The European Research Journal 2023;9(6):1380-1391 Original Article

DOI: 10.18621/eurj.1238842 *Pediatric Emergency Medicine*

Differential diagnosis for multiple systemic inflammatory syndrome in children: clinical and laboratory clues

Yüksel Bıcılıoğlu[1], Tuğçe Nalbant[1], Alper Çiçek[2], Esin Ergönül[3], Gamze Gökalp[1], Gülşah Demir[2], Şefika Bardak[2], Emel Berksoy[2]

[1]Department of Pediatric Emergency Medicine, Izmir Katip Çelebi University Faculty of Medicine, Izmir, Turkey; [2]Department of Pediatric Emergency Medicine, Izmir Tepecik Training and Research Hospital, Izmir, Turkey; [3]Department of Medical Education, Dokuz Eylul University School of Medicine, Izmir, Turkey

ABSTRACT

Objectives: We aimed to identify biochemical markers and clinical findings with high sensitivity and specificity that can be used in the differential diagnosis of patients suspected of having Multisystem Inflammatory Syndrome in Children (MISC) in the pediatric emergency department (PED). Moreover, we also examined early warning signs for predicting severe MIS-C patients requiring admission to intensive care unit (ICU).

Methods: We conducted a retrospective analysis of patients presenting to the PED with suspected MIS-C. Patient records were assessed for initial complaints, physical examination findings, laboratory and ımaging test results, diagnoses, and follow-up plans. Patients diagnosed with MIS-C were categorized as the MIS-C group, while others were categorized as the non-MIS-C group. Comparisons were made between these two groups.

Results: A total of 266 patients were included, with 68 diagnosed with COVID-19-associated MIS-C, including 20 monitored in the pediatric ICU. MIS-C patients had higher mean age, hospitalization, and ICU admission rates compared to non-MIS-C. MIS-C group showed higher prevalence of respiratory symptoms, hematological involvement, and shock. We observed lymphopenia, thrombocytopenia, hyponatremia, and elevated levels of blood C-reactive protein (CRP), procalcitonin, triglycerides, troponin, Brain Natriuretic Peptide (BNP), D-dimer, and fibrinogen in the MIS-C group. ICU patients had higher procalcitonin, aspartate aminotransferase, alanine aminotransferase, triglycerides, troponin, BNP, and ferritin levels, and lower sodium levels.

Conclusions: COVID-19-associated MIS-C group had higher rates of respiratory symptoms, hematological involvement, and shock. Lymphopenia, thrombocytopenia, elevated CRP, and D-dimer can guide MIS-C differential diagnosis. Additional tests (procalcitonin, troponin, BNP, triglycerides, ferritin) are recommended for high-suspicion cases. Patients with elevated BNP levels may require ICU admission.

Keywords: Multisystem inflammatory syndrome in children (MIS-C), COVID-19-associated multisystem inflammatory syndrome, pediatrics, SARS-CoV-2, pediatric emergency medicine

Received: ***January 22, 2023;*** *Accepted:* ***July 26, 2023;*** *Published Online:* ***August 18, 2023***

How to cite this article: *Bıcılıoğlu Y, Nalbant T, Çiçek A, Ergönül E, Gökalp G, Demir G, Bardak Ş, Berksoy E. Differential diagnosis for multiple systemic inflammatory syndrome in children: clinical and laboratory clues. Eur Res J 2023;(6):1380-1391. DOI: 10.18621/eurj.1238842*

Address for correspondence: *Yüksel Bıcılıoğlu, MD., Associate Professor, Izmir Katip Çelebi University Faculty of Medicine, Department of Pediatric Emergency Medicine, Gazeteci Hasan Tahsin Street, Basın Sitesi, 35360 Karabağlar, İzmir, Turkey. E-mai: lozcelebiyuksel@hotmail.com, Phone: +90 232 244 44 44, Fax: +90 232 243 01 55*

e-ISSN: 2149-3189

Throughout the COVID-19 pandemic declared in March 2020, children and adolescents constituted 1-2% of all cases. The vast majority of reported pediatric patients experienced asymptomatic or mild manifestations of the disease [1]. In contrast, Multisystem Inflammatory Syndrome in Children (MIS-C), which was defined during the pandemic, has resulted in severe clinical presentations requiring intensive care monitoring in children. The first case was reported in the United Kingdom in April 2020 [2]. Subsequently, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) promptly established diagnostic criteria to define the clinical syndrome. The CDC's case definition criteria are shown in Table 1 [3]. MIS-C shares many similarities with various diseases, most notably Kawasaki disease (KD), as it features fever, conjunctivitis, rash, hyperemia in the oropharynx, and cardiac involvement. Clinical and laboratory findings of MIS-C also emerge in many infectious, inflammatory, and allergic/reactive diseases apart from KD. Because the treatment of diagnosed diseases can vary significantly, it is crucial to distinguish MIS-C from other potential diseases [4].

The finding that serological tests are positive in 80-90% of patients, and polymerase chain reaction (PCR) tests are positive in 20-40%, supports the hypothesis that COVID-19 associated MIS-C is an immunological phenomenon related to hyperinflammation that develops following symptomatic or asymptomatic COVID-19 infection [5]. However, some patients exhibit positivity in both serology and PCR tests. This situation poses a confusing question: Is it an active COVID-19 infection, or is it MIS-C? In other words, the differential diagnosis of active COVID-19 infection, MIS-C, KD, and other infectious, inflammatory, and allergic/reactive diseases continues to challenge physicians when evaluating patients in the pediatric emergency department (PED). Despite the emergence of new studies defining clinical and laboratory markers for differential diagnosis between COVID-19, MIS-C, and other diseases, the optimal diagnostic criteria are yet to be determined [4, 5].

