Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2023

Research Article / Araştırma Makalesi

Evaluation of Multisystem Inflammatory Syndrome in Children (MIS-C) Cases: Clinical Features and Cardiologic Findings

Multisistemik İnflamatuvar Sendrom (MIS-C) Olgularının Klinik Özelliklerinin ve Kardiyolojik Bulgularının Değerlendirilmesi

[1]Yalçın Kara, [1]Mahmut Can Kızıl, [2]Gürkan Bozan, [2]Eylem Kıral, [3]Ayşe Sülü, [3]Pelin Köşger, [1]Ömer Kılıç, [3]Birsen Uçar, [2]Ener Çağrı Dinleyici

[1]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Eskişehir, Turkey
[2]Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care, Eskişehir, Turkey
[3]Eskişehir Osmangazi UniversityFaculty of Medicine, Department of Pediatrics, Division of Pediatric Cardiology, Eskişehir, Turkey

Abstract: Multisystem inflammatory syndrome in children (MIS-C) is a disease characterized by hyperinflammation with multiple organ involvement that develops after COVID-19 infection. In this study, we aimed to assess the clinical characteristics, cardiologic findings, and cardiac magnetic resonance imaging (MRI) results of MIS-C cases. Thirty-one patients diagnosed with MIS-C and followed up at Eskişehir Osmangazi University Faculty of Medicine between November 2020 and June 2022 were included in the study. The clinical and epidemiological characteristics and cardiological findings of the patients were evaluated retrospectively. Fifty-five percent of the thirty-one MIS-C cases were male and the mean age was 102 (2-204) months. The most common presenting symptoms were fever, rash, conjunctivitis, and abdominal pain. The most common cardiac findings were left ventricular dysfunction, myocarditis, and coronary artery dilatation. Cardiac MRI was performed in 4 of 8 patients with severe cardiac findings, and no pathologic findings were noted. Patients who had hypotension and cardiogenic shock at the time of admission, who had high ferritin, D-dimer, and IL -6 levels on laboratory tests, and who had left ventricular dysfunction and myocarditis on echocardiography had a high rate of ICU admission. The degree of cardiovascular involvement is important in following up on the disease and determining the treatment regimen. All patients should be monitored by echocardiography and cardiac MRI for possible permanent cardiac damage. Although MIS-C can lead to serious, life-threatening cardiac manifestations, early diagnosis and appropriate treatment can prevent the risk of serious cardiac morbidity and mortality in the future.
Keywords: MIS-C, cardiac involvement, cardiac MRI, echocardiography

Özet: Çocuklarda multisistemik inflamatuvar sendrom (MIS-C), COVID-19 enfeksiyonu sonrası gelişen, çoklu organ tutulumuyla giden hiperinflamasyonla karakterize bir hastalık tablosudur. Bu çalışmada, MIS-C olgularının klinik özelliklerinin, kardiyolojik bulgularının ve kardiyak manyetik rezonans görüntüleme (MRG) sonuçlarının değerlendirilmesi amaçlanmıştır. Çalışmaya Eskişehir Osmangazi Üniversitesi Tıp Fakültesi'nde, Kasım 2020-Haziran 2022 tarihleri arasında takip edilen MIS-C tanılı 31 olgu dahil edildi. Olguların klinik, epidemiyolojik özellikleri ve kardiyolojik bulguları retrospektif olarak değerlendirildi. Çalışmaya dahil edilen 31 olgunun 17'si (%55) erkek, 14'ü (%45) kız idi. Yaş ortalaması 102 (2-204) ay idi. En sık başvuru semptomları sırasıyla ateş, döküntü, konjunktivit ve karın ağrısıydı. En sık kardiyolojik bulgular ise; sol ventrikül disfonksiyonu, myokardit ve koroner dilatasyondu. Ağır kardiyolojik bulguları olan 8 olgunun 4'üne kardiyak MRG yapıldı, patolojik bulgu saptanmadı. Hipotansiyon ve şok bulguları olan, laboratuvar tetkiklerinde ferritin, D-dimer, IL-6 yüksekliği olan, ekokardiyografide sol ventrikül disfonksiyonu ve myokardit bulguları olan hastaların, yoğun bakım yatış oranları daha yüksekti. Kardiyovasküler tutulumun derecesi hastalığın takibinde ve tedavi rejiminin belirlenmesinde önemlidir. Olası kalıcı kardiyak hasar açısından tüm hastalar ekokardiyografi ve kardiyak MRG ile izlenmelidir. MIS-C ciddi, yaşamı tehdit eden kardiyak belirtilere yol açabilse de, erken tanı ve uygun tedavi gelecekte ciddi kardiyak morbidite ve mortalite riskini önleyebilir.
Anahtar Kelimeler: MIS-C, pediatrik, ekokardiyografi, MRG

