JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1244076
J Contemp Med 2023;13(2):270-276

Original Article / Orijinal Araştırma

Gastrointestinal System Involvement of Multisystem Inflammatory Syndrome in Children (MIS-C): A Single Center Experience of 47 cases

Pediatrik Multisistem İnflamatuvar Hastalıkta (MIS-C) Gastrointestinal Sistem Tutulumu: 47 Olgunun Tek Merkez Deneyimi

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Abstract

Aim: Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory syndrome which was newly described during the coronavirus disease 2019 (COVID-19) pandemic in children and characterized by fever, inflammation, multiorgan dysfunction. One of the major clinical presentation is gastrointestinal system involvement. The aim of the study is to evaluate the clinical course and outcome according to the severity of gastrointestinal presentation, focusing on MIS-C cases with gastrointestinal system involvement.

Material and Method: We performed a retrospective study of 47 MIS-C patients with gastrointestinal involvement in our clinic between October 2020 and March 2022. The patients were divided into two groups according to the severity of gastrointestinal involvement. The groups were compared in terms of demographic characteristics, gastrointestinal symptoms, laboratory parameters, other system involvement, length of hospital stay, treatment modalities, and clinical outcomes.

Results: According to the severity of gastrointestinal system involvement, 44.7% (n=21) of the cases were mild to moderate, 55.3% (n=26) were severe. The most common gastrointestinal symptoms at presentation were abdominal pain (78.7%), vomiting (59.6%), and nausea (55.3%). Transaminase elevation was present in 29.8% of the cases. The most common radiological findings were ascites (36.2%) and pancreatic edema (27.7%). In cases presenting with acute pancreatitis (n=9), intensive care unit admission rates (n=6) were statistically significantly higher. Brain natriuretic peptide (p=0.020) and d-dimer (p=0.032) were statistically significantly higher in the severe group than in the mild to moderate group.

Conclusion: In a significant part of the MIS-C cases with gastrointestinal involvement, severe findings is observed. Especially in cases presenting with pancreatitis, a more severe clinical course may be observed. Therefore, when managing patients presenting with gastrointestinal symptoms, the evaluation for pancreatitis is essential.

Keywors: Multisystem inflammatory syndrome in children, gastrointestinal involvement, pancreatitis

Öz

Amaç: Pediatrik multisistem inflamatuvar hastalık (MIS-C), koronavirüs 2019 (COVID-19) pandemisi sırasında yeni tanımlanan, ateş, inflamasyon ve çoklu organ yetmezliği ile karakterize hiperinflamatuvar bir sendromdur. Başlıca klinik prezentasyonlardan birisi gastrointestinal sistem tutulumudur. Çalışmanın amacı, gastrointestinal sistem tutulumu olan MIS-C olgularına odaklanarak, gastrointestinal tablonun şiddetine göre klinik seyir ve sonucu değerlendirmektir.

Gereç ve Yöntem: Ekim 2020-Mart 2022 tarihleri arasında kliniğimizde gastrointestinal tutulumu olan 47 MIS-C hastasının retrospektif bir çalışmasını gerçekleştirdik. Hastalar gastrointestinal tutulumun şiddetine göre iki gruba ayrıldı. Gruplar demografik özellikler, gastrointestinal semptomlar, laboratuvar parametreleri, diğer sistem tutulumları, hastanede kalış süreleri, tedavi yöntemleri ve klinik sonuçlar açısından karşılaştırıldı.

Bulgular: Gastrointestinal sistem tutulumunun ciddiyetine göre olguların %44.7'si (n=21) hafif-orta, %55.3'ü (n=26) şiddetli idi. Başvuru anında en sık görülen gastrointestinal semptomlar karın ağrısı (%78.7), kusma (%59.6) ve bulantı (%55.3) idi. Olguların %29.8'inde transaminaz yüksekliği mevcuttu. En sık radyolojik bulgu asit (%36.2) ve pankreas ödemi (%27.7) idi. Akut pankreatit ile başvuran olgularda (n=9), yoğun bakıma yatış oranları (n=6) istatistiksel olarak anlamlı derecede yüksekti. Brain natriüretik peptid (p=0.020) ve d-dimer (p=0.032), şiddetli grupta, hafif-orta gruba göre istatistiksel olarak anlamlı derecede yüksekti.

