Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20229803 • *J Pediatr Inf 2022;16(2):e77-e86*

Organ Involvement in Multisystem-Inflammatory Syndrome in Children Admitted to a Tertiary Hospital in Turkey

Türkiye'de Üçüncü Basamak Bir Hastaneye Başvuran Multisistem Enflamatuvar Sendromlu Çocuklardaki Organ Tutulumları

Esra Akyüz Özkan[1] (İD), Emine Hafize Erdeniz[2] (İD)

[1] *Department of Pediatrics, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye*
[2] *Division of Pediatric Infectious Diseases, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye*

Cite this article as: Akyüz Özkan E, Erdeniz EH. Organ involvement in multisystem-inflammatory syndrome in children admitted to a tertiary hospital in Turkey. J Pediatr Inf 2022;16(2):e77-e86.

Abstract

Objective: Multisystem inflammatory syndrome (MIS-C) in children is a newly defined and serious health problem that develops after SARS-CoV-2 infection. Our aim is to report epidemiological, clinical, laboratory and radiological features of children with MIS-C.

Material and Methods: Forty patients who applied to our hospital from October 2020 to February 2021 and met the MIS-C criteria were included in the study. Patients with gastrointestinal involvement (GIS), cardiac involvement and Kawasaki Disease (KD)-like MIS-C were examined clinically and laboratory.

Results: The mean age of the patients was 8.2 ± 4.2 years and male patients were in the majority (70%). The most common symptoms were fever (100%) and fatigue (90%). Gastrointestinal symptoms were present in 71%, cardiac involvement in %40, Kawasaki-like patients in %52.5, shock symptoms in 59%. Elevated levels of C-reactive protein, D-dimer, and ferritin were found in 100%, 97.5%, and 67.5% of the patients, respectively. Patients with cardiac involvement had higher mean age and lower lymphocyte levels. Shock findings were higher in patients with KD-like MIS-C. Also, INR and ferritin levels were higher in KD-like MIS-C patients (p= 0.028). The mean platelet count (p= 0.004) and albumin levels were lower (p= 0.048) in shock group.

Conclusion: MIS-C is a hyperinflammatory syndrome with cardiac, GIS, and lung involvement. Cardiac findings were not common in patients presenting with KD-like MIS-C, but a poor prognosis was observed in KD-like MIS-C patients. Patients with cardiac involvement were older and their lymphocyte count was lower.

Keywords: COVID-19, multisystem inflammatory syndrome in children(mis-c), Kawasaki disease, organ involvement

Öz

Giriş: Çocuklarda multisistem enflamatuvar sendrom (MIS-C), SARS-CoV-2 enfeksiyonu sonrası gelişen, yeni tanımlanmış ve ciddi bir sağlık sorunudur. Amacımız MIS-C'li çocukların epidemiyolojik, klinik, laboratuvar ve radyolojik özelliklerini bildirmektir.

Gereç ve Yöntemler: Çalışmaya Ekim 2020-Şubat 2021 tarihleri arasında hastanemize başvuran ve MIS-C kriterlerini karşılayan 40 hasta dahil edildi. Gastrointestinal tutulum (GIS), kardiyak tutulum ve Kawasaki Hastalığı (KD) benzeri MIS-C olan hastalar klinik ve laboratuvar özelliklerine göre incelendi.

Bulgular: Hastaların yaş ortalaması 8.2 ± 4.2 yıl olup, erkek hastalar çoğunluktaydı (%70). En sık görülen semptomlar ateş (%100) ve yorgunluk (%90) idi. Gastrointestinal semptomlar %71, kalp tutulumu %40, Kawasaki benzeri hastalık %52.5, şok semptomları %59 idi. Hastaların sırasıyla %100, %97.5 ve %67.5'inde yüksek C-reaktif protein, D-dimer ve ferritin seviyeleri bulundu. Kardiyak tutulumu olan hastaların yaş ortalaması daha yüksek ve lenfosit seviyeleri daha düşüktü. Kawasaki hastalığı benzeri MIS-C hastalarında şok bulguları daha fazlaydı. Ayrıca KD benzeri MIS-C hastalarında INR ve ferritin düzeyleri daha yüksekti (p= 0.028). Ortalama trombosit sayısı (p= 0.004) ve albümin düzeyleri şok grubunda daha düşüktü (p= 0.048).

Sonuç: Çocuklarda multisistem enflamatuvar sendrom kalp, GİS ve akciğer tutulumu ile seyreden hiperenflamatuvar bir sendromdur. Kawasaki hastalığı benzeri MIS-C ile başvuran hastalarda kardiyak bulgular yaygın değildi, ancak KD benzeri MIS-C hastalarında kötü prognoz gözlendi. Kardiyak tutulumu olan hastaların yaş ortalaması daha fazla ve lenfosit sayıları daha düşüktü.

Anahtar Kelimeler: COVID-19, multisistem-enflamatuvar sendrom (mis-c), Kawasaki hastalığı, organ tutulumu

Correspondence Address/Yazışma Adresi

Esra Akyüz Özkan

Ondokuz Mayıs Üniversitesi Tıp Fakültesi,
Çocuk Sağlığı ve Hastalıkları Anabilim Dalı
Samsun-Türkiye

E-mail: uzdresra@gmail.com

Received: 06.09.2021 **Accepted:** 01.12.2021 **Available Online Date:** 30.06.2022

Introduction

Several months after the onset of the SARS-CoV-2 virus pandemic, an increase in hospitalizations of children and adolescents with clinical features similar to toxic shock and Kawasaki disease (KD) began to be reported (1). On 14 May 2020, the United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) announced new case definitions called 'multisystem inflammatory syndrome in children' (MIS-C) (2,3).