ORCID ID of the authors: YK. 0000-0003-0569-1106, MCK. 0000-0002-6231-4238, GB. 0000-0001-5041-8892, EK.0000-0003-2245-5340, AS. 0000-0001-6384-3935, PK. 0000-0002-3926-9002, OK. 0000-0003-0168-4080, BU. 0000-0002-7746-6058, ECD. 0000-0002-0339-0134.

Received 03.10.2022 ***Accepted*** .03.01.2023 ***Online published*** 05.01.2023

Correspondence: Yalçın KARA- Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Eskişehir, Turkey e-mail: dryalcinkara@hotmail.com

Kara Y, Kizil MC, Bozan G, Kiral E, Sülü A, Kosger P, Kilic O, Ucar B, Dinleyici EC, Evaluation of Multisystem Inflammatory Syndrome in Children (MIS-C) Cases: Clinical Features and Cardiologic Findings, Osmangazi Journal of Medicine, 2023, ***Doi:*** *10.20515/otd.1183749*

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, a newly identified member of the coronavirus family, was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (1,2). The incidence in children is lower than in adults, and symptoms are known to be milder. Beginning in April 2020, as the incidence of COVID-19 increased in many countries, pediatric cases admitted to hospitals in Europe and the United States began to be reported with multisystem symptoms somewhat similar to Kawasaki disease and toxic shock syndrome (3-7). Subsequently, similar cases continued to be reported from around the world, and this inflammatory reaction was named multisystem inflammatory syndrome in children (MIS -C) by WHO and the Centers for Disease Control and Prevention (CDC), and diagnostic criteria were established (8,9). Persistent fever, multiorgan involvement (cardiovascular, gastrointestinal, neurologic, pulmonary, hematologic, renal, dermatologic), elevated inflammatory markers, evidence of past or current SARS-CoV-2 infection, and lack of any other alternative diagnosis to explain the current clinical picture were defined as the main criteria of MIS-C. The differential diagnosis of diseases such as Kawasaki disease, sepsis, macrophage activation syndrome, and toxic shock syndrome should be carefully performed before making the diagnosis in all patients because they cause similar clinical manifestations (8,9). MIS -C has a wide clinical spectrum, ranging from mild symptoms to severe shock and multiorgan failure requiring admission to the intensive care unit. The most important parameter determining the prognosis and mortality and morbidity of the disease is the degree of cardiac involvement (7,10). MIS-C most commonly results in left ventricular dysfunction, coronary artery dilatation, myocarditis, and less commonly valvulitis and valvular disease (10,11). The aim of this study was to analyze the epidemiological, clinical, laboratory, and echocardiography and cardiac magnetic resonance imaging (MRI) findings of cardiac involvement in MIS-C patients.

2. Materials and Methods

MIS-C cases followed between November 2020 and June 2022 in Eskişehir Osmangazi University Faculty of Medicine, Child Health and Diseases Clinic were included in the study. Thirty-one MIS-C patients with SARS-CoV-2 antibody or PCR positivity who were diagnosed with MIS-C according to WHO and CDC criteria were included in the study. Epidemiologic and clinical characteristics, COVID-19 contact history, underlying chronic disease, laboratory and radiologic findings, echocardiography findings, intensive care hospitalization (ICU), oxygen and inotrope support, treatment regimens, cardiologic findings, and 6-month follow-up cardiac MRI results were retrospectively evaluated. Patients with SARS-CoV-2 antibody or PCR positivity and clinical findings similar to MIS-C but compatible with any of the other alternative diagnoses such as sepsis, Kawasaki disease, and toxic shock syndrome were excluded. All patients were followed up with echocardiography intermittently after discharge. Cardiac magnetic resonance imaging was performed in the 6th month for the patients who received severe cardiological findings, intensive care hospitalization, and inotropic support at the time of diagnosis. Standard echocardiographic measurements were made according to American Society of Echocardiography guidelines. Coronary artery abnormalities were classified as follows: normal < 2, dilatation ≥ 2 to < 2.5, aneurysm ≥ 2.5. The study was initiated after the approval of the Ethics Committee of Eskişehir Osmangazi University.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. Continuous variables were expressed as median (minimum-maximum). After assessing normal distribution with the Kolmogorov-Smirnov test, parameters were compared between groups with the Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. P

values < 0.05 were considered statistically significant.

