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Article

A Comparison of Kawasaki Disease during the SARS-CoV-2 Pandemic with Multisystem Inflammatory Syndrome in Children

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Abstract: Objectives: This study aimed to compare the similarities and differences between the Kawasaki disease (KD) during the SARS-CoV-2 pandemic and multisystem inflammatory syndrome in children (MIS-C). Methods: The medical records of patients diagnosed with KD and MIS-C at a single center between July 2020 and November 2021 were retrospectively reviewed. Results: The study included 39 MIS-C patients (84.6% male) with a median age of 138 months and 17 KD patients (58.8% male) with a median age of 36 months. Compared with the KD patients, MIS-C patients were older ($p<0.001$), had longer hospital stays ($p=0.023$), elevated neutrophil count ($p<0.001$), C-reactive protein ($p<0.001$), procalcitonin ($p<0.001$), interleukin-6 ($p<0.014$), ferritin ($p<0.001$), fibrinogen ($p<0.001$), troponin I ($p=0.001$), NT-proBNP ($p<0.001$), and, D-dimer levels ($p<0.001$). They had more hypotension ($p=0.024$), decreased left ventricular function ($p=0.023$), and a greater need for corticosteroids ($p<0.001$), enoxaparin ($p=0.045$), and therapeutic plasma exchange ($p<0.001$). Patients with KD displayed a higher frequency of rash ($p<0.001$), oral mucosal changes ($p<0.001$), conjunctival injection ($p<0.001$), extremity changes ($p<0.001$), and cervical lymphadenopathy ($p<0.001$). They had a longer duration of fever ($p<0.001$), elevated white blood cell count ($p<0.001$), platelet count ($p<0.001$), and alanine aminotransferase level ($p<0.001$). The two groups were similar in terms of hemoglobin levels, erythrocyte sedimentation rate, albumin levels, or the frequency of coronary dilation/aneurysm, myocarditis, pericarditis, invasive mechanical ventilatory support, and intravenous immunoglobulin treatment. Conclusions: Older patient age, a greater presence of gastrointestinal and cardiac findings associated with hypotension, increased NT-proBNP levels, decreased left ventricular function, the use of various treatment modalities, and longer hospital stays suggest MIS-C, whereas a longer duration of fever and classical clinical features of KD favor KD.

Keywords: Kawasaki disease; multisystem inflammatory syndrome in children; SARS-CoV-2

1. Introduction

After the outbreak of the COVID-19 pandemic, an inflammatory multisystem syndrome in children has been reported from Europe and the USA with clinical features overlapping those of Kawasaki disease (KD) presenting weeks after SARS-CoV-2 infection [1-7]. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have created case definitions for this entity [8,9]. Several terminologies have been used to describe it and this article will use the term multisystem inflammatory syndrome in children (MIS-C) to refer to this condition. According to WHO and CDC definitions, MIS-C diagnosis requires fever, involvement of ≥2 systems/organs, elevated inflammatory markers, past SARS-CoV-2 infection or exposure, and exclusion of other possible causes (Table 1).

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Table 1. Diagnostic criteria for classical and atypical KD, MIS-C.

MIS-C	Individuals aged <21 years presenting with fever; laboratory evidence of inflammation; clinical evidence of severe illness requiring hospitalization; multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or gastrointestinal); • No plausible alternative diagnoses; And • People aged <21 years who have a fever, laboratory evidence of inflammation, clinical evidence of a serious illness requiring hospitalization, multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or gastrointestinal); who have no logical alternative diagnoses and who are positive for current or recent SARS-CoV-2 infection by reverse transcription-polymerase chain reaction, serology, or antigen test; or who were exposed to a patient with suspected or confirmed COVID-19 within 4 weeks before the onset of symptoms. Similarly, a fever of at least 38.0 °C for a full day or a report of a subjective fever lasting a full day that includes one or more of the following: elevated levels of CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6; low levels of albumin; and elevated counts of neutrophils, lymphocytes, and neutrophil-associated proteins. If they fit the MIS-C case definition, certain individuals who either fully or partially matched the KD criteria were reported. When evidence of SARS-CoV-2 infection was found in a juvenile mortality case, MIS-C was considered.
Classical KD	Patients with persistent fever for ≥5 days (or until the day of intravenous immunoglobulin administration, if administered before day 5 of fever) and exhibiting at least four of the following five clinical signs: • Changes in peripheral extremities; • Rash presentation; • Cervical lymphadenopathy of at least 1.5 cm diameter; • Changes in the oral mucosa; • Bilateral conjunctival injection.
Atypical KD	Patients whose disease did not meet the abovementioned KD criteria but who had a fever and coronary artery abnormalities. The diagnostic criteria were as follows: fever persisting for ≥5 days and meeting two to three diagnostic criteria or infants presenting with idiopathic fever for ≥7 days. • When the CRP level was <3 mg/dL, the ESR was <40 mm/h, and fever persisted, serial clinical and laboratory assessments were conducted. However, when peeling began, echocardiography was performed. • When the CRP level was ≥3 mg/dL and the ESR was ≥40 mm/h, coupled with a positive echocardiography finding, or the presence of three or more of the following laboratory findings:

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	1. Anemia; 2. Albumin level of ≤3 g/dL; 3. Fever with an increased alanine aminotransferase level; 4. Platelet count of 450,000/mm3 after day 7 of idiopathic onset; 5. White blood cell count of ≥15,000 mm3; 6. If the urine white blood cell count was >10/hpf, therapy was recommended.

Kawasaki disease is a febrile pediatric systemic vasculitis that typically affects children under five years old and its cause is unknown. [10]. The diagnostic method for KD is clinical criteria. Patients with a fever lasting five days or longer and at least four of the following five features are diagnosed with Kawasaki disease; injections in both conjunctiva, alterations in the lips and oral cavity, cervical lymphadenopathy, alterations in the extremities, and polymorphous rash. [10]. A child is diagnosed with incomplete (atypical) KD if they exhibit two or three of these symptoms along with a fever that lasts for five days or more [10] (Table 1). Due to mucocutaneous symptoms, MIS-C was initially referred to as a "Kawasaki-like" disease. Certain clinical features of MIS-C and KD are similar. These include fever, rash, conjunctival injection, erythema and edema of the extremities, and cervical lymphadenopathy. The similarity of certain clinical aspects suggests that MIS-C and KD may be part of the same spectrum of inflammatory disorders [2-4]. There are, however, clinical features where MIS-C and KD diverge. Patients with MIS-C are more likely to experience gastrointestinal problems such as shock and coagulopathy, while traditional KD is less likely [11]. Patients with MIS-C commonly present with prominent cardiac involvement manifested by left ventricular systolic and diastolic dysfunction, myocardial inflammation, and coronary artery dilations [12]. Classic KD is prevalent in North East Asian countries, but MIS-C is more common in patients of African, Hispanic, or Latino ethnicities. KD is more common in children under 5 years old, while MIS-C is more prevalent in older children (9). The documented distinctions between MIS-C and KD in epidemiology, pathology, inflammation, and immunity suggest these two illnesses are distinct entities [1-7,12,13]. During the SARS-CoV-2 pandemic, it has been difficult for pediatricians to distinguish between patients with MIS-C and those with KD [14,15]. Although numerous studies compared pre-pandemic KD with MIS-C, few studies investigated the differences between pandemic KD and MIS-C [2,10,16-21]. This study aims to identify the unique features facilitating differentiation between pandemic KD and MIS-C.

2. Materials and Methods

2.1. Study Population and Protocol

The study was conducted with the approval of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Research Ethics Committee (Date: 10.02.2021, Decision No: 2021/125). All procedures were carried out according to the ethical rules and the principles of the Declaration of Helsinki. Patient consent was waived as our study was retrospective.

This is a retrospective single-center study of patients who were hospitalized with KD and MIS-C between July 2020 and November 2021, at the Departments of Pediatrics of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital. The study included 17 KD patients admitted to the Pediatric Cardiology outpatient clinic and 39 MIS-C patients in intensive care and pediatric inpatient clinics. All MIS-C patients met the criteria set by WHO or CDC, while all KD patients met the criteria established by the American Heart Association [8-10] (Table 1). Demographic characteristics, clinical features, laboratory findings, echocardiographic findings at admission, treatments, duration of fever, and hospitalization duration of both KD and MIS-C patients were obtained from the hospital database. Patients with KD and MIS-C were compared concerning all of these characteristics.

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Laboratory findings on admission included white blood count (WBC), neutrophil percentage, hemoglobin (Hgb), platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, interleukin-6 (IL-6), alanine aminotransferase (ALT), ferritin, fibrinogen, D-dimer, troponin, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), as well as COVID-19 PCR and COVID-19 IgM and IgG results. Echocardiographic findings investigated compromised coronary dilation/aneurysm, left ventricular function, myocarditis, and pericarditis. Treatments included intravenous immunoglobulin (IVIG) 2 g/kg intravenous infusion, corticosteroids (Methylprednisolone) 1-4 mg/kg intravenous, enoxaparin 1 mg/kg subcutaneous, anakinra 2-4 mg/kg subcutaneous, therapeutic plasma exchange, and invasive mechanical ventilatory support.

