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CLINICAL RESEARCH ARTICLE

Mortality risk factors among critically ill children with MIS-C in PICUs: a multicenter study

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BACKGROUND: This study evaluated of clinical characteristics, outcomes, and mortality risk factors of a severe multisystem inflammatory syndrome in children admitted to a the pediatric intensive care unit.
METHODS: A retrospective multicenter cohort study was conducted between March 2020 and April 2021 at 41 PICUs in Turkey. The study population comprised 322 children diagnosed with multisystem inflammatory syndrome.
RESULTS: The organ systems most commonly involved were the cardiovascular and hematological systems. Intravenous immunoglobulin was used in 294 (91.3%) patients and corticosteroids in 266 (82.6%). Seventy-five (23.3%) children received therapeutic plasma exchange treatment. Patients with a longer duration of the PICU stay had more frequent respiratory, hematological, or renal involvement, and also had higher D-dimer, CK-MB, and procalcitonin levels. A total of 16 patients died, with mortality higher in patients with renal, respiratory, or neurological involvement, with severe cardiac impairment or shock. The non-surviving group also had higher leukocyte counts, lactate and ferritin levels, and a need for mechanical ventilation.
CONCLUSIONS: In cases of MIS-C, high levels of D-dimer and CK-MB are associated with a longer duration of PICU stay. Non-survival correlates with elevated leukocyte counts and lactate and ferritin levels. We were unable to show any positive effect of therapeutic plasma exchange therapy on mortality.

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IMPACT:

- MIS-C is a life-threatening condition.
- Patients need to be followed up in the intensive care unit.
- Early detection of factors associated with mortality can improve outcomes.
- Determining the factors associated with mortality and length of stay will help clinicians in patient management.
- High D-dimer and CK-MB levels were associated with longer PICU stay, and higher leukocyte counts, ferritin and lactate levels, and mechanical ventilation were associated with mortality in MIS-C patients.
- We were unable to show any positive effect of therapeutic plasma exchange therapy on mortality.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first defined in China at the end of 2019 and spread around the world within months, resulting in high rates of mortality and morbidity. On March 11, 2020, the World Health Organization (WHO) declared it a pandemic.[1,2] The rate of severe acute respiratory syndrome among children identified as infected with coronavirus 2 (SARS-CoV-2) at that time was 2–6%.[3,4] From April 2020, cases of pediatric patients epidemiologically related to SARS-CoV-2 were reported in Europe and the USA presenting with fever, severe systemic hyperinflammation, and cardiovascular shock.[5–8] Fever, rash, hyperinflammation, gastrointestinal symptoms, myocardial dysfunction, shock, and serologic evidence for SARS-CoV-2 became common characteristics of the emerging disease.

Although the course of COVID-19 was milder in children than in adults, this pediatric inflammatory disease frequently resulted in severe illness with multiorgan failure and shock and the need for pediatric intensive care unit (PICU) admission. With the increase in cases, on May 14, 2020, the Centers for Disease Control and Prevention (CDC) issued a national health advisory to report on cases meeting the criteria for multisystem inflammatory syndrome in children (MIS-C).[9]

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Children with MIS often improve rapidly with intensive monitoring and supportive care.[10,11] Some, however, deteriorate rapidly, requiring cardiac or respiratory support, with poor prognosis related to involvement of the cardiovascular system accompanied by systemic inflammation, severe cardiac disease, shock, and disease of the coronary arteries.

Our aim in this study was to describe the demographic characteristics, presenting symptoms, clinical course, laboratory findings, and the therapies received in case of MIS-C. We also aimed to identify clinical and biological markers that predicting severe disease and mortality among children and adolescents meeting the CDC case definition of MIS-C.

METHODS

Study design

This was a retrospective multicenter study conducted on cases in 41 PICUs in Turkey. The patients included in the study had all been diagnosed as having MIS-C according to the CDC criteria and admitted to PICUs between March 2020 and March 2021. Demographic characteristics, clinical and laboratory data, immunomodulatory therapies, respiratory and cardiovascular support modalities (vasoactive drugs and/or extracorporeal membrane oxygenation [ECMO]), and extracorporeal therapies, such as renal replacement therapy and therapeutic plasma exchange (TPE), were all recorded. All laboratory examinations and treatment decisions were made by the attending physicians in each unit.

