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Comparison of early characteristics of multisystemic inflammatory syndrome and Kawasaki disease in children and the course of Kawasaki disease in the pandemic

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Abstract

Introduction Multisystemic inflammatory syndrome (MIS-C) is a newly described disease manifestation in children associated with the novel coronavirus SARS-CoV-2 infection and can be easily confused with Kawasaki disease with its clinical and laboratory findings. In this study, the clinical findings, organ involvements, similarities, and differences in laboratory and imaging of the children with MIS-C and KD at the time of admission will be revealed in detail, and the treatment methods and follow-up results will be revealed.

Material and method Our study was a single-center study and included pediatric patients who were treated with a diagnosis of MIS-C between March 2020 and July 2023 in the pediatric cardiology, pediatric emergency, pediatric infection, and pediatric intensive care clinics at Celal Bayar University and who were treated with a diagnosis of KD (complete/incomplete) between January 2015 and July 2023. MIS-C diagnosis was made according to the Turkish Ministry of Health COVID-19 guidelines. Sociodemographic characteristics, clinical, laboratory, and echocardiography findings, treatments given, and clinical course of all patients included in the study were evaluated.

Results The median age was 30 months (7–84) in KD and 96 months (6-204) in MIS-C, and it was significantly higher in the MIS-C group ($p=0.000$). Symptom duration was significantly longer in the MIS-C group ($p=0.000$). In terms of clinical features, gastrointestinal syndrome findings (nausea, vomiting, abdominal pain) and respiratory findings (dyspnea) were significantly higher in the MIS-C group ($p=0.007$, $p=0.000$, $p=0.002$, respectively). Regarding cardiovascular system involvement, coronary involvement was significantly higher in the KD group. However, valvular involvement, left ventricular systolic dysfunction, and pericardial effusion were significantly higher in the MIS-C group ($p=0.000$, $p=0.001$, $p=0.003$, $p=0.023$, respectively). In terms of laboratory findings, white blood cell count was higher in KD ($p=0.000$), absolute lymphocyte count, platelet level, blood sodium, and albumin levels were lower in MIS-C group ($p=0.000$, $p=0.000$, $p=0.000$, $p=0.000$, $p=0.003$, respectively), ferritin and troponin levels were significantly higher in MIS-C group. These results were statistically significant ($p=0.000$, $p=0.000$, respectively). D-dimer and fibrinogen levels were high in both groups, and no significant statistical difference was detected

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between the two groups. There was no significant difference between the two groups regarding the length of hospitalization and mortality, but steroid use was significantly higher in the MIS-C group ($p = 0.000$).

Conclusion In conclusion, this study has demonstrated the similarities and differences between MIS-C and KD regarding clinical findings, organ involvement, and laboratory and imaging results. The results of our study have important implications in terms of contributing to the data in the existing literature on these two diseases and for the correct diagnosis and better management of pediatric patients presenting with these disorders.

What is known Multisystemic inflammatory syndrome (MIS-C) is a newly described disease manifestation in children associated with the novel coronavirus SARS-CoV-2 infection and can be easily confused with Kawasaki disease with its clinical and laboratory findings.

What is new Although MIS-C and KD have many similarities, their symptoms, disease processes, possible complications, and treatment regimens may differ.

Keywords Multisystemic inflammatory syndrome, Kawasaki disease, SARS-CoV-2 infection

Introduction

Multisystemic inflammatory syndrome (MIS-C) is a newly described disease entity in children associated with novel coronavirus SARS-CoV-2 infection. It is characterized by hyperinflammation with multi-organ involvement. Considering the clinical and laboratory diagnostic criteria, it can be easily confused with Kawasaki disease (KD) since it has many similar findings.

The incidence of MIS-C is 2/100.000, and it is frequently seen in school-age children and adolescents [1]. MIS-C is more prevalent in Europe and the USA than in East Asian countries such as Japan, China, and Korea and has affected children of African or Hispanic origin more frequently than white children in Europe and the USA [1, 2], suggesting an association with racial, environmental, or socioeconomic factors. In contrast, classic KD typically affects infants and young children and has a higher incidence in East Asia and in children of Asian descent [3].