3. Results

Forty-one patients who were followed up with a preliminary diagnosis of MIS-C at Eskişehir Osmangazi University Pediatrics Clinic between November 2022 and June 2022 were included in the study. Ten patients diagnosed with sepsis, bacteremia, pyelonephritis, and Kawasaki Disease during the follow-up were excluded from the study. Of 31 cases, 17 (55%) were male and 14 (45%) were female. The mean age was 102 (range 2-204) months. Twenty-six (83%) of the patients were previously healthy, 2 had obesity, 1 had cerebral palsy, 1 had epilepsy, and 1 had autism. The most common presenting symptoms were fever, rash, conjunctivitis and abdominal pain. Sixty-one percent of cases had hypotension and 31% had a cardiogenic shock. The most common system involvement was gastrointestinal system, followed by the cardiologic, and neurologic systems. Among laboratory tests, acute phase reactants were elevated in 100%, lymphopenia in 70%, thrombocytopenia in 42%, hyponatremia in 70%, pro-BNP elevation in 90%, D-dimer elevation in 96%, ferritin elevation in 90%, and IL -6 elevation in 33% (Table 1 and table 2). Of 16 patients with cardiac findings, 8 had left ventricular dysfunction, 7 had myocarditis and 3 had coronary dilatation. Sixty-five percent of cases were followed up in the ICU and 35% in the ward and the mean duration of hospitalization was 10.9 (range 6-30) days (Table 3). Patients who had ICU admission had significantly higher rates of hematologic involvement, hypotension, tachycardia, shock, abdominal symptoms, left ventricular dysfunction in echocardiography, and higher levels of - ferritin, D-dimer, and IL-6 (Table-2). Cardiac MRI was performed in 4 of 8 patients with serious cardiac findings at month 6, and no pathologic findings were detected (Table 4). Coronary computed tomography (CT) angiography was performed on one patient and coronary ectasia was detected. Intravenous immunoglobulin (IVIG) was administered in all patients, steroids in 84%, acetylsalicylic acid (ASA) in 80%, low molecular weight heparin in 32%, antibiotic treatment in 96%, inotropic support in 48%, plasma exchange in 6.5%. 51% of patients were ventilated with masks, 10% with high-flow oxygen, and 6.5% with mechanical ventilatory support. All patients were discharged with a cure, and none of the patients died (Table 1)

Table 1. Clinical and Epidemiological Characteristics of MIS-C Cases

	n:31 (%)		n:31 (%)
Gender		**Admission**	
Boy	17 (55)	**Intensive Care**	20 (64)
Girl	14 (45)	**Inpatient**	11 (36)
Age (month)	102 (2-204)	**Chronic Disease**	6 (19)
Symptoms-Signs		**Laboratory Findings**	
Fever	31 (100)	**COVID Lg G (+)**	31 (100)
Rash	24 (77)	**COVID PCR (+)**	2 (6.5)
Conjunctivitis	23 (74)	**APR↑**	31 (100)
Abdominal Pain	21 (68)	**Lymphopenia**	22 (77)
Vomiting	19 (61)	**Thrombocytopenia**	13 (32)
Diarrhea	18 (58)	**Hyponatremia**	22 (70)
Confusion	14 (45)	**D-dimer ↑**	30 (96)
Acute Abdomen	6 (19)	**Ferritin ↑**	28 (90)
Tachicardia	24 (77)	**Pro-BNP ↑**	28 (90)
Hypotension	19 (61)	**IL-6 ↑**	8 (25)
Cardiogenic Shock	10 (32)		
Radiological Findings		**Treatment**	
Chest X-ray	31 (100)	**IVIG**	31 (100)
Pneumonic Consolidation	7 (23)	**Steroid**	26 (84)
Pulmonary Effusion	2 (6.5)	**Low dose (2/mg/kg)**	22 (71)
Thorax CT	10 (32)	**Pulse steroid(30 mg/kg)**	4 (13)
Pneumonic Consolidation	6 (19)	**Acetylsalicylic acid**	25 (81)
Pulmonary Effusion	4 (13	**LMWH**	10 (32)
Cardiac MRI	4 (13)	**Antibiotic**	30 (96)