Sonuç: Gastrointestinal tutulumu olan MIS-C olgularının önemli bir kısmında ciddi bulgular görülmektedir. Özellikle pankreatit ile başvuran olgularda daha ağır bir klinik seyir gözlenebilir. Bu nedenle gastrointestinal semptomlarla prezente olan hastalarda pankreatit açısından değerlendirme gereklidir.

Anahtar Kelimeler: Pediatrik multisistem inflamatuvar hastalık, gastrointestinal tutulum, pankreatit

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Received *(Geliş Tarihi)*: 29.01.2023 **Accepted *(Kabul Tarihi)*:** 24.02.2023

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a newly recognized severe clinical condition which affects multiple systems and may result in shock and death. The most common organ involvements are cardiovascular, respiratory, renal, neurologic, hematologic and gastrointestinal systems.[1] Some patients with MIS-C with gastrointestinal system involvement may present with a clinic resembling viral gastroenteritis such as abdominal pain, nausea and vomiting. But, a considerable number of serious gastrointestinal manifestations such as diffuse mesenteric lymphadenitis, appendicitis, pancreatitis and terminal ileitis have also been reported in the literature.[2] In the literature, the presence of gastrointestinal symptoms at presentation was associated with a more severe clinical course for MIS-C.[3] The aim of this study is to describe the MIS-C patients presenting with gastrointestinal system involvement (clinical/radiological findings) and to evaluate patients according the severity of gastrointestinal involvement and its relationship with clinical course and outcome.

MATERIAL AND METHOD

In this study, the files of 53 patients followed with a diagnosis of MIS-C in the pediatric infectious diseases service of Necmettin Erbakan University Meram Medical Faculty between October 2020 and March 2022 were evaluated retrospectively. The diagnosis of MIS-C was made according to the CDC criteria:

1. Age < 21 years.
2. Clinical presentation in accordance with MIS-C, including all of the following:

Fever: Documented fever > 38.0°C (100.4 °F) for> 24 hours or report of subjective fever lasting> 24 hours.

Laboratory evidence of inflammation, including any of the following:

- Elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, IL-6 level.
- Neutrophilia, lymphocytopenia, hypoalbuminemia.

Multisystem (≥2) organ involvement:

- Cardiovascular (e.g., shock, elevated troponin, elevated brain natriuretic peptide (BNP), abnormal echocardiography, arrhythmia).
- Respiratory (e.g., pneumonia, ARDS, pulmonary embolism).
- Renal (renal failure).
- Neurologic (e.g., seizure, stroke, and aseptic meningitis).
- Hematologic (e.g., coagulopathy).
- Gastrointestinal (e.g., abdominal pain, vomiting, diarrhea, elevated liver enzymes, and ileus).

Severe illness requiring hospitalization.

3. No alternative potential diagnosis.
4. Evidence of infection with SARS-CoV-2 including positive SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) or positive serology.[4]

Demographic data, clinical features, laboratory parameters, radiological findings, treatment options and clinical outcome of the patients were retrospectively scanned from hospital records. MIS-C divided into three groups according to clinical severity as mild, moderate and severe:

- **Mild MIS-C:** No vasoactive requirement or respiratory support and minimal organ injury.
- **Moderate MIS-C:** Mild or isolated organ injury.
- **Severe MIS-C:** Moderate or severe organ injury, including moderate-to-severe ventricular dysfunction and requirement of inotropic support.[5]

Gastrointestinal involvement was determined by evaluating symptoms, laboratory and imaging findings at admission. The symptoms were nausea, vomiting, abdominal pain, diarrhea, hematemesis, and hematochezia. A transaminase level elevated more than twice the upper limit of normal was accepted as increased. The diagnosis of acute pancreatitis was made by evaluating clinical, laboratory and radiological findings in accordance with the recommendations of the International Study Group Of Pediatric Pancreatitis: In Search For A Cure consortium.[6] The liver size, findings consistent with pancreatitis (heterogeneity, edema), gallbladder wall thickening, wall thickening in the terminal ileum and/or cecum, findings compatible with appendicitis, presence of ascites and diffuse mesenteric lymphadenitis were examined by abdominal ultrasonography and computed tomography.

