



# Which Findings Make multisystem Inflammatory Syndrome in Children Different from the Pre-Pandemic Kawasaki Disease?

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## Abstract

Multisystem Inflammatory Syndrome in Children associated with COVID-19 infection attracted attention because some features overlapped with Kawasaki disease. And due to these overlapping features with Kawasaki disease, it has become difficult to diagnose both disorders. Therefore, this study focused on the differences between the patients diagnosed with MIS-C after COVID-19 and Kawasaki patients analyzed, particularly during the pre-pandemic period. In this way, it is aimed to reduce the dilemmas experienced in Diagnosis. In this descriptive study, 98 patients diagnosed with MIS-C throughout the pandemic were compared to 37 patients diagnosed with Kawasaki Disease during the pre-pandemic period.

The patients in the MIS-C group were older children and clinically suffered from more headaches, vomiting, diarrhea, abdominal pain, and chest pain than Kawasaki patients. Signs of shock such as hypotension and tachycardia were more remarkable. Also, myocarditis and mitral regurgitation were detected at a higher rate in the MIS-C group. Besides, in the laboratory, lymphopenia, hypoalbuminemia, and creatinine elevation were more apparent.

In conclusion, our present study findings support that although the MIS-C and Kawasaki share common features, they present with different clinical and laboratory features. And these differences are thought to be supportive in treatment and patient management.

**Keywords** Multisystem inflammatory syndrome in children · MIS-C · Kawasaki disease · Children

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## Introduction

Following the COVID-19 pandemic, in April 2020, a new pediatric hyperinflammatory syndrome was described in the United Kingdom [1]. These cases attracted attention because they were associated with COVID-19 infection and overlapped with Kawasaki disease, the leading cause of acquired heart disease in children [2]. Although the triggers of Kawasaki disease are unknown, the most likely reasons are infections and genetic factors. Concurrently, cases with fever, cough, rash, an elevated acute-phase reactant, hypoalbuminemia, hyponatremia, and thrombocytosis were reported from other countries, and even increased rates and severity of Kawasaki disease [3, 4].

On the other hand, it was observed that this syndrome, which was newly defined by clinical studies, had specific differences from Kawasaki disease, such as age, race, cardiac involvement, and laboratory results. Eventually, US Centers for Disease Control and Prevention (CDC) and the World Health Organization gave this newly identified syndrome the name Multisystem Inflammatory Syndrome in Children (MIS-C) [5].

Hyperinflammation plays a leading role in the pathogenesis of MIS-C and Kawasaki disease [2]. For this reason, anti-inflammatory treatments are included in management. Although there are similarities in treatment management, it is important to distinguish from Kawasaki disease due to MIS-C course, complications, and higher mortality risk. For instance, in patients with MIS-C, administration of steroids and enoxaparin are more common than KD treatment. And differential diagnosis for these two diseases is crucial in preventing possible undesirable side effects secondary to corticosteroids and financial burden and predicting cardiac complications for both disorders.

This study planned to compare Kawasaki patients in the pre-pandemic period and patients diagnosed with MIS-C after the pandemic with all features such as clinical, laboratory, response to treatment, and complications, and to reveal the differences.

## Patients and Methods

This study was conducted at the University of Health Sciences Dr. Behcet Uz Children's Hospital, a referral center for pediatric infectious diseases in the Aegean Region of Turkey. Patients who were followed up with the Diagnosis of Kawasaki disease before the COVID-19 pandemic from January 2017 to December 2019 and were followed up with the Diagnosis of MIS-C from March 2020 to January 2022 were included in the study.

The patients were divided into two main groups: the patients diagnosed with Kawasaki disease as Group I, and the patients diagnosed with MIS-C as Group II.

All hospitalized patients aged under 18-year-old and diagnosed with complete or incomplete Kawasaki disease or MIS-C were included in the study. According to the American Heart Academy guidelines, a persistent fever is defined as complete KD over five days associated with at least four of the five following criteria: conjunctivitis, cervical lymphadenopathy, polymorphous skin rash, red and cracked lips, inflammation of hands and feet. Children who do not meet the entire Kawasaki disease criteria, including fever  $\geq 5$  days plus two or three compatible above-mentioned clinical criteria, or fever  $\geq 7$  days with no other explanation, are accepted as incomplete/atypical KD. In addition, laboratory and echocardiographic findings were considered supportive for diagnosis [6].