In MIS-C patients, elevations have been detected in at least four inflammatory markers (C-reactive protein (CRP), neutrophil count, ferritin, procalcitonin, fibrinogen, interleukin-6, and triglycerides) in most cases. Furthermore, studies have reported thrombocytopenia (40%) and lymphopenia (30%). Elevations in cardiac biomarkers such as troponin (64-95%), Brain Natriuretic Peptide (BNP), and pro-BNP (73-95%) are prominent in patients with cardiac involvement [6].

One of the challenges faced by pediatric emergency physicians is distinguishing MIS-C, which carries the potential for serious illness requiring hospital admission, from other diseases that may not require such admission, all the while avoiding unnecessary tests. At this stage, it's crucial to identify distinctive complaints, physical examination findings, and laboratory parameters [7,8,9]. Our study aims to determine clinical features and laboratory parameters with high sensitivity and specificity that could be used in diagnosing COVID-19 associated MIS-C. Moreover, we also examined early warning signs for predicting severe MIS-C patients requiring admission to intensive care.

METHODS

The population of the study consisted of 266 patients who presented to the PED with a fever between May 2020 and February 2022 and were investigated for suspected MIS-C. Throughout the pandemic, our hospital's PED used the CDC's case definition [3] to diagnose COVID-19 related MIS-C, and a differential diagnostic approach was applied as described below to diagnose children presenting with fever. Patients with a persistent fever of 38° C or higher for over 24 hours, for whom the cause of fever could not be determined through history, physical examination, or initial laboratory tests (complete blood count, CRP, blood glucose, urea, creatinine, uric acid, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Lactate Dehydrogenase (LDH), sodium, potassium, calcium, chloride, albumin, amylase, lipase, and full urine examination), and who had high inflammatory markers were investigated for COVID-19 infection. SARS-COV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) IGM/IGG and COVID PCR tests were performed on patients with active COVID-19 symptoms or a history of COVID-19 infection, or those who had contact with a person infected with COVID-19 in the past four weeks. Additionally, tests were conducted for procalcitonin, sedimentation, triglycerides, ferritin, troponin, BNP, Prothrombin Time (PT), Activated Par-

tial Thromboplastin Time (APTT), International Normalized Ratio (INR), and D-Dimer. An Electrocardiogram (EKG) was performed. Cardiology consultation was requested, and an Echocardiogram (ECHO) was performed on patients suspected of having cardiac involvement. Lung radiographs were taken from patients with respiratory symptoms. Following all these results, a diagnosis of MIS-C was made or ruled out considering the CDC case definition. Patients were followed up on an outpatient basis, or admitted to the ward or intensive care, depending on their clinical condition. As our study was planned as a retrospective, descriptive type, a list of patients requested for SARS-COV-2 IgM/IgG from the PED was obtained from the hospital information automation system to access patient information. The digital records of patients in the were reviewed. Presentation complaints, physical examination, laboratory results, lung radiograph, EKG, ECHO findings, diagnosis, and follow-u plans were recorded in the case report form. Patients diagnosed with MIS-C were categorized as the MIS-C group, while others were categorized as the non-MIS-C group. Comparisons were made between these two groups.

Ethical approval was received from the committee of Izmir Katip Çelebi University Non-Interventional Research Ethics Committee (approval Number/ID: 24.02.2022/0041).

Statistical Analysis

Statistical Analysis: Continuous variables such as age and laboratory results were characterized using mean, standard deviation, IQR and median values. The Mann-Whitney U test was utilized to examine the correlation between laboratory results and MIS-C. Conformity to the normal distribution was evaluated with the Shapiro-Wilk t-test. The Pearson Chi-square test was used to analyze the correlation between demographic data like gender, presenting complaints, and MIS-C. Subsequently, ROC curves were established to evaluate the prediction of MIS-C diagnosis and the need for intensive care admission based on the patient's laboratory results. Analyses were conducted on IBM SPSS Statistics version 29 (IBM Corporation, Armonk, NY), with a confidence interval of 95% and a 5% margin of error.

RESULTS

A total of 266 patients were included in the study. Out of the patients undergoing investigations for the cause of fever, 68 (34.3%) were diagnosed with COVID-19 associated MIS-C. The distribution of diagnoses among 198 patients who did not receive a MIS-C diagnosis is presented in Fig. 1.