2.2. Echocardiographic Assessment

Philips Affiniti 50 c echocardiography system (Philips Healthcare, Andover, MA, USA) was used for transthoracic echocardiography. The same pediatric cardiologist evaluated all subjects. Standard echocardiographic modes used included M-mode, 2D, color, pulsed and continuous-wave Doppler, and tissue Doppler. The absolute dimensions (in millimeters), systolic function, and z-scores of the proximal coronary arteries including the left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery were assessed. Reduced left ventricle systolic function was defined as fractional shortening < 28%. Coronary aneurysms were defined using z-scores per American Heart Association Kawasaki guidelines (small aneurysm z-scores ≥ 2.5 to <5.0, medium aneurysm z-score ≥ 5 to <10, and absolute dimension < 8 mm, and large aneurysm z-score ≥ 10, or absolute dimension ≥ 8 mm) [10].

2.3. Statistics

The statistical analysis was performed using the Statistical Package for Social Science Statistics software, version 17.0 (IBM Corp., Armonk, NY, USA). Normality was evaluated by Kolmogorov–Smirnov test and histograms . The data were expressed as mean, standard deviation, median, minimum, maximum, frequency, percentage and the Interquartile Range (IQR). The categorical variables were compared with Pearson's chi-squared or Fisher's exact test. Continuous variables that did not have a normal distribution were compared with Mann–Whitney U test. Statistical significance was established for P-values less than 0.05. The effect size was calculated as d: 1.185 in the power analysis conducted using the G Power 3.1.9.7 (Franz Faul, Germany) program. With the determined effect size and a 5% margin of error, the power of the study was found to be 97.96%.

3. Results

There were thirty-nine MIS-C patients and seventeen KD patients in the study. The median ages of patients with MIS-C and KD at diagnosis were 138 (7-214) and 36 (18-48) months, respectively. MIS-C patients were older than KD patients (p<0,001). Twenty-three MIS-C patients (58.9%) and 10 KD patients (58.8%) were male, there was not a statistical difference in terms of sex between the MIS-C and KD patients (P = 0,992). Table 2 summarizes the characteristics of both MIS-C and KD patients.

Table 2. Characteristics, Symptoms, and Findings of Patients Diagnosed with Multisystem Inflammatory Syndrome in Children and Kawasaki Disease**.**

	MIS-C Patients (n = 39)	KD Patients (n = 17)	p
Age, months			
Median (min-max)	138 (7-214)	36 (18-48)	**<0.001**
IQR (P 25-P 75)	(97-182)	(32-42)	
Sex, n (%)			
Male	33 (84.6)	10 (58.8)	0,992

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Female	6 (15.3)	7 (41.1)	
Clinical symptoms			
Days of fever Median (min-max) IQR (P 25-P 75)	3 (1-7) (3-5)	6 (5-7) (5-6)	**<0.001**
Rash, n (%)	2 (5.1)	12 (70.5)	**<0.001**
Oral mucosal changes n (%)	4 (10.2)	14 (82.3)	**<0.001**
Bilateral conjunctival injection, n (%)	6 (15.3)	12 (70.5)	**<0.001**
Erythema and edema of extremities, n (%)	0 (0)	6 (35.2)	**<0.001**
Cervical lymphadenopathy, n (%)	6 (15.3)	15 (88.2)	**<0.001**
Acute gastrointestinal symptoms, n (%)	22 (66.6)	2 (11.7)	**<0,001**
Acute respiratory symptoms, n (%)	17 (43.5)	0 (0)	**0.001**
Hypotension, n (%)	11 (28.2)	0 (0)	**0.024**

Thirty-three patients with MIS-C (84.6%) showed positive SARS-CoV-2 serology, and six (15.3 %) exhibited positive PCR results. Twenty-nine of MIS-C patients (74.3%) reported being exposed to SARS-CoV-2. There was no COVID-19 or SARS-CoV-2 exposure history in any of the patients with KD. They did not show positive SARS-CoV-2 serology or exhibited positive PCR results. At least two of the five main clinical characteristics of KD—rash, changes in the oral mucosa, bilateral conjunctival injection, cervical lymphadenopathy, and erythema and edema of the extremities—were present in eight patients (20.5%) with MIS-C. Three (17.6%) of the 17 patients with Kawasaki disease were diagnosed with atypical Kawasaki disease.

The frequency of rash (P <0.001), oral mucosal changes (P <0.001), cervical lymphadenopathy (P <0.001), bilateral conjunctival injection (P <0.001), and erythema and edema of extremities (P <0.001) was higher in patients with KD. In contrast, the frequency of acute gastrointestinal symptoms (P <0.001), acute respiratory symptoms (P =0,001), and hypotension (P=0.024) was higher in patients with MIS-C (Table 2). Patients with MIS-C had higher neutrophil percentage (P <0.001), CRP (P <0.001), procalcitonin (P <0.001), ferritin (P <0.001), fibrinogen (P <0.001), D-Dimer (P <0.001), IL-6 (P =0.014), troponin I (P =0.001) and BNP values (P <0.001). On the other hand, days of fever (P <0.001), white blood cell count (P <0.001), platelet count (P <0.001), and ALT values (P <0.001) were higher in patients with KD. There was no statistical difference in terms of Hgb, ESR, and albumin between patients of KD and MIS-C (Table 3).