MIS-C inclusion criteria were according to the definition of the Turkish Ministry of Health COVID-19 guideline and CDC guideline [7–9]. According to these guidelines, inclusion criteria were children under 18 years of age with a fever for at least 24 h  $\geq 38.0$  °C, severe illness necessitating hospitalization, and two or more organ systems affected (e.g., cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, and neurological), and one or more of the laboratory findings. In addition, exposure to a suspected or confirmed COVID-19 case within four weeks before the onset of clinical manifestations was investigated. Positive test results for current or recent SARS-CoV-2 infection were evaluated by Real-Time Polymerase Chain Reaction (RT-PCR) or serology.

Patients for whom another diagnosis was confirmed during the follow-up were excluded.

Data from both groups were recorded and collected from the hospital's electronic medical records. The data included demographic characteristics, presenting signs and symptoms, laboratory and echocardiographic findings, clinical data, and treatment management.

Presenting signs and symptoms included the duration of fever before admission, cough, shortness of breath, tachycardia, hypotension, chest pain, vomiting, diarrhea, abdominal pain, rash, desquamation of the skin, conjunctivitis, unilateral/cervical lymphadenopathy, peripheral edema of extremity, and headache.

Admitting laboratory values included serum white blood cell (WBC) count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet (PLT) count, hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, ferritin, albumin, creatinine, D-dimer, fibrinogen were evaluated.

Finally, in the echocardiographic examination, the percentage of ejection fraction (EF), presence of mitral regurgitation, coronary dilatation/aneurysm, myocarditis, and

pericarditis were recorded for both disease groups. Echocardiographically, the presence of left ventricular dysfunction and low EF were considered signs of myocarditis [10]. Patients with pericardial effusion in the absence of myocardial dysfunction echocardiographically were considered as pericarditis [11]. According to the American Heart Association (AHA) guidelines, coronary artery dilatation was defined as a localized dilation of the internal lumen diameter but  $< 4$  mm, or if the child is  $\geq 5$  years of age, dilation but with an internal diameter of a segment measuring  $\leq 1.5$  times that of an adjacent segment. Coronary artery aneurysm was defined as an internal lumen diameter  $> 4$  mm, or if the child is  $\geq 5$  years of age, an internal diameter of a segment measuring  $> 1.5$  times that of an adjacent segment [12].

All laboratory values and echocardiography findings on admission were compared in both disease groups.

Requirements for Intravenous immunoglobulin (IVIG), corticosteroid, enoxaparin, and acetylsalicylic acid treatments were evaluated. The duration of fever after IVIG treatment was recorded.

## Statistical Methods

Categorical variables were analyzed using relative frequencies and numerical variables using median or mean (depending on whether they show normal distribution) values. Categorical variables were compared using Pearson  $\chi^2$  and Fisher's exact tests. Numerical variables were compared using the *t*-test or the nonparametric Mann–Whitney *U* test. Eventually, the characteristics of patients diagnosed with MIS-C and the classical KD cohort were compared using the Fisher's exact test for categorical variables and the Mann–Whitney *U* test for quantitative variables. A two-sided *p*-value  $< 0.05$  was considered statistically significant.

## Ethical Consent

This study was approved by the Local Ethical Committee of Dr. Behcet Uz Children's Training and Research Hospital (decision no: 2022–03.03).

## Results

### Comparison of Demographic Data and Clinical Findings of Kawasaki Disease and MIS-C

Thirty-seven patients with the Diagnosis of Kawasaki disease were defined as Group I. While thirty-two of them fulfilled the complete Kawasaki criteria, the remaining five patients met the atypical Kawasaki criteria.

Ninety-eight patients with MIS-C were included in the study as Group II. Twenty-three (62.2%) patients in group I were male, and 14 (37.8%) were female. Sixty-eight (69.4%) of these patients were male, and 30 (30.6%) were female in Group II. There was no significant difference between the two groups in terms of gender ( $p > 0.05$ ).