Case definition

The CDC case definition of MIS-C was used.[9] Cardiovascular involvement was defined as follows: need for vasopressors or vasoactive support to maintain blood pressure (BP) within normal limits for age, ejection fraction (EF) by echocardiographic of below 55%, dilated coronary arteries, pericarditis or pericardial effusion, and high troponin or N-Terminal pro-brain natriuretic peptide (NT-proBNP) levels or cardiac arrhythmia. Left ventricular EF (LVEF) measurement was based on the modified Simpson's method and categorized as either normal (≥55%), or mild (45–54%), moderate (30–44%), or severe impairment (<30%).[12] Patients were clinically diagnosed as being in shock when their BP was lower than the fifth percentile of the normal values for age, they needed for vasoactive medication to maintain normal BP, or they showed symptoms of hypoperfusion despite adequate fluid resuscitation.[12,13] Patients with clinical presentations of Kawasaki-like disease (KLD) were categorized as such according to the 2017 KD criteria of the American Heart Association (AHA).[13]

Elevation of creatinine levels more than twice the normal by age was the criterion for renal dysfunction; coagulation abnormality or thrombocytopenia (<100,000/mm^3) was regarded as hematological dysfunction; tachypnea, dyspnea, pneumonia, and acute respiratory distress syndrome (ARDS) or pleural effusion were regarded as respiratory disease. Illness severity was estimated using the Pediatric Risk of Mortality III (PRISM III) and Pediatric Logistic Organ Dysfunction 2 (PELOD-2) scores.[14,15] For the PRISM III score, various variables were recorded at 24 h of admission (heart rate, systolic BP, temperature, mental status, pupillary response, acidosis, pH, pCO2, total CO2, PaO2, glucose, potassium, creatinine, blood urea nitrogen [BUN], white blood cell [WBC] count, platelet count, and prothrombin and partial thromboplastin time [PT and PTT]). The Pediatric Logistic Organ Dysfunction (PELOD) score consists of ten variables used to represent five organ dysfunctions (neurological, cardiovascular, renal, respiratory, and hematologic).

Study approval

This study was approved by the Scientific Research Platform of the Turkish Republic Ministry of Health and ethically approved by Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation board (2021-02/16).

Statistical analyses

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah) program was used for statistical analyses. Descriptive statistical methods were used for demographic data (mean, standard deviation, median, first and third quartiles, frequency, percentage, and minimum and maximum). The normality of quantitative data distributions was tested using the Shapiro–Wilk test and graphics. Comparisons between groups of quantitative data were made using the independent samples *t* test if distributed normally or the Mann–Whitney *U*-test if skewed. Pearson's Chi-square and Fisher's exact test were used for comparisons of qualitative data. Diagnostic screening tests and ROC analysis were used to determine the cut-off point for leukocyte, ferritin, and lactate measurements according to mortality. p Values of <0.05 were accepted as significant.

RESULTS

Demographic and clinical characteristics

Between March 1, 2020 and March 31, 2021, 322 children met the criteria for confirmed MIS-C in 41 PICUs in Turkey and were included in the analyses; demographics and baseline clinical characteristics, clinical presentation, and comorbidities are presented in Table 1. The total number of patients admitted to the PICUs during this period was 17,423 (mortality rate 9%, $n = 1569$). The patient medians for age and weight were 119.4 ± 53.8 months and 38.9 ± 22.1 kg. Of the 322 patients, 185 (57%) were male, and 275 (85.4%) had no previous disease. The largest number of patients were admitted in December 2020 (39.1%, $n = 126$).

RT-PCR and antibody status by clinical subphenotype

A total of 249 (77.3%) children had microbiological or serological evidence of SARS-CoV-2 infection; 36 (11.1%) had a positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR), 230 (71.4%) were positive for SARS-CoV-2 immunoglobulin (Ig)-M or IgG, and 17 (5.2%) patients tested positive for both RT-PCR and antibodies. All patients without serological evidence had evidence of infection in the previous 4 weeks or a history of contact with a positive family member. The duration of PICU stay was longer in patients who were PCR-positive than in those with seropositivity. Respiratory disease was more common in PCR-positive patients, and cardiovascular disease was more common in seropositive patients.