Table 3. Laboratory findings of Patients Diagnosed with Multisystem Inflammatory Syndrome in Children and Kawasaki disease.

Laboratory findings Median (min-max) IQR (P 25-P 75)	MIS-C Patients	KD Patients	p
White blood cell count ($\times 10^3/\mu L$)	7600 (500-31000) (4800-11300)	15000 (12200-17600) (14400-16000)	**<0.001**

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Hemoglobin, g/dL	10,4 (7-15,4) (9,3-12,9)	11 (10-12) (10,5-11,3)	0.568
Neutrophil (%)	85 (26-95) (75-90)	57 (43-75) (49-65)	**<0.001**
Platelet count (×10³/uL)	180 (7-446) (99000-263000)	290 (220-400) (270000-360000)	**<0.001**
C-reactive protein, mg/dL (<0.5)	113 (1,5-329) (18-190)	14 (9-35) (12-17)	**<0.001**
Erythrocyte sedimentation rate, mm/h (<20)	34 (4-114) (23-68)	40 (24-48) (35-43)	0.859
Procalcitonin ng/ml (<0,05)	3,18 (0,01-168) (0,47-16)	0,02 (0,01-0,05) (0,01-0,03)	**<0.001**
Interleukin-6, pg/mL (<5.9)	100 (2,48-2000) (12-280)	28 (6-45) (14-38)	**0.014**
Alanine aminotransferase, IU/L (<39)	22 (5-381) (14-38)	60 (40-84) (55-67)	**<0.001**
Albumin g/L (38-54)	31 (11,1-48) (28-39)	30 (20-42) (24-35)	0.208
Ferritin, ng/ml (<207)	454 (27-3381) (198-1143)	80 (20-145) (45-120)	**<0.001**
Fibrinogen mg/L (<400)	485 (176-724) (408-585)	280 (210-550) (230-400)	**<0.001**
D-Dimer, mg/L (<0.5)	3.4 (0.34-35) (1,8-5,19)	0.8 (0.2-1.4) (0,5-1)	**<0.001**
Troponin I, picogram/ml (<0.14)	60 (0-106695) (22-146)	10 (3-18) (6-12)	0.001
NT-proBNP pg/mL (<100)	980 (10-35000) (300-2010)	45 (12-90) (34-75)	**<0.001**

Abbreviations: NT-proBNP, N terminal pro-brain natriuretic peptide.

Considering the echocardiographic findings, even though the frequency of decreased left ventricle function was higher in patients with MIS-C (P=0.023), there was no statistical difference in terms of coronary dilation/aneurysm, myocarditis, and pericarditis between patients of KD and MIS-C (P=0.309, P=0.088, and P=0.546) (Table 4).

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Table 4. Echocardiographic Findings, Treatments, and Hospitalization Duration of Patients Diagnosed with Multisystem Inflammatory Syndrome in Children and Kawasaki Disease.

Echocardiographic findings, n (%)	MIS-C Patients	KD Patients	p
Coronary dilation/aneurysm	5 (12.8)	0 (0)	0.309
Decreased left ventricular function	10(25.6)	0 (0)	**0.023**
Myocarditis	7 (17.9)	0 (0)	0.088
Pericarditis	3 (7.69)	0 (0)	0.546
Treatments, n (%)			
Intravenous immunoglobulin	33 (84.6)	17 (100)	0.087
Corticosteroids	30 (76.9)	0 (0)	**<0.001**
Subcutaneous enoxaparin	9 (23)	0 (0)	**0.045**
Anakinra	3 (7.69)	0 (0)	0.546
Therapeutic plasma exchange	22 (56.4)	0 (0)	**<0.001**
Invasive mechanical ventilatory support	7 (17.9)	0 (0)	0.088
Hospitalization duration, days, median (min-max)	6 (1-12)	4 (2-6)	**0.023**

The treatments applied and the number of subjects that received treatments are depicted in Table 4. Although 35 (89.7%) MIS-C patients required intensive care, none of the Kawasaki patients needed intensive care. Of these MIS-C patients needing intensive care, 22 (62.8%) received therapeutic plasma exchange treatment. Three patients with MIS-C (7.6%) were placed on extracorporeal membrane oxygenation. All KD patients received IVIG treatment while 84.6% of MIS-C patients did. Patients with KD did not receive intravenous corticosteroids, subcutaneous enoxaparin, anakinra, invasive mechanical ventilatory support, or therapeutic plasma exchange treatments. The number of subjects that received intravenous corticosteroids (P <0.001), subcutaneous enoxaparin (P=0.045), and therapeutic plasma exchange (P <0.001) was higher in patients with MIS-C. There was no statistical difference in terms of IVIG, anakinra treatment, and invasive mechanical ventilatory support between patients of KD and MIS-C (Table 4).