The mean age of children with MIS-C is  $91.2 \pm 55.7$  months (ranging from 5 to 204 months), and the mean age of children with Kawasaki disease was  $36.3 \pm 35.2$  months (ranging from 2.5 to 132 months), and it was significantly higher in the MIS-C group ( $p < 0.001$ ).

The duration of fever before Diagnosis was  $6.6 \pm 3.0$  days (minimum 1 day – maximum 14 days) in patients with Kawasaki disease and  $5.0 \pm 2.3$  days (minimum 0 day—maximum 12 days) in patients with MIS-C, and the duration of fever was significantly longer in the Kawasaki group ( $p = 0.043$ ).

The proportion of presence of unilateral/cervical lymphadenopathy, peripheral edema of extremity, desquamation of the skin, and the rash was significantly higher in Group I compared to Group II ( $p = 0.010$ ,  $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.001$ , respectively). The proportion of headache, vomiting, diarrhea, abdominal pain, hypotension, tachycardia, and chest pain was significantly higher in Group II compared to Group I ( $p = 0.018$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.01$ , respectively). There was no significant difference in the rates of cough, shortness of breath, and conjunctivitis between the two groups. ( $p > 0.05$ ). Demographic data and clinical features are reviewed at Table 1.

On the other hand, any patients diagnosed with MIS-C did not fulfill the complete Kawasaki disease criteria regarding fever and other accompanying symptoms. During the pandemic, 20 patients were hospitalized with the diagnosis of complete/incomplete Kawasaki Disease.

### Comparison of laboratory findings of Kawasaki Disease and MIS-C

The mean white blood cell count, absolute lymphocyte count, absolute neutrophil count, platelet count, and hemoglobin value were significantly higher in Group I compared to group II ( $p = 0.005$ ,  $p < 0.001$ ,  $p = 0.006$ ,  $p < 0.001$ , and  $p = 0.008$ , respectively) (Table 2). The laboratory findings are reviewed in Table 2. The mean albumin value was significantly low in Group II compared to Group I (3.62 g/dL vs. 4.67 g/dL,  $p = 0.006$ ). The median creatinine value was significantly higher in Group II compared to Group I (0.64 mg/dL vs. 0.48 mg/dL  $p = 0.046$ ) (Table 2). There was no statistically significant difference between the two groups in CRP, ESR, ferritin, and D-dimer values ( $p > 0.05$ ). All laboratory findings of both groups are reviewed in Table 2.

**Table 1** The comparison of demographic data and clinical features of Group I and Group II

	Patients diagnosed with Kawasaki disease at pre-pandemic period Group I n: 37	Patients diagnosed with MIS-C Group II n: 98	p value
Demographic data			
Gender, n (%)			
Male	23 (62,2%)	68 (69,4%)	> 0.05
Female	14 (37,8%)	30 (30,6%)	> 0.05
Age, months (mean ± SD)	36.31 ± 35.21	91.20 ± 55.70	0.000*
Duration of fever before the diagnosis, days (mean ± SD)	6.59 ± 2.99	5.030 ± 2.28	0.043*
Presenting signs and symptoms n (%)			
Cough	5(13.5%)	9(9.2%)	> 0.05
Shortness of breath	3(8.1%)	7(7.1%)	> 0.05
Conjunctivitis	5(13.5%)	9(9.2%)	> 0.05
Unilateral/cervical lymphadenopathy	7(18.9%)	10(10.2%)	0.010*
Peripheral edema of extremity	12(32.4%)	16(16.3%)	0.000*
Desquamation of the skin	16(43.2%)	8(8.2%)	0.000*
Rash	33(89.2%)	32(32.7%)	0.000*
Headache	1(2.7%)	8(8.1%)	0.018*
Vomiting	4(10.8%)	37(37.8%)	0.000*
Diarrhea	4(10.8%)	28(28.6%)	0.000*
Abdominal Pain	4(10.8%)	35(35.7%)	0.000*
Hypotension	1(2.7%)	21(21.4%)	0.000*
Tachycardia	2(5.4%)	21(21.4%)	0.000*
Chest pain	0	4(4.1%)	0.010*