Laboratory and echocardiographic findings

One hundred forty-three (44.4%) children had thrombocytopenia and lymphopenia was found in 255 (79.2%). Overall, the majority of cases had markedly elevated inflammatory markers: C-reactive protein (CRP) (97.8%), ferritin (83.5%), procalcitonin (68.6%), and erythrocyte sedimentation rate (ESR) (51.2%). Elevated levels of fibrinogen were found in 74.8% of patients, and hypoalbuminemia was identified in 215 patients (66.8%). The majority of patients had elevated levels of NT-proBNP (60.2%), and 66.1% had elevated troponin levels. The laboratory parameters are shown in Table 2.

During hospitalization, at least one echocardiogram was obtained for 300 (93.2%) patients, of whom 134 (41.6%) had decreased LVEF (<55%), and 84 (28%) had pericardial effusion. Of the patients with decreased LVEF, 36 (11%) had an EF of <30%, and 98 (30%) had an EF of between 30 and 55%. In total, 28 patients had cardiac arrhythmias and 2 had intracardiac thrombosis.

Among the 322 children with MIS-C, 32 (10%) had overlapping features with KD and were defined as having KLD. Shock was seen in 11 children. Twenty-two children (6.8%) with a diagnosis of KLD were found to have coronary artery abnormalities on echocardiography during PICU admission, including 6 with *z* scores >2.5. Giant coronary artery aneurysms (*z* score >10) were documented in one patient. All 32 patients with a KLD diagnosis received high-dose intravenous immunoglobulin (IVIG) (2 g/kg). Patients with KLD were younger than the patients without KLD (8.5 years [IQR 4–12] vs. 10.1 years (IQR 6.5–14), $p = 0.047$). Nevertheless, there were no significant differences between the two groups in terms of laboratory parameters, duration of stay, mechanical ventilation, or mortality.

Management and clinical outcomes

Treatments and outcomes are shown in Table 1. Seventy-five (23.3%) children were treated with TPE, and 19 (5.9%) received

Table 1. Demographic and clinical characteristics of patients.

Characteristic	*n* (%)
Sex	
Female	137 (43)
Male	185 (57)
Age, months	119.44 ± 53.8
PRISM	9 (4–15)
PELOD	10 (6–14)
VIS	15 (10–30)
Mean fever time (days)	4.5 (2–6)
SARS-CoV-2 antigen PCR positive	30 (9)
SARS-CoV-2 serology positive	240 (74.5)
SARS-CoV-2 antigen PCR and serology positive	13 (4)
Length of stay PICU, days	6 (3–9)
Clinical presenting features	
Fever	322 (100)
Shock	215 (66.8)
Tachypnea or dyspnea	196 (60.8)
Skin rash	182 (57)
Abdominal pain	176 (54.6)
Conjunctival changes	168 (52.1)
Nausea/vomiting	150 (46.6)
Comorbidities	47 (14.6)
Obesity	22 (6.8)
Congenital heart disease	6 (1.9)
Neuromuscular disease	6 (1.9)
Malignancy	8 (2.5)
Rheumatological disease	3 (0.9)
Asthma	2 (0.6)
The most commonly involved organ systems	
Cardiovascular	274 (85)
Hematological	267 (82.9)
Gastrointestinal	201 (62.4)
Mucocutaneous	190 (59)
Respiratory	163 (50.6)
Renal	68 (21.1)
Neurological	88 (27.3)
Therapy	
Mechanical ventilation	55 (17)
Non-invasive MV	68 (21.1)
HFNC	97 (30.1)
ECMO	11 (3.4)
TPE	75 (23.3)
CRRT	19 (5.9)
Vasopressor support	228 (70.8)
Milrinone	129 (40)
Epinephrine	117 (36.3)
Norepinephrine	102 (31.7)
Dopamine	27 (8.4)
IVIG	294 (91.3)
Systemic glucocorticoids	266 (82.6)
Low dose (2 mg/kg/day)	139 (43.2)
Medium dose (10 mg/kg/day)	22 (6.8)
High dose (30 mg/kg/day)	105 (32.6)
IVIG+ glucocorticoids	255 (79.2)
Interleukin-1Ra inhibitor	72 (22.4)
Interleukin-6 inhibitors	11 (3.4)
Anticoagulation (LMWH)	225 (69.9)
Aspirin	127 (39.4)

PRISM pediatric risk of mortality, *PELOD* pediatric logistic organ dysfunction, *VIS* vasoactive inotropic score, *PCR* polymerase chain reaction, *MV* mechanical ventilation, *HFNC* high flow nasal cannula, *ECMO* extracorporeal membrane oxygenation, *TPE* therapeutic plasma exchange, *CRRT* continuous renal replacement treatment, *IVIG* intravenous immunoglobulin, *LMWH* low molecular weight heparin.