Normal	4 (13)	**Inotrope**	15 (48)
Coronary CT Angiography	1 (3.5)	**Plasmapheresis**	2 (6.5)
Coronary Ectasia	1 (3.5)		
Echocardiography	16 (55)	**G.I. Involvement**	23 (74)
Left Ventricular Dysfunction	8 (25)	**Acute G.I. Involvement**	6 (19)
Myocarditis	7 (19)	**AcuteAppendicitis**	3 (10)
Coronary Dilatation	3 (10)	**Ileus**	2 (6.5)
Pericardial Effusion	2 (6.5)	**Invagination**	1 (3.5)
Cardiac Involvement	16 (52)	**OxygenSupport**	21 (68)
Neurological Involvement	14 (45)	**Mask**	16 (52)
Pulmonary Involvement	9 (29)	**HFO**	3 (10)
Hematological Involvement	5 (16)	**MV**	2 (6.5)
Renal Involvement	2 (6.5)		

APR: acute phase reactant, IL-6: interleukin-6, IVIG: intravenous immunoglobulin, LMWH: low molecular weight heparin, HFO: high flow oxygen, MV: mechanical ventilation

Table 2. Comparison of Clinical Characteristics of Intensive Care Patients

	Intensive Care (n:20) (%)	**Service (n:11) (%)**	**P**
Gender			
Boy	11 (65)	6 (35)	0,66
Girl	9 (64)	5 (36)	
Age (month)	114 (20-204)	80 (2-150)	0,08*
Chronic Disease	4 (80)	1 (20)	0,43
Cardiac Involvement	11 (68)	5 (32)	0,44
GIS Involvement	16 (70)	7 (30)	0,28
Neurological Involvement	11 (68)	5 (32)	0,44
Pulmonary	8 (89)	1 (11)	0,07
Hematological	5 (100)	0 (0)	0,02**
Renal	2 (66)	1 (33)	0,71
Hypotension	16 (84)	3 (16)	0,006
Tachicardia	18 (75)	6 (25)	0,03
Cardiogenic Shock	10 (100)	0	0,003
Acute GIS Involvement	6 (100)	0	0,05
Leukocyte	14110 ± 8824	9760 (4800-17000)	0,08*
Lymphocyte	982 ± 555	1510 ± 1269	0,21*
Platelets	194.000 ± 119.466	204.000 ± 78.000	0,81*
CRP	183 (19-601)	130 (28-257)	0,55**
Procalcitonin	24 (0,2-100)	8.3 (0.8-43)	0,32**
Na	134 (124-142)	132 (130-135)	0,28**
Ferritin	528 (78-3245)	352 (51-784)	0,05**
D-dimer	5.6 (1,2-27)	2.8 (1,1-13)	0,04**
Pro-BNP	4876 (10-35.000)	3100 (64-15500)	0,13**
IL-6	163 (3.9-12000)	2.2 (1.6-2.9)	0,03**
Echocardiography			
LV Dysfunction	6 (75)	2 (25)	
Myocarditis	6 (85)	1 (15)	0,04*
Coronary Dilation	0	3 (100)	
Pericardial Effusion	2 (12,5)	0	

*: *Chi-square, **: Mann Whitney U*
GIS: Gastrointestinal System, CRP: C-reaktive Protein, BNP: Brain Natriuretic Peptide, IL-6: Interleukin-6, LV: Left Ventricular

Table 3. Clinical and Epidemiological Characteristics of Cases with Cardiac Findings

	n:16 (%)
Age (month)	113 (36-172)
Gender	
Girl	9 (56)
Boy	7 (44)
Chronic Disease	4 (25)
Admission	
Intensive Care	11 (69)