Patients were divided into 3 groups according to the severity of gastrointestinal involvement:

a. Severe gastrointestinal involvement: cases with clinical and radiological findings suggesting appendicitis, diffuse adenomesenteritis, ascites, terminal ileitis and acute pancreatitis, which require surgical consultation
b. Mild to moderate gastrointestinal involvement: cases with symptoms such as nausea, vomiting, abdominal pain, and diarrhea, without severe gastrointestinal findings and/or mild findings such as liver enzyme elevation, and gallbladder wall thickening
c. Cases without gastrointestinal symptoms and signs.[7]

According to this classification scheme, 6 patients without gastrointestinal involvement were excluded from the study. The remaining 47 patients were divided into two groups as mild to moderate group and severe group. The groups were compared in terms of demographic characteristics, gastrointestinal symptoms, laboratory parameters, other system involvement, length of hospital stay, treatment modalities, and clinical outcomes.

The study protocol was approved by the Ethics Committee of Necmettin Erbakan University Meram Medical Faculty (approval no:2022/4060) and conformed to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Statistical Method

The data were analyzed by using IBM-Statistical Package for Social Sciences (IBM-SPSS Inc., Chicago, IL, USA) 22.0 package program. The conformity to the normal distribution was examined by using the 'Shapiro-Wilk test'. Continuous variables were expressed as mean ± standard deviation or median (25-75 percentile) and categorical variables were expressed as frequency (percentage ratio). In the analysis of continuous variables, when parametric test assumptions were met the 'Independent Sample T-test' was used and when parametric test assumptions were not met the 'Mann-Whitney U test' was used. In the analysis of categorical variables Chi-square Test or Fischer's Exact Test were used. Logistic regression analysis was used to identify possible independent risk factors for severe gastrointestinal involvement. A value of $p<0.05$ was accepted as statistically significant level.

RESULTS

The study was conducted on 47 patients with MIS-C with gastrointestinal system involvement. The mean age was 126.53±44.88 months and, 27 (57.4%) patients were male and 20 (42.6%) were female. All cases were previously healthy. According to the severity of the MIS-C clinic, 27.7% of the cases were considered as mild, 46.8% moderate and 25.5% severe. According to the severity of gastrointestinal involvement, 44.7% (n=21) of the cases were mild to moderate and 55.3% (n=26) were severe.

The most common gastrointestinal symptoms at admission were abdominal pain (78.7%), vomiting (59.6%), and nausea (55.3%). Seventeen (36.2%) children presented with diarrhea. Gastrointestinal bleeding was observed in 2 patients. Transaminase elevation was present in 29.8% of the patients. Cholestatic hepatitis was not observed in any of the cases. Additionally, acute liver failure was not observed in any of these cases. Abdominal USG was performed in all cases. Abdominal computed tomography was performed in 7 cases. The most common radiological findings were ascites (36.2%) and pancreatic edema (27.7%). Other radiological findings were mesenteric lymphadenitis (12.8%), hepatomegaly (10.6%), gallbladder wall thickness (8.5%), terminal ileitis (6.4%), and appendicitis (4.3%). MIS-C symptoms developed after appendectomy in one of 2 patients who had an clinical findings of acute abdomen and had radiological findings consistent with appendicitis. The other patient had clinical and laboratory findings of MIS-C at the first presentation and appendectomy was not performed. 3 patients had radiographic findings similar to those seen in inflammatory bowel disease, such as bowel wall thickening. These findings improved in 2 of patients, but persisted in a patient and were diagnosed with inflammatory bowel disease 3 months later.

Median duration of hospitalization was 9 days (25-75 percentiles, 7–11). All patients received intravenous immunoglobulin and methylprednisolone. 45 (95.7%) patients received acetylsalicylic acid and 35 (74.5%) patients received enoxaparin. Interleukin-1 receptor antagonist was administered to 22 patients (46.8%) and interleukin-6 receptor inhibitor was administered to a patient (2.1%). 9 children (19.1%) required intensive care unit admission and 2 of those who need hospitalization in the intensive care unit died. 95.7% of MIS-C cases with gastrointestinal presentation were discharged. Gastrointestinal symptoms and findings, treatment methods and clinical outcome of the cases are shown in **Table 1**.

Table 1. Gastrointestinal symptoms and findings, treatment, clinical outcomes in MIS-C patients with gastrointestinal involvement.

