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ORIGINAL ARTICLE

Clinical features and outcomes of 76 patients with COVID-19-related multi-system inflammatory syndrome in children

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Abstract

Objectives Multi-system inflammatory syndrome in children (MIS-C) is a less understood and a rare complication of coronavirus disease-2019 (COVID-19). Given the scarce data regarding this novel disease, we aimed to describe the clinical features and outcomes of our patients with MIS-C and to evaluate the associated factors for the pediatric intensive care unit (PICU) admission.

Methods The MIS-C patients under 18 years old diagnosed and treated in three referral centers between July 2020 and March 2021 were included. Data of the patients were retrospectively obtained from their medical records.

Results Overall, 76 subjects (24 females) with a mean age of 8.17 ± 4.42 years were enrolled. Twenty-seven (35.5%) patients were admitted to the PICUs. The two most common systemic involvement patterns were cardiac and gastrointestinal. There was only one lethal outcome in a patient with underlying acute lymphoblastic leukemia. Those with higher procalcitonin levels at admission were found to stay longer in the hospital ($r=0.254$, $p=0.027$). The risk of PICU admission increased with age (aOR: 1.277; 95% CI: 1.089–1.498; $p=0.003$) and with decreased initial serum albumin levels (aOR: 0.105; 95% CI: 0.029–0.378; $p=0.001$).

Conclusion Although there is a wide clinical variability among the patients with MIS-C, we suggest that those with older age and lower initial serum albumin levels merit close monitoring due to their higher risk for PICU admission.

Key Points

- *Although there is a wide variability regarding the management process among clinicians, MIS-C is a rare, severe, less understood complication of COVID-19 that may cause rapid clinical deterioration in the patients.*
- *Clinicians should be aware of this condition in children with persistent fever and a family history of COVID-19.*
- *Older age and low serum albumin levels are the independent predictors for the pediatric intensive care unit admission among MIS-C patients.*

Keywords COVID-19 · MIS-C · Pediatric intensive care unit · Rheumatology · SARS-CoV-2

Introduction

Although data gathered on the early days of the pandemic revealed that fever, dry cough, fatigue, and myalgia are the most common symptoms of coronavirus disease-2019 (COVID-19), severe complications such as acute respiratory syndrome (ARDS) even death have been observed [1]. In contrast with adults, children were considered to unlikely get the virus, and likely to have an asymptomatic or mild disease course [2]. Therefore, pediatric population was thought to be in a favorable position during the pandemic.

However, in April 2020, eight children with Kawasaki-like symptoms such as fever, conjunctivitis, peripheral edema, and gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were reported

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from the United Kingdom (UK). While refractory shock developed in all of these patients, significant pulmonary symptoms were absent [3]. Following the UK, children with SARS-CoV-2 induced hyperinflammatory states which highly resemble toxic shock syndrome (TSS), macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), and Kawasaki disease (KD) were reported from many other countries [4–6]. A growing body of evidence suggested that this hyperinflammatory condition which is caused by SARS-CoV-2 is a unique disease. The condition is named as multi-system inflammatory syndrome in children (MIS-C) by the Centers for Disease Control and Prevention (CDC) [7]. Therefore, new concerns whether children may be vulnerable to the virus more than thought before have been raised.

Given the recent data regarding a broad spectrum of variabilities in clinical and immunologic findings, a complex immune mechanism probably influenced by geographical and ethnic circumstances was thought to play the role in the pathogenesis of MIS-C [8]. Therefore, further clinical and observational studies and case series from all around the world are required for better understanding of disease pathogenesis. Moreover, although there are several studies describing MIS-C patients which were admitted to the pediatric intensive care unit (PICU) [9–11], there is a scarce data regarding the predictors of PICU admission. Thus, in the present study, we aimed to evaluate the clinical characteristics and the outcomes in a relatively large population of children with MIS-C. Additionally, we aimed to examine possible predictors of PICU admission among MIS-C patients.

Materials and methods

Patients and data collection

MIS-C patients under 18 years old diagnosed and treated in three referral centers between July 2020 and March 2021 were included in the study.

For the definition of MIS-C, we used criteria established by CDC: (a) an individual aged < 21 years presenting with fever (≥ 38.0 °C for ≥ 24 h, or report of subjective fever lasting ≥ 24 h), laboratory evidence of inflammation (one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin (IL)-6; elevated neutrophils; reduced lymphocytes; and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological), (b) no alternative plausible diagnoses, and (c) positivity for current or recent SARS-CoV-2 infection established by RT-PCR, serology, or antigen test or COVID-19 exposure within the 4 weeks before the onset of symptoms [12].