The etiology of these diseases is unclear and multifactorial, but infections (mainly viral) play a vital role in both cases. Notably, most reported cases of MIS-C have positive serologic tests for SARS-CoV-2 and less frequently positive real-time reverse transcription polymerase chain reaction (RT-PCR) tests, suggesting the post-infectious nature of this syndrome [4]. Current evidence suggests that MIS-C results from an exaggerated innate and adaptive immune response, characterized by a cytokine storm and likely triggered by previous exposure to SARS-CoV-2 in susceptible children [5].

Although many clinical and epidemiological features of KD suggest that an infectious agent causes the disease, its etiology is still unclear because a microbiological pathogen is not associated with KD so far [6]. The infrequent occurrence of MIS-C in China and other Asian countries affected by COVID-19, except for very few case reports, has led to speculation about coronavirus variations or increased susceptibility or genomic variation in these populations [1, 7, 8]. Previous theories that a specific unidentified infectious pathogen triggered the disease have been more or less obsolete. Instead, a genetic predisposition associated with conventional viral agents and an abnormal immune system response to a common stimulus is thought to play a role in the development of the disease.

Although both pathological conditions have many common features in etiology and pathophysiology, as well as clinical manifestations, diagnosis, and treatment, they are defined as different diseases due to differences in their epidemiology and the pathophysiological processes involved in the development and frequency of some clinical manifestations. Although there are similarities in treatment management, it is crucial to distinguish MIS-C from KD due to its course, complications, and high mortality risk.

In this study, we aimed to reveal the clinical findings, organ involvement, similarities and differences in laboratory and imaging findings at the time of presentation, treatment modalities, and follow-up results of pediatric patients with MIS-C and KD (incomplete-complete KD) followed in our clinic.

Material and method

Our study is a single-center study that included pediatric patients who were treated with a diagnosis of MIS-C in children between March 2020 and July 2023 in the pediatric cardiology, pediatric emergency, pediatric infection, and pediatric intensive care clinics at Celal Bayar University and who were treated with a diagnosis of KD (complete/incomplete) between January 2015 and July 2023.

In addition to fever lasting five days or longer, the diagnosis of KD was made if 4 or 5 of the following criteria were present after excluding similar diseases: 1-Bilateral nonpurulent conjunctivitis, 2- Erythematous and chapped lips, strawberry tongue appearance, hyperemia in the oropharynx, 3- Polymorphous exanthema (morbilliform, maculopapular or scarlatiniform), 4- Edema in the hands and feet, hyperemia in the palms and soles,

5- Cervical lymphadenopathy (larger than 1.5 cm in diameter). Incomplete KD was considered in patients with a fever exceeding five days and meeting two or three criteria if the diagnosis was supported by laboratory and echocardiographic findings [9, 10].

MIS-C diagnosis was made according to the Turkish Ministry of Health COVID-19 guidelines. Based on the guidelines, the diagnosis of MIS-C was considered valid when the patient's age ranged from 0 to 21 years, and they exhibited either a body temperature exceeding 38,0 °C for more than 24 h or the family reported the existence of fever along with laboratory test results indicating inflammation (with at least two or more pieces of evidence). Additionally, a severe disease course necessitating hospitalization, involvement of multiple organ systems (with at least two or more), the absence of an alternative diagnosis, and evidence of past or recent SARS-CoV-2 infection (within six days) were also considered [11]. Age, gender, presence of chronic diseases, symptoms and physical examination findings at presentation, duration of symptoms, dates of presentation, laboratory findings (complete blood count, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], serum albumin, sodium and complete urine examination), electrocardiography and echocardiography findings, treatments given and clinical course of the cases included in the study were recorded.

BNP and NT-proBNP values for cardiac functions could not be included in the study because they were not studied in most patients due to technical reasons.

All symptoms, clinical findings, laboratory values, echocardiography findings, and treatments applied at the time of admission were compared for both groups.

Statistical methods

All results were analyzed using the Windows SPSS v.22.0 program. Descriptive statistics were shown as mean±standard deviation for variables with normal distribution, median (minimum-maximum) for variables with non-normal distribution, and number of people (n) and (%) for nominal variables. Differences in numerical variables among patient groups were assessed through the Student t Test or Mann-Whitney U Test. Nominal variables were analyzed using the Pearson chi-square or Fisher exact test. Statistical significance was considered achieved if the p-value was <0.05.

Ethical approval

This study was approved by the Manisa Celal Bayar University Local Ethics Committee (date-decision no: 28.08.2023-530).

Results

Demographic characteristics

The distribution of diseases according to years in our study is shown in Fig. 1.