Symptoms N (%)	Abdominal Pain	37 (78.7%)
	Vomiting	28 (59.6%)
	Nausea	26 (55.3%)
	Diarrhea	17 (36.2%)
	Hematemesis	1 (2.1%)
	Hematochezia	1 (2.1%)
Findings N (%)	Ascites	17 (36.2%)
	Pancreatic Edema	13 (27.7%)
	Mesenteric lymphadenitis	6 (12.8%)
	Hepatomegaly	5 (10.6%)
	Gallbladder wall thickness	4 (8.5%)
	Terminal Ileitis	3 (6.4%)
	Appendicitis	2 (4.3%)
Clinical Course and Outcomes N (%) or median (25-75 persentile)	Hospitalization Time (days)	9 (7-11)
	Hospitalization in the ICU	9 (19.1%)
	Inotrope Support	12 (25.5%)
	Invasive or Noninvasive MV support	10 (21.3%)
	Acetylsalicylic acid	45 (95.7%)
	IVIG	47 (100%)
	Methylprednisolone	47 (100%)
	Enoxaparin	35 (74.5%)
	IL-1 receptor antagonist	22 (46,8%)
	Il-6 receptor inhibitor	1 (2.1%)
	Mortality	2 (4.3%)
	Discharge	45 (95.7%)

The severe gastrointestinal presentations such as pancreatitis, adenomesenteritis, ascites, appendicitis were compared according to the clinical courses and outcomes (intensive care unit hospitalization requirement, inotropic support, invasive or noninvasive mechanical ventilation requirement, mortality). It was found that the rate of intensive care unit admission was statistically significantly higher in cases presenting with acute pancreatitis (p=0.008). 2 patients died and these patients had acute pancreatitis and ascites. There was no significant difference between the other severe clinical presentations (ascites, diffuse mesenteric lymphadenitis, terminal ileit, appendicitis) in terms of clinical course and outcome (**Table 2**).

Table 2. The severe gastrointestinal presentations according to the clinical courses and outcomes

		Ascites			Pancreatitis			Mesenteric lymphadenitis			Terminal Ileit			Appendicitis		
		Yes	No	p	Yes	No	p	Yes	No	P	Yes	No	p	Yes	No	p
ICU admission	Yes	5 (55.4)	4 (45.4)	0.168	6[a] (66.7)	3[b] (33.3)	0.008*	1 (11.1)	8 (88.9)	0.678	0 (0)	9 (100)	0.520	0 (0)	9 (100)	0.650
	No	12 (31.6)	26 (68.4)		7[a] (18.4)	31[b] (81.6)		5 (4.9)	33 (86.8)		3 (7.9)	35 (92.1)		2 (5.3)	36 (94.7)	
Inotrop support	Yes	6 (50)	6 (50)	0.208	6 (50)	6 (50)	0.055	0 (0)	12 (100)	0.151	0 (0)	12 (100)	0.404	0 (0)	12 (100)	0.550
	No	11 (31.4)	24 (68.6)		7 (20)	28 (80)		6 (12.8)	29 (82.9)		3 (8.6)	32 (91.4)		2 (5.7)	33 (94.3)	
MV	Yes	4 (40)	6 (60)	0.526	5 (50)	5 (50)	0.087	1 (10)	9 (90)	0.622	0 (0)	10 (100)	0.479	0 (0)	10 (100)	0.616
	No	13 (35.1)	24 (64.9)		8 (21.6)	29 (78.4)		5 (13.5)	32 (86.5)		3 (8.1)	34 (91.9)		2 (5.4)	35 (94.6)	
Mortality	Yes	2 (100)	0 (0)	0.126	2 (100)	0 (0)	0.072	0 (0)	2 (100)	0.759	0 (0)	2 (100)	0.875	0 (0)	2 (100)	0.916
	No	15 (33.3)	30 (66.7)		11 (24.4)	34 (75.6)		6 (13.3)	41 (87.2)		3 (6.7)	42 (93.3)		2 (4.4)	45 (95.7)	

*: significant at 0.05 level according to Fischer's Exact test. a,b: same superscript letters in each row denote the significant pairwise comparison of columns. ICU: Intensive Care Unit, MV: Mechanical Ventilation (invasive or/and noninvasive)

When the patients were evaluated according to the severity of gastrointestinal involvement, it was found that there was no statistically significant difference between the groups in terms of age (p=0.427) and gender (p=0.579). Body mass index was lower in the severe group, but the difference was not statistically significant (p=0.627). The most common gastrointestinal complaint was abdominal pain in both groups. There was no statistically significant difference between the groups in terms of the distribution of symptoms (p>0.05 for all) (**Table 2**). It was found that respiratory (p=0.284) and cardiovascular involvement (p=0.181) were more common in the severe group, however the difference was not statistically significant. Neurological involvement was significantly higher in the severe group (p=0.037) (**Table 3**).

