) | 324 (40–4845) |
| Fibrinogen (g/L) | >3.93; 17 (38.6) | 3.5 (0.7–8.3) |
| Albumin (g/L) | <38; 40 (93) | 27.8 (15.9–43.4) |

N=number of patients; %=column percentage; SD=standard deviation; min=minimum; max=maximum; MIS-C=multisystem inflammatory syndrome in children.

abdominal pain (59%), and diarrhoea (50%). All cases had fever above 38°C on admission except one case with an immunodeficiency syndrome. The most common concomitant system involvements were the gastrointestinal (77.2%) and mucocutaneous systems (65.9%). Clinical characteristics of all cases are shown in Table 1.

All cases had positive severe acute respiratory syndrome coronavirus 2 serology and four cases also had polymerase chain

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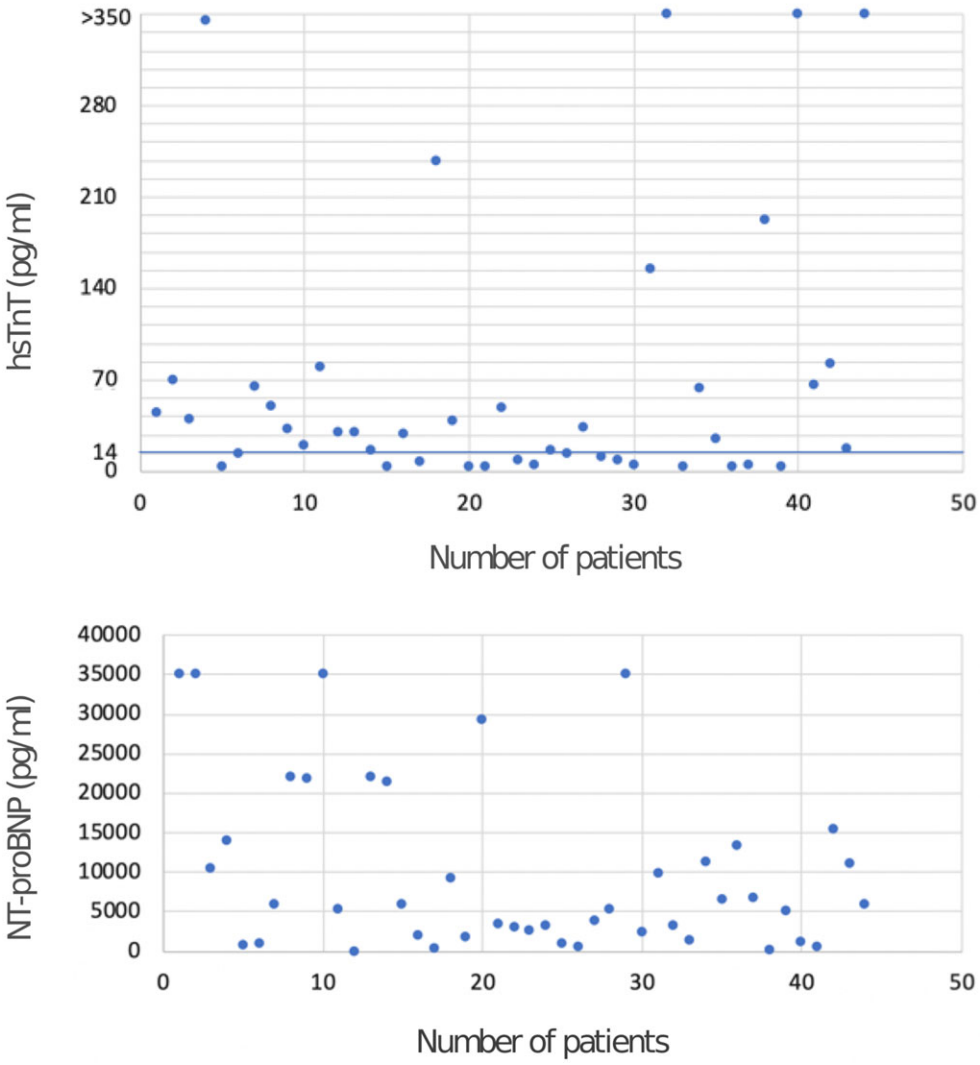



**Figure 1.** The distribution of hsTnT and NT-proBNP.

reaction positivity at the same time. The laboratory findings are shown in Table 1. All the cases had elevated N-terminal pro-B-type natriuretic peptide levels while high-sensitivity cardiac troponin T levels were elevated in 28 (63.6%) cases. The mean high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide levels were 162 ± 444.4 pg/ml and 10,054 ± 11,604 pg/ml, respectively. The distribution of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide is shown in Fig 1. There was a significant positive correlation between high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide ($p < 0.01$). The N-terminal pro-B-type natriuretic peptide levels were also positively correlated with the severity of MIS-C ($p < 0.05$).