\*statistically significant findings ( $p < 0.005$ )

**Table 2** The comparison of the laboratory findings between Group I and Group II

	Patients diagnosed with Kawasaki disease at pre-pandemic period Group I n: 37 (mean ± SD)	Patients diagnosed with MIS-C Group II n: 98 (mean ± SD)	p value
WBC (cells/mL)	17.168 ± 8.134	11.041 ± 5.064	0.005*
ANC (cells/mL)	11.766 ± 7.396	8.073 ± 3.973	0.000*
ALC (cells/mL)	3.864 ± 2.739	2.147 ± 1.870	0.006*
PLT (cells/mL)	403.972 ± 186.530	214.459 ± 92.749	0.000*
Hemoglobin (g/dl)	12.8 ± 16.93	11.54 ± 1.44	0.008*
Creatinine (mg/dL)	0.48 ± 0.10	0.64 ± 0.30	0.046*
Alb (g/dL)	4.67 ± 7.51	3.62 ± 0.50	0.006*
CRP (mg/dL)	10.59 ± 7.93	13.89 ± 9.70	> 0.05
ESR (mm/h)	69.70 ± 32.52	70.23 ± 27.68	> 0.05
Ferritin (mg/L)	1.110 ± 2960	1.294 ± 4.188	> 0.05
D-dimer (ng/mL)	1.859 ± 2.710	1.249 ± 1.750	> 0.05

WBC white blood cell count, ANC absolute neutrophil count, ALC absolute lymphocyte count, PLT platelet, CRP C-reactive protein, ESR erythrocyte sedimentation rate, ml milliliter, g gram, mg milligram, dl deciliter, mm millimeter, h hour, l liter, ng nanogram

\*statistically significant findings ( $p < 0.005$ )

### Comparison of Echocardiographic Findings of Kawasaki Disease and MIS-C

There was a statistically significant difference in the echocardiographic findings between Group I and Group II. Coronary

dilatation rate in echocardiography was statistically higher in Group I compared to Group II (11 (29.7%), 4 (4.1%), respectively;  $p < 0.001$ ). The rate of mitral regurgitation was 43.9% (43) in Group II versus 29.7% (11) in Group I, the rate of myocarditis was 10.2% (10) in Group II versus 0% (0) in

Group I, and the rate of perimyocarditis was 2% (2) in Group II versus 0% (0) in Group I and it was statistically higher ( $p=0.001$ ,  $p<0.001$ , and  $p<0.001$ , respectively). There was no statistically significant difference between ejection fractions in both patient groups ( $p>0.05$ ). Echocardiographic findings and treatment managements are summerized in Table 3.

### Comparison of Treatment Managements of Kawasaki Disease and MIS-C

There was a statistically significant difference in the treatment management between Group I and Group II. IVIG treatment rate was 100% (37) in Group I versus 96.9% (95) in group 2, the rate of acetylsalicylic acid administration was 94.6% (35) in Group 1 versus 68.4% (67) in Group 2 ( $p=0.028$ ,  $p<0.01$ , respectively). The mean time of IVIG administration was  $47.27 \pm 64.78$  h in Group 1 versus  $18.84 \pm 22.05$  h in Group 2 ( $p<0.01$ ). The rate of corticosteroid treatment in Group II was 58.2% (57) compared to 10.8% (4) in Group I, and the rate of enoxaparin treatment was 68.4% (67) in Group II compared to 8.1% (3) in Group I. ( $p<0.00$ ,  $p<0.001$  respectively).

### Discussion

Large clinical studies evaluating the similarities and differences between MIS-C and Kawasaki disease were limited. Therefore, in this descriptive study, we compared 98 patients diagnosed with MIS-C throughout the pandemic

and 37 patients diagnosed with Kawasaki disease during the pre-pandemic period. We found statistically significant differences between the two groups. These differences included that patients in the Kawasaki group had a younger age and a more longer pre-diagnosis fever period epidemiologically. Additionally, among the clinical findings, the presence of unilateral/cervical lymphadenopathy, peripheral edema of extremity, desquamation of the skin and rash, presence of laboratory differences such as leukocytosis and thrombocytosis, and coronary dilatation in terms of cardiac involvement were the most striking differences.