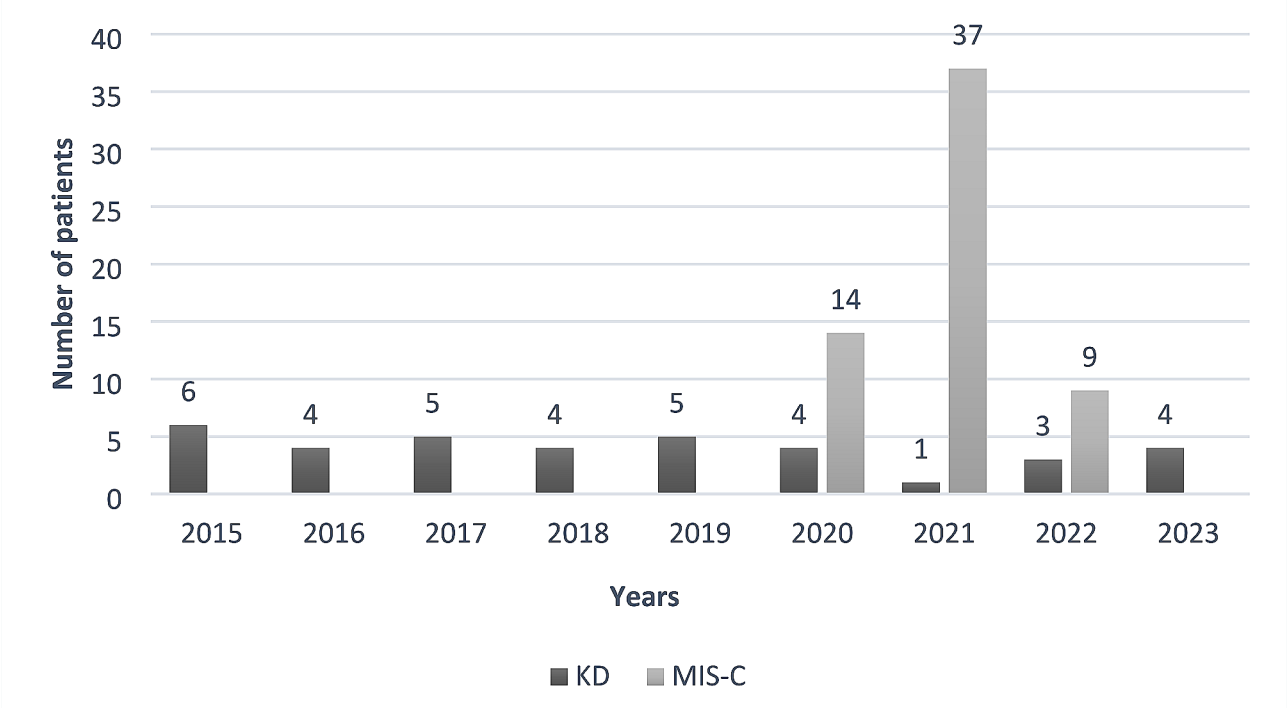

Fig. 1 The distribution of diseases according to years in our study

In our study, 60 (62.5%) patients fulfilled the diagnostic criteria for MIS-C and 36 (37.5%) patients fulfilled the diagnostic criteria for KD, and a total of 96 patients were included in the study. Of the KD patients, 23 (64%) had incomplete KD, and 13 (36%) had complete KD. There was no difference regarding gender between both groups ($p=0.874$). The female/male ratio was 1.06 in the MIS-C group, and the female/male ratio was 1.00 in the KD group. Median age was 30 months (7–84 months) in KD and 96 months (6-204 months) in MIS-C and was found to be statistically significantly higher in MIS-C ($p<0.001$) (Table 1). In the triple comparison of complete - incomplete KD and MIS-C patients, age was significantly higher in MIS-C patients (Table 2) ($p<0.001$). There was no difference between complete and incomplete KD patients.

When evaluated in terms of clinical findings

The duration of fever was shorter in the MIS-C group with a median of 4.5 days (min-max: 1–10 days) and in the KD group with a median of 7 days (min-max: 5–20 days), and this finding was statistically significant ($p<0.001$). When evaluated in terms of comorbidities, the presence of a co-morbid condition in the MIS-C group was significant ($p=0.042$). Co-morbid diseases were obesity and asthma. All patients had fever and fatigue. Both groups had no significant difference regarding rash and conjunctivitis ($p=0.673$, $p=0.092$, respectively). Regarding gastrointestinal syndrome findings, nausea, vomiting, and abdominal pain were significantly higher in the MIS-C group ($p=0.007$, $p<0.001$, respectively). Respiratory finding (dyspnea) was significantly higher in the MIS-C group ($p=0.002$) (Table 1).