The system involvements were defined as follows: (a) respiratory involvement: respiratory distress findings (such as tachypnea and intercostal retractions), requirement of respiratory support (such as free-flow oxygen and invasive/non-invasive mechanic ventilation), and screening evidence of lung involvement (such as consolidation, infiltration, ground-glass opacities, and pleural effusion); (b) cardiac involvement: shock signs requiring fluid resuscitation (such as tachycardia, hypotension, prolonged capillary re-filling time), requirement of inotropic agents, biochemical or screening evidence of myocarditis (such as suggestive echocardiographic findings, elevated n terminal pro-B type natriuretic peptide and troponin levels), and other echocardiographic abnormalities (such as coronary dilatations, pericardial effusion, and decreased systolic functions); (c) renal involvement: anuria, oliguria, acute kidney injury/renal failure (detected by monitoring daily urine output and serum creatinine levels), and dialysis requirement; (d) hematologic involvement: thrombocytopenia, prolonged conventional coagulation tests, active bleeding, and thrombosis; (e) dermatologic involvement: rashes, desquamations, and other skin changes; (f) gastrointestinal involvement: nausea-vomiting, diarrhea, hepatic involvement (elevated liver enzymes or bilirubin levels), pancreatitis (proven by screening findings and elevated amylase and lipase), and appendicitis (proven by physical examination signs, elevated inflammatory markers, and screening findings); (g) neurologic involvement: altered mental status, irritability, confusion, lethargy, stupor, coma, pupil dilatation, meningismus, and convulsion.

The diagnosis of KD was established based on the diagnostic criteria defined by the American Heart Association (AHA) [13]. All of the patients were examined by at least one general pediatrician, one pediatric cardiologist, one pediatric rheumatologist, and one PICU intensivist if suspicion of PICU requirement has occurred. Moreover, patients with appendicitis or pancreatitis were also examined by pediatric surgeons. Echocardiography was performed in all of the patients by pediatric cardiologists. Standard criteria were followed while measuring the diameters of coronary arteries, indexed with Z scores. The Z scores of > 2.5 Z scores were defined as coronary artery dilatation [13, 14]. We performed IL-6 testing by the electrochemiluminescence immunoassay (ECLIA) method on the cobas® e 801 immunoassay analyzers.

The clinical guidance suggested by the American College of Rheumatology (ACR) was followed for the planning of the treatment regimens of the patients: all

of the patients received intravenous immunoglobulin (IVIG) ± steroids as first-line treatment. Those whose fever and/or any other systemic involvement finding persisted despite the first-line treatment were defined as non-responders while those who were unresponsive to any type of medical treatment were considered medically resistant. Anakinra or high-dose steroids were given to non-responders. Anticoagulants such as acetyl-salicylic acid were also given to all of the patients except for those with active bleeding or thrombocyte count ≤ 80 000/mm^3 [15]. Plasmapheresis was performed in medically resistant patients.

The indication for the admission to PICU was established by the PICU intensivists. The patients with hemodynamic instability which were refractory to high-volume resuscitation and requiring inotropic agents, myocardial dysfunction, severe arrhythmia, acute respiratory failure, encephalopathy, and progressive clinical worsening despite the standard treatment were admitted to the PICUs.

Data of the patients were retrospectively obtained from their medical records, and the parents of all of the patients approved the informed consent for the study. The institutional ethics committee of our center approved the study protocol (01/07/21–29,430,533-601.01–01-163,882). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed. We obtained informed consent from the caregivers of all of the participants in the study.

SARS-CoV-2 RNA screening via molecular methods

SARS-CoV-2 RNA from nasopharynx and/or oropharynx swab samples were taken from children admitted to the hospital with suspected MIS-C. In accordance with the manufacturer's instructions, children whose RNA presence could be detected before the cut-off Ct values were evaluated as SARS-CoV-2 RNA positive.

Anti-SARS-CoV-2-IgG Screening via Serological Assays

CLIA and/or ELISA-based tests have been applied to determine whether children have had SARS-CoV-2 infection. CLIA-based SARS-CoV-2 IgG (Abbott, Illinois-USA) assay was performed on Architect *i*1000 (Abbott, Illinois-USA) device. ELISA-based SARS-CoV-2 IgG (Vircell, Granada-Spain) assay was performed on Triturus (Grifols, Barcelona-Spain) device. In the CLIA-based test, index values above 1.4 S/C are positive, while values below 1.4 S/C are negative. In the ELISA-based test, antibody index values above 6 were determined as positive, values below 4 determined as negative, and values between them were determined as equivocal.

Statistical analysis

The statistical analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL). Categorical variables were expressed as numbers (percentages). Continuous variables were given as mean ± standard deviation or median (minimum–maximum) according to their distribution which was measured by using the Kolmogorov–Smirnov test. Categorical variables were compared by using Chi-square test or Fisher's-exact test, when available. Continuous variables were compared using the Mann–Whitney *U* test.

To assess the correlation between ages, initial inflammatory markers, fever duration before admission, and length of hospital stay, Spearman rank correlation coefficients test were used. Logistic regression analysis was performed to determine which variables were predictive for PICU admission.

Receiver-operating characteristic (ROC) curve and area under the ROC curve (AUC) of the significant associated factors for PICU admission which were detected in regression analysis were estimated for the patients. After ROC analysis, the best cut-off point was determined by using Youden Index for initial serum albumin levels. The sensitivity and specificity were calculated according to the best cut off point. Statistical significance was defined as $p < 0.05$.