In contrast, the patients in the MIS-C group were older children and clinically from more headaches, vomiting, diarrhea, abdominal pain, and chest pain than patients with Kawasaki disease. Signs of shock such as hypotension and tachycardia were more remarkable. Also, myocarditis and mitral regurgitation were detected at a higher rate in the MIS-C group. Besides, in the laboratory, lymphopenia, hypoalbuminemia, and creatinine elevation were more apparent. Among these findings, the creatinine value is thought to be related to the older age of the patients in the MIS-C group. On the other hand, creatinine levels in the all KD group were within the normal range for age, whereas creatinine levels in 5 (5.1%) MIS-C patients were above the normal range for age.

The current study revealed that the mean age in the MIS-C group was significantly higher than in the Kawasaki group. The result was consistent with the other reports in the literature [13, 14]. In the multi-center study conducted by Ciftdogan et al. [13], the median age of the patients with MIS-C was nine years. However, the median age was seven

**Table 3** The comparison of the echocardiographic findings and treatment management between Group I and Group II

	Patients diagnosed with Kawasaki disease at pre-pandemic period Group I n: 37	Patients diagnosed with MIS-C Group II n: 98	p value
Echocardiographic findings			
Percent of Ejection Fraction (mean $\pm$ SD)	68.67 $\pm$ 6.05	65 $\pm$ 8.75	> 0.05
Mitral Regurgitation (n,%)	11 (29.7%)	43(43.9%)	0.001*
Coronary dilation	11(29.7%)	4(4.1%)	0.000*
Myocarditis	0(0%)	10(10.2%)	0.000*
Pericarditis	0(0%)	2(2%)	> 0.05
IVIG treatment (n,%)	37(100%)	95(96.9%)	0.028*
Time of IVIG administration (hour, mean $\pm$ SD)	47.27 $\pm$ 64.78	18.84 $\pm$ 22.05	0.000*
IVIG repeated course (n,%)	3(8%)	0	0.000*
Corticosteroids	4(10.8%)	57(58.2%)	0.000*
Enoxaparin	3(8.1%)	67(68.4%)	0.000*
Acetylsalicylic acid	35(94.6%)	67(68.4%)	0.000*
ICU admission	3(8.1%)	25(25.5%)	0.000*

ICU Intensive care unit

\*statistically significant findings ( $p<0.005$ )

in MIS-C patients overlapping with Kawasaki disease. Ultimately, age has been recognized as one of the essential demographic differences. Similar to the current study, Kawasaki disease typically affects young children under the age of five, whereas MIS-C has been reported in children ranging from 1.6 to 20 years, with a median age of 6–11 years [15–17]. Male predominance was observed in other MIS-C studies [5, 18]. Although our findings were similar, male predominance was present in both disease groups, and no significant statistical difference was observed.

According to this study, the duration of fever before diagnosis was shorter in MIS-C, which is consistent with other studies. Furthermore, in other studies, the fever resolved in a shorter period [19]. One of the most important factors affecting this result is thought to be the difference in diagnostic criteria.

Gastrointestinal symptoms such as vomiting, diarrhea, nausea, severe abdominal pain suggestive of appendicitis, and headache were more prevalent in MIS-C patients. These findings were consistent with many studies, reviews, and case series in the literature. Gastrointestinal findings were among the most remarkable clinical findings in the majority of the MIS-C group and were significantly different from patients diagnosed with Kawasaki disease [18, 20, 21]. In the studies conducted by Ciftdogan et al. [13, 22], it was stated that gastrointestinal symptoms were more dominant at presentation in MIS-C patients. When classified according to the age groups of these patients, it was noted that gastrointestinal complaints such as nausea were primarily detected in older children. The reason was attributed to the fact that the younger age group may be insufficient to express the complaints [13]. It also can be considered that similar reasons may also be valid for patients diagnosed with Kawasaki disease by age group. As a result, according to reports, including our own, gastrointestinal symptoms are more common in MIS-C, such as the study of Abraham et al. [23], which had more than 80% of MIS-C cases present with gastrointestinal symptoms. In reality, cases of appendectomy performed due to misdiagnosis have been reported in the literature [19, 24].