Multisystem inflammatory syndrome in children which occurs 2-6 weeks after SARS-CoV-2 infection, can affect multiple organ systems, including cardiac, gastrointestinal, hematological, dermatological, neurological, respiratory and renal systems (4).

The current study aimed to report epidemiological, clinical, laboratory and radiological features of children with MIS-C followed up in a tertiary care hospital in Samsun, Turkey.

Materials and Methods

This is a retrospective study involved children aged 0-18 years and applied to Ondokuz Mayıs University Medical Faculty Hospital between the dates of 01/10/2021-30/02/2021 and met the MIS-C criteria.A confirmed case of COVID-19 is defined as a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal samples or a positive SARS-CoV-2 antibody test. In current study covid antibody tests of all patients were positive.

The definition of the CDC was used to define MIS-C. The CDC's definition of MIS-C is:

1) fever> 38.0°C for ≥24 h (objective or subjective);

2) laboratory evidence of inflammation, including, but not limited to, one or more of the following: High values of C-reactive protein (CRP) (>5 mg/L), erythrocyte sedimentation rate (ESR) (>40 mm/hr), fibrinogen (>400 mg/dL), procalcitonin (>2 ng/mL), D-dimer (>3 ng/mL), ferritin (>500 ng/mL), lactic acid dehydrogenase (LDH) (>200 U/L), or interleukin 6 (IL-6); elevated neutrophils, reduced lymphocytes (<1000 cells/uL), and low albumin (<3 gr/dL);

3) no alternative plausible diagnosis;

4) current or recent SARS-CoV-2 infection diagnosed by a positive reverse transcription polymerase chain reaction (RT-PCR) or positive serological tests (IgM, IgG or IgA), or exposure to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms (2).

The study was approved by the ethics committee of Ondokuz Mayıs University Faculty of Medicine (No: 2021/141).

Based on the clinical severity, we classified our cases as mild, moderate and severe. Mild cases were defined as those patients who had a fever and two or more organ involvement with normal vital signs, while the patients with moderate MIS-C were defined based on receiving supportive treatment for organ failure, including oxygen support with a mask for lung involvement, ursodeoxycholic acid support because of high liver enzymes, and intact vital signs. Patients in the severe group were the ones with hypotensive and unresponsiveness to fluid therapy or in need of inotropes, intensive care or had severe involvement.

Demographic, clinical, laboratory and radiologic results and outcome data were recorded and compared according to the following groups: KD-like disease, cardiac involvement and gastrointestinal system (GIS) involvement. In addition, patients with shock findings such as hypotension, tachycardia, and prolonged capillary refill time were compared with those without shock characteristics.

As a treatment in these patients; supportive therapy, monitoring of lung, liver, kidney and heart functions, fever control, antiviral treatments, oxygen therapy, Intravenous immunoglobulin (IVIG), immunomodulators, corticosteroids, anticoagulation therapy (LMWH) and empirical antibiotic therapy was used.

In the treatment approach; in patients with mild clinic, according to fever and clinical findings, IVIG 1-2 g/kg, IVIG 1-2 g/kg and 2 mg/kg methylprednisolone or only methylprednisolone 1-2 mg/kg were given.

In patients with moderate clinic IVIG 1-2 g/kg and 2 mg/kg methylprednisolone, and if unresponsive, methylprednisolone was increased to 10 mg/kg. In patients with severe clinical findings, IVIG was started with 2 g/kg, and an additional dose of IVIG was given when necessary. Methylprednisolone was started as 2 mg/kg, but for those with severe clinical persistence, 10 mg/kg or pulse methylprednisolone therapy was given. Anakinra was administered to patients who did not respond to them clinically or laboratory.

Statistical Analysis

Data were analyzed with IBM SPSS 23. Conformity to normal distribution was analyzed using the Shapiro-Wilk test. Chi-square and Fisher's exact tests were used to compare categorical variables according to groups. Independent two-sample t test was used to compare normally distributed data according to paired groups, and Mann-Whitney U test was used to compare non-normally distributed data. One-way analysis of variance was used to compare normally distributed data according to three and more groups, and multiple comparisons were made with Tamhane's T2 test. The Kruskal Wallis test was used

to compare data that were not normally distributed according to groups of three or more. Analysis results are presented as mean ± standard deviation for quantitative data. The categorical data were presented as frequency (percentage). The significance level was taken as p< 0.050.

Results

The clinical and treatment frequency distributions of the patients are given in Table 1. Forty patients were included in the study. The mean age of the patients was 8.2 ± 4.2 years and 28 were boys (70%). COVID-19 was proven by serologically in all patients. 67.5% had covid contact within four weeks. 65% had household contact.

Clinical findings at the time of admission include: Fever in all patients (100%), cough in 6 (15%), sore throat in 3 (7.5%), myalgia in 19 (47.5%), nausea and vomiting in 23 (57.5%), abdominal pain in 27 (67.5%), diarrhea in 27 (67.5%), fatigue in 36 (90%), bilateral bulber conjunctivitis in 20 (50%), strawberry tongue in 21 (52.5%), rash in 22 (55%), desquamation in 2 (5%), arthritis/arthralgia in 2 (5%), was observed (Table 1). Rhinorrhea and anosmia were not detected.

