POSTGRADUATE MEDICINE
https://doi.org/10.1080/00325481.2021.1987732

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CLINICAL FEATURES
ORIGINAL RESEARCH

The clinical course and short-term health outcomes of multisystem inflammatory syndrome in children in the single pediatric rheumatology center

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ABSTRACT

Objectives: Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe condition resulting in excessive response of the immune system after SARS-CoV-2 infection. We report a single-center cohort of children with MIS-C, describing the spectrum of presentation, therapies, clinical course, and short-term outcomes.

Methods: This is a prospective observational study from to a tertiary pediatric rheumatology center including patients (aged 1 month to 21 years) diagnosed with MIS-C between April 2020-April 2021. Demographic, clinical, laboratory results and follow-up data were collected through the electronic patient record system and analyzed.

Results: A total of 67 patients with MIS-C were included in the study. Fever was detected in all patients; gastrointestinal system symptoms were found in 67.2% of the patients, rash in 38.8%, conjunctivitis in 31.3%, hypotension in 26.9% myocarditis, and/or pericarditis in 22.4%, respectively. Respiratory symptoms were only in five patients (7.5%). Kawasaki Disease like presentation was found 37.3% of the patients. The mean duration of hospitalization was 11.8 7.07 days. Fifty-seven patients (85%) received intravenous immunoglobulin (IVIG), 45 (67%) received corticosteroids, 17 (25.3%) received anakinra, and one (1.5%) received tocilizumab. Seven of the patients (10.4%) underwent therapeutic plasma exchange (TPE). In 21 (31.3%) patients, a pediatric intensive care unit (PICU) was required in a median of 2 days. The first finding to improve was fever, while the first parameter to decrease was ferritin (median 6.5 days (IQR, 4–11.2 days)). Sixty-five patients were discharged home with a median duration of hospital stay of 10 days (IQR, 7–15 days).

Conclusion: Patients with MIS-C may have severe cardiac findings and intensive care requirements in admission and hospital follow-up. The vast majority of these findings improve with effective treatment without any sequelae until discharge and in a short time in follow-up. Although the pathogenesis and treatment plan of the disease are partially elucidated, follow-up studies are needed in terms of long-term prognosis and relapse probabilities.

ARTICLE HISTORY
Received 2 June 2021
Accepted 28 September 2021

KEYWORDS
Multisystem inflammatory syndrome in children; pediatric; COVID-19; outcome 4

Introduction

The coronavirus 2019 (COVID-19) outbreak has caused major changes in daily life and routine activities in societies all over the world. Fortunately, SARS-CoV-2 often causes mild illness in children. Multisystem inflammatory syndrome in children (MIS-C) and MIS-N in the newborn is a rare but severe condition resulting in excessive response of the immune system after SARS-CoV-2 infection. Overall, MIS-C is a rare complication of SARS-CoV-2. In the multicenter study, COVID-19 reported an incidence of MIS-C of 0.14% in children with infection [1]. Although MIS-C occurs in a wide age spectrum from infancy to young adulthood, it is typically reported at school age [2–6]. MIS-C is a life-threatening condition that is characterized by severe inflammation of one or more parts of the body, particularly the lungs, heart, and gastrointestinal tract. It begins several weeks after exposure to SARS-CoV-2. Then patients with MIS-C have symptoms of persistent fever, often accompanied by gastrointestinal symptoms (abdominal pain, vomiting, diarrhea), mucocutaneous changes (rash, conjunctivitis), and cardiac changes (myocarditis, left ventricular dysfunction). Rarely, neurological symptoms (headache, meningismus) have been reported in patients [2–7]. MIS-C signs and symptoms that occur in children may overlap with other time-sensitive diagnoses, such as sepsis, toxic shock syndrome, Kawasaki disease (KD), macrophage activation syndrome, appendicitis, or meningitis. MIS-C patients had a negative PCR for SARS-CoV-2, while they had positive antibody test results [4,8,9].

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MIS-C is characterized by a cytokine storm, which is caused by unconventional T cell activation, resulting in intense activation of other immune cells and the release of cytokines, such as interleukins (IL-1,6,18), TNF-α and INF-gamma [10]. Also, MIS-C shows findings like Toxic shock syndrome, hemophagocytic lymphocytosis (HLH) or macrophage activation syndrome (MAS) observed in various rheumatic disorders, such as systemic juvenile idiopathic arthritis [10,11].