Inpatient	5 (31)
Echocardiography	
Left Ventricular Dysfunction	8 (50)
Myocarditis	7 (44)
Coronary Dilatation	3 (18)
Pericardial effusion	2 (12)
Electrocardiography	
Arrhythmia	3 (18)
Tachicardia	15 (94)
Hypotension	12 (75)
Cardiogenic Shock	5 (31)
Treatment	
IVIG	16 (100)
Steroid	13 (81)
Acetylsalicylic acid	13 (13)
LMWH	5 (31)
Plasmapheresis	2 (12.6)
Inotrope	8 (50)
Pro-BNP ↑	14 (88)
Cardiac MR	4 (25)
Normal	4 (25)
Coronary CT Angiography	1 (6)
Coronary Ectasia	1 (6)

IL-6: interleukin-6, IVIG: intravenous immunoglobulin, LMWH: low molecular weight Heparin
CT: Computed Tomography, MR: Magnetic Resonance

Table 4. Cardiac MRI Findings of the Cases with Severe Cardiac Findings

	Age (month)	Echocardiography	Treatment	Cardiac MRI
Case-1	144	Pericardial Effusion Pulmonary Hypertension Tricuspid Regurgitation Aortic Regurgitation Mitral Regurgitation	IVIG Pulse Steroid LMWH Acetylsalicylic Acid Plasmapheresis Inotropic	Normal
Case-2	168	Coronary Artery Dilatation Left Ventricular Dysfunction Mitral Regurgitation	IVIG Pulse Steroid LMWH Acetylsalicylic Acid Plasmapheresis Inotropic	Normal
Case-3	180	Myocarditis	IVIG Pulse Steroid LMWH Acetysalicylic acid Plasmapheresis	Normal
Case-4	146	Coronary Artery Dilatation Left Ventricular Dysfunction	İVİG Steroid (2 mg/kg) Acetysalicylic acid	Normal

MRI: magnetic resonance imaging, IVIG: intravenous immunoglobulin, LMWH: low molecular weight heparin

4. Discussion

The aim of this study is to evaluate the clinical and epidemiological features and especially cardiac findings of MIS-C cases. Previous studies reported that MIS-C cases were more common in males and school children aged 7.5-10 years, and most patients were previously healthy (6,7). MIS -C patients present with a wide clinical spectrum at the time of admission. However, the most common symptoms in studies are fever, followed by gastrointestinal symptoms such as diarrhea, abdominal pain, and vomiting;

Kawasaki syndrome-like symptoms such as rash, conjunctivitis, and lymphadenopathy; and neurologic symptoms such as headache and confusion. Feldstein et al. reported that all patients had a high fever and 92% had gastrointestinal symptoms, Whittaker et al. showed that the most common symptoms at the time of admission were high fever (100%), rash (52%), abdominal pain (53%), and conjunctivitis (45%) (3,7). In our country, Yılmaz-Çiftdoğan et al. reported fever in all patients, fatigue in 81%, gastrointestinal findings in 77%, rash in 54%, conjunctivitis in 49%, respiratory symptoms in 34%, and headache in 24% (12). In our study, the most common symptoms on admission were fever, rash, conjunctivitis, and gastrointestinal symptoms such as abdominal pain and diarrhea, and fatigue. In addition, the gastrointestinal system (74%), heart (52%), neurological system (45%), pulmonary system (29%), and hematological system (16%) were most commonly affected. When MIS-C was first defined, only cases such as Kawasaki disease and toxic shock syndrome were commonly diagnosed. Over time, the diagnosis rate of MIS-C by clinicians has increased as specific diagnostic criteria have been established in all countries. Therefore, different rates of systemic involvement have been reported in different studies.