When the groups were compared according to the severity of MIS-C, it was found that the rate of mild to moderate gastrointestinal involvement was significantly higher in cases with mild MIS-C. Similarly, severe gastrointestinal involvement was significantly higher in cases with moderate and severe MIS-C (p=0.002).

When the groups were evaluated in terms of clinical course and outcome, it was found that there was no statistically significant difference between the groups. However, intensive care unit requirement (26.9%, p=0.160), inotropic support (30.8%, p=0.360), invasive or noninvasive mechanical ventilation requirement (26.9%, p=0.475) and mortality rates (7.7%, p=0.475) were higher in the group with severe gastrointestinal involvement compared to the group with mild to moderate gastrointestinal involvement (9.5%, 19%, 14.3%, 0%, respectively) (**Table 3**).

When the groups were compared according to laboratory parameters, it was found that BNP (p=0.020) and d-dimer (p=0.032) levels were statistically significantly higher in the severe group compared to the mild to moderate group. The median BNP level was 8,632 ng/mL (2.252-16,414 ng/mL) in the severe group, it was 2,227 ng/mL (909-5,444 ng/mL) in the mild to moderate group. D-dimer level was 3,771 ng/mL (2.005-4.800 ng/mL) [median (25-75 percentiles)] in the severe group and it was 2,022 ng/mL (725-3,100 ng/mL) [median (25-75 percentiles)] in the mild to moderate group. In addition, lymphocyte count (p=0.195) and albumin levels (p=0.334) were lower in the severe group, but the difference was not statistically significant. Additionally, there was no statistically significant difference between severe and mild to moderate groups in terms of other laboratory parameters such as hemoglobin, white blood cell count, platelet count, erythrocyte sedimentation rate, C-reactive protein, interleukin-6, aspartate transaminase, alanine transaminase, fibrinogen and ferritin. (**Table 3**).

DISCUSSION

Gastrointestinal symptoms, which were thought to be less common in the early stages of the COVID-19 pandemic, have been reported more frequently after the identification of MIS-C.[3] It is increasingly recognized that gastrointestinal symptoms and signs are the most common clinical presentation of MIS-C.[8] Cases ranging from mild gastrointestinal symptoms such as isolated nausea and vomiting to severe manifestations such as terminal ileitis, pancreatitis, and acute abdomen have been reported.[9-11] Our study focused on MIS-C cases with gastrointestinal system involvement and evaluated the severity of gastrointestinal involvement, clinical features, laboratory findings, and clinical outcome.

In a meta-analysis in which 8 studies including a total of 440 MIS-C cases were evaluated, it was reported that the age of the cases ranged from 7 to 10 years, with a dominance of male gender 59%.[12] Sayed et al., in their study, which evaluated gastrointestinal involvement in patients with SARS-CoV-2 infection and MIS-C, reported that the mean age of MIS-C cases with gastrointestinal involvement was approximately 8 years higher compared to those without gastrointestinal involvement and there was no significant difference in terms of gender.[13] Vecchio et al evaluated the severity of gastrointestinal findings in children with SARS-CoV-2 infection. They reported that the mean age of the patients with severe gastrointestinal findings was higher in their cohort, which also included cases with MIS-C and age was a risk factor for severe gastrointestinal involvement.[7]

Table 3. Demographic characteristics, clinical and laboratory parameters according to the severity of gastrointestinal involvement