Table 2. Admission and peak laboratory test results.

	Median (IQR)
WBC ($\times 10^3$/L)	10.9 (7.1–15.9)
Peak WBC ($\times 10^3$/L)	6.4 (4.4–9.1)
ALC ($\times 10^3$/L)	0.9 (0.6–1.6)
Minimum ALC ($\times 10^3$/L)	0.7 (0.4–0.9)
Platelets ($\times 10^9$/L)	160 (108.6–250)
D-dimer (μg/mL)	3.2 (1.4–5.9)
Lactate, mmol/L	2 (1.5–3)
Peak lactate, mmol/L	2.9 (2.01–4.4)
Serum creatinine, mg/dL	0.6 (0.4–0.8)
Sodium meq/L	133.3 (131–137)
Albumin, g/dL	3.1 (2.8–3.7)
AST, U/L	35.5 (24–58)
ALT (U/L)	27 (17–50)
Ferritin ng/mL	513.3 (282–974)
Peak ferritin ng/mL	673 (400–1325)
Troponin, ng/mL	0.1 (0.02–0.3)
CK-MB, ng/mL	3.3 (1.1–14)
NT-pro-BNP pg/mL	3077 (624–12802.5)
Peak NT-pro-BNP pg/mL	5000 (1124–16054)
CRP mg/dL	23.2 (11.9–99.2)
Peak CRP mg/dL	27.8 (16.6–156.5)
Procalcitonin ng/mL	4.2 (1.1–22.4)
Peak procalcitonin ng/mL	8.1 (2.3–33)
IL-6 pg/mL	70.5 (20.1–355)
Peak IL-6 pg/mL	107 (28.8–585)
ESR mm/h	45 (23–76)
Fibrinogen ng/mL	455 (258.2–622.5)
Peak fibrinogen ng/mL	500 (361.5–662)

WBC white blood cell count, *ALC* absolute lymphocyte count, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CK-MB* creatine kinase isoenzyme, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *CRP* C-reactive protein, *IL-6* interleukin 6, *ESR* erythrocyte sedimentation rate.

continuous renal replacement therapy (CRRT). Several parameters were significantly higher in the TPE group (Table 3).

The median length of PICU stay was 6 (3–9) days. Patients with longer duration of PICU stay (defined as >6 days) had more frequent respiratory, hematologic, or renal involvement and also

Table 3. Comparison between the TPE (−) and TPE (+) groups.

	TPE (−) ($n = 247$) Mean ± SD (median)	TPE (+) ($n = 75$) Mean ± SD (median)	
Age (months)	114.33 ± 52.32	136.27 ± 55.52	0.001*
PICU duration	5 (3–8)	7 (5–12)	0.002*
PRISM III score	9 (6–16)	15 (8–28)	<0.001*
PELOD score	10 (5–11)	15 (11–29)	0.002*
Number of organ system disease	4 (3–5)	4 (3–6)	[a]0.001*
VIS	15 (10–25)	20 (12–55)	0.001*
Presence of shock	156 (63.2%)	59 (78.7%)	[b]0.013*
Severe cardiac impairment EF <30%	7 (2.8%)	9 (12%)	[c]0.004*
Mechanical ventilation	24 (9.7%)	31 (41.3%)	[b]<0.001*
Immunomodulatory treatment—anakinra	42 (17%)	30 (40%)	[b]<0.001*
Immunomodulatory treatment—tocilizumab	4 (1.6%)	7 (9.3%)	[c]0.004*

TPE therapeutic plasma exchange, *PRISM* pediatric risk of mortality, *PELOD* pediatric logistic organ dysfunction, *VIS* vasoactive inotropic score, *EF* ejection fraction.
*$p < 0.05$.
[a]Mann–Whitney *U*-test; shown in the table as the median (Q1–Q3).
[b]Pearson chi-square test.
[c]Fisher's exact test.

had higher D-dimer, CK-MB, and procalcitonin levels. Logistic regression analysis showed that elevated D-dimer (odds ratio [OR] = 1.041, 95% confidence interval [CI]: [1.008–1.074]; $p = 0.015$) and CK-MB (OR = 2.264, 95% CI: [1.060–4.835]; $p = 0.035$) levels were significantly associated with longer duration of PICU stay.