No significant differences were observed between

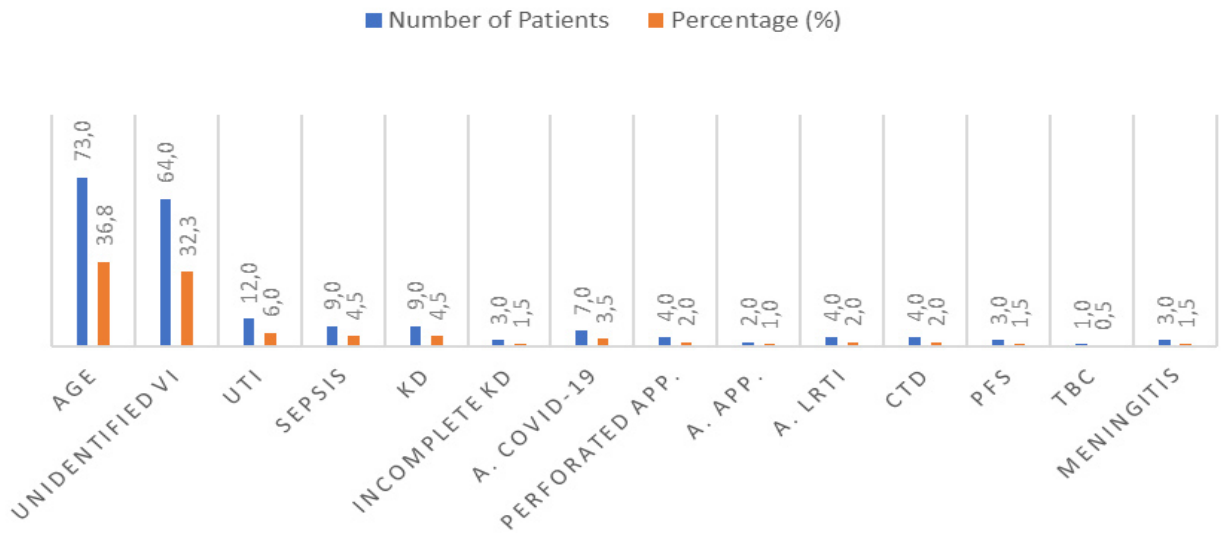

Fig. 1. The distribution of diagnoses among 198 patients in non-MIS-C group. AGE = Acute Gastroenteritis, Unidentified VI = Unidentified viral infection, UTI = Urinary tract infection, KD = Kawasaki disease, A. COVID-19 infection = Acute COVID-19 infection, Perforated App. = Perforated appendicitis, A. App. = Acute appendicitis, A. LRTI = Acute lower respiratory tract infection, CTD = Collagen tissue disease, PFS = Periodic fever syndrome, Tbc = Tuberculosis

Table 1. CDC case definition of multisystem inflammatory syndrome in children

	Criteria
1	**Age under 21 years**
2	**The patient must satisfy all of the following clinical criteria:**
	- Persistent fever of ≥ 38°C for ≥ 24 hours
	- Elevated levels of CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, and presence of neutrophilia, lymphocytopenia, hypoalbuminemia
	- Multisystem involvement (2 or more organ systems) including:
	• Cardiovascular (e.g., shock, elevated troponin, elevated BNP)
	• Respiratory (e.g., pneumonia, ARDS, pulmonary embolism)
	• Renal (e.g., AKI, kidney failure)
	• Neurologic (e.g., seizure, stroke, aseptic meningitis)
	• Hematologic (e.g., coagulopathy)
	• Gastrointestinal (e.g., abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding)
	• Dermatologic (e.g., erythroderma, mucositis, other rash)
	- Severe illness requiring hospitalization
3	**No alternative plausible diagnoses**
4	**Recent or current exposure to SARS-CoV-2, indicated by any of the following:**
	- Positive SARS-CoV-2 RT-PCR test
	- Positive serology test
	- Positive antigen test
	- Exposure to COVID-19 within the 4 weeks prior to the onset of symptoms

CDC = Centers for Disease Control and Prevention, CRP = C-Reactive Protein, ESR = Erythrocyte Sedimentation Rate, LDH = Lactate Dehydrogenase, IL-6 = Interleukin 6, BNP = Brain Natriuretic Peptide, ARDS = Acute Respiratory Distress Syndrome, AKI = Acute Kidney Injury, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, RT-PCR = Real-Time Polymerase Chain Reaction, COVID-19 = Coronavirus Disease 2019, PT = Prothrombin Time, PTT = Partial Thromboplastin Time.

the MIS-C and non-MIS-C patients in terms of gender and nationality. However, the mean age of the MIS-C group was significantly higher compared to that of the non-MIS-C group (Mann-Whitney U test, $p = 0.02$). Among all patients, the most common presenting symptoms were diarrhea, vomiting, and abdominal pain, indicative of gastrointestinal involvement. No significant difference in these presenting symptoms was observed between the two groups (Chi-square test, $p > 0.05$). Similarly, no significant difference was noted in the duration of fever between the two groups. However, hematological involvement and hypotension were significantly more common in the MIS-C group (Mann-Whitney U test, $p < 0.001$) (Table 2).

SARS-CoV-2 IgG results were positive in 44 patients (64.7%) in the MIS-C group, and both SARS-CoV-2 IgG and IgM values were negative in 6 (8.8%) patients. Eighteen patients (26.4%) had positive results for both IgG and IgM. PCR tests of these 18 patients were negative. These results were evaluated together with clinical findings and other laboratory tests, and none of them were diagnosed with acute COVID-19 infection (Table 3).