Prism software (Prism 8, GraphPad Software, San Diego, California) was used to analyze and graph data.

Results

Characteristics of the patients

A total of 76 patients (24 females) were included in the study. The mean age was 8.17 ± 4.42 years. Twelve (15.8%) patients had an underlying chronic disease (asthma: 2, acute lymphoblastic leukemia (ALL): 2, familial Mediterranean fever (FMF): 1, cerebral palsy: 1, morbid obesity: 1, obsessive–compulsive disorder: 1, cyanotic congenital heart disease: 1, cardiac rhythm disturbance: 1, type 1 diabetes mellitus:1, tuberous sclerosis: 1), and 5 of 12 were under a long-term medication (anti-epileptic drugs: 1, insulin: 1, colchicine: 1, chemotherapy: 1, selective serotonin reuptake inhibitor: 1). At the onset of MIS-C, the attacks of the patient with FMF were under control by colchicine. The parents of fifty-three (69.7%) patients declared that they had followed the general isolation measures.

The median febrile days before admission was 4 (1–15). While anti-SARS-CoV-2 immunoglobulin (Ig) G positivity was seen in 59 (77.6%) patients, 17 (22.4%) had a negative result. Among 17 patients with a negative IgG result, SARS-CoV-2 polymerase-chain reaction (PCR) test was positive in

5, contact history with a known COVID-19 case within the 4 weeks before admission was present in 8, and both of the contact history and PCR positivity was present in 4 patients. Among 59 patients with a positive IgG result, SARS-CoV-2 PCR test was positive in 3, negative in 49, and not available in 7. The frequency of system involvements were as follows: cardiac ($n=71$, 93.4%), gastrointestinal ($n=65$, 85.5%), dermatologic ($n=40$, 52.6%), respiratory ($n=34$, 44.7%), hematologic ($n=16$, 21.1%), neurologic ($n=14$, 18.4%), and renal ($n=8$, 10.5%).

Besides, the frequencies of laboratory evidences of inflammation were as follows (patients without available data were not included into the analysis): elevated CRP ($n=74$, 97.4%), elevated ESR ($n=41$, 74.5%), elevated fibrinogen ($n=52$, 78.7%), elevated procalcitonin ($n=76$, 100%), elevated D-dimer ($n=73$, 96.1%), elevated ferritin ($n=64$, 94.1%), elevated LDH ($n=9$, 12.5%), elevated IL-6 ($n=28$, 96.5%), neutrophilia ($n=45$, 59.2%), lymphocytopenia ($n=54$, 71.1%), and hypoalbuminemia ($n=8$, 10.5%). Daily changes in the inflammatory markers of the patients are given in Fig. 1.

Eight (10.5%) patients fulfilled the diagnostic criteria of KD. Twenty-eight (36.8%) patients had cardiac murmur, twenty-two (28.9%) patients had hepatomegaly, eleven (14.4%) patients had splenomegaly, and four (5.2%) patients had musculoskeletal findings such as arthralgia, myalgia, and arthritis. While the echocardiographic abnormalities were found in 46 (60.5%) patients (valve insufficiency: 36, decreased systolic function: 14, pericardial effusion: 13, myocarditis: 7, coronary dilatation: 6), all of these findings were regressed completely in their follow-ups.

While chest computed tomography (CT) abnormalities were found in 15 patients (ground-glass opacities: 10, infiltration: 6, pleural effusion: 2, consolidation: 2, atelectasis: 1, pulmonary emboli: 1), 13 patients had abnormal abdomen CT findings (mesenteric lymphadenopathy: 8, intraabdominal fluid collection: 3, appendicitis: 2, pancreatitis: 1). Active bleeding was seen in the cranial CT screenings of one patient.

All of the patients received broad-spectrum antibiotic, and additional antifungal agents were given to 4 (5.2%) patients. While IVIG was used in all of the patients, steroids were given to 74 (97.3%) patients. Besides, anakinra was used in 3 (3.9%) refractory cases, and plasmapheresis was performed in 14 (18.4%) medically resistant patients. Four (5.2%) patients required dialysis. Moreover, anticoagulants, inotropic agents, and favipiravir were given to 70 (92.1%), 22 (28.9%), and 7 (9.2%) patients. Although 75 (98.6%) patients recovered, unfortunately one patient with ALL has died due to intracranial bleeding possibly caused by disease-related thrombocytopenia. Clinical characteristics of the patients according to the age groups are given in Table 1.

Length of hospital stay

The median length of hospital stay of the patients was 8 days (2–22). Patients with higher procalcitonin levels at admission ($r=0.254$, $p=0.027$), with myocarditis ($p=0.019$), with decreased systolic functions ($p=0.011$), and those who required inotropic agents ($p=0.022$) were found to stay longer in the hospital. Correlations between initial inflammatory markers and length of hospital stay of the patients are given in Fig. 2.