On admission: The average duration of fever was five days, one patient (2.5%) had seizure, 13 had (32.5%) had headache, 1 (2.5%) had tachipnea, 2 (5%) was lethargic, 14 (35%) had tachycardia, 9 (22.5%) had hypotension, 5 (12.5%) had prolonged capillary refill time. Four patients (10%) had heart failure, 2 had (5%) respiratory failure, 7 had (17.5%) acute liver failure. 4 patients (10%) were admitted to intensive care at the time of admission. One of them (2.5%) had high flow theraphy. Three of them (7.5%) received inotropic support (Table 1).

Five patients (12.5) had leukopenia [<4000 (4500-12500) cells/uL], 16 (40%) had leukocytosis (>10.000 cells/uL), 15 had (37.5%) lymphopenia (<1000 cells/uL), 4 (10%) had neutropenia (<1500 cells/uL), 4 (10%) had anemia (<9 g/dL), 21 (52.5%) had thrombocytopenia (<150 x $10^9/L^3$), all of them had high CRP levels (>5 mg/L), 17 (42.5%) had elevated procalcitonin levels (>2 ng/mL), 24 (60%) had high ESR levels (>40 mm/hr) d-, 39 (97.5%) had high D-dimer (>3 ng/mL), 11 (27.5%) had high INR levels (>1.1), 27 (67.5%) had high ferritin levels (>500 ng/mL), 12 patients (30%) had high troponin levels (>0.1 ng/mL), 7 had (17.5%) hypoalbuminemia (<3 gr/dL), 9 had (22.5%) hyponatremia (<130 mEq/L).

GIS findings were observed most frequently at admission (72.5%). The mean age of those with GIS involvement was 8.27 ± 4.38 years, while those without GIS involvement were 8.09 ± 4.04 years. (p= 0.907). Among the symptoms of GIS= 24 patients had nausea (65%), 23 vomiting (57.5%), 26 abdominal pain (89.7%), and 27 had diarrhea (93.1%). Two patients were followed for pancreatitis and three patients were followed for perforated appendicitis. There was no difference in shock findings such as hypotension, tachycardia and other clinical features between two groups.

In terms of laboratory findings: The average lymphocyte value of those without GIS involvement was lower than those with involvement,but it was within normal limits in both groups. There was no difference between the two groups in the other laboratory values (Table 2).

Sixteen patients had cardiac involvement (40%). The mean age of those with cardiac involvement was 9.9 ± 4.4 years, while those without cardiac involvement were 7.0 ± 3.7 years (p= 0.038). Four patients had endocarditis (25%), four had myocarditis (25%), one patient had pericardial effusion (6.2%), one patient had right coronary dilatation (6.2%), five had left coronary dilatation (31.2%), and one had right and left coronary dilatation (6.2%). There was no difference in clinical findings between those with and without cardiac involvement. Kawasaki disease findings (strawberry tongue, rash, conjunctivitis) and cough, myalgia, vomiting, diarrhea, abdominal pain, hypotension and tachycardia was similar between two groups. Laboratory findings of patients with and without cardiac involvement were compared; while the mean lymphocyte count was lower in those with cardiac involvement (p= 0.042), urea (p= 0.036) and creatinine (p= 0.010) were higher (Table 2). Laboratory comparison is shown graphically in Figure 1.

Twenty one patients were admitted to the complete-incomplete KD clinic (52.5%) (11 complet, 10 incomplete KD). Complete KD, incomplete KD and non-KD were compared with their clinical characteristic. The conjunctivitis, lip fissure, strawberry tongue, rash, tachycardia, hypotension, and prolonged capillary refill time were more common in patients with KD-like MIS-C (Table 3). Three of the 21 KD-like MIS-C patients had coronary dilatation (14.2%). There were no signs of KD in four patients with coronary dilatation. Three out of four patients with myocarditis had KD-like MIS-C.

The INR values of 5.3% of non-KD-like MIS-Cs, 60% of the incomplete group and 27.3% of the complete group were found to be higher than normal limits (>1.1). Likewise, the ferritin value of 10.5% of non-KD-like MIS-Cs, 70% of the incomplete group and 63.6% of the complete group were obtained as higher than normal limits (>500 ng/mL) (p= 0.028) (Table 4). Laboratory comparison is shown graphically in Figure 2.

When our patients with and without shock findings were compared, platelet count and albumin levels were lower in the group with shock. While the mean platelet value was 107 ± 41 x $10^9/L^3$ in the group with shock, it was 200 ± 123 x $10^9/L^3$ in the group without shock (p= 0.004). The albumin value was 3.1 ± 0.35 gr/dL in the group with shock symptoms and 3.6 ± 0.65 gr/dL in the group without shock symptoms (p= 0.048). Patients followed up with shock findings were compared in terms of clinical characteristics.

Table 1. Clinical characteristics, organ involvement and treatment features of the patients with MIS-C

	Frequency (n)	Percentage (%)
Cardiac involvement	16	40.0
Gastrointestinal system involvement	29	72.5
Gender		
Male	28	70.0
Female	12	30.0
COVID-19 case contact with in 4 weeks	27	67.5
Fever	40	100
Cough	6	15.0
Runny nose	0	0.0
Sore throat	3	7.5
Myalgia	19	47.5
Nausea	26	65.0
Vomiting	23	57.5
Abdominal pain	27	67.5
Diarrhea	27	67.5
İleus	4	10.0
Fatigue	36	90.0
Anosmia	0	0.0
Conjunctivitis	20	50.0
Fissure on the lips	23	57.5
Strawberry tongue	21	52.5
Rash	22	55.0
Desquamation	2	5.0
Arthritis/arthrals	2	5.0
Bleeding	1	2.5
Seizure	1	2.5
Headache	13	32.5
Tachipnea	1	2.6
Consciousness restless	6	15.4
Normal	32	82.1
Asleep	1	2.6
Lethargic	2	5.0
Tachicardia	14	35.0
Hypotension	9	22.5
Prolonged capillary refill time	5	12.5
Dehydration		
Severe	2	5.0
Mild	26	65.0
Moderate	11	27.5
No	1	2.5
Toxic shock	0	0.0
Macrophage activation syndrome	1	2.5
Acute kidney failure	0	0.0