Among the patients in the non-MIS-C group, 157 (79.2%) had negative results for both COVID-19 IgM and IgG, 28 patients (14%) had positive COVID-19 IgG results, and 13 patients (6.5%) showed positive results for both IgG and IgM. Out of these 13 patients with positive serology (IgG and IgM), 3 were confirmed to have acute COVID-19 infection through

Table 2. Comparison of demographic and clinical characteristics, and hospitalization rates between with MIS-C and Non-MIS-C group

	Total (n = 266)	MIS-C (n = 68)	Non-MIS-C (n = 198)	*p* value
Age (months), mean ± SD	88 ± 60.4	102.6 ± 53	83 ± 62	**0.02**[a]
Gender (M/F)	122/144	25/43	97/101	0.08[a]
Nationality (TC/Syria)	241/25	63/5	178/20	0.50 [a]
Diarrhea, n (%)	120 (45)	28 (41)	92 (46)	0.45[b]
Vomiting, n (%)	114 (42)	33 (48.5)	81 (40.9)	0.27[b]
Cough, n (%)	36 (13.5)	10 (14.7)	26 (13)	0.74[b]
Dermatological involvement, n (%)	60 (13.5)	20 (29.4)	40 (20)	0.11[b]
Mucous membrane involvement, n (%)	33 (12.4)	11 (16)	22 (11)	0.27[b]
Gastrointestinal system involvement, n (%)	184 (69)	50 (73.5)	134 (67.6)	0.36[b]
Respiratory system findings, n (%)	33 (12.4)	15 (22)	18 (9)	0.05[b]
Neurological system involvement, n (%)	13 (4.8)	4 (5.8)	9 (4.5)	0.43[b]
Cardiac involvement, n (%)	12 (4.5)	6 (8.8)	6 (3)	0.056[b]
Presence of hypotension, n (%)	31 (11.6)	19 (27.9)	12 (6)	**< 0.0001**[b]
Hematological system involvement, n (%)	221 (83)	20 (29.4)	6 (3)	**< 0.0001**[b]
Outpatient follow-up, n (%)	76 (28.5)	0	76 (38)	**< 0.0001**[b]
Admitted to the ward, n (%)	164 (61.6)	48 (70.5)	116 (58.5)	**< 0.0001**[b]
Admitted ICU, n (%)	26 (9.7)	20 (29.4)	6 (3)	**< 0.0001**[b]

[a]Mann-Whitney U Test, [b]Chi-Square Test

positive PCR testing (Table 3). Diagnoses for the remaining 10 patients were as follows: 5 patients with unidentified viral infections, 1 patient with tuberculosis, 1 patient with a collagen tissue disease, and 3 patients with gastroenteritis. None of the serologically tested patients had been vaccinated against COVID-19. Serological positivity was significantly higher in the group diagnosed with MIS-C compared to the group non - MIS-C (Chi-square test, $p < 0.001$).

A total of 7 patients were diagnosed with acute COVID-19. Among these, 3 patients had both serological and PCR positivity, whereas the remaining 4 patients had negative serology but tested positive on PCR.

In patients diagnosed with MIS-C, Absolute lymphocyte Count (ALC), platelet, and sodium levels were significantly lower, while triglyceride, troponin, BNP, PT, D-Dimer, and fibrinogen levels were significantly higher compared to those compared to the group non-MIS-C (Mann Whitney-U test, $p < 0.05$) (Table 4).

ROC curves were constructed for ALC, platelet count, CRP, procalcitonin, triglyceride, troponin, BNP, ferritin, PT, D-Dimer, fibrinogen, and sodium values,

Table 3. Comparison of serology test result in MIS-C and Non-MIS-C patients

Group	COVID-19 IgG (+)	COVID-19 IgM and IgG (+)	COVID-19 IgM and IgG (-)	Total patients
MIS-C	44 (64.7%)	18 (26.4%)	6 (8.8%)	68
Non-MIS-C	28 (14%)	13 (6.5%)	157 (79.2%)	198

Table 4. Comparison of laboratory parameters of patients diagnosed with MIS-C and Non-MISC group.

Laboratory Markers	Normal range	MISC (n = 68) Median (IQR)	Non-MISC (n = 198) Median (IQR)	*p* value*
WBC (×10³/uL)	4.2-10.6	10.0 (8.9) (n = 68)	11.2 (8.0) (n = 198)	0.40
ANS (×10³/uL)	2-6.9	8200 (6300) (n = 68)	7150 (7400) (n = 198)	0.13
ALC (×10³/uL)	0.6-3.4	1000 (1200) (n = 687	1800 (2350) (n = 197)	**< 0.0001**
Hemoglobin (gr/dL)	12.2-16.2	11.7 (1.8) (n = 68)	11.8 (2.2) (n = 198)	0.95
Platelets (×10³/uL)	140-400	225 (175) (n = 68)	278 (130) (n = 198)	**0.01**
CRP (mg/dL)	0-5	127 (112) (n = 68)	70.6 (104) (n = 198)	**< 0.01**
Procalcitonin (ng/mL)	0-0.1	1.28 (4.74) (n = 68)	0.39 (2.3) (n = 189)	**0.002**
ESR (mm/h)	0-20	40.5 (32.5) (n = 12)	62.5 (74.5) (n = 40)	0.192
AST (u/L)	0-35	30 (24) (n = 68)	28 (16) (n = 197)	0.40
ALT (u/L)	0-35	19 (26.5) (n = 68)	16 (11) (n = 197)	0.14
Triglycerides (mg/dL)	32-158	102 (72.7) (n = 60)	86.5 (76) (n = 130)	**0.032**
Urea (mg/dL)	10-38	25.5 (14) (n = 68)	22 (11) (n = 198)	0.48
Creatinine (mg/dL)	0.5-1.2	0.6 (0.3) (n = 68)	0.5 (0.3) (n = 198)	0.39
Troponin (ng/mL)	0.0-0.06	3.7 (33) (n = 66)	2.5 (0.0) (n = 169)	**< 0.0001**
BNP (ng/L)	2-100	180 (325) (n = 31)	18 (22.3) (n = 23)	**< 0.0001**
Ferritin (µ/L)	6-320	175 (198) (n = 58)	112 (130) (n = 157)	**0.001**
PT (sec)	10.8-15	13.6 (2.2) (n = 68)	13 (1.85) (n = 189)	**0.011**
APTT (sec)	21-36	25.3 (4.0) (n = 68)	25 (5.0) (n = 189)	0.51
INR	0.8-1.2	1.1 (0.17) (n = 65)	1.08 (0.13) (n = 192)	0.16
D-Dimer (ng/mL)	0-440	2050 (2288) (n = 66)	1240 (1990) (n = 183)	**0.005**
Fibrinogen (mg/dL)	170-420	466 (257) (n = 68)	397 (193) (n = 160)	**0.004**
Sodium (mmol/L)	35-148	133 (5) (n = 68)	135 (4) (n = 198)	**< 0.0001**
Albumin (gr/dL)	3.5-5.2	30.5 (35.5) (n = 68)	32 (35.9) (n = 195)	0.192
LDH (u/L)	110-295	294 (131) (n = 68)	292 (96) (n = 196)	0.51