Pediatric intensive care unit admission

The mean age of the patients with and without PICU admission was 10.44 ± 4.87 and 6.92 ± 3.63 years, respectively. The patients with PICU admission were found to be significantly older ($p=0.001$). The frequencies of neurologic involvement ($p=0.027$), renal involvement ($p=0.002$), respiratory involvement ($p=<0.001$), myocarditis ($p=0.007$), and decreased systolic functions ($p=0.027$) were found to be significantly higher in patients with PICU admission.

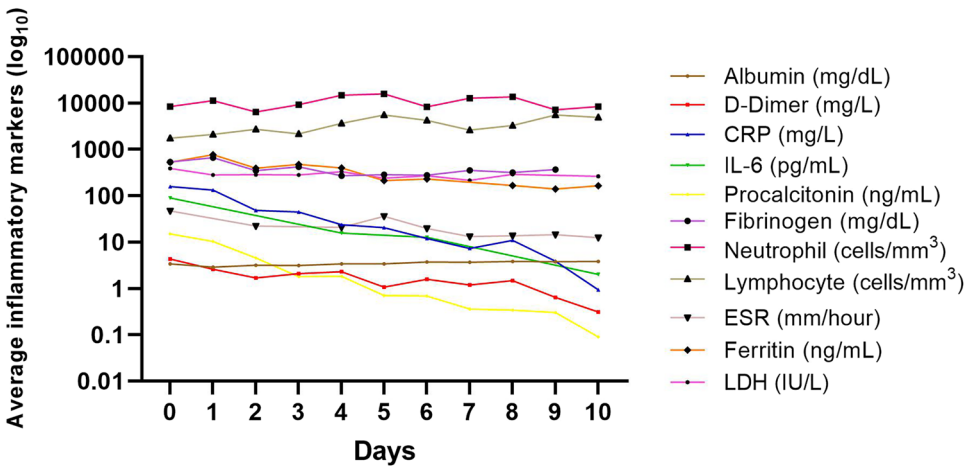


Fig. 1 Monitoring of the inflammatory markers of the patients

Table 1 Characteristics of the patients according to the age groups

	0–5 age group ($n=29$)	6–12 age group ($n=33$)	13–18 age group ($n=14$)	p value
Demographic findings				
Gender				0.776
Female (n, %)	10 (34.5%)	9 (27.3%)	5 (35.7%)	
Male (n, %)	19 (65.5%)	24 (72.7%)	9 (64.3%)	
Isolation measures during pandemic				0.276
Not followed (n, %)	10 (34.5%)	7 (21.2%)	6 (42.9%)	
Followed (n, %)	19 (65.5%)	26 (78.8%)	8 (57.1%)	
Chronic disease (n, %)	1 (3.4%)	6 (18.2%)	5 (35.7%)	0.021
Long-term medication (n, %)	1 (3.4%)	2 (6.1%)	2 (14.3%)	0.402
Diagnostic criteria of MIS-C				
1: Febrile days before admission (median (min–max))	4 (1–15)	2 (5–14)	1 (3–10)	0.053
2: SARS-CoV-2 evidence				
Positive IgG (n, %)	25 (86.2%)	27 (81.8%)	7 (50%)	0.021
Negative IgG (n, %)	4 (13.8%)	6 (18.2%)	7 (50%)	
PCR positivity (n, %)	1 (25%)	1 (16.7%)	3 (42.9%)	
Contact history (n, %)	3 (75%)	4 (66.6%)	1 (14.2%)	
Both (n, %)	–	1 (16.7%)	3 (42.9%)	
3: Multisystem involvement				
Cardiac (n, %)	28 (96.6%)	32 (97%)	11 (78.6%)	0.096
Gastrointestinal (n, %)	26 (89.7%)	29 (87.9%)	10 (71.4%)	0.295
Dermatologic (n, %)	17 (58.6%)	17 (51.5%)	6 (42.9%)	0.616
Neurologic (n, %)	6 (20.7%)	7 (21.2%)	1 (7.1%)	0.483
Renal (n, %)	2 (6.9%)	3 (9.1%)	3 (21.4%)	0.340
Respiratory (n, %)	11 (37.9%)	13 (39.4%)	10 (71.4%)	0.084
Hematologic (n, %)	5 (17.2%)	5 (15.2%)	6 (42.9%)	0.084
*4: Laboratory evidence of inflammation**				
Elevated CRP (n, %)	29 (100%)	32 (97%)	13 (92.9%)	0.479
Elevated ESR (n, %)	19 (76%)	18 (72%)	4 (80%)	1
Elevated fibrinogen (n, %)	19 (76%)	23 (79.3%)	10 (83.3%)	0.874
Elevated procalcitonin (n, %)	29 (100%)	33 (100%)	14 (100%)	–
Elevated D-dimer (n, %)	29 (100%)	31 (93.9%)	13 (92.9%)	0.401
Elevated ferritin (n, %)	28 (100%)	26 (89.7%)	10 (90.9%)	0.213
Elevated LDH (n, %)	3 (10.3%)	3 (10%)	3 (23.1%)	0.514
Elevated IL-6 (n, %)	14 (93.3%)	10 (100%)	4 (100%)	1
Neutrophilia (n, %)	18 (62.1%)	21 (63.6%)	6 (42.9%)	0.384
Lymphocytopenia (n, %)	19 (65.5%)	22 (66.7%)	13 (92.9%)	0.137
Hypoalbuminemia (n, %)	5 (17.2%)	3 (9.1%)	0 (0%)	0.260
Additional data				
Fulfilled Kawasaki disease criteria (n, %)	3 (10.3%)	5 (15.2%)	0 (0%)	0.386
Echocardiographic findings				
Valve insufficiency (n, %)	11 (37.9%)	19 (57.6%)	6 (42.9%)	0.282
Myocarditis (n, %)	1 (3.4%)	2 (6.1%)	4 (28.6%)	0.041
Pericardial effusion (n, %)	6 (20.7%)	6 (18.2%)	1 (7.1%)	0.664
Coronary dilatation (n, %)	2 (6.9%)	4 (12.1%)	0 (0%)	0.554
Decreased systolic function (n, %)	4 (13.8%)	5 (15.2%)	5 (35.7%)	0.180
Other screening findings				
Chest X-ray abnormality (n, %)	4 (13.8%)	6 (18.2%)	5 (35.7%)	0.228
Chest CT abnormality (n, %)	3 (10.3%)	7 (21.2%)	5 (35.7%)	0.141
Abdomen CT abnormality (n, %)	6 (20.7%)	6 (18.2%)	1 (7.1%)	0.664