Parameters		Mild to moderate (n:21)	Severe (n:26)	p value
Demographic characteristics	*Age (months)	120.67±48.65	131.27±41.96	0.427
	‡2-5 years of age	4(19%)	1(3.8%)	0.158
	‡>5 years of age	17(81%)	25(96.2%)	
	§Male	13(61.9%)	14(53.8%)	0.579
	§Female	8(38.1%)	12(46.2%)	
	*BMI SDS	0.26±1.31	0.07±1.26	0.627
Symptoms	Nausea	12 (46.2%)	14 (53.8%)	0.528
	Vomiting	13 (46.4%)	15 (53.6%)	0.503
	Abdominal pain	17 (45.9%)	20 (54.1%)	0.512
	Diarrhea	7 (41.2%)	10 (58.8%)	0.478
	Hematemesis	0 (0.0%)	1 (100%)	0.553
	Hematochezia	0 (0.0%)	1 (100%)	0.553
MIS-C severity	Mild	11(84.6%)a	2(15.4%)a	0.002
	Moderate	8(36.4%)b	14(63.6%)b	
	Severe	2(16.7%)b	10(83.3%)b	
Other system involvement	Neurological	5(23.8%)	14(53.8%)	0.037
	Respiratory	5(23.8%)	10(38.5%)	0.284
	Cardiac	8(38.1%)	15(57.7%)	0.181
	Renal	3(14.3%)	3(11.5%)	1
Clinical course	†Hospitalization duration	9(7-10)	11(8-13)	0.093
	‡Hospitalization in the ICU	2(9.5%)	7(26.9%)	0.160
	§Inotrop	4(19%)	8(30.8%)	0.360
	‡Invasive/Noninvasive MV	3(14.3%)	7(26.9%)	0.475
Clinical outcomes	Mortality	0(0%)	2(7.7%)	0.495
	Discharge	21(100%)	24(92.3%)	
Laboratory parameters	*Hemoglobin (g/dL)	12.16±2.18	12.25±1.31	0.859
	*White blood cell (µg/L)	8,409±3,807	10,744±5,175	0.171
	†Platelet count (109/L)	140 (122-195)	161 (121-206)	0.669
	†Lymphocyte count (µg/L)	0.850 (0.640-1.220)	0.730 (0.600-0.970)	0.195
	*Neutrophil count (µg/L)	6,748±3,582	9,482±5,077	0.069
	†Erythrocyte sedimentation rate (>20mm/h)	55 (40-73)	40 (26-78)	0.624
	†AST (U/L)	27.3 (13.0-48.0)	27.5 (16.3-87.0)	0.556
	†ALT (U/L)	30.0 (17.4-43.0)	31.5 (16-72)	0.889
	†Albumin (g/dL)	3.5(3.0-3.8)	3.1 (2.8-3.6)	0.334
	†BNP (>25 ng/mL)	2,227 (909-5,444)	8,632 (2,252-16,414)	0.020
	†IL-6 (>6.4 pg/mL)	51.35 (8.30-230)	96.85 (56.55-1,253.5)	0.187
	*C- reactive protein (mg/L)	177.49±96.31	201.74±84.24	0.362
	†D-dimer (>500 ng/mL)	2,022 (725-3,100)	3,771 (2,005-4,800)	0.032
	†Fibrinogen (>400 mg/dL)	457 (334-547)	481.5 (437-732)	0.149
	†Ferritin >336 ng/mL)	601(410-903)	854 (551-1080)	0.239

* Independent Sample T-test, † Mann-Whitney U test, ‡ Fischer's Exact test, §Chi-Square test. Continuous variables were expressed as mean±SD or median (25-75 percentiles), while categorical variables were presented as N (%). BMI SDS: Body mass index standard deviation score; ICU: Intensive care unit; MV: Mechanical ventilation

In our study, the mean age and male dominance (57.4%) were similar to the previously reported MIS-C cases. However, the mean age of mild to moderate involvement and severe involvement groups were very close to each other. In addition, there was no difference between the severity groups in terms of gender.

The most common gastrointestinal symptoms of MIS-C include abdominal pain vomiting, and diarrhea. Radia et al., in their review analyzed the results of 35 studies conducted on a total of 783 MIS-C cases. They reported that 36% of cases with MIS-C had abdominal pain, 27% had diarrhea, and 25% had vomiting.[14] In our study, the most common symptoms of the cases with gastrointestinal involvement were abdominal pain (78.7%) and vomiting (59.6%). When the groups according to the severity of gastrointestinal involvement were compared no statistically significant difference was found in terms of presenting symptoms. The results of our study findings show that patients may present with different gastrointestinal symptoms regardless of the severity of gastrointestinal involvement.

It has been reported that elevated liver enzymes are frequent in MIS-C and associated with more severe clinical manifestations.[15] Giannattasio et al., in their study evaluating acute liver injury in MIS-C cases, reported that

16 (29%) of 55 MIS-C cases had increased transaminases and cholestasis findings were accompanied in 2 cases at admission and no acute liver failure developed in any of the patient.[16] In our study, consistent with the literature, increased transaminases were present in 29.8% of our cases. No cholestasis or acute liver failure was detected in any of the patients included in our study. There was no difference between the mild to moderate and severe gastrointestinal involvement groups in terms of transaminase levels. The results of our study suggest that there is no relationship between increased transaminase levels and severity of gastrointestinal involvement.