Even though the number of days with fever in patients with KD is statistically more than in patients with MIS-C (P <0.001), patients with MIS-C stayed in the hospital longer (P=0.023) (Tables 2 and 4).

4. Discussion

Several researchers have analyzed the differences between MIS-C and classical KD, comparing MIS-C patients to pre-pandemic KD patients as well as pre-pandemic KD to pandemic KD patients [2,11,1-23]. On the other hand, the number of studies comparing MIS-C to pandemic KD is scarce including studies comparing MIS-C to pre-pandemic plus pandemic KD [24-28]. The findings from our study provide insights into the comparative features of pandemic KD and MIS-C, especially in

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the context of the COVID-19 pandemic. Both conditions share some overlapping clinical features but exhibit distinct differences that are crucial for accurate diagnosis and management.

The patient's age may be useful in differentiating between the two conditions. The demographic differences observed in our study of MIS-C patients—being older—support previous reports [11,12,20,21]. These findings are also consistent with the literature comparing MIS-C patients with pandemic patients with KD [24,27,28].

Our study supports existing knowledge about the differences in clinical features between pre-pandemic KD and MIS-C. It shows that rash, conjunctival injection, oral mucosal changes, and extremity changes are more common in KD patients than in MIS-C patients [16,20,21]. Conversely, gastrointestinal symptoms, acute respiratory problems, and low blood pressure are much more common in MIS-C patients than in KD patients [16,21]. The duration of fever is also longer in KD patients [16,20,21]. However, clinical features may overlap between MIS-C and KD. The study conducted by Phi et al. found that the prevalence of diffuse skin rash, hand and foot edema or erythema, and gastrointestinal signs was significantly higher in patients with MIS-C [17]. There were no significant differences between MIS-C and KD patients in terms of conjunctivitis and skin rash in the study conducted by Yavuz et all. They also found that oropharyngeal signs, cracked lips, edema of the hands and feet, and cervical lymphadenopathy were more prevalent in patients with KD [20]. When the studies comparing patients with pandemic KD and MIS-C are taken into consideration, the duration of fever is longer in KD patients in line with our study [24,28]. Consistent with similar studies hypotension and acute gastrointestinal symptoms were more frequent in MIS-C patients in comparison to KD patients [24,26,28]. However, even though the frequency of clinical features of rash, oral mucosal changes, bilateral conjunctival injection cervical lymphadenopathy, and erythema and edema of extremities is higher in patients with KD than patients with MIS-C in our study, studies by Şener et all. did not find a significant difference in terms of conjunctival injection and changes in the extremities between KD and MIS-C patients in their study [24]. The difference between the findings of the two studies may be due to the fact that in the study by Şener et all, the patients with MIS-C who were included in the study were selected from those with KD-like symptoms whereas in our study, only 20.5% of the patients with MIS-C had at least two major clinical features of KD. Moreover, a study by Alkan et al. using a methodology similar to ours also found no significant difference regarding rash and conjunctivitis between KD and MIS-C patients in their study [28]. These findings may support the overlapping nature of clinical features between MIS-C and KD.

Our study showed that MIS-C patients exhibited lower WBC and platelet counts while displaying elevated levels of neutrophil, CRP, procalcitonin, IL-6 ferritin, fibrinogen, and d-dimer, compared to KD patients indicating hyperinflammation and cardiovascular involvement. Our data was largely consistent with most of the studies in the literature [1,2,11,18,24,26,28,29]. However, there are also contradicting results in the literature comparing patients with pre-pandemic KD with MIS-C patients. There was no significant difference in both groups in terms of ferritin, CRP, ESR, and D-dimer values in the study conducted by Cem et al., and WBC, platelet, ALT, and CRP values in the study by Phi et al. [17,21]. Yavuz et. all also did not find a significant difference between the two groups in CRP, ALT, fibrinogen, and D-dimer values, even the mean ESR level in KD patients was significantly higher than that in MIS-C patients in their study [20]. We interpreted the studies comparing patients with pandemic KD and MIS-C patients in terms of laboratory data. Şener et all. in line with our study, did not find a significant difference between the two groups in ESR, and ALT whereas Mehrban et all. found higher fibrinogen and ESR levels in KD patients and no statistical difference between groups in terms of d-dimer and CRP levels [24-27]. Discrepancies regarding laboratory data between various studies may be related to different geographies and ethnicities the studies were conducted. Compared to the USA and Europe, the incidence of KD is higher in Asian nations including Japan, South Korea, China, and Taiwan (10). Asian children had the lowest incidence of MIS-C, while children of Hispanic or Black ethnicity had the highest frequency [12]. Although CRP, ferritin, fibrinogen, and D-dimer values did not differ between the groups in the studies above, our study found statistical differences regarding these data between the two groups of KD and MIS-C. The reason for this could be that 89.7 % of our MIS-C patients were treated in the