Table 1 (continued)

	0–5 age group ($n=29$)	6–12 age group ($n=33$)	13–18 age group ($n=14$)	p value
Treatments				
IVIG (*n*, %)	29 (100%)	33 (100%)	14 (100%)	–
Steroid (*n*, %)	28 (96.6%)	32 (97%)	14 (100%)	1
Anakinra (*n*, %)	2 (6.9%)	0 (0%)	1 (7.1%)	0.296
Inotropic agents (*n*, %)	6 (20.7%)	8 (24.2%)	8 (57.1%)	0.035
Anticoagulants (*n*, %)	27 (93.1%)	31 (93.9%)	12 (85.7%)	0.643
Favipiravir (*n*, %)	0 (0%)	3 (9.1%)	4 (28.6%)	0.009
Plasmapheresis (*n*, %)	2 (6.9%)	5 (15.2%)	7 (50%)	0.002
Outcomes				
Length of hospital stay (days, median (min–max))	8 (5–21)	9 (3–22)	8 (2–21)	0.606
PICU admission (*n*, %)	5 (17.2%)	11 (33.3%)	11 (78.6%)	<0.001

*Patients without available data were not included into the analysis

CRP, C-reactive protein; *CT*, computed tomography; *ESR*, erythrocyte sedimentation rate; *IgG*, immunoglobulin G; *IL-6*; interleukin 6; *LDH*, lactate dehydrogenase; *MIS-C*, multiinflammatory syndrome in children; *PCR*, polymerase chain reaction; *PICU*, pediatric intensive care unit; *SARS-CoV-2*, severe acute respiratory coronavirus-2