Among the 16 (5%) patients who died, eight were male (50%), and the median age was 127.4 ± 61.1 months. Eight of these patients had diagnoses of underlying conditions (acute lymphocytic leukemia, malignancy, congenital heart diseases, cerebral palsy), and five received ECMO support. All of them received systemic glucocorticoids, 14 received IVIG, and 8 received immunomodulators.

The percentages of patients with neurological or respiratory symptoms were higher among non-survivors, and there was an increased incidence of severe cardiac impairment (EF < 30%) compared with survivors. The presence of renal involvement, need for mechanical ventilation, and shock were also significantly more common in non-survivors. The serum levels of D-dimer, ferritin, lactate, and CRP were significantly raised, and lymphopenia was more common in non-survivors than survivors. A comparison of laboratory parameters of survivors and non-survivors is presented in Table 4. Logistic regression analysis showed that the non-surviving group had higher leukocyte counts, lactate levels, ferritin levels, and a need for mechanical ventilation. The cut-off value was calculated for the factors associated with mortality (leukocyte, lactate, ferritin) (Table 5). ROC curve for leukocyte, lactate and ferritin have shown in Figs. 1 and 2.

DISCUSSION

Our study of pediatric patients with MIS-C in Turkey, describes a febrile hyperinflammatory syndrome currently seen worldwide that has gastrointestinal, dermatologic, mucocutaneous, hematological, and respiratory manifestations associated with cardiac dysfunction. Although multiple reports have been published internationally on MIS-C, there are a limited number of studies evaluating patients with severe disease admitted to the PICU.

Similar to other reports, most of the patients in our study were male (57%).[16–18] This higher frequency of males can be understood as an effect of the biological differences between the sexes of sensitivity to infections, adaptive immune response, immune regulation, inflammation, and tissue repair.[19]

Because the case definition is nonspecific and confirmatory laboratory testing does not exist, it may be difficult to distinguish MIS-C from other conditions with overlapping clinical manifestations such as severe acute COVID-19. In a study by Godfred et al.[20] in which the patients were classified into three groups according to clinical characteristics, in class 1 patients, cardiovascular system disease was prominent, and SARS-CoV-2 serology was positive in 98%, while class 2 patients had mainly respiratory system disease and the highest rate of SARS-CoV-2 positivity in PCR (84%). These class 2 patients also had a longer duration of ICU stay. Similarly, the rate of cardiovascular system findings in our study was higher in patients with positive SARS-CoV-2 serology, and respiratory system disease was more frequent in patients testing positive for SARS-CoV-2, and the latter had a longer duration of PICU stay.

The rates of patients diagnosed with MIS-C and being admitted to the ICU have been reported at between 68 and 80%,[10,17,21] and mortality rates are 1.7–2.6%.[7,17,18,20,21] In a study by Son et al.,[22] 385 out of 518 patients with MIS-C were admitted to the ICU, and 9 (2.3%) died (although there are studies reporting mortality rates as high as 27% and even 66%).[23,24] The mortality rate was 5% in our study. This relatively higher rate can be explained by the study population being comprised of patients admitted to the ICU, but it may also be the result of possible challenges in diagnosis and referral for a relatively new syndrome resulting in delays in treatment. Some patients were transferred from other cities, while others were transferred to the PICU only when they deteriorated clinically and displayed an emerging need for mechanical ventilation or ECMO, both of which would affect the prognosis negatively. Mortality increases with delayed admittance to the PICU and delayed referral to centers with ICUs.

Although there are numerous studies on MIS-C, factors associated with mortality rates are rarely commented on. Maheshwari et al. reported that non-survivors had more neurocognitive and respiratory symptoms and an increased incidence of myocarditis than survivors. Furthermore, the presence of acute kidney injury, need for ventilation, and shock was significantly more common in non-survivors.[23] Similarly, in our study, non-survivors had more neurologic and respiratory symptoms and an increased incidence of severe cardiac

Table 4. Comparison of the survivor and non-survivor groups.