In patients with MIS-C abdominal imaging findings are rarely normal. Frequently reported imaging findings include mesenteric lymphadenitis, ascites, intestinal wall thickening including terminal ileum and/or cecum, hepatomegaly, and gallbladder wall thickening.[17,18] The some clinical and radiological features in gastrointestinal involvement of MIS-C can lead to an unneccesary surgery or late-diagnosis of some disease such as inflammatory bowel disease, as in our cohort.[9] Ilieva et al evaluated abdominal imaging findings in a cohort of 51 patients with MIS-C. They reported ascites in 65% of cases, mesenteric lymphadenitis in 37%, and ileitis and/or colitis in 35%.[19] The most common findings in our study were ascites (36.2%) and pancreatic edema (27.7%). The patients with severe findings including ascites, pancreatitis, diffuse mesenteric lymphadenitis and terminal ileitis were included in the severe group. When the relationships between these findings and parameters related to poor clinical outcome, such as intensive care admission, inotropic support, invasive/noninvasive mechanical ventilation requirement, and mortality were examined, it was found that the rate of intensive care hospitalization was significantly higher, especially in the presence of pancreatitis.

Liu et al., investigated the expression of angiotensin-converting enzyme 2 (ACE2) receptors of SARS-CoV-2 in the pancreas and they showed that ACE2 receptors are more abundant in the pancreas than in the lung.[20] Acharyya et al., reported that 53% of 17 patients with MIS-C had acute pancreatitis at admission. In addition, they reported that 55% of the cases with acute pancreatitis required hospitalization in the ICU and 22% resulted in mortality. Acharya et al. suggested that pancreatitis should be included in the MIS-C diagnostic criteria, due to its frequency and poor clinical course.[10] In our study, similar to the literature, we found that the rate of hospitalization in the intensive care unit is higher in the presence of acute pancreatitis.

The results of our study showed that neurological involvement was significantly higher in MIS-C cases with severe gastrointestinal involvement. It has been suggested that neuroinvasion of the central nervous system by SARS-CoV-2 may worsen the clinical course.[21] In addition, it has been shown that two proteinases required for neuroinvasion (ACE2 and TMPRSS2) are expressed in the enteric nervous system and the blood brain barrier and have been implicated in neurological findings.[22] The fact that neurological involvement is more frequent in MIS-C cases with severe gastrointestinal involvement may be the clinical reflection of this expression.

Vecchio et al. found that leukocyte, C-reactive protein, and ferritin levels were higher in MIS-C cases with severe gastrointestinal involvement.[7] In our study, there was no difference between the severe and mild to moderate groups, in terms of these inflammatory biomarkers. We found that BNP and d-dimer levels were higher in MIS-C with severe gastrointestinal involvement group compared to the mild to moderate group. In the literature, it has been reported that BNP and d-dimer levels are associated with the severity of MIS-C.[23] In our study, we observed that severe MIS-C clinic was significantly more common in patients with severe gastrointestinal involvement and we suggest that these findings may be related to the severity of the MIS-C. In a study evaluating the severity of gastrointestinal involvement in children with SARS-CoV-2 infection, it was reported that severe gastrointestinal findings are associated with MIS-C, prolonged hospitalization, and increased need for hospitalization in the intensive care unit.[7] Sayed et al. reported that the rate of critical illness was higher in patients with MIS-C, in the presence of gastrointestinal involvement. However, the severity of gastrointestinal involvement was not evaluated in this study.[13] Our study focused only on MIS-C cases with gastrointestinal involvement and showed that severe gastrointestinal involvement was more common in severe MIS-C cases. The rates of need for hospitalization in the intensive care unit, inotropic support, need for invasive/noninvasive mechanical ventilation, and mortality were higher in patients with MIS-Cs with severe gastrointestinal involvement; however, the differences were not statistically significant. We think that the lack of statistically significant results is due to the small number of patients in the groups, which we formed according to severity.

The limitations of the study are its retrospective design and single-center study. Although the number of patients in the groups seems to be small, this is the study with the largest patient cohort from a single center on a specific aspect of MIS-C in the current literature. We focused only on cases with MIS-C with gastrointestinal involvement and evaluated the severity of gastrointestinal system involvement along with clinical course and outcome.