When evaluated in terms of laboratory findings

White blood cell count (WBC) was significantly higher in the KD group ($p<0.001$). In comparison, absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were lower in the MIC-C group, with a statistically

Table 1 The comparison of demographic data and clinical features of subgroup Kawasaki and MIS-C patients

	Kawasaki group (*n* = 36)	**MIS-C group (*n* = 60)**	***P****
Demographic data			
Gender, n(%)			
Male	18 (50%)	31 (51.7%)	0.874
Female	18 (50%)	29 (48.3%)	
Age, months, median (range)	30 (7–84)	96 (6-204)	< 0.001*
Duration of fever, median (range)	7.00 (5.00–20.00)	4.50 (1.00–10.00)	< 0.001*
Komorbidite	0 (0.00%)	7 (11.9%)	0.042*
Presenting signs and symptoms n (%)			
Fever	36 (100%)	60 (100%)	-
Fatigue	36 (100%)	60 (100%)	-
Rash	19 (52.8%)	29 (48.3%)	0.673
Conjunctivitis	22 (61.1%)	26 (43.3%)	0.092
Nausea-vomiting	7 (19.4%)	28 (46.7%)	0.007*
Diarrhea	5 (13.9%)	17 (28.3%)	0.103
Abdominal Pain	10 (27.8%)	41 (68.3%)	< 0.001*
Dyspnea	0 (0.00%)	14 (23.3%)	0.002*
Headache	4 (11.1%)	9 (15.0%)	0.761
Cardiovascular system involvement*, *n (%)	26 (72.2%)	44 (73.3%)	0.906
Myocarditis	0 (0.00%)	31 (51.7%)	< 0.001*
Coronary involvement	24 (66.7%)	4 (6.7%)	< 0.001*
Valvular involvement	4 (11.1%)	28 (46.7%)	0.001*
Mitral regurgitation	4 (12.1%)	29 (48.3%)	< 0.001*
Aortic regurgitation	0 (0.00%)	4 (6.7%)	0.293
Ejection Fraction < 55%	0 (0.00%)	12 (20%)	0.003*
Pericardial effusion	0 (0.00%)	8 (13.3%)	0.023*
Hypotension	0 (0.00%)	31(51.6%)	< 0.001*
Treatment management and hospitalization			
Length of hospitalization	7.50 (3.00–20.00)	9.00 (4.00–28.00)	0.155
IVIG treatment	36 (100%)	58 (96.7%)	0.526
Acetylsalicylic acid	35 (97.2%)	60 (100%)	0.375
Corticosteroids	3 (8.3%)	60 (100%)	< 0.001*
LMWH	1 (2.8%)	9 (15%)	0.084
Inotrope support	0 (0.0%)	31 (51.6%)	< 0.001*

LMWH: low-molecular-weight Heparin, *statistically significant findings ($p<0.05$)

Table 2 The comparison of the laboratory findings between Kawasaki and MIS-C patients