Table 1. Clinical characteristics, organ involvement and treatment features of the patients with MIS-C (continue)

	Frequency (n)	Percentage (%)
Acute liver failure	7	17.5
Heart failure	4	10.0
Respiratory failure	2	5.0
ARDS	1	2.5
Shock	9	22.5
IVIG	38	95.0
Steroid	39	97.5
İnotropic support	3	7.5
Anti-viral		
Favipiravir	2	5.0
Liponavir/ritonavir	2	5.0
No	36	90.0
Anticoagulant	40	100
Anakinra	4	10.0
Oxygen administration		
Cpap	1	2.6
Nasal cannula	1	2.6
Face mask	1	2.6
Plasma exchange	0	0.0
PICU admission	4	10.0

ARDS: Acuteres piratory distress syndrome. PICU: Pediatric intensive care unit, IVIG: Intravenous immunoglobulin.

While there was a difference between the two groups in terms of fatigue, tachycardia, hypotension, and capillary filling, there was no difference in KD findings such as strawberry tongue, conjunctivitis, and rash.

The average length of stay was 7.35 ± 3.15 days, average intensive care stay was 4.25 ± 4.03 days. Thirty eight patients (95%) received IVIG therapy. Thirty nine patients (97.5) received varying doses of steroid therapy, depending on the clinic severity. Four patients (10%) received Anakinra treatment, none of the patients received plasma exchange and ECMO theraphy. All patients received empiric systemic antibacterial therapy. No growth was detected in the blood culture. All patients were discharged, no patients died.

Discussion

Multisystem inflammatory syndrome is a hyperinflammatory condition with cardiac, GIS, respiratory and dermatological involvement.A study involved eight children and showed symptoms of KD, was first published in the UK and is now being seen worldwide (5).

Forty patients diagnosed with MIS-C and proven to have PCR or serologically had COVID-19 were included in the study. In accordance with the literature, male patients were in majority in the study (6,7). Most of them had no underlying diseases. Four of them were followed up in PICU (10%) and had signs of shock and required inotrope treatment, and one patient was followed up with high flow. Although nine patients (22.5%) had hypotension at presentation, three patients (7.5%) required inotropic support. In the study conducted by Torres et al (8) 59% of the patients required intensive care hospitalization at presentation and 44% of patients required mechanical ventilation and inotrope support. No death was detected. Dufort et al (7) reported an 80% PICU admission rate.

The striking finding was that, unlike COVID-19 disease, patients with MIS-C had high GIS and cardiac involvement, and respiratory symptoms were not much. Five patients had radiological abnormalities (12.5%), four patients had ground glass appearance and one patient had atelectasis on thorax CT, only one patient with chest radiography abnormal had lower respiratory tract symptoms (2.5%). In the study of Hameed et al (9), they found central bronchial wall thickening in 34% of patients with MISC without lower respiratory tract symptoms and thought that this might be due to airway inflammation. Abnormal chest radiography findings can also be observed in KD, and it was thought that this could be secondary to lower respiratory tract inflammation or pulmonary arteritis (10).

Table 2. Comparison of patients with and without cardiac and gastrointestinal involvement