The rate of admission to the intensive care unit ranges from 30% to 80% in different studies (7,12-14). In our country, the rates of admission to the ICU were reported to be 37.6% by Yılmaz-Çiftdoğan et al, 25.9% by Kıymet et al, and 31.3% by Sözeri et al (14-16). In our study, there was a higher rate of ICU admission (64%) compared to the data of our country. In a study comparing the clinical and laboratory examinations of the patients with intensive care admission, it was demonstrated that the patients who required intensive care had more cardiac involvement, the fever lasted longer, hypotension and oxygen requirements were more frequent at the time of admission (17). Regarding laboratory findings, patients requiring intensive care were reported to have higher CRP, IL-6, troponin, ferritin, and pro-BNP levels, and lower lymphocyte and platelet counts (17). Another study found that ICU patients were older than ward patients, respiratory findings such as dyspnea and shortness of breath on admission, gastrointestinal findings such as abdominal pain, and cardiac findings such as cardiogenic shock and left ventricular dysfunction were more common (11). Regarding laboratory findings, CRP, D-dimer, ferritin, and pro-BNP levels were reported to be higher (11). In another study conducted in our country, no association was found between gastrointestinal, cardiac, and neurological system involvement and ICU admission; however, it was found that patients with respiratory system findings and hypotension required more intensive care at the time of admission (14). Similar to previous studies, the average age of patients requiring intensive care was higher in our study, whereas hypotension, tachycardia, and cardiogenic shock were more common. No correlation was found between gastrointestinal, pulmonary, neurologic, and renal system involvement and ICU admission. However, patients with hematologic involvement such as coagulopathy and patients with left ventricular dysfunction and myocarditis required more intensive care. Laboratory findings of patients with intensive care admission had higher ferritin, D-dimer, and IL -6 levels. There are many different reports on the rate of critical care admission and the correlation between critical care admission and system involvement, which can be explained by the fact that the critical care capacity of centers varies and the criteria for ICU admission may vary from center to center. When MIS-C was first defined, most cases diagnosed were those with Kawasaki-like symptoms and predominant cardiac involvement. With the widespread use of the MIS-C diagnosis and treatment guidelines in all centers, the diagnosis has increased in patients presenting with different system findings. This may have contributed to the change in ICU admissions and cardiac involvement.

Cardiac involvement is the most common systemic involvement in MIS -C patients and plays an important role in disease prognosis and treatment plans. The rate of cardiac involvement varies from 50-95% in different studies (3,7,10,13,18-20). Valverde et al. found that 93% of the patients had cardiac

involvement and the most common cardiological findings were cardiogenic shock (40.2%), arrhythmia (35%), mitral regurgitation (38%), ventricular dysfunction (34%), pericardial effusion (27.9%) and coronary artery dilatation (24%) (10). Feldstein et al. reported that cardiac findings were present in 80% of patients, and the most common findings were hypotension/shock (48%) requiring inotropic agents, left ventricular dysfunction (38%), pericardial effusion/pericarditis (26%), arrhythmia (12%), and coronary dilation (8%) (7). In laboratory tests, the most common findings were elevated BNP (73%) and elevated troponin (50%) (7). In studies conducted in our country, Yılmaz-Çiftdoğan et al. found cardiac findings such as valvulitis, myocarditis, pericarditis, left ventricular dysfunction, and coronary artery dilatation in 75.6% of 614 MIS-C patients (12). Kavurt et al. in their study of 50 MIS-C patients, found pericardial effusion in 72%, pleural effusion in 52%, left ventricular dysfunction in 52%, mitral regurgitation in 50%, and coronary artery dilatation in 4% (21). In our study, 52% of the patients had cardiological findings, and the most common were left ventricular dysfunction, myocarditis, coronary dilatation, and pericardial effusion. In our study, cardiological findings were also less common than those reported in the literature. The most common cardiac finding was left ventricular dysfunction, which is also found in the literature, whereas coronary dilatation was less common. It has been reported that patients with hypotension, shock, and myocarditis are admitted to the ICU more frequently than patients with coronary dilatation/aneurysm (7,10,11,22,23). Laboratory tests show that pro-BNP and troponin levels are higher during ICU admission (10-11, 22-23). In our study, no difference was found between the patients with and without cardiac involvement in relation to ICU admission. However, it was found that patients with left ventricular dysfunction, myocarditis, and cardiogenic shock required more intensive care compared with patients with coronary artery dilatation, which is consistent with the literature. This can be explained by the fact that more patients presented with hypotension and cardiogenic shock in our study and that these patients were followed up in the intensive care unit because of the need for inotropics and impaired hemodynamic parameters.