	Incomplete Kawasaki group, (*n* = 23)	Complete Kawasaki group, (*n* = 13)	MIS-C group, (*n* = 60)	*p*
Demographic data				
Gender,*n*(%)				
Male	9 (39.1%)	9 (69.2%)	31 (51.7%)	0.219
Female	14 (60.9%)	4 (30.8%)	29 (48.3%)	
Age, months, median (range)	30.00[b] (7.00–84.00)	36.00[b] (8.00–74.00)	96.00[a] (6.00-204.00)	< 0.001*
Duration of fever, median (range)	7.00[b] (5.00–16.00)	6.00[b] (5.00–20.00)	4.50[a] (1,00–10,00)	< 0.001*
Presenting signs and symptoms n (%)				
Fever	23[b] (100%)	13[b] (100%)	60[a] (100%)	< 0.001*
Fatigue	10 (43.5%)	9 (69.2%)	29 (48.3%)	0.304
Rash	12 (52.2%)	10 (76.9%)	26 (43.3%)	0.087
Conjunctivitis	4[b] (17,4%)	3[b] (23.1%)	28[a] (46.7%)	0.026*
Nausea-vomiting	3 (13.0%)	2 (15.4%)	17 (28.3%)	0.261
Diarrhea	3[b] (13.0%)	7[a] (53.8%)	41[a] (68.3%)	< 0.001*
Abdominal Pain	0[b] (0.0%)	0[b] (0.0%)	14[a] (23.3%)	0.004*
Dyspnea	3 (13.0%)	1 (7.7%)	9 (15.0%)	0.912
Headache	23[b] (100%)	13[b] (100%)	60[a] (100%)	< 0.001*
***Cardiovascular system involvement*, *n* (%)**	17 (73.9%)	9 (69.2%)	44 (73.3%)	0,480
Laboratory findings				
WBC (cells/mL)	13,900[b] (6,900 – 40,870)	15,430[b] (7,822 – 26,500)	9,665[a] (910 – 25,410)	< 0.001*
ANC (cells/mL)	9,300 (3,000–25,590)	9,900 (3,000–18,100)	7,765 (700 – 20,000)	0.588
ALC (cells/mL)	3,870[b] (940 – 10,680)	4,200[b] (1,260-7,100)	980[a] (190-7,400)	< 0.001*
Hemoglobin (g/dl)	10.70[a, b] (7.80–12.90)	9.60[b] (8.80–11.90)	11.05[a] (6.70–16.80)	0.004*
PLT (cells/mL)	434,000[b] (248,000-778,000)	511,000[b] (225,000-987,000)	178,500[a] (212–557,000)	< 0.001*
CRP (mg/dL)	5.99[b] (1.76–30.36)	10.00[b] (0.12–34.70)	16.70[a] (2.85–62.30)	0.001*
ESR (mm/h)	82.26[b] ± 24.07	88.15[b] ± 31.41	50.88[a] ± 22.71	0.001*
Troponin	4.00[b] (1.00–40.00)	6.00[b] (2.30-9.00)	27.00[a] (2.30–8395.00)	< 0.001*
Sodium (mEq/L)	136.00 (129.00-141.00)	136.00 (129.00-139.00)	132.00 (123.00-142.00)	0.001*
Albumin (g/dL)	3.52[b] ± 0.55	3.38[b] ± 0.50	3.10[a] ± 0.54	< 0.001*
Treatment management and hospitalization				
Length of hospitalization	7.00 (4.00–20.00)	8.00 (3.00–18.00)	9.00 (4.00–28.00)	0.242
IVIG treatment	23 (100%)	13 (100%)	58 (96.7%)	> 0.050*
Acetylsalicylic acid	22 (95.7%)	13 (100%)	60 (100%)	> 0.050*
Corticosteroids	2[b] (8.7%)	1[b] (7.7%)	60[a] (100%)	< 0.001*

WBC white blood cell count, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *PLT* platelet, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, LMWH: low-molecular-weight Heparin

*statistically significant findings ($p < 0.05$)

significant decrease in ALC ($p < 0.001$). Hemoglobin level was especially lower in the complete KD group ($p = 0.004$), and blood platelet level was higher in both KD groups than in the MIS-C group ($p < 0.001$). In the MIS-C group, ferritin, CRP level, and sedimentation level were significantly higher in KD ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). Regarding renal functions, creatinine and urea levels were significantly higher in the MIS-C group than in the KD groups ($p < 0.001$, $p = 0.034$, respectively). Blood sodium and albumin levels were statistically lower in the MIS-C group ($p < 0.001$, $p = 0.003$, respectively). Troponin level was significantly higher in the MIS-C group compared to both KD groups ($p < 0.001$). Fibrinogen and D-Dimer increased in both MIS-C and KD, and no statistical difference was detected between the groups ($p = 0.843$, $p = 0.095$, respectively). In terms of liver functions, no statistical difference was detected between the two groups regarding ALT and AST levels ($p = 0.594$ and $p = 0.261$, respectively). There was no difference between the two groups regarding urine WBC, urine red blood cell, and urine protein ($p = 0.339$, $p = 0.187$, $p = 0.284$, respectively) (Table 2).

When evaluated in terms of cardiovascular system involvement

On echocardiographic evaluation, coronary involvement was significantly higher in the KD group, while valvular involvement, left ventricular systolic dysfunction, and pericardial effusion were significantly higher in the MIS-C group ($p < 0.001$, $p = 0.001$, $p = 0.003$, $p = 0.023$, respectively) (Table 1).