The fact that hyperinflammatory or cytokine storm develops after infection or by delayed parainfectious mechanism in MIS-C supports the existence of nonspecific T cell activation, autoantibodies, immunocomplexes, and antibody-dependent enhancement of immune reactions in disease pathogenesis [9,12–14].

The long-term prognosis of MIS-C is unknown. According to previous reports, median length of stay in hospital is 7 days, need for intensive care in 68% of the patients and mortality rate is 1.7% [15]. In a study conducted with a small number of patients, it was reported that cardiac involvement observed during the follow-up period improved in most of the patients [16]. We report a single-center cohort of children with MIS-C, describing the spectrum of presentation, therapies, clinical course, and short-term outcomes.

Materials and methods

This is a prospective observational study of pediatric patients (aged 1 month to 21 years) with a confirmed infection with SARS-CoV-2 who meet criteria for MIS-C admitted from April 2020 to April 2021, to a tertiary pediatric rheumatology center. The study protocol was reviewed and approved by the Ethics Committee (EC) of the University of Health Sciences, Umraniye Training and Research Hospital (Approval No: B.10.1TKH.4.34.H.GP.0.01/9) with the ethical principles laid down in the Declaration of Helsinki. Five patients were reported previously described in a recently published letter [17].

A confirmed case of COVID-19 was defined as a positive result from real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab for SARS-CoV-2 or positive SARS-CoV-2 antibody assay or exposure with patients with COVID-19.

The Centers for Disease Control and Prevention case definition for MIS-C was used to define a confirmed case of MIS-C [18]. Demographic, clinical, laboratory results and follow-up data were collected through the electronic patient record system.

The Statistical Package for the Social Sciences (SPSS) (version 26.0, SPSS-Inc., Chicago, IL, USA) was used for statistical analysis. The normality of the distribution of the variables was assessed by visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk\vs test). Descriptive analyses were presented as percentages, mean ± standard deviation, medians, minimum (min), maximum (max), and interquartile range (IQR) values. A p value < 0.05 was considered as statistically significant.

Results

A total of 67 patients with MIS-C were included. The median follow-up time was 3 months (IQR, 2–4 months). Mean age was 9 ± 5.2 years (min -max: 1–18 years) and 71.6% (n = 48) were male. Comorbid diseases were detected in 32.8% of the patients (n = 12). 75% of these 12 patients were obesity (n = 9), 50% (n = 6) autoimmune or autoinflammatory disease, 17% (n = 2) immunodeficiency and 17% (n = 2) epilepsy.

Fever was detected in all patients; mean duration of fever was 4.4 days (min-max: 1–15 days). 59.7% of the patients (n = 40) had fever for more than four days at the time of admission. The second most common symptoms of presentation were gastrointestinal system symptoms (67.2%, N = 45), among them abdominal pain (80%, n = 36) and diarrhea (64.4%, n = 29). Various rash and conjunctivitis were detected in 26 and 21 patients, respectively. KD-like presentation was found 37.3% of patients (n = 25) in this cohort. Respiratory symptoms were only in five patients in our study. At admission, 31 patients had cardiac abnormalities; among these patients, two have coronary arter dilatation (6.45%). %26.9 (n = 18) of patients had hypotension, among these patients 15 patents had myocarditis and/or pericarditis. The median left ventricular ejection fraction (LVEF) was 67% (IQR, 62.2–70%). 7.5% of the patients had mild-moderate cardiac dysfunction, which was defined as the depletion of the LVEF (30–50%) at the time of admission. Demographic and clinical findings were presented in Table 1. The patients with cardiac pathologies were found older (median age was 11.25 vs 5.5 years, p = 0.04) Cardiac involvements were found similar both gender (p = 0.33). Among the presenting symptoms, the presence of conjunctivitis was found to be associated with cardiac findings, while gastrointestinal, rash, and long fever duration (>4 days) were not found to be stastistically significance (p = 0.04 vs p = 0.53, p = 0.13, and p = 0.45, respectively). High levels of neutrophile lymphocyte ratio were detected in the patients with cardiac pathologies (9.5 ± 7.3 vs 6.2 ± 5.8, p = 0.04).

Most patients (n = 52 [77.6%]) tested positive only for SARS-CoV-2 antibody; 9 (13.4%) tested positive for both RT-PCR and antibodies, and 6 patients (18%) were accepted contact. The median white blood cell count was found 10,040/mL (IQR, 7080–14,780 /mL), lymphocyte was 1390 (IQR, 870–2260) and neutrophile lymphocyte ratio was (NLR) 5.3 (IQR, 2.4–11).