	Cardiacİnvolvement			GIS involvement			
	Without cardiac involvement (mean + standard deviation)	With cardiac involvement (mean + standard deviation)	p	Without GIS involvement (mean + standard deviation)	With GIS involvement (mean + standard deviation)		p
Duration of fever (day)	4.52 ± 2.27	5.00 ± 1.51	0.207	4.64 ± 1.75	4.75 ± 2.10	U= 150	0.899
Heart rate (beats/min)	107.92 ± 15.87	118.44 ± 23.50	0.188	112.73 ± 18.49	111.90 ± 20.46	U= 150	0.768
Respiratory rate (breaths/min)	24.29 ± 2.93	24.50 ± 4.97	0.808	24.18 ± 1.47	24.45 ± 4.41	U= 154	0.863
Systolic blood pressure (mmHg)	107.92 ± 5.88	103.69 ± 10.40	0.132	108.18 ± 6.03	105.48 ± 8.80	U= 136	0.307
Diastolic blood pressure (mmHg)	68.33 ± 5.65	66.13 ± 7.50	0.168	68.18 ± 6.03	67.17 ± 6.69	U= 147	0.542
Oxygen saturation (%)	97.58 ± 1.53	95.94 ± 3.21	0.027	97.36 ± 2.11	96.76 ± 2.59	U= 137.5	0.340
Hemoglobin (g/dL)	11.01 ± 1.69	11.28 ± 1.52	0.611	11.03 ± 1.40	11.16 ± 1.70	t= 0.222	0.825
White blood cell count (cells/uL)	24714.58 ± 76638.04	9757.50 ± 4046.01	0.473	8796.36 ± 3496.92	22500.34 ± 69657.63	U= 139	0.535
Platelet count ($x10^9/L^3$)	190.67 ± 119.34	187.00 ± 124.25	0.804	195.55 ± 129.06	186.17 ± 118.56	U= 157	0.940
Lymphocyte count (cells/uL)	4295.00 ± 12761.76	1025.63 ± 612.62	**0.042**	1993.64 ± 1195.56	3364.14 ± 11687.61	U= 94.5	**0.049**
Neutrophil count (cells/uL)	6720.42 ± 3460.54	8130.00 ± 3634.89	0.224	6109.09 ± 2591.20	7730.00 ± 3801.30	t= 1.539	0.135
Eosinophil count	132.08 ± 151.05	87.50 ± 106.74	0.846	182.73 ± 197.24	88.28 ± 95.36	U= 118	0.206
CRP (mg/L)	112.68 ± 69.93	178.31 ± 123.61	0.159	96.32 ± 49.00	155.09 ± 108.80	U= 110.5	0.138
Procalcitonin (ng/mL)	5.35 ± 9.42	10.17 ± 10.13	0.110	3.22 ± 5.06	8.58 ± 10.84	U= 95.5	0.223
ESR (mm/hr)	46.50 ± 30.95	46.36 ± 36.72	0.901	45.90 ± 32.81	46.71 ± 33.16	t= 0.064	0.949
Sodium (mEq/L)	134.48 ± 3.13	132.44 ± 4.23	0.091	134.64 ± 3.67	133.25 ± 3.72	t= -1.052	0.300
ALT (U/L)	78.73 ± 183.02	32.00 ± 22.31	0.679	116.36 ± 261.96	38.67 ± 47.99	U= 117.5	0.203
AST (U/L)	111.63 ± 260.30	38.69 ± 21.51	0.772	147.36 ± 347.69	57.83 ± 110.79	U= 131	0.388
LDH (U/L)	560.57 ± 673.70	337.50 ± 87.30	1.000	451.70 ± 433.16	479.20 ± 573.75	U= 112.5	0.648
Ferritin (ng/mL)	936.71 ± 2166.79	608.40 ± 436.75	0.237	802.82 ± 1109.34	813.43 ± 1918.17	U= 148	0.851
INR	1.15 ± 0.17	1.26 ± 0.29	0.176	1.13 ± 0.19	1.21 ± 0.24	U= 103	0.225
D-dimer (ng/mL)	5.46 ± 3.31	6.01 ± 2.97	0.577	4.46 ± 2.93	6.16 ± 3.15	U= 107.5	0.145
Fibrinojen (mg/dL)	267.42 ± 174.01	332.80 ± 257.04	0.792	266.50 ± 143.39	303.94 ± 228.13	U= 35.5	0.966
Albumin (g/dL)	3.50 ± 0.57	3.60 ± 0.73	0.654	3.59 ± 0.68	3.53 ± 0.63	t= -0.259	0.797
Troponin (ng/mL)	16.50 ± 74.81	0.22 ± 0.16	0.113	0.14 ± 0.10	12.91 ± 65.97	U= 108.5	0.275
Urea (mg/dL)	11.10 ± 6.32	14.00 ± 5.97	**0.036**	10.95 ± 4.09	12.76 ± 6.92	U= 135	0.458
Creatinin (mg/dL)	0.43 ± 0.12	0.61 ± 0.31	**0.010**	0.45 ± 0.12	0.53 ± 0.26	U= 116.5	0.230
Lactat (mmol/L)	1.29 ± 0.45	1.45 ± 0.42	0.367	1.41 ± 0.45	1.35 ± 0.44	U= 41.5	0.668
Length of stay in hospital (day)	6.23 ± 2.60	9.00 ± 3.23	**0.006**	6.10 ± 2.28	7.81 ± 3.33	U= 94.5	0.163

t: Independent two sample t test statistics, U: Mann-Whitney U test statistics, INR: International normalized ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ALT: Alanine aminotransferase, AST: Aspartat aminotransferase, LDH: Lactate dehydrogenase.

Leukocytosis, lymphopenia, and thrombocytopenia were common laboratory findings consisted with the literature. Also, CRP, ESR and ferritin values were high in accordance with the literature, which is one of the MISC definition criteria and as expected in hyperinflammatory events (11).

Gastrointestinal involvement involvement was observed most frequently at admission (72.5%). Of our patients with GIS involvement, two had pancreatitis, three had appendicitis, four had mesentery lymphadenopathy, one had ileitis, one had hepatomegaly and two had free fluid in the abdomen. Nausea, vomiting, abdominal pain, and diarrhea were higher in those with GIS involvement, as expected. No significant difference was observed in the laboratory. In a study with a case series from 26 US states, GIS involvement was reported as 80%, and a study from France reported GIS involvement in all patients with MIS-C (7,12). In the study by Hameed et al. (9), 54% of GIS symptoms were detected and 47% showed features of right iliac fossa mesenteric inflammation and lymphadenopathy on-abdominal USG. In current study four patients had mesentery lypphadenopathy (10%). It is thought that this lymphadenitis