The American College of Rheumatology recommended that all patients be evaluated by echocardiography and cardiac MRI no earlier than 2-6 months after diagnosis to determine the long-term cardiac effects of MIS-C cases (24). Capone et al. performed cardiac MRI in 11 of 50 MIS-C patients 2-4 weeks after discharge and found no signs of fibrosis or myocardial edema in any of the cases (25). Dominguez et al. detected myocardial edema, pericardial effusion and left ventricular dysfunction in 12 patients who underwent cardiac MRI on the day 5 to 100 after discharge (26). On the other hand, Aslan et al. performed cardiac MRI in 31 of 34 MIS-C patients 3-6 months after discharge and reported that they detected at least one cardiac pathology in 61% of the patients, such as pericardial effusion (45.2%), right ventricular dysfunction (19.4%), and left ventricular dysfunction (16.7%) (22). Similarly, in our study, cardiac MRI was performed in only 4 of 31 patients 6 months after discharge, and no cardiac pathology was detected in 4 patients. The fact that different cardiac MRI findings have been noted in the literature can be explained by the fact that in some studies it was performed in the acute phase and the long-term continuation of the treatment process. As in our study, it has been revealed that MIS-C can be cured without permanent cardiac damage with an appropriate protocol and appropriate treatment duration depending on the degree of cardiac involvement and disease on admission.

Treatment of MIS -C patients requires a multidisciplinary approach, and the mainstay of treatment is IVIG, steroids, and anticoagulants. Valverde et al. reported in their study of 286 MIS-C patients that 78.3% of patients received IVIG, 28% systemic steroids, 74.1% acetylsalicylic acid, and 30% inotropic support (10). Yılmaz-Çiftdoğan et al. reported that 614 MIS-C patients were treated with IVIG (93%), steroids (83%), acetylsalicylic acid (66%), anticoagulants

(59%), inotropics (19%), biologic agents (6.4%), and plasma exchange (1.6%) (12). In our study, all patients were administered IVIG, 84% steroids, 81% acetylsalicylic acid, 32% low-molecular-weight heparin (LMWH), 96% empiric antibiotics, 48% inotropics, and 6% plasma exchange treatment. Although there are differences in treatment regimens from center to center, the presence of hypotension and shock findings, the degree of left ventricular dysfunction, the presence of coronary dilation for anticoagulant therapy, and blood D-dimer, ferritin, and pro-BNP levels may guide the treatment regimen. This study had several limitations, including the fact that it was retrospective with single-center data, the small number of patients, and the infrequency of cardiac MRI scans.

In conclusion, multisystemic inflammatory syndrome is an autoinflammatory disease in children with manifestations involving multiple systems, particularly the cardiovascular system. Age, hypotension, cardiogenic shock and laboratory findings such as high ferritin, D-dimer, IL-6 levels, presence of left ventricular dysfunction and myocarditis on echocardiography are guiding factors in determining the need for intensive care. The degree of cardiovascular involvement is important in the follow-up of the disease and in determining the treatment regimen. All patients should be followed up via echocardiography and cardiac MRI for potential permanent cardiac damage. Although MIS-C can lead to serious life-threatening cardiologic manifestations, early diagnosis and appropriate treatment can prevent the risk of serious cardiologic morbidity and mortality in the future.

REFERENCES

1. Dong Y, Mo X, Hu Y et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020; 145: e20200702
2. World Health Organization. Corona virüs disease 2019 (COVID-19) situation reports; 2021. [Cited: 19 May 2021] Available from URL: https://wwwwhoint/emergencies/diseases/novel-coronavirus-2019/situation-reports.
3. Whittacker E, Bamford A, Kenny J et al (2020) Clinical characteristics of 58 children with a pediatri cinflammatory multisystem syndrom etemporallyas sociated with SARS-CoV-2. *JAMA* 324:259–269.
4. Riphagen S, Gomez X, Gonzalez-Martinez C et al. Hyper inflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; 23: 1607–8.
5. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasakilike disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771–1778.
6. Dufort EM, Koumans EH, Chow EJ et al (2020) Multisystem inflammatory syndrome in children in New York State. *N Engl J Med* 383:347–358.
7. Feldstein LR, Rose EB, Horwitz SM et al (2020) Multisystem inflammatory syndrome in U.S. children andadolescents. *N Engl J Med* 383:334–346.
8. 8. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with corona virus disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp (3 August 2021,date lastaccessed).
9. World Health Organization. Multisystem inflammatory syndrome in children and adolescentstemporallyrelatedto COVID-19 (2020), WHO reference number:WHO/2019 nCoV/Sci_Brief/Multisystem_Syndrome_Children/2020.1https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and adolescents with-covid-19 (3August 2021,date lastaccessed).
10. Valverde I, Singh Y, Sanchez-de-Toledoet al. Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe. Circulation.2021 Jan 5;143(1):21-32.
11. Abrams JY, Oster ME, Godfred-Cato SE, et al.Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health.* 2021;5:323-331.
12. Yilmaz Ciftdogan D, Ekemen Keles Y,Cetin BS, et al. COVID-19 associated multisystem icinflammatory syndrome in 614 children with and with out over lap with Kawasaki disease-Turk MIS-C study group. *Eur J Pediatr*. 2022;181:2031-2043.
13. Torres JP, Izquierdo G, Acu~na M, et al. Multisystem inflammatory syndrome in children (MIS-C): report of the clinicaland epidemiological characteristics of cases in Santiago de Chiled uring the SARS-CoV-2 pandemic. *Int J Infect Dis* 2020;100:75–81.