Table 1. Demographic and clinical characteristics of patients.

Demographic Characteristics	Total (n = 67)	
Gender (F/M)	19/48	
Age (mean±SD)	9 ± 5.2	
Follow up duration (median (IQR))	3 (1.5–3)	
Comorbid diseases (n/%)	n	%
Obesity	9	13.4
Autoimmune or autoinflammatory disease	6	8.9
Immunodeficiency	2	3
epilepsy	2	3
Clinical findings (n/%)	n	%
Fever	67	100
Fever >4 days	40	59.7
Duration of fever (mean (min-max))	4.4 (1–15)	
Abdominal pain	36	53.7
Diarrhea	29	43.2
Various rash	26	38.8
Conjunctivitis	21	31.3
KD- like presentation	25	37.3
Respiratory symptoms	5	7.4
Hypotension	18	26.8
Altered consciousness	5	7.5
Myocarditis and/or pericarditis	15	22.3
Mild-moderate cardiac dysfunction	5	7.5

The median C reactive protein (CRP) was 13.2 mg/dL (IQR, 17.9–20.4 mg/dL), and ferritin 340.7 ng/mL (IQR, 201–671 ng/mL). The median troponin was 0.005 ng/mL(IQR, 0.003–0.044 ng/mL) and brain natriuretic peptide (BNP) 228 pg/mL (IQR, 87.5–1296 pg/mL). The median d-dimer was 2380 mg/mL (IQR, 1255–4127 mg/mL). Hyponatremia and hypoalbuminemia were detected in 46.3% of patients (n = 31). Macrophage activating syndrome was detected in 15 patients (22.4%). We measured IL-6 level in 20 patients, the median IL-6 levels were found 45. 5 (IQR, 11.7–197.5) pg/ml. Laboratory characteristics of patients are shown in Table 2.

The mean duration of hospitalization was 11.8 ± 7.07 days (min-max: 1–37 days). Fifty- seven patients (85%) received intravenous immunoglobulin (IVIG) and 45 (67%) received corticosteroids (median 23 days). The first IVIG dose (2 g/kg) was administered in 24 hours to 70% of the patients, and 20 of these patients were given concurrent steroids. 17 (25.3%) patients received anakinra (median 8 days), and one (1.5%) received tocilizumab (10 mg/kg). The median (IQR) dose of anakinra was 3 mg/kg/day (IQR, 2–4 mg/kg/day). Seven of the patients (10.4%) underwent therapeutic plasma exchange (TPE). Vasoactive medications mostly used norepinephrine were used in 14 patients (21%). The median duration of vasopressor use was 5 days (IQR,1–6 days). Prophylactic dosing with enoxaparin was used in 42 (63%) patients. The median duration of anticoagulant use was 7.5 days (IQR, 3.75–11).

In 21 (31.3%) patients, a pediatric intensive care unit (PICU) was required within a median of 2 days, of which two patients (9.5%) required invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Nineteen patients were discharged from PICU with an average stay of 4.7 days (IQR, 4–8 days) and two patients (3%) died (Table 2). The patients who need a PICU were older than others (11 vs 8 years, p = 0.04). The presence of rash, bradycardia, hypoalbuminemia and high levels of N/L ratio was noted in patients who needed intensive care and biologic therapy (Table 4). Therefore, the patients who treated only IVIG were younger than other (median 4.75 years vs 11.2 years).

During the hospitalization period, the first finding to improve was fever, while the first parameter to decrease was ferritin (median 6.5 days (IQR, 4–11.2 days)). The recovery time of other laboratory parameters is in Table 3. Sixty-five patients were discharged home with a median duration of hospital stay of 10 days (IQR, 7–15 days).

Table 2. Laboratory characteristics, treatment, and outcomes of patients.