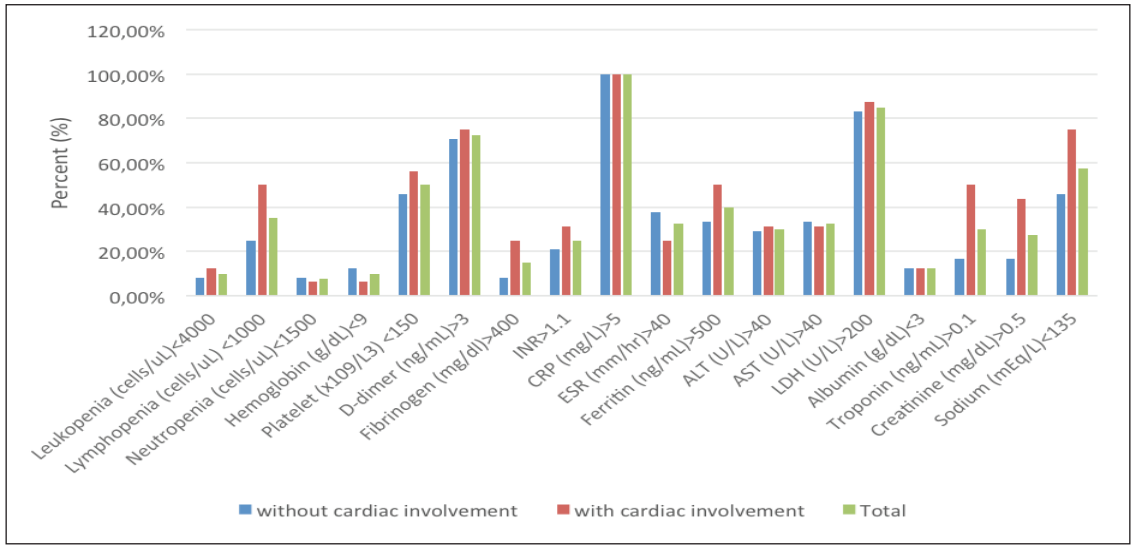

Figure 1. Distribution of laboratory parameters according to cadiac involvement.

Table 3. Comparison of clinical characteristics of complete Kawasaki disease, incomplete Kawasaki disease and non-Kawasaki disease patients with MIS-C

	Complete KD MIS-C (n)	İncomplete KD MIS-C (n)	Non-KD MIS-C (n)	p
Nausea	8	5	13	0.504
Vomiting	6	5	12	0.772
Abdominal pain	7	6	14	0.718
Diarrhea	7	6	14	0.718
Fatigue	10	10	16	0.401
Anosmia	11	10	19	0.132
Conjunctivitis	11[a]	4[b]	5[b]	**0.000**
Fissure on the lips	11[a]	6[b]	6[b]	**0.001**
Strawberry tongue	8[a]	7[ab]	6[b]	**0.041**
Rash	11	4	7	**0.002**
Desquamation	2	0	0	0.062
Arthritis	1	1	0	0.384
Headache	5	3	5	0.548
Tachipnea	0	0	1	0.567
Chest pain	1	0	1	0.632
Lethargic	2	0	0	0.062
Tachicardia	8[a]	3[b]	3[b]	**0.006**
Hipotension	6[a]	1[b]	2[b]	**0.011**
Prolonged capillaryre fill time	4[a]	0[b]	1[b]	**0.018**
Chi-square test statistics, a-b: There is no difference between groups with the same letter. p< 0.05 is significant.				

may be direct virus invasion or secondary reactive hyperplasia (13). In another study, nonspecific inflammation was detected in US performed in eight patients whose examination findings mimicked appendicitis and all of them reported normal on CT (14). In current study three had appendicitis and get surgery. It has been reported that GIS symptoms seen in MIS-C may be due to ischemia secondary to vasculitis (15). In the study of Hameed et al (9), two children had splenic infarcts. They also saw free fluid, gallbladder wall thickening, and pericholecystic and periportal edema, possibly due to systemic inflammation, hypoalbuminemia, serositis, fluid overload and/or heart failure. Two patients had free fluid in the abdomen in present study (5%).

Hypotension, tachycardia, and prolonged capillary refill

Table 4. Comparison of labaratory findings of complete Kawasaki disease, incomplete Kawasaki disease and non-Kawasaki disease patients with MIS-C

	Non-KD MIS-C	Incomplete KD MIS-C	Complete KD MIS-C	Total	Statistical analysis	p
Leukopenia (cells/uL)< 4000	1 (5.3)	1 (10)	2 (18.2)	4 (10)		
Lymphopenia (cells/uL)< 1000	6 (31.6)	4 (40)	4 (36.4)	14 (35)		
Neutropenia (cells/uL)< 1500	1 (5.3)	0 (0)	2 (18.2)	3 (7.5)		
Hemoglobin (g/dL)< 9	1 (5.3)	2 (20)	1 (9.1)	4 (10)		
Platelet (x10^9/L3)< 150	8 (42.1)	7 (70)	5 (45.5)	20 (50)		
D-dimer (ng/mL)> 3	12 (63.2)	8 (80)	9 (81.8)	29 (72.5)		
Fibrinojen (mg/dL)> 400	3 (15.8)	0 (0)	3 (27.3)	6 (15)		
INR> 1.1	1 (5.3)[b]	6 (60)[a]	3 (27.3)[ab]	10 (25)		
CRP (mg/L)> 5	19 (100)	10 (100)	11 (100)	40 (100)		
ESR (mm/hr)> 40	6 (31.6)	3 (30)	4 (36.4)	13 (32.5)	χ= 53.927	**0.028**
Ferritin (ng/mL)> 500	2 (10.5)[a]	7 (70)[b]	7 (63.6)b	16 (40)		
ALT (U/L)> 40	5 (26.3)	3 (30)	4 (36.4)	12 (30)		
AST (U/L)> 40	5 (26.3)	4 (40)	4 (36.4)	13 (32.5)		
LDH (U/L)> 200	17 (89.5)	8 (80)	9 (81.8)	34 (85)		
Albumin (gr/dL)< 3	0 (0)	1 (10)	4 (36.4)	5 (12.5)		
Troponin (ng/mL)> 0.1	3 (15.8)	4 (40)	5 (45.5)	12 (30)		
Creatinine (mg/dL)> 0.5	4 (21.1)	5 (50)	2 (18.2)	11 (27.5)		
Sodium (mEq/L)< 135	10 (52.6)	6 (60)	7 (63.6)	23 (57.5)		

Chi-square test statistics, a-b: There is no difference between groups with the same letter, p< 0.05 issignificant.
INR: International normalized ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ALT: Alanine aminotransferase, AST: Aspartat aminotransferase, LDH: Lactat dehydrogenase.