Twenty-three (52.3%) cases had mild, nine (20.5%) had moderate, and twelve (27.3) had severe disease. Medical treatment was determined according to the severity of MISC. All cases were treated with intravenous immunoglobulin (2 g/kg), methylprednisolone, and acetylsalicylic acid (3–5 mg/kg/day). Methylprednisolone dose was adjusted according to the severity of MIS-C.[11] Low molecular weight heparin therapy was administered to 17 cases. Anakinra was used in only two cases with multi-organ failure and unresponsive to the intravenous immunoglobulin and methylprednisolone treatment. Twenty-four cases were followed up in the paediatric intensive care unit. The mean length of paediatric intensive care unit stay was 6.7 ± 6.36 days. Respiratory support (invasive and non-invasive) was required in 22 (50%) cases, and 18 cases (40%) required inotropic support. Two cases had haemodialysis and one case had plasma exchange. None of the cases needed mechanical circulatory support. The mean duration of hospitalisation was 13.52 ± 17.5 days.

Thirty-four (77.2%) cases had an electrocardiographic abnormality during hospitalisation. The electrocardiographic abnormalities are shown in Table 2. The most common finding was sinus tachycardia (50%) as expected. Sinus bradycardia was observed in 18 (40%) cases and eight cases with bradycardia had previously tachycardia. Sinus bradycardia appeared on a median of 3.5 days (min.–max.: 2–14). In only one case, frequent ventricular extrasystoles developed 6 months after discharge as a late manifestation.

Thirty-one (70.4%) cases had an echocardiographic abnormality. The echocardiographic findings are shown in Table 2. Twelve cases (27.3%) had left ventricular systolic dysfunction (left ventricular ejection fraction < 55%): nine (20.4 %) with mild (left ventricular ejection fraction 41–55%) and three (6%) with moderate (left ventricular ejection fraction 31–40%) left ventricular systolic dysfunction. The lowest left ventricular ejection fraction

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**Table 2.** Electrocardiographic, echocardiographic, and cardiac magnetic resonance findings of cases with MIS-C.

| | | | n (%) |
|---|---|---|---|
| **Electrocardiographic findings (n = 44; 100%)** | Electrocardiographic abnormality | | 34 (77.2) |
| | Sinus tachycardia | | 22 (50) |
| | Sinus bradycardia | | 18 (40.9) |
| | Arrhythmias | | 6 (13.6) |
| | ST-T changes | | 6 (13.6) |
| **Echocardiographic findings (n = 44; 100%)** | Echocardiographic abnormality | | 31 (70.4) |
| | LV systolic dysfunction Simpson's biplane LVEF <55% | | 12 (27.3) |
| | Coronary dilation (Z-score >2.5 or wall irregularity) | | 2 (4.5) |
| | Pericardial effusion | | 14 (31.8) |
| | Aortic valve regurgitation | | 6 (13.6) |
| | Mitral valve regurgitation | | 25 (56.8) |
| | TAPSE, mm | <15, n (%) | 7 (15.9) |
| | MAPSE, mm | <10, n (%) | 9 (20.4) |
| | TAPSE Z-score | <−2 | 9 (20.4) |
| | Mitral E/A | <1 | 2 |
| | | 1–2 | 41 |
| | | >2 | 1 |
| | E/e' | <8 | 25 |
| | | 8–15 | 15 |
| | | >15 | 4 |
| ***Cardiac magnetic resonance imaging* (n = 28; 63.6%)** | Late gadolinium enhancement | | 3 (10.7) |
| | Pericardial effusion | | 7 (25) |
| | LV systolic dysfunction | LVEF 50–55% | 8 (28.5) |
| | | LVEF 40–49% | 2 (7.1) |
| | | LVEF 30–39 % | 1 (3.5) |

n=number of patients; %=column percentage; LV=left ventricle; LVEF=left ventricular ejection fraction; MIS-C=multisystem inflammatory syndrome in children.