CONCLUSION

Gastrointestinal involvement is one of the major findings of MIS-C. In a significant part of the cases severe gastrointestinal system involvement is observed. Patients with pancreatitis may have more severe course. However,

pancreatitis is not one of the organ involvements in the MIS-C diagnostic criteria. We think that, clinic and laboratory evaluation for pancreatitis should be part of the management of MIS-C with gastrointestinal presentations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of the Ethics Committee of Necmettin Erbakan University Medical Faculty (protocol code:2022/4060 and date of approval: 02.12.2022).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Patel JM. Multisystem Inflammatory Syndrome in Children (MIS-C). Curr Allergy Asthma Rep 2022;22(5):53-60.
2. Santos MO, Goncalves LC, Silva PAN, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J) 2022;98(4):338-49.
3. Jimenez DG, Rodríguez-Belvís MV, Gonzalez PF, et al. COVID-19 Gastrointestinal Manifestations Are Independent Predictors of PICU Admission in Hospitalized Pediatric Patients. Pediatr Infect Dis J 2020;39(12):459-62.
4. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69(32):1074-80.
5. Genceli M, Akcan Metin O, Erdogan KN, et al. Clinical and Laboratory Evaluations of Patients Diagnosed as Having Multisystem Inflammatory Syndrome Associated with Coronavirus Disease 2019 in Children: A Single Center Experience from Konya. J Pediatr Infect Dis 2023;18(1):17-24.
6. Morinville VD, Husain SZ, Bai H, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr 2012;55(3):261-5.
7. Vecchio AL, Garazzino S, Smarrazzo A, et al. Factors Associated With Severe Gastrointestinal Diagnoses in Children With SARS-CoV-2 Infection or Multisystem Inflammatory Syndrome. JAMA Netw Open 2021;4(12):e2139974.
8. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. Children (Basel) 2020;7(7):69.
9. Gomez IJA, Lopez PP, Duque DC, et al. Abdominal manifestation of multisystemic inflammatory syndrome in children. J Pediatr Surg Case Rep 2021;74:102042.
10. Acharyya BC, Dutta M, Meur S, Das D, Acharyya S. Acute Pancreatitis in COVID-19-associated Multisystem Inflammatory Syndrome of Children-A Single Center Experience. JPGN Rep 2021;3(1):e150.
11. Sahn B, Eze OP, Edelman MC, et al. Features of Intestinal Disease Associated With COVID-Related Multisystem Inflammatory Syndrome in Children. J Pediatr Gastroenterol Nutr 2021;72(3):384-7.
12. Abrams JY, Godfred-Cato SE, Oster ME, et al. Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review. J Pediatr 2020;226:45-54.
13. Sayed IA, Bhalala U, Strom L, et al. Gastrointestinal Manifestations in Hospitalized Children With Acute SARS-CoV-2 Infection and Multisystem Inflammatory Condition: An Analysis of the VIRUS COVID-19 Registry. Pediatr Infect Dis J 2022;41(9):751-8.
14. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev 2021;38:51-7.
15. Cantor A, Miller J, Zachariah P, DaSilva B, Margolis K, Martinez M. Acute hepatitis is a prominent presentation of the multisystem inflammatory syndrome in children: a single-center report. Hepatology 2020;72(5):1522-27.
16. Giannattasio A, Maglione M, D'Anna C, et al. Liver and Pancreatic Involvement in Children with Multisystem Inflammatory Syndrome Related to SARS-CoV-2: A Monocentric Study. Children (Basel) 2022;9(4):575.
17. Hameed S, Elbaaly H, Reid CEL, et al. Spectrum of Imaging Findings at Chest Radiography, US, CT, and MRI in Multisystem Inflammatory Syndrome in Children Associated with COVID-19. Radiology 2021;298(1):E1-E10.
18. Ucan B, Kaynak Sahap S, Cınar HG, et al. Multisystem inflammatory syndrome in children associated with SARS-CoV-2: extracardiac radiological findings. Br J Radiol 2022;95(1129):20210570.
19. Ilieva E, Kostadinova V, Tzotcheva I, Rimpova N, Paskaleva Y, Lazova S. Abdominal and Thoracic Imaging Features in Children with MIS-C. Gastroenterol Insights 2022;13(4):313-25.
20. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol 2020;18(9):2128-30.
21. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020;92(6):552-5.
22. Deffner F, Scharr M, Klingenstein S, et al. Histological Evidence for the Enteric Nervous System and the Choroid Plexus as Alternative Routes of Neuroinvasion by SARS-CoV2. Front Neuroanat 2020;14:596439.
23. Alkan G, Sert A, Tuter Oz SK, Emiroglu M, Yılmaz R. MIS-C Clinical features and outcome of MIS-C patients: an experience from Central Anatolia. Clin Rheumatol 2021; 40(10):4179-89.