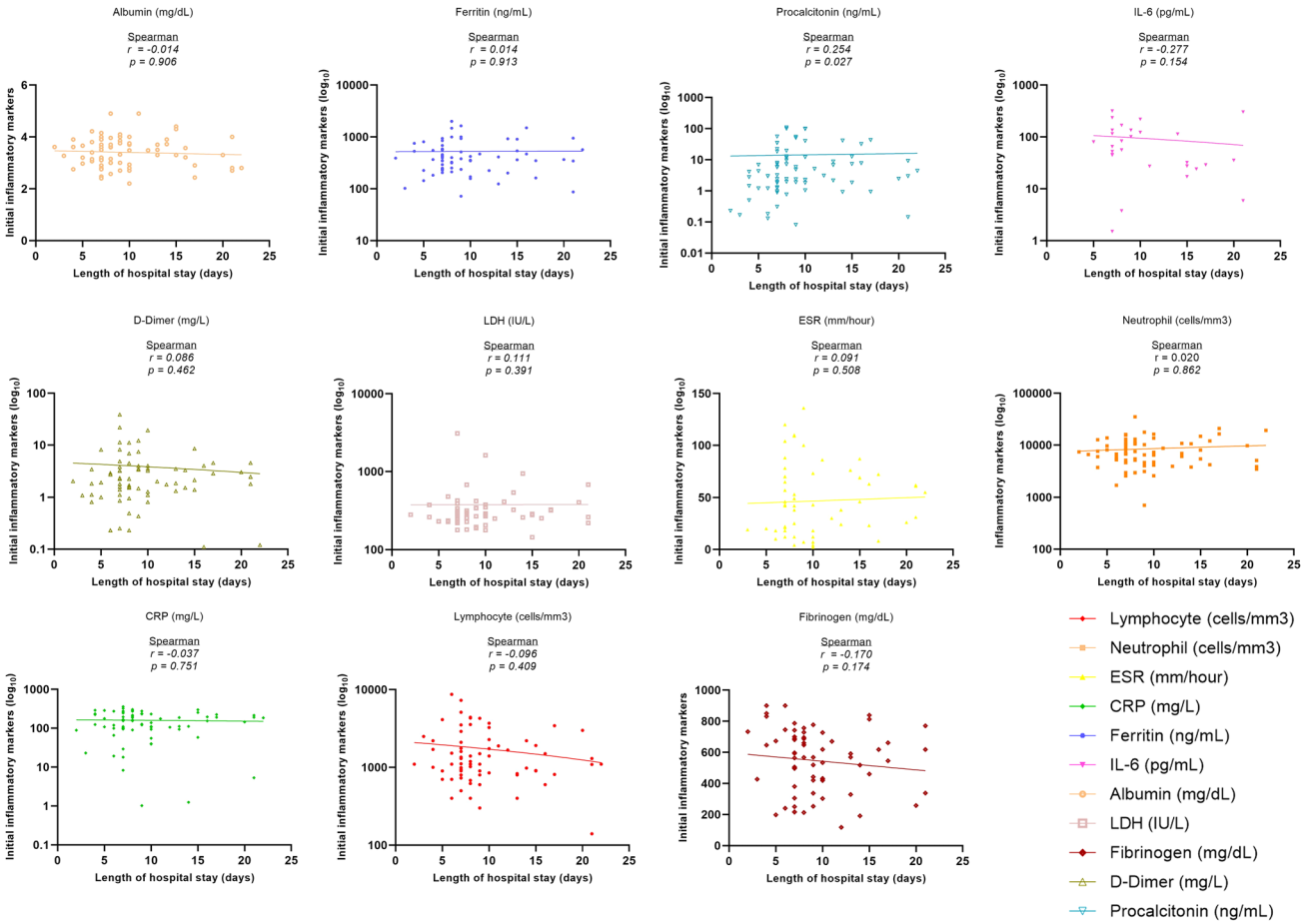


Fig. 2 The correlations between initial inflammatory markers and length of hospital stay

Table 2 Tested variables for the length of hospital stay and pediatric intensive care unit admission

	PICU admission		
	Yes ($n=27$, 35.5%)	No ($n=49$, 64.4%)	p value
Demographic findings			
Age (years) (mean ± SD)	10.44 ± 4.87	6.92 ± 3.63	0.001
Male Gender (*n*, %)	18 (66.7%)	34 (69.4%)	1
Isolation measures followed (*n*, %)	18 (66.7%)	35 (71.4%)	0.864
Chronic disease (*n*, %)	7 (25.9%)	5 (10.2%)	0.101
Receiving long-term medication (*n*, %)	3 (11.1%)	2 (4.1%)	0.340
Diagnostic criteria of MIS-C			
1: Febrile days before admission (median (min–max))	4 (1–15)	4 (1–12)	0.848
2: SARS-CoV-2 antibody			0.047
Positive IgG (*n*, %)	17 (63%)	42 (85.7%)	
Negative IgG (*n*, %)	10 (37%)	7 (14.3%)	
3: Multisystem involvement			
Cardiac (*n*, %)	24 (88.9%)	47 (95.9%)	0.249
Gastrointestinal (*n*, %)	22 (81.5%)	43 (87.8%)	0.506
Dermatologic (*n*, %)	11 (40.7%)	29 (59.2%)	0.193
Neurologic (*n*, %)	9 (33.3%)	5 (10.2%)	0.027
Renal (*n*, %)	7 (25.9%)	1 (2%)	0.002
Respiratory (n, %)	22 (81.5%)	12 (24.5%)	< 0.001
Hematologic (*n*, %)	8 (29.6%)	8 (16.3%)	0.286
*4: Initial inflammatory markers**			
CRP (mg/L) (mean ± SD)	167.88 ± 88.46	155.08 ± 89.25	0.550
ESR (mm/h) median (min–max)	42 (8–100)	42 (2–136)	0.904
Fibrinogen (mg/dL) (mean ± SD)	583 ± 234.97	523.7 ± 183.9	0.332
Procalcitonin (ng/mL) median (min–max)	4.42 (0.08–100)	3.1 (0.143–110)	0.323
D-dimer (mg/L) median (min–max)	2.83 (0.11–38.75)	1.93 (0.23–21.94)	0.168
Ferritin (ng/mL) median (min–max)	395.35 (72–2000)	378.5 (102–2000)	0.614
LDH (IU/L) median (min–max)	290 (178–3092)	286 (144–684)	0.572
IL-6 (pg/mL) median (min–max)	83.4 (24–303)	56 (1.5–317)	0.694
Neutrophil (cells/mm^3) median (min–max)	6910 (700–20,950)	6780 (2550–35,130)	0.944
Lymphocyte (cells/mm^3) median (min–max)	910 (140–7300)	1350 (400–8700)	0.015
Albumin (mg/dL) (mean ± SD)	3.14 ± 0.5	3.59 ± 0.56	0.001
Additional data			
Fulfilled Kawasaki disease criteria (*n*, %)	3 (11.1%)	5 (10.2%)	1
Echocardiographic findings			
Valve insufficiency (*n*, %)	15 (55.6%)	21 (42.9%)	0.412
Myocarditis (*n*, %)	6 (22.2%)	1 (2%)	0.007
Pericardial effusion (*n*, %)	3 (11.1%)	10 (20.4%)	0.359
Coronary dilatation (*n*, %)	1 (3.7%)	5 (10.2%)	0.413
Decreased systolic function (*n*, %)	9 (33.3%)	5 (10.2%)	0.027
Treatments			
IVIG (*n*, %)	27 (100%)	49 (100%)	–
Steroid (*n*, %)	26 (96.3%)	48 (98%)	1
Anakinra (*n*, %)	2 (7.4%)	1 (2%)	0.286
Inotropic agents (*n*, %)	18 (66.7%)	4 (8.2%)	< 0.001
Anticoagulants (*n*, %)	23 (85.2%)	47 (95.9%)	0.178
Favipiravir (*n*, %)	6 (22.2%)	1 (2%)	0.007
Plasmapheresis (*n*, %)	14 (51.9%)	0 (0%)	< 0.001