Laboratory Characteristics	
SARS-Cov-2 Antibody Positivity (n/%)	52/77.6
Both Serologic And RT-PCR Test Positivity (n/%)	9/13.4
With Contact History (n/%)	6/18
White Blood Cell Count *	10,040 (7080–14,780)
Lymphocyte *	1390 (870–2260)
Neutrophile Lymphocyte Ratio	5.3 (2.4–11)
C Reactive Protein (mg/dL) *	13.2 (17.9–20.4)
Ferritin (ng/mL)*	340.7 (201–671)
Troponine (ng/mL)*	0.005 (0.003–0.044)
IL-6 level (pg/ml)*	45. 5 (11.7–197.5)
Brain Natriuretic Peptide (pg/mL)*	228 (87.5–1296)
D-Dimer (mg/mL FEU)*	2380 (1255–4127)
Treatments	
Corticosteroids (n/%)	45/67
Intravenous Immunoglobulin (n/%)	58/85
Anakinra (n/%)	17/25.3
Treatment Duration of Anakinra *	8 (6.5–13)
Tocilizumab (n/%)	1/1.5
Vasoactive Medications (n/%)	14/21
Enoxaparin (n/%)	42/63
Outcomes	
Duration of Hospitalization (days)#	11.8 ± 7.07
Admission of PICU (n/%)	21/31.3
Duration of PICU (median (IQR))	4.7 (4–8)
Utilization of mechanical ventilator (n/%)	2/3
Utilization of ECMO (n/%)	2/3
Mortality (n/%)	2/3

*(median (IQR)) # mean±SD, IQR: Interquartile range, PICU: Pediatric Intensive Care Unit, ECMO: Extracorporeal Membrane Oxygenation

Post-Discharge Follow-Up

All patients were invited to outpatient clinic control within the first 2 weeks for clinical evaluation, and management of therapy (steroid and anticoagulant). Patients came to the first outpatient clinic on the median 11th day. Lymphopenia was detected in three patients, elevated ferritin in four patients and elevated d-dimer was in three patients. After the first control, all patients who received prophylactic heparin treatment were discontinued and aspirin was started. 26 of 31 (84%) patients with cardiac pathology improved during follow-up. While coronary artery (CA) dilatation continued in two patients, and mitral valve insufficiency persisted in one patient.

Table 4. Comparison of clinical and laboratory indicators in patients based on the anakinra treatment and intensive care hospitalization.

	PICU Admission			Anakinra therapy		
	Present (n = 21)	Absent (n = 46)	p	Present (n = 17)	Absent (n = 50)	p
Age (months)*	132.48	98.6	0.04	134	95	0.07
NLR	13.0	5.31	0.00	9.4	4.2	0.00
Hyponatremia (n/%)	16/76.1	15/32.6	0.01	14/82.3	17/34	0.00
Bradicardia (n/%)	8/38	0/0	0.00	7/41.1	1/2	0.00
Myocarditis (n/%)	13/61.9	10/21.7	0.02	8/47	15/30	0.16
Rash (n/%)	12/57.1	14/66.6	0.03	11/64.7	15/30	0.01
Hypoalbuminemia (n/%)	20/95.2	11/52.3	0.00	16/94.1	11/22	0.00

*median, PICU: Pediatric intensive care unit, NLR: Neutrophil/Lymphocyte ratio

Table 3. Recovery features and normalization period of laboratory findings of patients*.

	median (IQR)
Ferritin	6.5 (4–11.2)
Neutrophile Lymphocyte Ratio	7 (3–10)
Lymphocyte	5 (3–7)
D-Dimer	7 (4.75–12)
C Reactive Protein	10 (7–13)
Brain Natriuretic Peptide	10 (10–19.5)

*The period (days) for laboratory parameters to return to their normal range of from the start of treatments (median – IQR)

Discussion

In this study, we aim to present our disease findings and treatment results in a large cohort of patients with a diagnosis of MIS-C. Consistent with the literature, the patients were children in the 7–8 age group, who were previously healthy, and there was male gender predominance [2,3,15,19–21].

The majority of patients (61 [91%]) were tested positive for SARS-CoV-2 infection by RT-PCR, antibody testing, or both. Six (9%) patients had an epidemiologic link to a person with Covid-19. In our study, the number of patients diagnosed only with epidemiological connection was lower than in other reported case series (30% in Feldstein et al, 27% in Dhanalakshmi et al. and 34% in Jain et al. series) [3,22,23]. We think that the presence of laboratory evidence is very important to avoid overdiagnosis. Since other infections were rarely seen during the pandemic period in our daily practice, a small number of patients whose clinical findings fully overlap with MISC were diagnosed with only an epidemiological link. In our series, 13.4% of children had RTPCR positive, among these five patients has symptomatic COVID infection previously. In such patients it is necessary to distinguish between MIS-C and severe COVID infections. Feldstein et al. showed that findings such as cardiovascular or mucocutaneous rash are more common than respiratory symptoms in MIS-C [3].