WBC = White blood cell, ANC = Absolute neutrophil count, ALC = Absolute lymphocyte count, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, BNP = brain natriuretic peptide, PT = prothrombin time, PTT = partial prothrombin time, INR = International Normalized Ratio, LDH = lactate dehydrogenase

*Mann-Whitney U test.

which were significant according to the Mann Whitney U analysis. Upon examining the laboratory values with ROC curves, it was observed that the calculated AUC values for five laboratory values were statistically significant. These include Procalcitonin (AUC 0.719, $p = 0.022$), Triglyceride (AUC 0.690, $p = 0.047$), Troponin (AUC 0.698, $p = 0.039$), BNP (AUC 0.853, $p < 0.0001$), and Sodium (AUC 0.792, $p = 0.002$). However, upon examination of these laboratory parameters using a Logistic Regression model, they were not found to be significant in predicting the diagnosis of MIS-C.

Out of the 68 patients diagnosed with MIS-C, 42 (61.7%) had normal ECHO results obtained in the PED. Six patients (8.8%) were found to have heart failure, three patients (4.4%) had pericardial effusion, three patients (4.4%) exhibited mitral valve insufficiency, five patients (7.3%) had myocarditis and coronary dilation, and two patients (2.9%) showed aortic valve insufficiency. Seven patients did not receive an ECHO in the PED. All patients diagnosed with heart failure, one patient with pericardial effusion, two patients with concurrent myocarditis and coronary dilation, and one patient with mitral valve insufficiency were admitted to the pediatric ICU. All these patients had BNP values measured above 240 ng/L.

Sixty eight patients diagnosed with MIS-C were compared with 12 patients diagnosed with KD. The average age of patients diagnosed with KD was 46.3 months, whereas it was 102.6 months for those diagnosed with MIS-C, and this difference was significant (Mann-Whitney U test, $p = 0.001$). When compared in terms of gender, a significant difference was detected. All of those diagnosed with KD were male (Fisher's Exact Test, $p = 0.014$). When the physical examination findings at the first presentation were compared, tachycardia was significantly more common in the MIS-C group (Fisher's Exact Test, $p = 0.03$). Although hypotension was more frequently observed in the MIS-C group in the comparison made in terms of the presence of hypotension, the p-value was determined as 0.06. When comparing laboratory parameters; differences were found between the two groups in terms of averages for ALC, platelet count, troponin, and BNP (Mann Whitney-u test). In Kawasaki patients, ALC and platelet counts were higher than in MIS-C patients. In the MIS-C group, BNP and troponin were found to be significantly higher than in Kawasaki patients ($p = 0.014$, $p = 0.003$, $p = 0.006$, and $p = 0.014$; respectively).

All patients diagnosed with COVID-19 associated MIS-C were hospitalized. Of these patients, 20 (29.4%) were monitored in the pediatric ICU. The rates of hospitalization and intensive care need were significantly higher in patients diagnosed with MIS-C compared to those diagnosed with non-MIS-C (Chi-square test, $p < 0.0001$).

The average age of patients monitored in the ICU with a diagnosis of MIS-C was significantly higher compared to others (Mann Whitney U test, $p = 0.008$). When comparing laboratory parameters, procalcitonin, AST, ALT, triglyceride, troponin, BNP, and ferritin values were significantly higher, while sodium values were significantly lower in patients requiring intensive care monitoring (Table 5). Upon generating ROC curves, the calculated AUC values for these eight laboratory values were found to be statistically significant: Procalcitonin (AUC 0.668, $p = 0.03$), Triglycerides (AUC 0.772, $p = 0.001$), Troponin (AUC 0.709, $p = 0.07$), BNP (AUC 0.728, $p = 0.035$), Sodium (AUC 0.658, $p = 0.041$), Ferritin (AUC 0.776, $p = 0.003$), AST (AUC 0.660, $p = 0.039$), and ALT (AUC 0.694, $p = 0.012$). However, these laboratory parameters were not found to be significant in predicting intensive care admission in the logistic regression model.

DISCUSSION

Children observed for COVID-19 associated MIS-C are predominantly previously healthy individuals who have experienced a mild or asymptomatic course of COVID-19 infection. Patients most frequently present with gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) and mucocutaneous inflammation signs (rashes, conjunctivitis, oromucosal changes). Upon examination, lymphopenia and elevated inflammatory markers are typically identified. However, a subset of patients develops severe illness manifestations, including hypotension/shock and cardiac involvement such as myocarditis, myocardial dysfunction, and coronary artery changes [4].