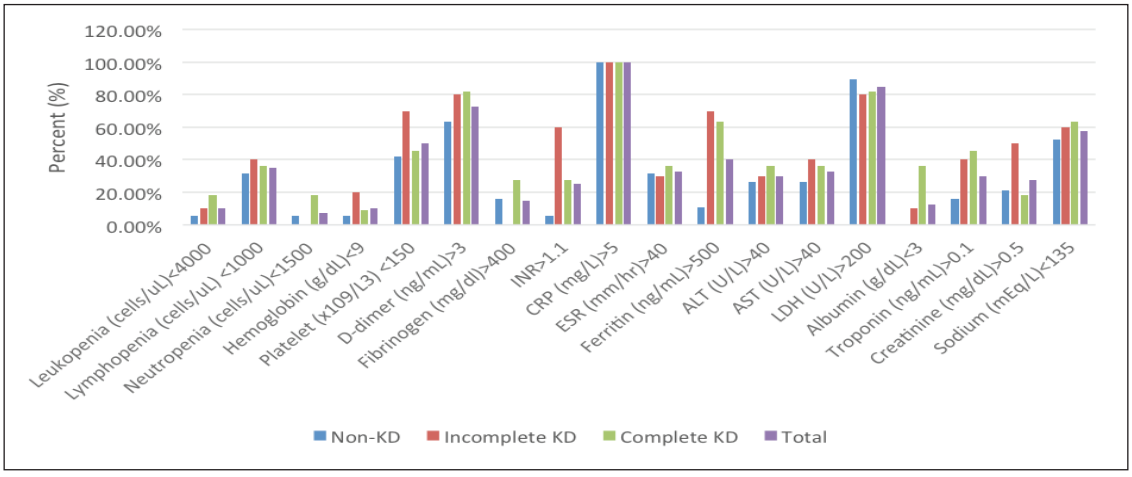

Figure 2. Distribution of laboratory parameters according to Kawasaki disease features.

time are defined as symptoms of shock. In the study of Lima-Setta et al. (11) 59% of patients had symptoms of shock, mainly tachycardia (43%), hypotension (30%) and prolonged capillary refilling (29%). In current study shock was present in nine patients (22.5%), hypotension (22.5%), tachycardia (35%), prolonged capillary refilling time (12.5%). The mean platelet count (p= 0.004) and albumin values (p= 0.048) were lower in the group with shock findings than in the group without. Caution should be exercised in terms of shock in patients with MIS-C with thrombocytopenia and hypoalbuminemia. In the study of Torres et al (8) severe MIS-C group had lower hemoglobin and albumin levels, decreased platelet counts, and higher D-dimer. In another study comparing severe and nonsevere MIS-C patients, there was no difference in platelet values (16).

Kawasaki disease is acute medium vessel vasculitis with a preference for coronary arteries, which is more common in infants; is the most common cause of childhood acquired heart disease. Characteristics that define KD include fever, rash, cervical lymph node enlargement and ocular and oral mucosal changes, as well as involvement of other organs such as the liver, lungs, gastrointestinal system, central nervous system, and joints (17).

Although it has been reported in the literature that patients with KD-like MIS-C may be younger than five years, similar to KD, in this study there was no statistical difference between the mean age of those with KD-like MIS-C and those who did not (17,18). The average age of KD-like MIS-Cs was 8.5 years. In the literature, the rate of MIS-C patients meeting KD criteria has been reported between 22% and 64% (6,15,19). In current study 21 patients had clinical signs of KD (52.5%). Eleven (27.5%) of them were evaluated as complete and 10 (25%) as incomplete according to KD criterias of American Heart Association (17). Only three of our 21 patients with KD-like MIS-C had coronary dilatation (14.2%). Three of four patients with myocarditis had signs of KD.

Hypotension, tachycardia, and prolonged capillary refill time were higher in patients with KD-like MIS-C compared to patients with nonKD-like MIS-C. This means that shock symptoms are more common in patients with KD-like MIS-C and they may have a more severe course.

While inflammation markers are high in KD as KD-like MIS-C, thrombocytosis is mostly observed in KD, while thrombocytopenia is common in KD like MIS-C (20). In this study, the number of patients with thrombocytopenia was similar between those with KD-like MIS-C and non-KD MIS-C. When laboratory values were compared among these groups, only INR length and high value of ferritin were statistically significant. Since the shock findings are higher in patients with KD-like MIS-C, higher levels of ferritin and INR may be associated with poor prognosis.

In this study, 16 patients had cardiac involvement (40%). Four patients (25%) had endocarditis, 4 (25%) had myocarditis, 1 (6.3%) had pericardial effusion, and 7 (43.7%) had coronary dilatation. The mean age of those with cardiac involvement was 9.91 ± 4.44 years, while those without cardiac involvement were 7.09 ± 3.75 years (p= 0.038). The rate of heart involvement increases with age. Cardiac involvement was 44.4% in the study of Torres et al (8) and 80% in the study of Felstein et al. (6).