in the first week was used for the statistical analyses. Also, in nine (20.4 %) cases, mitral annular plane systolic excursion was under 10 mm. The mean tricuspid annular plane systolic excursion value was 18.2 ± 3.4 and nine (20.4%) cases had a tricuspid annular plane systolic excursion Z-score of <−2. To assess left ventricular diastolic dysfunction, E/A ratio, mitral lateral and septal e' velocity, and E/e' ratio were evaluated. The distribution of cases with a Z-score of <−2 for tissue Doppler index was as follows: mitral lateral: E'(n:11;25%), A'(n:2;4.5%), and S'(n:3;6.8%); septal: E' (n:9;20%), A'(n:3;6.8%), and S'(n:7;15.9%); and tricuspid: E' (n:2;4.5%), A'(n:3;6.8%), and S'(n:12;27%). However, Z-scores of tissue Doppler velocities of all cases were within normal range at discharge. The most common valvular abnormality was mitral regurgitation (n:25;56.8%). Pericardial effusion was detected in only 14 cases (31.8%) on admission, all of which was completely resolved during the course of hospitalisation. None of the cases with pericardial effusion had signs of cardiac tamponade. Simpson's biplane left ventricular ejection fraction was significantly correlated with mitral E, septal E, tricuspid annular plane systolic excursion Z-score, paediatric intensive care unit, and hospitalisation duration (respectively, p: 0.007, 0.006, <0.000, 0.016, 0.009). There was a significant relationship between E/e' value and N-terminal pro-B-type natriuretic peptide, hospitalisation duration, and paediatric intensive care unit follow-up days (respectively p = 0.029, 0.037, <0.001). The univariate logistic regression analysis' results for left ventricular ejection fraction are shown in Table 3.

The N-terminal pro-B-type natriuretic peptide was significantly higher in cases who necessitated inotropic support and paediatric intensive care unit requirement (p < 0.001). The N-terminal pro-B-type natriuretic peptide and high-sensitivity cardiac troponin T were negatively correlated with Simpson's biplane left ventricular ejection fraction and M-mode left ventricular fractional shortening (respectively, p < 0.001, p = 0.005). When Receiver operating characteristic analysis was performed for N-terminal pro-B-type natriuretic peptide, according to left ventricular systolic dysfunction (left ventricular ejection fraction < 55), the value under the curve was 0.784, and the standard error value for this area was 0.075, and it was statistically significant (p = 0.004). The most ideal cut-off value for N-terminal pro-B-type natriuretic peptide was 8023 pg/ml according to Youden Index. When Receiver operating characteristic analysis was performed for high-sensitivity cardiac

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**Table 3.** Univariate logistic regression results for left ventricular ejection fraction.

| Variables (references) | Beta coefficient | Standard error | p value | Odds ratio (OR) | 95% confidence intervals for OR | |
|---|---|---|---|---|---|---|
| | | | | | Lower limit | Upper limit |
| **NT-proBNP** | 0.001 | 0.001 | **0.012*** | 1.001 | 1.001 | 1.002 |
| **HsTnT** | 0.001 | 0.001 | 0.142 | 1.001 | 0.999 | 1.003 |
| **Inotropic support** | 2.708 | 0.876 | **0.002*** | 15.000 | 2.696 | 83.445 |
| **TDI mitral E'** | −0.501 | 0.295 | 0.090 | 0.606 | 0.340 | 1.080 |
| **TDI mitral A'** | −0.239 | 0.251 | 0.342 | 0.788 | 0.482 | 1.288 |
| **TDI mitral S'** | −0.491 | 0.423 | 0.246 | 0.612 | 0.267 | 1.402 |
| **TDI septal E'** | −0.926 | 0.392 | **0.018*** | 0.396 | 0.184 | 0.855 |
| **TDI septal A'** | −0.506 | 0.299 | 0.090 | 0.603 | 0.336 | 1.083 |
| **TDI septal S'** | −0.425 | 0.282 | 0.131 | 0.654 | 0.376 | 1.135 |
| **TAPSE Z-score** | −1.061 | 0.352 | **0.003*** | 0.346 | 0.174 | 0.690 |
| **MAPSE** | −0.280 | 0.157 | 0.074 | 0.756 | 0.556 | 1.028 |
| **LVEDD Z-score** | −1.012 | 0.425 | **0.017*** | 0.364 | 0.158 | 0.837 |
| **Sex** | 0.085 | 0.685 | 0.901 | 1.089 | 0.284 | 4.173 |
| **Age** | 0.004 | 0.006 | 0.474 | 1.004 | 0.992 | 1.016 |

NT-proBNP=N-terminal pro-B-type natriuretic peptide; HsTnT=high-sensitivity cardiac troponin T; TDI=tissue Doppler index; LVEDD=left ventricular end-diastolic diameter.
Bold* values denote statistical significance at the $p < 0.05$ level.