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intensive care unit. Of these, 62.8% were severe enough to receive therapeutic plasma exchange treatment, and three MIS-C patients were placed on extracorporeal membrane oxygenation as well, which elevated these serum markers leading to a more pronounced systemic inflammatory response in MIS-C compared to KD. Nevertheless, we suppose that more studies are required to determine the optimal cut-off values for these laboratory data to use them as markers for the comparison of both diseases as there are many conflicting results in terms of these data.

Cardiovascular complications are the most notable manifestations in patients with MIS-C. Consistent with both studies comparing patients with pre-pandemic or pandemic KD with MIS-C patients, a decrease in left ventricular systolic function, was more frequent in echocardiograms of MIS-C patients regarding KD patients in our study [7,20,24,27,28,30]. When the frequencies of coronary dilation/aneurysms were interpreted, there was no statistical difference between the groups in our study. When the pre-pandemic KD patients were compared with the MIS-C patients, coronary artery dilation or aneurysm was more frequently observed in patients with MIS-C in the study conducted by Phi et al [17]. Yavuz et al. also showed that the coronary diameter was higher in the MIS-C group than in the KD group, as the coronary diameter was greater than 2.5 mm in 71% of MIS-C patients. (20). Contrary to these findings, Cattalini et al and Matsubara indicated that compared to KD patients, children with MIS-C have fewer coronary artery anomalies, and those that do exist are nearly invariably temporary and recover quickly over time [12,18,30]. 16.5% of patients with MIS-C in a sizable cohort of 1,733 individuals in the US developed coronary artery abnormalities, a rate comparable to untreated KD. [31]. In line with these studies, coronary dilatation rate in echocardiography was statistically higher in KD patients in the study conducted by Cem et al. [21]. Data obtained from studies conducted with pandemic KD and MIS-C patients were consistent with our study. One revealed that coronary artery dilatation was less common in MIS-C patients and two other studies showed no statistically significant differences regarding coronary artery z scores between the KD and MIS-C groups [24,26,27,32]. There is only one study showing significantly higher coronary involvement in the pandemic KD patients [28]. The difference in the coronary dilation rate between pre-pandemic and pandemic KD patients may be explained by the early admission of KD patients during the pandemic, due to concerns about contracting COVID-19. This heightened awareness of Kawasaki-like disease among physicians likely led to the prompt recognition of the condition and treatment with IVIG within 10 days of fever onset. [33].

Our Study found that troponin and NT-proBNP and the frequency of hypotension were higher in MIS-C patients. There was not a significant difference in terms of myocarditis or pericarditis between KD and MIS-C patients. Studies found that 40–80% of MIS-C patients have symptomatic myocarditis [2,7,6,34]. However, studies comparing pre-pandemic KD patients with MIS-C patients regarding these data have conflicting results. A study conducted by Phi et all did not find a significant difference in terms of myocarditis or pericarditis whereas studies carried out by Cem et al. and Yavuz et al. showed that the rate of pericarditis and pericardial effusion was higher in MIS-C group. One study comparing pandemic KD patients with MIS-C patients did not find a significant difference in terms of myocarditis or pericarditis [24]. Conversely, another one found that pericardial effusion was significantly higher in the MIS-C group [28]. In MIS-C, cardiac biomarkers such as NT-pro-BNP and troponin levels are significantly higher than in previous KD cohorts, indicating heart failure and myocardial damage causing hypotension [11]. Studies comparing both pre-pandemic and pandemic KD patients with MIS-C patients showed that NT-pro-BNP and cardiac troponin levels are extremely high in MIS-C patients, and the prevalence of hypotension is elevated. This is consistent with our findings, although not all of these data points were examined in every study [1,7,11,18,21,24,26,28,29,32,34].