We found that mucocutaneous findings, conjunctivitis, lymphadenopathy, edema in the extremities, and skin involvement are more prominent in Kawasaki disease. In addition to fever, which is also included in the diagnostic criteria, these clinical findings such as rash, redness of eyes, cracked lips, strawberry tongue, erythema, swollen red palms, and soles were more pronounced symptoms in almost all studies in the literature [13, 25–27]. A recent update on Kawasaki disease reported that although significantly less common, other clinical manifestations may include vomiting, abdominal pain, myocarditis, and neurological findings not included in the diagnostic criteria [26, 27]. However, it should note that classical KD is a clinical diagnosis based on defined criteria without an alternative explanation [26].

In terms of laboratory, patients diagnosed with Kawasaki disease had significantly higher absolute leukocytes, absolute lymphocyte count, and platelet count than the MIS-C group in our study. Lymphopenia and thrombocytopenia have been reported in the literature to accompany MIS-C cases, as seen in our study, whereas leukocytosis was observed in Kawasaki patients. In addition, sedimentation, CRP, ferritin, and D-dimer levels were also higher as acute-phase reactants in patients with MIS-C in previous studies [4, 19, 28]. However, no significant difference was found between the two groups in our study from the standpoint of acute-phase reactants. Besides these results, hypoalbuminemia was detected in the MIS-C group of the current study, similar to the literature, and it should be noted that laboratory differences can be used as clinical support in the differential diagnosis [29, 30].

Kawasaki patients had significantly better clinical presentation, stability, and few cardiac abnormalities, except for coronary artery dilatations, according to studies [31]. On the other hand, patients with MIS-C had prominent fast progression myocarditis rather than coronary involvement, with shock findings such as hypotension and tachycardia, valve regurgitation, arrhythmia, and atrioventricular blocks being more common [19, 32]. A large study comparing MIS-C and Kawasaki Disease demonstrated decreased cardiac function, myocarditis, pericardiac effusion, mitral regurgitation, and pleural effusion occurred almost exclusively in patients with MIS-C. In contrast, patients with KD had the lowest rates of shock and hypotension [33]. In the literature, symptomatic myocarditis has been reported in 40–80% of patients with MIS-C [4, 28]. In contrast, it is seen in <5% of patients with Kawasaki disease [34]. Coronary artery abnormalities (CAAs) have been reported in 9–24% of MIS-C patients, typically in the form of dilatation or small-sized aneurysms [34, 35]. As in our study, it was stated cardiac failure is prominent in MIS-C patients. In the current study, ejection fraction (EF) levels were relatively lower in the MIS-C group. There was no statistically significant difference in EF levels observed between MIS-C and Kawasaki disease [19, 32]. On the other hand, while 25 MIS-C patients required intensive care, only three Kawasaki patients required intensive care, which was significantly higher in MIS-C patients. Of the patients diagnosed with MIS-C, 8 of them were admitted to the intensive care unit due to cardiac dysfunction (based on low ejection fraction and/or fractional shortening). Consistent with the literature, the coronary aneurysm was significantly higher in the Kawasaki group in this study. In contrast, tachycardia, hypotension, mitral regurgitation, myocarditis, and pericarditis rates were substantially higher in the MIS-C group. These findings suggested that cardiac dysfunction or failure was more common in MIS-C patients.

Besides these findings, chest pain was not detected in any of the patients who were followed up with Kawasaki

disease, while it was observed in the four patients diagnosed with MIS-C. Similarly, found no information in the literature on accompanying chest pain in the patients with Kawasaki disease, whereas in Belhadjer et al. [36], chest pain was reported in six cases diagnosed with MIS-C. For this reason, chest pain complaints among the clinical symptoms should be questioned in the differential diagnosis, and the importance of vital evaluation should be kept in mind.