The most common comorbidities reported in previous reports are being overweight (10–39%) and previous asthma history (5–18%) [2,8,19,20]. In our patient group, obesity was detected in 13.4% of patients. In addition, four of our patients used biological therapy due to various rheumatic diseases (such as juvenile idiopathic arthritis, deficiency of Adenosine deaminase enzyme −2) and one patient was diagnosed with immunodeficiency (Costman syndrome).

Initial clinical findings in patients with a diagnosis of MIS-C vary widely, high fever is often accompanied by gastrointestinal system dermatological and cutaneous pathologies [2,3,15,19–21,24,25]. In our reported patient group, abdominal pain was observed as the most common finding accompanying high fever. Mesenteric lap, severe diarrhea and vomiting, which may be bloody, were observed as other gastrointestinal system symptoms.

The prevalence of KD is significantly higher in East Asian countries, including Japan, Korea, China and Taiwan, but low in Europe and the USA [26,27]. In previous studies, especially involving European cohorts, most MIS-C patients were reported to have KD-like symptoms [8,28–31]. In other study from Turkey was reported 63.6% of 33 patients with MIS-C had KD-like syndrome (26). In contrast with these studies, KD-like presentation was found 37.3% of patients in our cohort. In the pathogenesis of both MISC and KD; abnormal or dysregulated immune reactions, and the release of large amounts of inflammatory cytokines (cytokine strome) can lead to similar clinical pictures in both diseases [12,32,33]. Considering our clinical observations and the literature, it suggests that both diseases are different entities. MIS-C patients have more specific features that are not present in patients with KD; especially severe abdominal pain mimicking acute appendicitis, bradycardia, myocardial involvement and lymphopenia, high pro-BNP and D-dimer levels.

In our cohort, 31.3% of patients required PICU admission, median 2 days. Nineteen patients were discharged from PICU with an average stay of 4.7 days (IQR, 4–8 days) and two patients (3%) died. In our cohort, the PICU requirement was higher than in both the Latin American (12.7%) and European cohorts (8%), and the mortality rate was like the Latin American cohort (4.2%) [10,19]. The percentage of patients admitted PICU 67% and 80% in the largest French and U.S. studies, respectively [3,34].

Looking at other studies, overall higher rates of serious illness and death have been reported in patients and their family members with economic and insurance instability, rough work, and home environments [4,19]. In our study, the risk factors associated with need of PICU admission were reported as older age, bradycardia, myocarditis, hyponatremia and/or hypoalbuminemia. Abrams et al. series decreased cardiac function, shock, and myocarditis was associated with PICU admission [35].

Cardiac involvement begins with bradycardia/hypotension and may end with myocardial dysfunction and cardiogenic shock [2,3,15,21,24,28,34,36]. In the reported patient groups, the frequency of left ventricular dysfunction is between 31% and 100% [37]. In a study by Kaushik et al., it was reported that 97% of the patients had an echocardiogram and the depressed LV ejection fraction (<50%) was 65% [15]. The possible mechanisms of myocardial damage in MIS-C include acute viral myocarditis, inflammation, hypoxia, stress cardiomyopathy, and ischemia due to CA involvement, which is rare compared to others [37]. In our cohort, myocarditis and/or pericarditis was seen in 27 patients, %52 of the patients (n = 14) progressed myocardial dysfunction and required inotropic agents in PICU. Two patients were needed ECMO support. The use of inotropic support in our cohort was lower than that reported by Belhadjer et al. in a cohort of 35 children in which 80% of patients had inotropic support [38]. The length of PICU stay of MIS-C cases was 4.7 days, which is similar to the Ozsurekci et al. report [25].

In the literature, rhythm abnormalities of varying severity have been described in 7–60% of patients, and coronary artery enlargement or aneurysms in 6–24% [37]. In our cohort, bradycardia occurring 2 days after the median hospitalization in 11 (16.4%) patients, coronary artery enlargement was observed in two patients. In our patient group, bradycardia was mostly observed in the adolescent age group. With this

determination, we think that closer monitoring of rhythm problems of patients at this age will positively affect the treatment outcome. This result needs to be confirmed by larger cohort studies.

Recovery of cardiac pathologies occurred in %84 of our cohort at hospital discharge. This result was found in report of Kausik et al. (95%) and in Belhadjer et al. (71%) [15,38]. The median recovery time was 8.5 days (IQR,5.5–17.7 days).