The symptoms, physical examination findings, and test results observed in MIS-C share common characteristics with many other diseases, making it

Table 5. Comparison of gender, age, and laboratory parameters of MIS-C patients admitted to the ICU and those admitted to the ward.

Parameter / Marker	Normal range	Ward admission (n = 48)	ICU admission (n = 20)	*p* value
Gender (F/M)		17/31	8/12	0.721
Age (months)		91	130	**0.008**
Fever value (°C)		38.4	38.7	0.252
WBC (×10³/uL)	4.2-10.6	11.915	11.240	0.957
ANC (×10³/uL)	2-6.9	9375	9335	0.549
ALC (×10³/uL)	0.6-3.4	1555	1055	0.178
Hemoglobin (g/dL)	12.2-16.2	11.7	12	0.835
Platelets (×10³/uL)	140-400	255	230	0.364
CRP (mg/dL)	0-5	128	146	0.270
Procalcitonin (ng/ml)	0-0.1	3.5	23.7	**0.030**
ESR (mm/h)	0-20	44.5	41	0.578
AST (u/L)	0-35	35	69	**0.039**
ALT (u/L)	0-35	29	58	**0.012**
Triglycerides (mg/dL)	32-158	107	198	**0.001**
Urea (mg/dL)	10-38	23	37	0.328
Creatinine (mg/dL)	0.5-1.2	0.59	1.0	0.182
Troponin (ng/ml)	0.0-0.06	135	3863	**0.006**
BNP (ng/L)	2-100	179	504	**0.035**
Ferritin (µ/L)	6-320	177	316	**0.003**
PT (s)	10.8-15	13.8	13	0.185
APTT (s)	21-36	25.7	25	0.479
INR	0.8-1.2	1.1	1.1	0.070
D-DIMER (ng/ml)	0-440	2940	3608	0.078
Fibrinogen (mg/dL)	170-420	477	499	0.505
Sodium (mmol/L)	35-148	133	130	0.040
Albumin (g/dL)	3.5-5.2	2.2	2.1	0.716
LDH (u/L)	110-295	290	366	0.060

WBC = White blood cell, ANS = Absolute neutrophil count, ALC = Absolute lymphocyte count, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, BNP = brain natriuretic peptide, PT = prothrombin time, PTT = partial prothrombin time, INR = International Normalized Ratio, LDH = lactate dehydrogenase

challenging to make a differential diagnosis in the PED. In the study aimed at investigating biochemical markers with high specificity and sensitivity to differentiate COVID-19 associated MIS-C from other diseases and reduce the confusion among physicians working in the PED, a total of 266 patients were evaluated. 68 of these patients were diagnosed with COVID-19 associated MIS-C, and 20 of them were

monitored in the pediatric ICU. The hospitalization and ICU admission rates of patients diagnosed with MIS-C were significantly higher compared to others.

In MIS-C patients, we detected a positivity rate of 64.7% (44 patients) for COVID-19 IgG, and 26.4% (18 patients) tested positive for both IgG and IgM. All of these patients had negative PCR results. Neutralizing antibody responses have been found in COVID-19 patients, but the relationship between SARS-CoV-2 antibody levels and disease severity is still debated. SARS-CoV-2 spike protein IgM and IgG levels are higher in severe and recovered COVID-19 patients, proportional to the time since symptom onset, reflecting a robust SARS-CoV-2-specific humoral response. SARS-CoV-2 IgG and IgM antibodies have been found at lower levels in asymptomatic SARS-CoV-2-positive individuals compared to COVID-19 patients. However, the exact timing of SARS-CoV-2 exposure in relation to MIS-C development and laboratory findings remains unclear [4]. Feldstein *et al*. [9] reported that 70% of patients had a positive RT-PCR (Real time polymerase Chain Reaction) or antibody test, with 30% being exposed to a COVID-19-positive individual in the past 4 weeks. In another study involving 52 MIS-C patients, 56% (28/50) had a positive PCR result for SARS-CoV-2 (acute infection), and 44% (22/50) tested positive for SARS-CoV-2 antibodies (post-acute) [1]. Considering these findings, although SARS-CoV-2 antibody testing is not routinely practiced in many centers, we use serological tests routinely in our center when diagnosing MIS-C to demonstrate its association with COVID-19, and we believe it can be a valuable aid in differential diagnosis.

While no significant differences were observed between the two groups in terms of gender, the mean age of the MIS-C group (102.6 months) was significantly higher. Additionally, the mean age of those in the ICU (130 months) was significantly higher compared to those admitted to the general ward for MIS-C. Our findings were consistent with the United Kingdom (UK) cohort [1] (median age 10.7 (8.3-14.1) vs. 1.6 (0.2-12.9); $p < 0.001$), Vogel *et al*. [4] (median age: 8.5 years), and Yasuhara *et al*. [10] systematic review (median age: 9.3). We believe that greater attention should be given to age criteria in the diagnosis of COVID-19 associated MIS-C. Increasing age should be considered in the clinical decision-making process when screening for MIS-C cases.