The treatment modalities employed also differed between the two groups in our study. All KD patients received IVIG, which is a standard treatment, while 84.6% of MIS-C patients did. MIS-C patients more frequently received intravenous corticosteroids, subcutaneous enoxaparin, and therapeutic plasma exchange. However, there was no statistical difference in the frequency of IVIG, anakinra, and invasive mechanical ventilatory support treatments. Three patients with MIS-C (13.6%) also required extracorporeal membrane oxygenation. A study comparing pre-pandemic KD patients

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with MIS-C patients showed that there was no significant difference in terms of IVIG, and low-molecular-weight heparin [28]. The MIS-C group had a significantly higher rate of steroid use. Neither intensive care nor inotropic support was necessary for the KD patients. On the contrary, the study by Ciftdogan et al. conducted with pandemic KD and MIS-C patients showed that IVIG treatment was more frequently administered in patients with clinical features overlapping with KD [26]. The study conducted by Şener et al. with pandemic KD and MIS-C patients found that intravenous corticosteroids, anakinra, and therapeutic plasma exchange use was significantly higher in the MIS-C group. The reason for the use of different treatment methods in the studies could be due to the involvement of different patient groups. Pre-pandemic KD patients, pandemic KD patients, and MIS-C patients with or without features overlapping with KD and with different treatment needs may be the reason for the use of different treatment methods in these studies. All these data reflect the more severe and complex nature of MIS-C, which often requires a multi-modal and patient-specific approach to manage the hyperinflammation and organ dysfunction associated with the syndrome [14]. In contrast, KD patients were primarily treated with IVIG, consistent with established guidelines [10].

One of the most striking difference is the duration of hospitalization in our study. Although KD patients experienced a longer duration of fever, MIS-C patients had a longer overall hospital stay. This could be attributed to the more severe and multi-systemic nature of MIS-C, which may require prolonged treatment and monitoring. This fact is also supported by studies conducted with pre-pandemic or pandemic KD patients versus patients with MIS-C [21,24,32]. However, a study by Yavuz et al. did not find a significant difference between groups concerning the duration of hospitalization [20].

5. Conclusions

In summary, while KD and MIS-C share several clinical features, our study underscores the importance of recognizing the distinct characteristics of especially pandemic KD and MIS-C. Older patient age, an increased presence of gastrointestinal and cardiac findings associated with hypotension, increased NT-proBNP levels, and decreased left ventricular function as well as various treatment modalities implied and longer hospital stay suggest MIS-C, whereas a longer duration of fever and classical clinical features of KD favor KD. Future research should continue to explore these differences and improve diagnostic criteria to enhance patient outcomes.

6. Limitations

The first limitation of our study was the small number of KD patients. The second limitation of our study is that not all our KD patients had overlapping features of KD. These two limitations may be related to the fact that the number of classic KD patients decreased significantly during the pandemic [35].

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References

1. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA. 2020, 324, 259-269.
2. Verdoni L, Mazza A, Gervasoni A, 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, 1771-1778.
3. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA. 2020, 324, 294–296.
4. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. BMJ. 2020, 369, m2094.
5. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020, 395, 1607–1608.
6. Belhadjer Z, Me´ot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context to global SARS-CoV-2 pandemic. Circulation. 2020, 142, 429–436.
7. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020, 383, 334–46.
8. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific Brief 2020. Available at: https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed August 17, 2024.
9. Centers for Disease Control and Prevention health alert network (HAN). Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Available at: https://archive.cdc.gov/#/details?url=https://emergency.cdc.gov/han/2020/han00432.asp. Accessed August 17, 2024
10. McCrindle BW, Rowley AH, Newburger JW, 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, 927–999.
11. Kabeerdoss J, R Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int. 2021, 41, 19-32.
12. Rivas MN, Arditi M. Kawasaki Disease and Multisystem Inflammatory Syndrome in Children Common Inflammatory Pathways of Two Distinct Diseases. Rheum Dis Clin North Am. 2023, 49, 647-659.
13. Godfred-Cato S, Abrams JY, Balachandran N, et al. Distinguishing multisystem inflammatory syndrome in children from COVID-19, Kawasaki Disease and toxic shock syndrome. Pediatr Infect Dis J. 2022, 41, 315–323.
14. Sharma C, Ganigara M, Galeotti C, et al. Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. Nat Rev Rheumatol. 2021, 17, 731-748.
15. Haslak F, Gunalp A, Kasapcopur O. A cursed goodbye kiss from severe acute respiratory syndrome-coronavirus-2 to its pediatric hosts: multisystem inflammatory syndrome in children. Curr Opin Rheumatol. 2023, 35, 6-16.
16. Bashir A, Bhat AA, Jan M, Wani KA. Kawasaki like illness in COVID versus Kawasaki disease in pre-COVID era. Int J Contemp Pediatr. 2023, 10, 484-487.
17. Phi DL, Dao TL, To MM, Nguyen TB, Nguyen DC, Gautret P, Hoang VT. Clinical and Laboratory Characteristics of Kawasaki Disease and COVID-19-Related Multisystem Inflammatory Syndrome in Children. J Korean Med Sci. 2023, 38, e410.
18. Cattalini M, Della Paolera S, Zunica F, et al. Defining Kawasaki disease and pediatric inflammatory multisystem syndrome-temporally associated to SARS-CoV-2 infection during SARS-CoV-2 epidemic in Italy: results from a national, multicenter survey. Pediatr Rheumatol Online J. 2021, 19, 29.
19. Bar-Meir M, Guri A, Godfrey ME, et al. Characterizing the differences between multisystem inflammatory syndrome in children and Kawasaki disease. Sci Rep. 2021, 11, 13840.
20. Yavuz L, AlHamdani S, Alasrawi S, et al. Kawasaki disease (KD) and multisystem inflammatory syndrome in children (MIS-C) in a Middle Eastern patient cohort. Pediatr Rheumatol Online J. 2023, 21, 64.
21. Cem E, Böncüoğlu E, Kıymet E, Şahinkaya Ş, Çelebi MY, Gülderen M, Kaçar P, Kara AA, Aydın A, Murat M, Yılmazer MM, Bayram N, Devrim İ. Which Findings Make multisystem Inflammatory Syndrome in Children Different from the Pre-Pandemic Kawasaki Disease? Pediatric Cardiology. 2023; 44, 424-432.
22. Ünlü AM, Holm M, Hafstrøm TK, Glerup M, Bjerre J, Herlin T. Changes in Kawasaki disease incidence and phenotype during the COVID-19 pandemic. Dan Med J. 2023, 70, A10220600.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 August 2024 doi:10.20944/preprints202408.1861.v1