Table 3 The comparison of demographic data and clinical features of subgroup Kawasaki and MIS-C patients

	Kawasaki group (*n* = 36)	MIS-C group (*n* = 60)	*p*
WBC (cells/mL)	14,450 (6,900 – 40,870)	9,665 (910 – 25,410)	< 0.001*
ANC (cells/mL)	9,340 (940 – 10,680)	7.765 (700 – 20,000)	0.327
ALC (cells/mL)	3,925 (940 – 10,680)	980 (190-7,400)	< 0.001*
Hemoglobin (g/dl)	10.40 (7.80–12.90)	11.05 (6.70–16.80)	0.004*
PLT (cells/mL)	475,000 (225,000-987,000)	178,500 (212–557,000)	< 0.001*
CRP (mg/dL)	6.18 (0.12–34.70)	16.70 (2.85–62.30)	< 0.001*
ESR (mm/h)	84.38 ± 26.66	50.88 ± 22.71	< 0.001*
Fibrinogen (mg/dL)	551.43 ± 180.49	573.78 ± 206.73	0.843
D-dimer (ng/mL)	699 (52-1170)	798 (124–3872)	0.095
Ferritin (ng/mL)	88.45 (42.40–196.00)	215.85 (42.60–1171.00)	< 0.001*
Sodium (mEq/L)	136.00 (129.00-141.00)	132.00 (123.00-142.00)	< 0.001*
Albumin (g/dL)	3.47 ± 0.53	3.10 ± 0.54	0.003*
BUN (mg/dL)	8.44 (3.70–18.00)	9.80 (4.20–50.50)	0.073
Urea (mg/dL)	18.00 (8.00–35.00)	21.00 (9.00-108.00)	0.034*
Creatinine (mg/dL)	0.26 (0.04–0.54)	0.41 (0.12–3.25)	< 0.001*
AST (IU/L)	37.00 (11–596)	39.50 (13.00-446.00)	0.594
ALT (IU/L)	35.50 (8-328)	30.50 (3.00-308.00)	0.261
Troponin (ng/L)	5.50 (1.00–40.00)	27.00 (2.30–8395.00)	< 0.001*
Urine-WBC (HPF)	2.50 (0.00-172.00)	2.00 (0.00–29.00)	0.339
Urine-blood (HPF)	3.00 (0.00–23.00)	2.00 (0.00-104.00)	0.187
Urine-protein (mg/d)	17 (47.2)	29 (48.3)	0.284

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, *d* day, *BUN* blood urea nitrogen, *AST* aspartate transferase, *ALT* Alanine transaminase

*statistically significant findings ($p < 0.05$)

When evaluated in terms of treatment

There was no significant difference in terms of IVIG, aspirin, and low-molecular-weight heparin (LMWH) use in both groups ($p = 0.526$, $p = 0.375$, $p = 0.084$, respectively). Steroid use was significantly higher in the MIS-C group ($p < 0.001$). 13.3% of patients with MIS-C needed intensive care, and 51.6% required inotropic support. Conversely, neither intensive care nor inotropic support was necessary for the KD group (Table 1).

Discussion

Although MIS-C and KD have many similarities, their symptoms, disease processes, possible complications, and treatment regimens may differ. Studies in the literature can also have differences and common similarities.

In our study, we found similar treatment responses to partially similar treatment interventions, as well as overlap in clinical features and elevated inflammatory markers at presentation between KD and MIS-C patients. Both complete and incomplete KD exhibited distinct characteristics, including cardiac involvement, leukocytosis, and thrombocytosis. Notably, coronary involvement was more prevalent in younger children. Additionally, we observed that MIS-C predominantly impacts older children, presenting with heightened gastrointestinal and respiratory symptoms, valvular involvement, and cardiac dysfunction. Lymphopenia was notably pronounced in this group, necessitating steroid support alongside aspirin and IVIG therapy. Furthermore, MIS-C patients often require intensive care. In our study, similar to the studies in the literature, we found that the mean age in the MIS-C group was significantly higher than in both complete and incomplete KD groups. This result was similar to other studies in the literature [12, 13]. Considering our study and other literature data, it can be said that age is one of the main demographic differences for these two diseases, considering that KD typically affects young children under the age of five [9, 12–14].