Table 2 (continued)

	PICU admission		
	Yes ($n=27$, 35.5%)	No ($n=49$, 64.4%)	p value
Respiratory support			
None (n, %)	10 (37%)	43 (87.8%)	< 0.001
Free-flow oxygen (n, %)	7 (25.9%)	4 (8.2%)	
Non-invasive ventilation (n, %)	7 (25.9%)	2 (4.1%)	
Invasive ventilation (n, %)	3 (11.1%)	0 (0%)	

*Patients without available data were not included into the analysis

CRP, C-Reactive protein; *CT*, computed tomography; *ESR*, erythrocyte sedimentation rate; *IgG*.: Immunoglobulin G; *IL-6*, interleukin 6; *LDH*, lactate dehydrogenase; *MIS-C*, multi-inflammatory syndrome in children; *PCR*, polymerase chain reaction; *PICU*, pediatric intensive care unit; *SARS-CoV-2*, severe acute respiratory coronavirus-2

Patients with PICU admission were found to have significantly lower lymphocyte counts ($p=0.017$) and lower serum albumin levels ($p=0.034$) at admission. Detailed data are given in Table 2.

Older age and lower initial albumin levels were found to be significant associated factors for predicting PICU admission in both the univariate and multivariate logistic regression analysis (Table 3). While ROC curve of age was determined significant ($p=0.002$) and AUC of the ROC curve was 0.715 (95% CI: 0.585–0.845), ROC curve of initial albumin level was determined significant ($p=0.001$) and AUC of the ROC curve was 0.726 (95%CI: 0.610–0.843) (Fig. 3). The performance of initial albumin level as a diagnostic test was found to be good with the best cut-off point as 3.36 mg/dL; the sensitivity and specificity of initial albumin level was 71.4% and 66.7%, respectively.

Discussion

As it was previously mentioned, MIS-C is a rare, severe, and less-understood complication of COVID-19. Due to its devastating consequences, studies focused on the management and monitoring of the disease are required to provide a high awareness among clinicians. Twenty-seven (35.5%) of 76 MIS-C patients required PICU admission in the present study. Lower serum albumin levels with the best cut-off point as 3.36 mg/dL and older age were found to be independent predictors for PICU admission. Seventy-five (98.6%) patients recovered without a significant sequel.

Although SARS-CoV-2 pandemic is originated from East Asia, most of the MIS-C cases were reported from Europe and the USA [16]. Similar to their geographical locations, Middle East and West Asia are in the middle of the line between East Asia and Western world regarding the number of reported cases [16–18]. Given the recent data suggesting that geographical circumstances may influence the development of the disease, large cohort studies from every single country are required for better understanding. This study is the third reported cohort from Turkey, and owing to its larger sample size, it may present contributions to the previous ones [18, 19]. Demographic findings of our study such as male predominance, prominently affected age group and survival rates were consistent with the current literature.

Although there was no significant difference between males and females regarding the PICU admission rates, there was a general male predominance with a percentage of 68.4% among our patients. This finding was consistent with previous reports [9, 20, 21]. Several molecular differences influenced by sex hormones between genders that play a pivotal role in the entrance of SARS-CoV-2 into the human body might be responsible for the severity of the disease in male [22].

Table 3 Logistic regression analysis of the risk factors of pediatric intensive care unit admission

	Univariate analysis			Multivariate analysis		
	aOR	95% CI	p value	aOR	95% CI	p value
Age	1.220	1.078–1.382	0.002	1.277	1.089–1.498	0.003
Initial inflammatory markers*						
Lymphocyte (cells/mm^3)	1	0.999–1	0.116	1	0.999–1	0.369
Albumin (mg/dL)	0.205	0.075–0.561	0.002	0.105	0.029–0.378	0.001