Those with and without cardiac involvement were compared according to clinical and laboratory values. When comparing those with cardiac involvement and those without involvement, KD characteristics (strawberry tongue, fissure of the lips, conjunctivitis, rash) and shock findings such as hypotension and tachycardia were not frequent in those with cardiac involvement. In other words, echocardiography is recommended even if there are no KD and shock findings.

Oxygen saturation and lymphocyte count were lower; urea and creatinine levels were higher in those with cardiac involvement. Patients with lymphopenia should be evaluated for cardiac involvement. Length of stay was also longer in this group.

Most of the patients in our series received IVIG (95%) and steroid (%97.5%) therapy. After the first IVIG dose, all children had a fever reduction except one patientand that one patient required a second IVIG dose. Feldstein et al (6) reported the rate of IVIG and steroid use as 48%, Toubiana et al (15) reported the use of IVIG as 77%, and the rate of steroid use as 49%. In the study conducted by Kaushik et al. (21), the rate of using IVIG was 54%, steroid 51%, Anakinra 12%, and inotrope 51%.

Conclusion

In conclusion, as expected, acute phase reactants were high in patients with MIS-C, which was defined as a hyperinflammatory event. The most commonly affected system was GIS. Cradiac involvement increased with age, and low lymphocytes were observed in these patients. Cardiac involvement was not high in patients presenting with a KD clinic. Shock findings were higher in KD-like MIS-C patients. Caution should be exercised in patients with MIS-C in terms of thrombocytopenia, hypoalbuminemia, hyperferritinemia and high INR.

Ethics Committe Approval: Ethical approval was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee (Decision no: B.30.2.ODM.0.20.08/180, Date:26.03.2021).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- EAÖ, EHE; Design- EAÖ; Supervision- EAÖ, EHE; Resource- EAÖ; Data Collection and/or Processing- EAÖ; Analysis and/or Interpretation- EAÖ; Literature Search - EAÖ, EHE; Writing- EAÖ, EHE; Critical Review- EHE.

Conflict of Interest: All authors declare that they have no conflicts of interest or funding to disclose.

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

References

1. *Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki disease: Novel virus and novel case. Hosp Pediatr 2020;10(6):537-40.* ***[CrossRef]***
2. *CDC. Health Alert Network (HAN): Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). 2020 Available from: https://emergency.cdc.gov/han/2020/ han00432.asp.*

3. *WHO. World Health Organization Scientific Brief: Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19. 2020 Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-1*
4. *Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, 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(5):323-31.* **[CrossRef]**
5. *Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607-8.* **[CrossRef]**
6. *Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383(4):334-46.*
7. *Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383(4):347-58.* **[CrossRef]**
8. *Torres JP, Izquierdo G, Acuña M, Pavez D, Reyes F, Fritis A, et al. Multisystem inflammatory syndrome in children (MIS-C): Report of the clinical and epidemiological characteristics of cases in Santiago de Chile during the SARS-CoV-2 pandemic. Int J Infect Dis 2020;100:75-81.* **[CrossRef]**
9. *Hameed S, Elbaaly H, Reid CEL, Santos RMF, Shivamurthy V, Wong J, et al. Spectrum of imaging findings at chest radiography, US, CT, and MRI in multisystem inflammatory syndrome in children associated with COVID-19. Radiology 2021;298(1):E1-E10.* **[CrossRef]**
10. *Umezawa T, Saji T, Matsuo N, Odagiri K. Chest x-ray findings in the acute phase of Kawasaki disease. Pediatr Radiol 1989;20(1-2):48-51.* **[CrossRef]**
11. *Lima-Setta F, Magalhães-Barbosa MC, Rodrigues-Santos G, Figueiredo EADN, Jacques ML, Zeitel RS, et al. Multisystem inflammatory syndrome in children (MIS-C) during SARS-CoV-2 pandemic in Brazil: A multicenter, prospective cohort study. J Pediatr (Rio J) 2020;97(3):354-61.* **[CrossRef]**
12. *Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324(3):259-69.* **[CrossRef]**
13. *Sivit CJ, Newman KD, Chandra RS. Visualization of enlarged mesenteric lymph nodes at US examination. Clinical significance. Pediatr Radiol 1993;23(6):471-5.* **[CrossRef]**
14. *Tullie L, Ford K, Bisharat M, Watson T, Thakkar H, Mullassery D, et al. Gastrointestinal features in children with COVID-19: An observation of varied presentation in eight children. Lancet Child Adolesc Health 2020;4(7):e19-e20.* **[CrossRef]**
15. *Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: Prospective observational study. BMJ 2020;369:m2094.* **[CrossRef]**
16. *Zhao Y, Yin L, Patel J, Tang L, Huang Y. The inflammatory markers of multisystem inflammatory syndrome in children (MIS-C) and adolescents associated with COVID-19: A meta-analysis. J Med Virol 2021;93(7):4358-69.* **[CrossRef]**
17. *McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. Circulation 2017;135(17):e927-e999.* **[CrossRef]**
18. *Shackelford PG, Strauss AW. Kawasaki syndrome. N Engl J Med 1991;324(23):1664-6.* **[CrossRef]**
19. *Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet 2020;395(10239):1771-8.* **[CrossRef]**
20. *Shulman ST. Pediatric coronavirus disease-2019-associated multisystem inflammatory syndrome. J Pediatric Infect Dis Soc 2020;9(3):285-6.* **[CrossRef]**
21. *Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): A multi-institutional study from New York City. J Pediatr 2020;224:24-9.* **[CrossRef]**