23. Iio K, Matsubara K, Miyakoshi C, Ota K, Yamaoka R, Eguchi J, Matsumura O, Okutani T, Ueda I, Nishiyama M. Incidence of Kawasaki disease before and during the COVID-19 pandemic: a retrospective cohort study in Japan. BMJ Paediatrics Open. 2021, 5, e001034.
24. Şener, S, Batu, ED, Akca ÜK, Atalay E, Cüceoğlu MK, Balık Z, Başaran Ö, Karagöz T, Özsürekçi Y, Bilginer Y, Özen S. Differentiating Multisystem Inflammatory Syndrome in Children from Kawasaki Disease During the Pandemic. Turk Arch Pediatr. 2024, 59, 150-156.
25. Sarı E, Erdede Ö. Comparison of Eosinophil Counts in Inflammatory Conditions: Multisystem Inflammatory Syndrome in Children, Kawasaki Disease, and Infectious Mononucleosis. Children (Bazel). 2024, 11, 204.
26. Ciftdoğan DY, Keles YE, Cetin BS et all. COVID-19 associated multisystemic inflammatory syndrome in 614 children with and without overlap with Kawasaki disease-Turk MIS-C study group. European Journal of Pediatrics. 2022, 181, 2031–2043.
27. Mehrban S, Tahghighi F, Moghadam EA, Ziaee V. Multisystem inflammatory syndrome in children and Kawasaki disease; comparison of their clinical findings and one-year follow-up—a cross-sectional study. Ital J Pediatr 2023, 49, 90.
28. Alkan F, Bircan O, Bal A, Bayturan S, Zengin N, Coskun S. Comparison of early characteristics of multisystemic inflammatory syndrome and Kawasaki disease in children and the course of Kawasaki disease in the pandemic. BMC Pediatrics. 2024, 24, 485.
29. Consiglio CR, Cotugno N, Sardh F, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020, 183, 968–981
30. Matsubara D, Kauffman HL, Wang Y, et al. Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States. J Am Coll Cardiol 2020, 76, 1947–61.
31. Belay ED, Abrams J, Oster ME, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA Pediatr. 2021, 175, 837-845.
32. Fridman DM, Tsoukas P, Jeewa A, Yeung RSM, Gamulka BD, McCrindle BW. Differentiation of COVID-19 Associated Multisystem Inflammatory Syndrome From Kawasaki Disease With the Use of Cardiac Biomarkers. Canadian Journal of Cardiology. 2023, 39, 815-823.
33. Marchesi A, Tarissi de Jacobis I, Rigante D, et al. Kawasaki disease: guidelines of Italian Society of Pediatrics, part II - treatment of resistant forms and cardiovascular complications, follow-up, lifestyle and prevention of cardiovascular risks. Ital J Pediatr. 2018, 44, 103.
34. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020, 79, 999–1006.
35. Kaya Akca U, Atalay E, Cuceoglu MK, et al. Impact of the COVID-19 pandemic on the frequency of the pediatric rheumatic diseases. Rheumatol Int. 2022, 42, 51-57.

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