While the presence of Anti-SARS-CoV-2 IgM or IgG was initially a useful marker for distinguishing KD (incomplete) and MIS-C early in the pandemic, the specificity of seropositivity as a diagnostic test for MIS-C decreases as population immunity increases due to continued exposure. Considering the epidemiological trend of SARS-CoV-2 infection and the prevalence of MIS-C in our society during our study, we observed that, in addition to SARS-CoV-2 seropositivity, older age, cardiac dysfunction, thrombocytopenia, and lymphopenia were important distinguishing features in MIS-C patients, differentiating them from KD.

When we evaluated in terms of gender, we did not see any difference between KD and MIS-C. There were also differences between studies in the literature regarding this result [13, 15, 16].

Fever is the main diagnostic criterion for these two diseases, and all patients in our study had a history of fever. We found that the duration of fever was lower in the MIS-C group. In another study, it was found that fever resolved in a shorter time [17]. This may be due to the fact that the MIS-C group is more symptomatic and has a worse course, and the diagnostic criteria are different.

Similar to the data in the literature, we found that GIS symptoms such as nausea, vomiting, and abdominal pain were more common in the MIS-C group [18, 19]. When these patients were classified according to age groups, Çiftdoğan et al. found that gastrointestinal complaints such as nausea were primarily detected in older children. Separate studies evaluating patients in the same age group are needed to determine whether GI symptoms are a clinical difference in MIS-C or whether KD patients have difficulty expressing these complaints at a younger age [16].

Again, the fact that a respiratory problem such as dyspnea was found more frequently in MIS-C in our study may suggest that similar reasons may be valid for patients diagnosed with KD who have difficulty expressing these complaints at a young age. Understanding this situation, it may be considered to include clinical symptoms of GI, respiratory, cardiovascular, neurological, musculoskeletal, and genito-urinary systems in addition to the diagnostic criteria in KD, especially for self-expressive children [20].

Classic symptoms of complete or incomplete KD, including rash, mucosal involvement, conjunctivitis, erythema/edema of the hands and feet, and cervical lymphadenopathy, were also found in 25-65.5% of patients with MIS-C symptoms, and no significant difference was found between the two diseases [21]. Our study found no difference between the groups regarding conjunctivitis, rash, and mucocutaneous involvement. However, in a study conducted by Ecem et al., these symptoms were more predominant in KD disease [12].

When evaluated in terms of laboratory findings, inflammatory markers were increased in both disease states. WBC was higher in KD ALC, and platelet levels were lower in MIS-C, and CRP was higher in MIS-C. In the literature, while lymphopenia and thrombocytopenia accompanied MIS-C cases, as observed in our study, leukocytosis was observed in KD, and CRP increase was found to be significantly higher in the MIS-C group [22, 23]. Sedimentation, CRP, ferritin, and D-dimer levels as acute phase reactants were also found to be higher in patients with MIS-C in the literature [17, 24]. However, we found that the sedimentation level was significantly higher in KD patients. D-dimer level increased in both cases, and there was no significant difference between the groups.

In addition to these results, hypoalbuminemia was found in the MIS-C group in our present study, similar to the literature, and hyponatremia was also significant in the MIS-C group, and it should be taken into consideration that laboratory differences may be used as clinical support in the differential diagnosis [12, 25].

In terms of cardiac involvement, coronary involvement, and partial valvular involvement were observed in KD, whereas myocarditis, valvular insufficiency, pericardial effusion, left ventricular systolic dysfunction, and consequently, hypotension requiring inotropic support were more common in patients with MIS-C than coronary involvement. While the need for inotropes was not detected in KD, it was present in 51.6% of the MIS-C group.

Similar to our study, a large comprehensive study by Godfred-Cato S. et al. comparing MIS-C and KD showed decreased cardiac function, myocarditis, pericardial effusion, mitral regurgitation, and reported that pleural effusion occurred almost exclusively in patients with MIS-C. In this MIS-C cohort, coronary artery dilatation or aneurysms were present in 18.6% of cases. In contrast, shock and hypotension were lower in patients with KD [26]. In the study of Feldestien et al., coronary aneurysm was found in 8.8% of the patients [1]. Çifdoğan et al. found coronary artery dilatation and aneurysm in 10.8% of MIS-C patients [16]. Cem et al. found coronary artery dilatation in 4.1% (n:4/98) of MIS-C patients [12]. In our study, we found coronary artery dilatation in 6.7% (n:4/60) of MIS-C patients and 66.7% of KD patients.