There were no significant differences in presenting complaints between the two groups; however, gastrointestinal symptoms were most commonly observed in the MIS-C group, followed by mucocutaneous involvement symptoms. Respiratory symptoms, hematological involvement (lymphopenia, thrombocytopenia, elevated D-dimer), and signs of shock (hypotensive shock) were significantly more frequent in the MIS-C group. We found hypotension in 27.9% of MIS-C patients at their initial presentation. While Roberts *et al*. [11] reported a low number of children presenting with hypotension as their initial vital sign, they identified hypotension within the first 12 hours as an indicator for MIS-C diagnosis.

While gastrointestinal symptoms tend to be predominant in the presentation of MIS-C, they are rare in traditional KD [4]. A systematic review by Panigrahy *et al*. [12], which included 875 MIS-C patients, concluded that gastrointestinal symptoms, including abdominal pain (52.8%), vomiting (44.8%), diarrhea (39.5%), and mucocutaneous symptoms (44.4%), were common. Respiratory distress (20.9%) and neurological involvement (17.5%) were less frequent. In an observational cohort study conducted in the UK, children with MIS-C had a higher rate of presenting with fatigue (51% vs. 28%); $p = 0.004$). Additionally, they had higher rates of headache (34% vs. 10%; $p < 0.001$), myalgia (34% vs. 8%; $p < 0.001$), sore throat (30% vs. 12%; $p = 0.003$), and lymphadenopathy (20% vs. 3%; $p < 0.001$) [1]. In our study, we also found that headache was the most common complaint after gastrointestinal symptoms and rash. Our observations regarding the clinical presentation of MIS-C were very similar to previously reported cases in the literature. Thus, notable differences distinguishing MIS-C from KD include older age, predominantly gastrointestinal symptoms, and a higher prevalence of shock and myocardial injury at presentation [13]. We believe that these differences, along with other factors, can be highly informative in the differential diagnosis between MIS-C and KD. However, it should be noted that in addition to the presence of fever, gastrointestinal symptoms such as vomiting, abdominal pain, and/or diarrhea, along with conjunctivitis and rashes, and headache, are not specific and can also occur in oncological diseases, non-infectious inflammatory conditions, or other infectious diseases [14]. In our

study group as well, patients other than those with MIS-C were most commonly diagnosed with invasive gastroenteritis and undetermined viral infections.

Consistent with findings reported in several MIS-C cohort studies [1, 7, 11, 15-19], we observed lymphopenia, thrombocytopenia, hyponatremia, and elevated levels of blood CRP, procalcitonin, triglycerides, troponin, BNP, D-dimer, and fibrinogen in the COVID-19 associated MIS-C group. Five laboratory (Procalcitonin, Triglyceride, Troponin, BNP, Sodium) values showed statistically significant AUC values. Although BNP had the highest significance (AUC 0.853, $p < 0.0001$), logistic regression analysis revealed that it was not significant in predicting MIS-C diagnosis. These important findings can aid in distinguishing this syndrome from other diseases, especially KD, where platelet counts typically increase. While platelet count is a discriminating feature, it was only mildly decreased in MIS-C patients. In the presence of systemic inflammation, thrombocytosis is typically observed. If mild thrombocytopenia is detected in the presence of systemic inflammation markers, and there are compatible clinical findings, MIS-C should be considered. [11]. MIS-C patients often exhibit elevated D-dimer levels (90%) [6]. Additionally, although high D-dimer levels have been associated with treatment-resistant KD, their significance in cardiac involvement in MIS-C remains uncertain [13]. Kline *et al*. [8] found that CRP > 4.5 mg/dL and ALC < 1.5 K/μL had 86% sensitivity and 91% specificity for identifying MIS-C cases. In our study, we found significant elevations in CRP, procalcitonin, triglycerides, troponin, BNP, and decreases in lymphocyte, platelet, and sodium levels, but we were unable to determine specific cutoff values.

Procalcitonin is often used as an indicator of bacterial infection and can also be elevated in severe viral infections. Elevated procalcitonin levels have also been reported in MIS-C [11]. In our study, procalcitonin levels were significantly higher in the MIS-C group compared to the non-MIS-C group. Furthermore, patients with MIS-C who were admitted to the ICU had significantly higher procalcitonin levels.

In MIS-C, elevated troponin and BNP-proBNP levels indicate cardiac involvement. Troponin and BNP are closely associated with disease activity [4]. Minocha *et al*. [20] demonstrated abnormality in at least one cardiac test in the majority of patients (78%). BNP levels have been suggested as early warning indicators for the need for inotropic/vasoactive treatment in MIS-C. Echocardiography in patients with elevated BNP levels may be useful in promptly identifying patients with cardiac dysfunction and adjusting treatment or considering alternative diagnoses [6]. We recommend using the BNP test as a screening tool in children with prolonged and unexplained fever to identify early cardiac involvement in MIS-C.

Hyponatremia, observed in a significant portion of MIS-C cases during admission, can occur secondary to dehydration, renal or cardiac failure. While hyponatremia has been identified as a predictor of poor prognosis in both COVID-19 and KD, its prognostic role in MIS-C remains uncertain [13]. In our study, we also found significantly lower sodium levels in both MIS-C patients and those requiring ICU admission. When comparing the laboratory parameters of patients admitted to the general ward and those admitted to the ICU within the MIS-C group, we observed higher procalcitonin, AST, ALT, triglyceride, troponin, BNP, and ferritin levels, as well as lower sodium levels, in the ICU group. These results were consistent with other studies in the literature [1, 10, 13, 20, 21]. However, we were unable to establish significance in predicting the need for ICU admission.