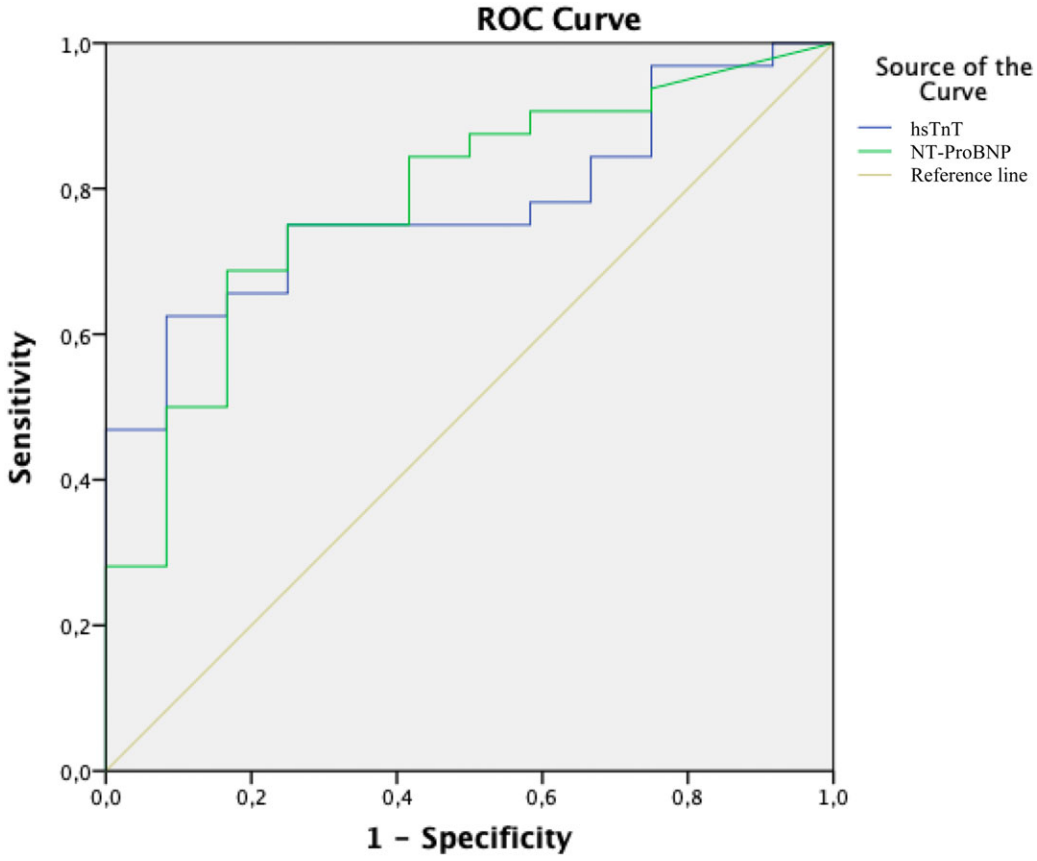



**Figure 2.** NT-proBNP and hsTnT's Receiver operating characteristic analysis results according to left ventricular systolic dysfunction.

troponin T, according to left ventricular systolic dysfunction (left ventricular ejection fraction < 55), the value under the curve was 0.776, and the standard error value for this area was 0.070, and it was statistically significant ($p = 0.005$). The most ideal cut-off value for high-sensitivity cardiac troponin T was 39.5 pg/ml, according to Youden Index (Fig 2).'