14. Kıymet E, Böncüoğlu E, Şahinkaya Ş, et al. A Comparative Study of Children with MIS-C between Admitted to the Pediatric Intensive Care Unitand Pediatric Ward: A One-Year Retrospective Study. *J Trop Pediatr*. 2021;8:67
15. Yilmaz Cift dogan D, Ekemen Keles Y, Karbuz A, et al. Multisystem inflammatory syndrome in children associated with COVID-19 in 101 cases from Turkey (Turk-MISC study). *J Paediatr Child Health*. 2022 58:1069-1078.
16. Sözeri B, Çağlayan Ş, Atasayan V, et al. The clinical course and short-term health out comes of multisystem inflammatory syndrome in children in the single pediatric rheumatology center. *Postgrad Med.* 2021;133:994-1000.
17. Tekin ZE, Sezer M, Çelikel E, et al. Factor saffecting diseases everity of multisystem inflammatory syndrome in children. *Pamukkale Medical Journal.* 2022: 15:595-602.
18. Miller AD, Zambrano LD, Yousaf AR, et al. Multisystem inflammatory syndrome in children-united states, february 2020-July 2021. Clin Infect Dis 2021:ciab1007.
19. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coranavirus 2019 pandemic: a caseseries. *J Pediatric Infect Dis Soc* 2020;9:393-398.
20. Radia T, Williams N, Agrawal P, et al. Multi-system inflammatory syndrome in children&adolescents (MIS-C): a system aticreview of clinical feature sandpre sentation. *Paediatr Respir Rev* 2021;38:51-57.
21. Kavurt AV, Bağrul D, Gül AEK, Özdemiroğlu N, et al. Echocardiographic Findingsand Correlation with Laboratory Values in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19. Pediatr Cardiol. 2022 Feb;43(2):413-425.
22. Arslan SY, Bal ZS, Bayraktaroglu S, et al. Cardiac Assessment in Children with MIS-C: Late Magnetic Resonance Imaging Features. *Pediatr Cardiol.* 2022; 2:1–10.
23. Cetin BS, Kısaarslan AP, Tekin S,et al. Evaluation of Baseline Characteristics and Prognostic Factors in Multisystemic Inflammatory Syndrome in Children: Is It Possibleto Foresee the Prognosis in the First Step? *J ClinMed.* 2022;11:4615.
24. Henderson LA, Canna SW, Friedman KG, et al. AmericanCollege of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 2. Arthritis Rheumatol. 2021;73:e13-e29.
25. Capone CA, Misra N, Ganigara M et al (2021) Sixmonth follow up of patients with multi-system inflammatory syndrome in children. *Pediatrics* 148:e2021050973.
26. Caro-Domínguez P, Navallas M, Riaza-Martin L et al. Imaging findings of multisystem inflammatory syndrome in children associated with COVID-19. *Pediatr Radiol* 51:1608–1620

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 01, Date: 02.02.2021).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: Design: YK, MCK, GB, EK, AS, PK, BU Data Collection or Processing: GB, EK, AS, PK, BU Analysis or Interpretation: YK, MCK, ÖK, ECD Literature Search: YK, MCK, ÖK, ECD Writing: YK, MCK, ÖK

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Peer-review: Internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

©Copyright 2023 by Osmangazi Tıp Dergisi - Available online at tip.ogu.edu.tr ©Telif Hakkı 2023 ESOGÜ Tıp Fakültesi - Makale metnine dergipark.org.tr/otd web sayfasından ulaşılabilir.