Cem et al. found that 25.5% of MIS-C patients and 8.1% of KD patients needed intensive care [12]. Lemis et al. found that 33% of MIS-C patients and 7.5% of KD patients needed intensive care [13]. In our study, patients with MIS-C tended to have a more severe course and had more intensive care hospitalization than KD patients. This patient group required third-step intensive care. We did not detect the need for intensive care in KD patients. These differences may be due to differences in intensive care levels. We followed up with all our patients who were considered for MIS-C under level 2 intensive care conditions, but level 3 intensive care support was needed in 13.3%.

IVIG and acetylsalicylic acid (ASA) are first-line treatments for KD. Patients with medium and large aneurysms are treated with combined antiplatelet and anticoagulant therapy. Glucocorticosteroids are recommended for high-risk KD patients and patients who do not respond to IVIG [27]. In our study, we applied. IVIG and aspirin to all KD patients; steroid support was given to 8.3%, and combined antiplatelet and anticoagulant treatment was given to 2.8%. Other treatment possibilities include infliximab, cyclosporine, and anakinra, but were not used in any patient.

Since the first reports of the disease, immunosuppressive drugs and immunomodulators have been the mainstay of MIS-C treatment [28]. Antithrombotic prophylaxis in MIS-C also includes low-dose ASA unless contraindicated and low molecular weight heparin in selected cases with high risk of thrombotic complications [28].

The recommended primary treatment for the management of patients with MIS-C is IVIG, and steroid therapy is also recommended as primary treatment in case of shock, IVIG non-response, and coronary involvement. In the absence of response to the primary available treatments, anakinra, tocilizumab, or infliximab treatments are also recommended to be considered [28, 29]. In our study, we applied IVIG to 96.7% of MIS-C patients, aspirin, and steroid support to all, and combined antiplatelet and anticoagulant treatment to 15%. Other treatment possibilities, including infliximab, tocilizumab, and anakinra, were not used.

In one recent study, corticosteroid administration without IVIG was found to be effective in treating MIS-C, except in severe cases and those with cardiac involvement [30].

In our study, we applied IVIG treatment to all MIS-C patients except for two patients. Although more studies are needed, considering the clinical conditions, single corticosteroid treatment may be an alternative.

Although we found a slight decrease in the incidence of KD during the pandemic, it is not clear whether this is related to the diagnostic overlap with MIS-C or to the changing environmental factors, pathogen infections, and dietary changes during the pandemic [31].

Limitations

Due to our study's single-center design, the findings may not be generalizable to other settings. A multicenter approach could provide more robust data. Additionally, the study's retrospective nature may introduce biases related to data recording and patient management over the years.

In conclusion, we have revealed the similarities and differences between MIS-C and KD in our study. We provide further evidence that MIS-C is a distinct condition from KD. Common symptoms of MIS-C include fever, KD-like features, gastrointestinal symptoms, shock, or coagulopathy. Many of these features are also found in cases of acute abdomen, toxic shock syndrome (TSS), septic shock, KD-shock syndrome, or multiple organ dysfunction syndrome (MODS) and sometimes cause diagnostic confusion in clinical practice [31]. Although a positive serological test for SARS-CoV-2 infection is the main factor distinguishing MIS-C from these entities, all these hyperinflammatory diseases may be sister diseases within a broader syndrome characterized by post-acute autoimmune febrile response to infections. However, the immune system's complex pathophysiology and mechanistic involvement remain unclear. Therefore, although not the same disease, understanding the similarities and differences between MIS-C and KD syndrome will provide useful clues to analyze the pathogenesis, treatment strategies, and long-term follow-up results of these hyperinflammatory diseases. Also, it is not known whether MIS-C can spread to populations like KD or whether it will re-exist under another name after the pandemic and its long-term effects. Therefore, long-term studies should continue to determine the characteristics of MIS-C.

Abbreviations

MIS-C	Multisystemic inflammatory syndrome
KD	Kawasaki disease
RT-PCR	Reverse transcription polymerase chain reaction
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
WBC	White blood cell count
ALC	Absolute lymphocyte count
IVIG	Intravenous immunoglobulin
LMWH	Low-molecular-weight Heparin

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Author contributions

F.A. contributed to the study's conception, and participated in data acquisition, data interpretation, and writing of the manuscript. O.B. and A.B. collected data. All authors contributed to the study's conception, participated in data acquisition, and approved the final version.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The need of informed consent is waived by the Ethics in Research Committee of the School of Medicine of the Celal Bayar University of Manisa (28.08.2023/530).

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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