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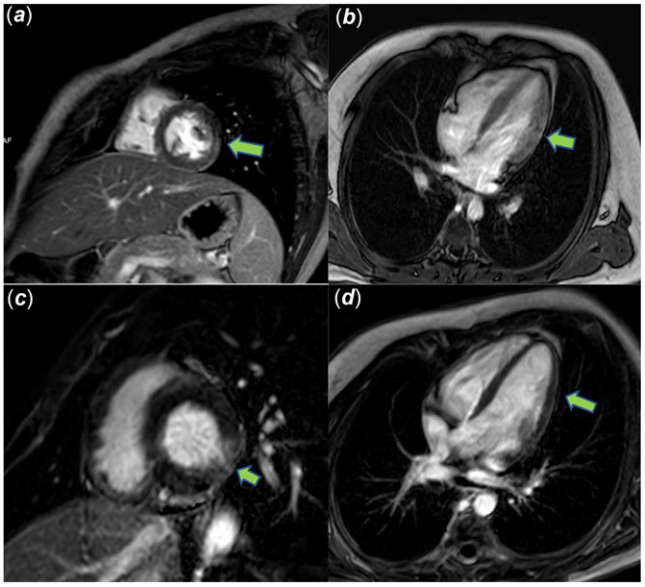



**Figure 3.** Late gadolinium enhancement, cardiac magnetic resonance images in MIS-C cases. (***a***) Left ventricular free wall (***b***) Left ventricular free wall lateral-basal area (***c***) Left ventricular lateral-basal area (***d***) Lateral subepicardial left ventricular wall (green arrows).

Cardiac magnetic resonance imaging was performed in 28 cases (63.6%) at a median duration of 2.3 months (min−max: 1−11 months) after discharge. As previously stated, only in one case, cardiac magnetic resonance was performed in the 18th month of the follow-up, because the initial cardiac magnetic resonance could not be performed. Thus, no statistical analysis related to the cardiac magnetic resonance of this patient was performed. Cardiac magnetic resonance revealed early and late gadolinium enhancement in the subepicardial area of the left ventricular free wall in one case. In this case, there was also a slight increase in intensity in the same area in T2-weighted images. Transmural late gadolinium enhancement was seen in the basal area of the left ventricle lateral wall in other two cases (Fig 3). Minimal pericardial effusion was present in seven cases. Five cases with pericardial effusion also had pericardial effusion on echocardiography at the time of admission, but there was no effusion in echocardiographic examinations at the time of cardiac magnetic resonance. Global left ventricular function measurement by cardiac magnetic resonance showed that 17 cases had normal function (ejection fraction > 55%), eight cases had borderline dysfunction (ejection fraction 50–55%), two cases had mild left ventricular dysfunction (ejection fraction 40–49%), and one case had moderate left ventricular dysfunction (ejection fraction 30–39%). Five of the cases with echocardiographic left ventricular systolic dysfunction on admission also had low cardiac magnetic resonance left ventricular ejection fraction. However, at the time of cardiac magnetic resonance, all patients had normal left ventricular systolic function by echocardiography.

The mean follow-up period was 17.5 ± 4.85 months. The cardiovascular abnormalities of all cases except two completely recovered during follow-up period. One of these cases died on the second day due to intractable shock and multi-organ failure. The second case also has leukocyte adhesion deficiency and he has ongoing left ventricular systolic dysfunction but clinically asymptomatic with medical treatment. The parents of this case did not give permission for initial cardiac magnetic resonance, but later on they accepted to participate in cardiac magnetic resonance because of ongoing left ventricular systolic dysfunction. Cardiac magnetic resonance performed at 18 months of follow-up revealed left ventricular ejection fraction of 48% and late gadolinium enhancement on the inferior, anterolateral, and inferolateral of left ventricle basal subepicardial area. Interestingly, in another case, frequent ventricular extrasystoles occurred 6 months after discharge. Although this case had no echocardiographic abnormality during follow-up, mild left ventricular systolic dysfunction (left ventricular ejection fraction was 44%) and pericardial effusion were detected at the cardiac magnetic resonance imaging. We did not observe any recurrence of cardiac abnormalities during the follow-up in the rest of the cases. Moreover, when the control cardiac magnetic resonance was performed in the 1st year of the follow-up to the three cases with myocardial involvement in initial cardiac magnetic resonance, we observed that previous cardiac magnetic resonance pathologies were completely recovered.