Intravenous immunoglobulin is the most effective treatment for reducing coronary artery complications in Kawasaki disease [37]. Because of the high level of inflammation, acetylsalicylic acid (A.S.A.) is recommended with an anti-inflammatory dose, in addition to IVIG [38]. Although the optimal management of MIS-C is still unknown, considering the clinical similarities and the underlying inflammatory process in both diseases, IVIG, corticosteroid, and anticoagulant treatments were primarily used in MIS-C cases [39]. Similarly, while all Kawasaki patients diagnosed before the pandemic received IVIG treatment, IVIG treatment was not provided in three of the MIS-C cases in our study. The reason is thought to be that the fever does not persist in these patients, and the clinical findings are stable. The current study also discovered that the time of IVIG administration was noticeably shorter in patients diagnosed with MIS-C than in those diagnosed with Kawasaki disease who required repeated IVIG replacement. It can be explained by the fact that the duration of fever in the definitions of MIS-C and Kawasaki, combined with the increased awareness caused by the pandemic, leads to an earlier diagnosis of MIS-C.

After IVIG, the other primary treatment for Kawasaki disease is acetylsalicylic acid usually given in a moderate or high dose until the patient is afebrile [40]. As a result, our research observed that the use of acetylsalicylic acid in conjunction with IVIG is significantly higher in Kawasaki patients. On the other hand, corticosteroid and enoxaparin administration were higher in the MIS-C group in the current study. It is thought that the risk of thrombosis will increase due to the tendency of COVID-19 infection and related processes and the accompanying obesity factor in these patients; therefore, enoxaparin treatment is used [41]. Similar to our study, in the review reported by Sharma et al., corticosteroids were used in the majority of the patients diagnosed with MIS-C [42]. During the varying treatment period, many guidelines recommended corticosteroid treatment with IVIG for MIS-C, but recently, comparative publications in terms of their use with IVIG alone or with corticosteroid use have begun to emerge. In one of the recent research, corticosteroid implementations without IVIG have been seen to be effective in the treatment of MIS-C, except for severe cases and those with cardiac involvement [43]. Although more research is needed, considering the clinical conditions, it is thought that single corticosteroid therapy may be an alternative, according to studies.

This study has several limitations due to the collection of data retrospectively. As a disadvantage of the retrospective study, cardiac enzymes were evaluated more broadly in MIS-C patients, whereas these values were not studied in Kawasaki patients, preventing a comparison. Troponin, for example, was routinely tested in patients with MIS-C but not in Kawasaki patients prior to the pandemic. Furthermore, because the investigation was in the acute period, the diagnosis of myocarditis confirmed by echocardiography, and magnetic resonance imaging (MRI) findings could not be obtained in this period. In addition, the sample of Kawasaki disease is small to generalize our findings. However, we include only the children with Kawasaki disease, which were followed up before the start of COVID-19 pandemic, thus avoid diagnostic dilemmas in diagnosis of Kawasaki disease and Kawasaki overlap syndrome during COVID-19 pandemic such as availability of accurate serological tests.

## Conclusion

In conclusion, our findings of the present study support that although the MIS-C and Kawasaki share common features, they present with different clinical and laboratory features. The MIS-C patients are older children than Kawasaki patients with a higher proportion of gastrointestinal symptoms in addition to hypotension and tachycardia. In addition, in patients with MIS-C, administration of steroids and enoxaparin are more common than KD treatment. And differential diagnosis for these two diseases is crucial in preventing possible undesirable side effects secondary to corticosteroids and financial burden and predicting cardiac complications for both disorders.

**Author contributions** EC, İD, NB: was responsible for the organization and coordination of the trial. EC and İD: were the chief investigators responsible for the data analysis. AA, EB, EK, MG, PK, AAK, ŞŞ, MYÇ, MD, MMY, MM and NB: developed the trial design. All authors contributed to the writing of the final manuscript. All authors contributed to the management or administration of the trial.

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## Declarations

**Conflict of interest** The authors have no example conflict of interest and no relevant financial relationships to disclose.

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