*Patients without available data were not included into the analysis

PICU, pediatric intensive care unit

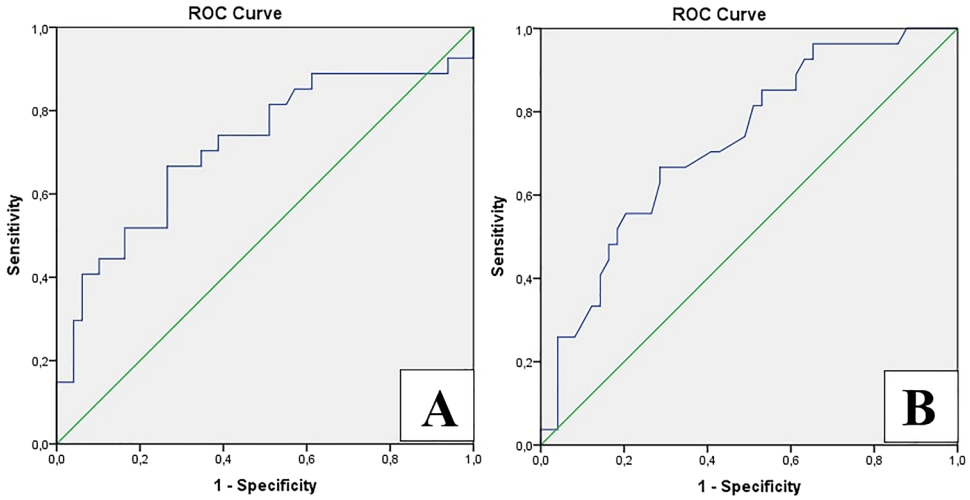


Fig. 3 Receiver-operating characteristic (ROC) curve analysis of the ages (**A**) and serum albumin levels (**B**) of the patients

As mentioned above, MIS-C shares many similarities with KD. However, in contrast with KD, which mainly affects children younger than 5 years old [23], 61.8% of our patients were older than 5. This finding was consistent with previous studies describing MIS-C patients [24, 25]. Moreover, while KD mostly affects Asian children, data regarding the MIS-C were predominantly obtained from western countries, so far [25–28]. These paradoxical data make us consider genetic differences of the hosts in the pathogenesis of MIS-C.

The overall interval between the peak of the COVID-19 outbreak and the emergence of patients with MIS-C was reported to be 4–5 weeks. Moreover, in most patients, while antibody testing results were positive, PCR tests were negative. These data suggest an uncontrolled post-infectious hyperinflammatory response in the pathogenesis of MIS-C instead of direct viral invasion [8]. Consistent with these findings, in fifty-six patients (73.6%), PCR was negative, while the SARS-CoV-2 IgG was positive.

Although studies describing MIS-C patients so far present a wide variability of clinical signs, most of the cases had cardiac dysfunction and gastrointestinal symptoms [18, 29]. Consistent with the previous reports, the two most common systemic involvements in our study were cardiac and gastrointestinal. Besides, respiratory, renal, and neurologic involvement rates were significantly higher in patients admitted to PICUs, as expected.

It was demonstrated in a recent study that children older than 5 years were more likely to be admitted to PICUs [30]. Similarly, in our study, older age was found to be an independent predictor for the PICU admission. There are several suggested explanations for the association between the clinical severity and the ages of patients. Firstly, younger children have a more "trained immunity" provided by the intense vaccination procedures which induces reprogramming the innate immune cells [31]. Secondly, it was previously shown that angiotensin converting enzyme 2 (ACE 2) protein expression which serves as a receptor for SARS-CoV-2 on the human cell surfaces was found to significantly lower in younger ages [32]. Thirdly, the immune system in early life is immature and insufficient for developing a hyperinflammatory response, which is substantially a part of the pathogenic mechanism of MIS-C [8, 33].

A significant relationship between severe disease course or PICU admission and several inflammatory markers including CRP, D-dimer, and ferritin levels was recently shown [30, 34]. In a recently published cohort, hypoalbuminemia was detected in half of the MIS-C patients [19]. Although present among CDC criteria, albumin levels have been evaluated as an outcome measure of MIS-C patients in the present study, for the first time. Thus, we revealed that PICU admission rates increased with decreasing levels of initial serum albumin levels. However, given that the best cut-off value was higher than the hypoalbuminemia's threshold, further studies are required to confirm this novel finding.

Since anakinra is widely used in the treatment of COVID-19, new restrictions and re-arrangement were performed by the health minister of our government. These new policies lead to a short-term shortage of anakinra. Therefore, although 14 patients did not respond to IVIG or steroids, anakinra could be given to only three of them, and plasmapheresis was performed in 11 of them.

The limitations were the retrospective manner of the study and the lack of some of the biomarkers such as IL-6 in several patients, due to the differences between laboratory circumstances of the centers.

In conclusion, the MIS-C represents the severe post-infectious complications of COVID-19 in pediatric patients. A take-home message from this and previous MIS-C studies is clinicians should be aware of this condition in children with persistent fever and a family history of COVID-19. Although there is a wide clinical variability among the patients with

MIS-C, we suggest that those with older age and those with lower initial serum albumin levels merits close monitoring due to their higher risk for PICU admission. Cross-cultural, prospective control studies with higher number of patients are required for further elucidation of our findings. Besides, almost a total recovery was noted in our study. This promising outcome should be also confirmed by the long-term follow-up of our cohort.

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Declarations

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