Limitations

Our study has several limitations. Firstly, it was designed retrospectively, so some laboratory tests were not performed on all patients. Specifically, due to the nighttime conditions in our PED, sedimentation rate tests were conducted on a limited number of patients, and we did not find significant elevations as observed in other studies. Additionally, although we screened patients who underwent SARS-CoV-2 IgM/IgG testing to identify those with a preliminary diagnosis of MIS-C, we may not have reached all patients through this method. Furthermore, during the screening period, there is a possibility that unnecessary tests were performed in order to avoid missing a diagnosis of MIS-C.

CONCLUSION

Children diagnosed with COVID-19-associated MIS-C were older, and gastrointestinal and mucocutaneous

involvement symptoms were predominant during presentation. Respiratory symptoms, hematological involvement (lymphopenia, thrombocytopenia, elevated D-dimer), and signs of shock were significantly more common in the MIS-C group. In the differential diagnosis of MIS-C, initial screening tests such as lymphopenia, thrombocytopenia, elevated CRP, and elevated D-dimer can be guiding factors. However, in patients with a high suspicion of MIS-C, additional tests including procalcitonin, troponin, BNP, triglycerides, and ferritin should be performed. It is important to keep in mind that patients with elevated BNP levels may require ICU admission.

Authors' Contribution

Study Conception: YB; Study Design: YB; Supervision: GG; Funding: N/A; Materials: GG; Data Collection and/or Processing: TN, AÇ; Statistical Analysis and/or Data Interpretation: EE, YB; Literature Review: ŞB, GD; Manuscript Preparation: YB and Critical Review: EB, YB.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The author disclosed that they did not receive any grant during conduction or writing of this study.

Acknowledgement

This study was partly presented as oral presantation at 18th National Pediatric Emergency Medicine and Intensive Care Congress, November 2-5, 2022, Antalya, Turkey.

REFERENCES

1. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020;;370:m3249.
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8.
3. HAN Archive - 00432 | Health Alert Network (HAN). (2021). Accessed 06 June 2022. https://emergency.cdc.gov/han/2020/han00432.asp
4. Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Moceri P, et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2021;39:3037-49.
5. Emeksiz S, Çelikel Acar B, Kibar AE, Özkaya Parlakay A, Perk O, Bayhan Gİ, et al. Algorithm for the diagnosis and management of the multisystem inflammatory syndrome in children associated with COVID−19. Int J Clin Pract 2021;75:e14471.
6. Giacalone M, Scheier E, Shavit I. Multisystem inflammatory syndrome in children (MIS-C): a mini-review. Int J Emerg Med 2021;14:50.
7. Karagol C, Tehci AK, Gungor A, Ekici Tekin Z, Çelikel E, Aydın F, et al. Delta neutrophil index and C-reactive protein: a potential diagnostic marker of multisystem inflammatory syndrome in children (MIS-C) with COVID-19. Eur J Pediatr 2022;181:775-81.
8. Kline JN, Isbey SC, McCollum NL, Falk MJ, Gutierrez CE, Guse SE, et al. Identifying pediatric patients with multisystem inflammatory syndrome in children presenting to a pediatric emergency department. Am J Emerg Med 2022;51:69-75.
9. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334-46.
10. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol 2021;56:837-48.
11. Roberts JE, Campbell JI, Gauvreau K, Lamb GS, Newburger J, Son MB, et al. Differentiating multisystem inflammatory syndrome in children: a single-centre retrospective cohort study. Arch Dis Child 2022;107:e3.
12. Panigrahy N, Policarpio J, Ramanathan R. Multisystem inflammatory syndrome in children and SARS-CoV-2: a scoping review. J Pediatr Rehabil Med 2020;13:301-16.
13. Sethuraman U, Kannikeswaran N, Ang J, Singer A, Miller J, Haddad R, et al. Multisystem inflammatory syndrome in children associated with novel coronavirus SARS-CoV-2: Presentations to a pediatric emergency department in Michigan. Am J Emerg Med 2021;39:164-7.
14. Hançerli Törün S, Yilmaz Çiftdoğan D, Kara A. Multisystem inflammatory syndrome in children. Turk J Med Sci 2021;51(SI-1):3273-3283.
15. Rostami-Maskopaee F, Ladomenou F, Razavi-Amoli SK, Navaeifar MR, Hajialibeig A, Shahbaznejad L, et al. Clinical characteristics and outcomes of the multisystem inflammatory syndrome in children (MIS-C) following COVID-19 infection in Iran: a multicenter study. PLoS One 2022;17:e0274104.
16. Alkan G, Sert A, Oz SKT, Emiroglu M, Yılmaz R. Clinical features and outcome of MIS-C patients: an experience from Central Anatolia. Clin Rheumatol 2021;40:4179-89.
17. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347-58.
18. Waseem M, Shariff MA, Tay ET, Mortel D, Savadkar S, Lee H, et al. Multisystem inflammatory syndrome in children. J Emerg Med 2022;62:28-37.

19. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259-69.
20. Minocha PK, Phoon CKL, Verma S, Singh RK. Cardiac findings in pediatric patients with multisystem inflammatory syndrome in children associated with COVID-19. Clin Pediatr (Phila) 2021;60:119-26.
21. Stankovic C, DeLaroche A, Arora R, Spencer P, Ehrman RR. Laboratory trends in severe MIS-C. Acad Emerg Med 2022;29:1258-60.