## Discussion

The severe acute respiratory syndrome coronavirus 2 infection in children causes a severe and potentially fatal disease known as MIS-C. MIS-C is defined as a disease with multiple system involvement in children that develops 2–6 weeks after severe acute respiratory syndrome coronavirus 2 infection. Variable degrees of abnormalities in cardiac enzymes, electrocardiography, echocardiography, and cardiac magnetic resonance imaging have been reported in children with MIS-C. In this study, we aimed to evaluate the cardiac manifestations of MIS-C and to evaluate the correlation of echocardiographic and cardiac magnetic resonance findings. The frequency of cardiovascular involvement was reported as 34–82% in MIS-C, and similarly, the rate of cardiovascular involvement was 61.9% in our study.

Left ventricular systolic dysfunction, coronary artery anomalies, valve regurgitation, and pericardial effusion are the most common cardiovascular abnormalities that have been observed in children with MIS-C. In our study, left ventricular systolic dysfunction, valvulitis, and pericardial effusion were the most common echocardiographic findings on admission in cases with MIS-C. In series with a large number of cases, the rate of left ventricular dysfunction is reported as 30–35%, and similarly, this rate was 27% in our study. In studies with a sample size, including more than 50 children with MIS-C, the incidence of coronary artery abnormalities, pericardial effusion, and valvular insufficiency was 14–28%, 9–28%, and 24-–48%, respectively.[20] Similarly, the rate of coronary artery abnormality, pericardial effusion, and valvular insufficiency in our study was 4.6%, 31.8%, and 56.8%, respectively. In our study, the rate of coronary abnormality was lower in comparison to other studies.[21] The low incidence of coronary dilatation may be due to the fact that our institution is a tertiary referral centre because patients requiring multidisciplinary approach rather than prominent cardiac involvement were more commonly referred to our institution and also the relatively higher mean age (8.5 ± 4.8 years) of the study group may be a contributing factor as coronary involvement is more common in younger ages. The decrease of tricuspid annular plane systolic excursion Z-score was observed in 20.4% of the cases and similarly, Valverde et al. reported that 33.4% of the cases had reduced right ventricular tricuspid annular plane systolic excursion (Z-score <−2) on admission.[22] Cardiac biomarkers are usually elevated in children with MIS-C.[22,23] Whittaker et al. reported the median troponin and N-terminal pro-B-type natriuretic peptide levels of cases that suffer shock as 45 (8–294) ng/L and 788 (174–10,548) pg/ml,

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respectively.[24] In our study, the median high-sensitivity cardiac troponin T level was 29.2 (3–2098) pg/ml and the median N-terminal pro-B-type natriuretic peptide level was 5222 (127–35,000) pg/ml. N-terminal pro-B-type natriuretic peptide level of 8023 pg/ml and high-sensitivity cardiac troponin T level of 39.5 pg/ml were determined as a cut-off value for determining left ventricular systolic dysfunction in our study. Although we failed to find any cut-off point for troponin and N-terminal pro-B-type natriuretic peptide in the literature, Soongswang et al. reported a level of 0.052 ng/ml is an appropriate cut-off point for cardiac troponin-T for the diagnosis of acute myocarditis.[25] Our study shows that an increase in N-terminal pro-B-type natriuretic peptide, rather than high-sensitivity cardiac troponin T, is more prominent in cases with MIS-C and left ventricular systolic dysfunction. Left ventricular systolic dysfunction may also be cause by acute myocarditis. Although this study does not compare troponin levels in acute myocarditis and MIS-C, to the best of our clinical expertise increase in troponin-T levels is more prominent in children with acute myocarditis in comparison to children with MIS-C.

In the last decades, cardiac magnetic resonance has been the diagnostic technique of choice in tertiary care facilities in patients with acute nonischaemic myocardial damage, and myocarditis is one of the most common reasons for cardiac magnetic resonance imaging in children.[26] Since MIS-C was first described, various studies about the cardiovascular involvement have been published but only a few of these studies have also evaluated cardiovascular involvement with cardiac magnetic resonance.