A standard clinical practice guideline for MIS-C therapy has been proposed by the American College of Rheumatology (ACR). According to this guideline, ACR has recommended the use of IVIG and/or corticosteroids as first-line therapy in these patients [39,40]. Approximately 30–80% patients do not respond to IVIG alone and may require adjunctive immunomodulatory therapy to control inflammation. The efficiency of IVIG treatment alone has been reported to be 30–80% in studies [28,33,41–44].

In the same guideline, high-dose anakinra (recombinant IL-1 receptor antagonist) (>4 mg/day) is recommended for MIS-C patients with resistant disease despite receiving IVIG and steroid therapy (34). Due to increased IL-6 levels and adverse outcomes in COVID-19, IL-6 neutralization with tocilizumab is also among the treatments applied [45]. Diorio et al. reported that serum IL-1, IL-2, and IL-6 levels were elevated in patinets with MIS-C [46]. IVIG resistance was found 55.2% of our patients, which was higher than KD that reported by Pilania et al [47]. In our study, IVIG resistant patients were older (median age 8.87 vs 10 years, $p = 0.2$). When the relationship between clinical findings at presentation and IVIG resistance and anakinra requirement was evaluated, a significant relationship was observed with cutaneous findings ($p = 0.004$ and $P = 0.006$, respectively). We treated 17 (25.3%) patients with anakinra, and one (1.5%) received tocilizumab before anakinra. This patient was currently followed up with a diagnosis of systemic JIA. After MIS-C developed, he was given tocilizumab first after IVIG and steroid because he also had pulmonary findings. He had high IL-6 levels (178 pg/ml). However, since there was no response to this treatment, TPE was performed in addition to high-dose anakinra (10 mg/kg/day).

TPE reduces mortality in serious and/or life-threatening MIS-C patients by reducing cytokines. In the report presented by Emeksiz et al., TPE was reported to decrease mortality [48]. In our population, TPE was applied to 10.4% of patients.

Diorio et al. reported increases in markers of endothelial dysfunction and vascular injury in MIS-C with elevated d-dimers and B-natriuretic proteins [46]. Per institutional protocols, MIS-C patients s would have received prophylactic anticoagulation [49,50]. We treated 45 (63%) patients with prophylactic enoxaprin during the symptomatic period and continued treatment with aspirin for 1 month after recovery. We terminated the treatment of the patient who did not have dimer elevation or signs of thrombosis in the control. Guidelines regarding the thrombotic evaluation and anticoagulation management of hospitalized children with MIS-C remains lacking [51].

In a systematic review by Kaushik et al. the median duration of hospitalization was 7 days, and intensive care was required in 68% of patients [13]. The mortality rate was reportedly 1.7% in the US and 1.4% in Europe [15]. Capone et al reported cardiac involvement experienced nearly full recovery [16]. The long-term prognosis of MIS-C is unknown as there are not many studies on the subject. In the follow-up results of the patients who were followed up for a median of 3 months in our study; median duration hospitalization was found 10 days and mortality rate was 2.9%. Majority of patients with cardiac involvement (84%) improved during follow-up. It was observed that coronary dilatation improved in one of our patients after 17 days and in the other after 110 days. These results show that MISC, which has a frightening course in clinical follow-up, does not cause permanent damage in most patients with appropriate treatment. Of course, this result needs to be confirmed in large cohorts.

Conclusions

In conclusion, patients in our cohort showed clinical features like KD or MAS, like as hundreds of patients with MIS-C diagnosed during the COVID-19 outbreak. Although these patients had severe cardiac findings and intensive care requirements, they recovered until their discharge and were followed up in the short term without any sequelae. Although the pathogenesis and treatment plan of the disease are partially elucidated, follow-up studies are needed in terms of long-term prognosis and relapse probabilities.

Acknowledgments

We are grateful to all participating children and their families.

Author contributions

Conception and design; BS, SÇ, VA, KU, TÇ, ÖPA, CHA, GA, ES, MK, TÖ, SE and FD, Analysis and interpretation of the data; BS and FD, Drafting of the paper or revising it critically for intellectual content; BS and FD, The final approval of the version to be published; BS, SÇ, VA, KU, TÇ, ÖPA, CHA, GA, ES, MK, TÖ, SE and FD, and all authors agree to be accountable for all aspects of the work.R

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