Decreased left ventricular ejection fraction, pericardial effusion, abnormal T2 myocardial values/hyperintense myocardium, and early and late gadolinium enhancement are the most common cardiac magnetic resonance findings in the studies conducted to show cardiovascular involvement and myocardial damage in MIS-C with cardiac magnetic resonance. In our study, we performed initial cardiac magnetic resonance in 28 cases and all cardiac magnetic resonance parameters were normal in 18/28 cases. Three cases had cardiac magnetic resonance findings that may be attributed to the presence of myocardial inflammation: one case had early and late gadolinium enhancement and increase of intensity in T2 sequence in the subepicardial area of the left ventricular free wall. The other two cases had transmural late gadolinium enhancement in the basal area on the lateral wall of the left ventricle. Pericardial effusion was observed in seven cases (32%). Valverde et al. evaluated 42 of 286 (14.7%) cases with MIS-C with cardiac magnetic resonance during hospitalisation (6–13 days) and reported T2 hyperintensity in 14 (33.3%), pericardial effusion in 10 (23.8%), early gadolinium enhancement in 1 (2.4%), and late gadolinium enhancement in 6 (14.3%) cases.[22]

Bermejo et al. evaluated 44 children with MIS-C, in whom cardiac magnetic resonance was performed between 12 and 72 days from the onset of symptoms. They reported that the left ventricular ejection fraction was mildly decreased in one case and small areas of late gadolinium enhancement were observed in two cases. Also, one case had an increased mean T1 value at the midventricular level, five cases had abnormal segmental T1 values, one case had higher T2 values in the apical lateral segment, and one case had abnormal T2 values at basal septum.[27] Theocharis et al. showed myocardial oedema and fibrosis in 50% of MIS-C cases ($n = 20$) regardless of cardiac function and timing of presentation.[28] Both oedema and fibrosis had global distribution patterns. Dilorenzo et al. reported mid-term cardiac magnetic resonance data in 13 children at 6–9 months following hospitalisation for MIS-C and one case had late gadolinium enhancement at the inferior insertion point and mid-ventricular inferolateral region, with normal ventricular function, no evidence of oedema or perfusion defects, and normal T1 and T2 times.[29] In a retrospective study, cardiac magnetic resonance was performed in 51 of 216 cases at a median time of 105 days (min.–max.:93–151 days). One case had a small area of mid myocardial late gadolinium enhancement in the basal inferior segment, another case had a thin area of subendocardial late gadolinium enhancement in the basal anterolateral segment, and none had elevated T2 values. Four cases had left ventricular ejection fraction < 55% (3 of 50–54%; 1 of 47%). There were no pericardial or pleural effusions in any of the cases. Webser et al. evaluated children diagnosed as MIS-C and coronavirus disease-2019 with cardiac magnetic resonance and reported that left and right ventricular ejection fractions were similar between cases and controls ($p = 0.66$ and 0.70, respectively).[30] Sirico et al. performed cardiac magnetic resonance imaging on 17 cases with MIS-C in the early acute phase (median 19 days after symptom's onset) and follow-up cardiac magnetic resonance was performed in 15 patients at 6 months after MIS-C diagnosis. Follow-up cardiac magnetic resonance showed the persistence of non-ischaemic late gadolinium enhancement in all patients with late gadolinium enhancement in the acute phase. However, quantitative analysis showed a reduction of the late gadolinium enhancement extension among the involved myocardial segments compared to the early phase. None of the cases had myocardial oedema on T2 sequences in the control cardiac magnetic resonance.[31,32] To the best of our knowledge, besides our study this is the only study in which control cardiac magnetic resonance was performed. Considering the findings of this study and our study, it may be more beneficial to perform follow-up cardiac magnetic resonance at the first year of follow-up if the patient is asymptomatic.

The most important parameter affecting the result of all these studies might be related to the examination time, as the timing of cardiac magnetic resonances varies from acute phase to long term in these studies. Another important factor is the selection bias for the cardiac magnetic resonance evaluation. There is no guideline about the role and timing of cardiac magnetic resonance in MIS-C; thus, most institutions have their own practices according to their clinical expertise. In our study, 28 of 44 cases were evaluated with cardiac magnetic resonance at a mean duration of 2, 5–3 months of admission and three cases with gadolinium enhancement were also evaluated at the 1 year of follow-up. It is well-known that MIS-C is a transient hyperinflammatory state and after successful management of the acute phase most abnormalities are completely resolved. Cardiac abnormalities of all cases except two cases (one case with left ventricular systolic dysfunction and one case who had died) were completely resolved. Although all the patients had normal left ventricular systolic dysfunction at the time of cardiac magnetic resonance except one case, cardiac magnetic resonance revealed borderline, mild, and moderate left ventricular systolic dysfunction in eight (18%), two (4.5%), and one (2.2%) cases, respectively. Chakraborty et al. evaluated 23 of 80 children with MIS-C at the 6 $^{th}$ month of follow-up. Although 76.2% of the children had left ventricular systolic dysfunction on admission, all had normal left ventricular systolic functions by echocardiography at the 6$^{th}$ month of follow-up. Similar to our study, although all cases had normal left ventricular systolic function by echocardiography at the time of cardiac magnetic resonance, cardiac magnetic resonance revealed abnormal left ventricular ejection fraction in 15% cases and persistent late gadolinium enhancement

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in 14.3% of the cases. In addition to this, none of the patients had myocardial oedema in T2-weighted image sequence. They concluded that these findings probably represent either ongoing subtle myocardial damage or results of previous scarring, resulting in abnormal myocardial tissue characteristics and that the recovery of real volumetric measurements of systolic function may be more slower than known, with subtle abnormalities lasting up to 6 months. [33] Benvenuto et al. evaluated 20 MIS-C patients with cardiac magnetic resonance at the median 3 months. Twenty percent had mildly reduced left ventricular ejection fraction, 15% had myocardial oedema or fibrosis at T1 sequence, 5% had prolonged T2 time, and 25% had minimal late gadolinium enhancement.[21] Three of the four cases with mildly reduced left ventricular ejection fraction in cardiac magnetic resonance had normal left ventricular ejection fraction by echocardiography. The discrepancy in left ventricular ejection fraction measured by echocardiography and cardiac magnetic resonance may be due to the fact that cardiac magnetic resonance is more sensitive in means of volumetric measurement, and the real recovery of systolic function may be more slower than known as concluded by Chakraborty et al., but on the other hand the inadequate reading techniques and the variations in cardiac magnetic resonance software's used for interpretation may contribute to disparities in measurement.

In our study, limited number of patients had gadolinium enhancement on cardiac magnetic resonance. Early and late gadolinium enhancement was observed in one patient with signal changes consistent with oedema in the subepicardial area of the left ventricular free wall in T2A sequence. Acute myocarditis was considered if contrast agent uptake was observed in early gadolinium enhancement. The other two cases had transmural late gadolinium enhancement in the basal area on the lateral wall of the left ventricle. As a result, lateral wall of left ventricle was the most common site of involvement in cardiac magnetic resonance. Although subepicardial late gadolinium enhancement is more common finding in postinfectious myocarditis, in our study, only one of three patients had subepicardial late gadolinium enhancement. The other two cases had transmural late gadolinium enhancement, which is more common in infiltrative and ischaemic diseases. Any further conclusion or comparison regarding gadolinium enhancement cannot be made based on our findings, because of the very low number of cases with late gadolinium enhancement. The 1st year cardiac magnetic resonance evaluation of these three cases was completely normal, and this finding supports the fact that cardiac involvement in MIS-C is mostly completely resolved.

## Conclusion

Our study showed that an increase in N-terminal pro-B-type natriuretic peptide is more prominent than troponin in children with MIS-C and cardiovascular involvement. Although left ventricular dysfunction is more common, right ventricular functions may also be affected. Even though the cases may present in a cardiogenic shock state, most of the cases have a rapid and complete recovery in a brief time with appropriate support and treatment. Cardiac magnetic resonance imaging is a valuable tool to evaluate myocardial involvement, but in our study, most of the cases with clinical, echocardiographic, and laboratory findings of cardiovascular involvement and dysfunction had no prominent cardiac magnetic resonance findings. Although the number of cases with cardiac magnetic resonance findings was not sufficient to make any concrete conclusion and it does not determine or change the treatment modalities, it is observed that children even with normal echocardiographic findings may have abnormal cardiac magnetic resonance findings such as fibrosis and oedema. Thus, cardiac magnetic resonance may be beneficial in selected cases, such as evaluation of patients who are willing to participate in sports.

### Study limitations

The relatively small sample size was the main limitation of our study. Due to technical difficulties/issues, we could not do cardiac magnetic resonance in all cases as some patients have refused the procedure due to claustrophobia or the risk of sedation. One case with late gadolinium enhancement on the cardiac magnetic resonance at 18 months was not included in the statistical analyses because the statistical analyses were performed according to the initial cardiac magnetic resonance findings.

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**Competing interests.** None.

**Ethical standard.** The authors assert that all procedures contributing to this work follow the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the ethics committee of Ankara University. (Date/No: 06.05.2021/ i4-274-21).

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