	Survivor ($n = 306$) Median (Q1, Q3)	Non-survivor ($n = 16$) Median (Q1, Q3)	[a]*p*
Age	110.2 ± 43.4	127.4 ± 61.1	0.145
PRISM score	9 (4–15)	24 (17–33)	<0.001*
PELOD	10 (5–12)	30 (15–40)	<0.001*
Organ system involvement	4 (3–5)	6 (4.5–6)	<0.001*
VIS	15 (10–25)	105 (55–144)	<0.001*
Leukocyte (on admittance)	10.92 (6.86–15.51)	16.06 (9.49–27.05)	0.019*
Lymphocyte (on admittance)	2.83 (0.9–4.42)	0.9 (0.6–1.44)	0.001*
D-dimer (Ug/mL) (on admittance)	3.24 (1.38–4.53)	9 (1.54–16)	0.024*
Lactate (on admittance)	2 (1.4–2.96)	4.5 (2.5–13)	<0.001*
Lactate (peak)	2.8 (2–4.1)	12.7 (5.2–20)	<0.001*
Ferritin (on admittance)	503 (278.45–900.5)	2216 (1084–18,090)	<0.001*
Ferritin (peak)	659 (400–1211)	10,956 (2834–21,320)	<0.001*
Troponin (on admittance)	0.07 (0.02–0.27)	0.24 (0.04–0.47)	0.173
CK-MB (on admittance)	3.25 (1.12–12.93)	5.52 (0.96–21.51)	0.639
NT-proBNP (on admittance)	3077 (634–12,405)	2676 (256–14,000)	0.739
CRP (on admittance)	14.1 (2.18–20.4)	23.76 (12.3–105.39)	0.008*
CRP (peak)	20.25 (15.15–35.1)	28.4 (16.68–160.6)	0.196
PCT (on admittance)	4.85 (1.31–22.36)	0.74 (0.43–58.3)	0.247
PCT (peak)	8.22 (2.41–31.8)	3.77 (1.7–58.3)	0.796
IL-6 (on admittance)	70 (19–355)	285 (35.85–652.5)	0.220
Sedimentation (on admittance)	45 (23–76)	60 (26.5–65)	0.964
Fibrinogen (on admittance)	461 (273–630)	309.5 (94–391)	0.028*
	n (%)	*n* (%)	*p*
Cardiac disease	259 (84.6)	15 (93.7)	[b]0.483
Renal disease	59 (19.3)	11 (68.7)	[b]<0.001*
Respiratory disease	151 (49.3)	12 (75)	[c]0.045*
Hematological disease	251 (82)	16 (100)	[b]0.084
Neurological disease	79 (25.8)	9 (56.2)	[b]0.017*
Severe cardiac impairment EF < 30%	27 (8.2)	9 (56.2)	[b]0.005*
Mechanical ventilation	42 (13.7)	13 (81.2)	[b]<0.001*

PRISM pediatric risk of mortality, *PELOD* pediatric logistic organ dysfunction, *VIS* vasoactive inotropic score, *CK-MB* creatine kinase isoenzyme, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *CRP* C-reactive protein, *PCT* procalcitonin, *IL-6* interleukin 6, *EF* ejection fraction.
*$p < 0.05$.
[a]Mann–Whitney *U*-test.
[b]Fisher's exact test.
[c]Pearson chi-square test.

impairment compared with survivors. The presence of renal involvement and the need for mechanical ventilation were significantly more common in non-survivors.

In proinflammatory states, including MIS-C, inflammatory markers levels, such as CRP, ESR, procalcitonin, D-dimer, and ferritin, may be raised.[5,24–26] Patients with severe MIS-C also have higher levels of WBCs, absolute neutrophil count (ANC), and ferritin, as well as CRP and D-dimer, and lower levels of absolute lymphocyte count (ALC) and fibrinogen than patients with non-severe MIS-C.[26–28] In our study, serum levels of D-dimer, CRP, lactate, and ferritin were significantly raised in non-survivors as compared with survivors. Also, non-survivors had lower ALC and low fibrinogen levels. This indicates a more severe inflammatory response in non-survivors. One of the distinctive features of our study was the definition of factors that associated with mortality and duration of stay in PICU. According to our data, high levels of D-dimer and CK-MB are related to longer duration of PICU stay; high leukocyte count, ferritin and lactate levels, and mechanical ventilation are all related to mortality.

In other reports of patients with MIS-C, the rates of shock at presentation were 50–84%,[7,29–31] inotropic support 25–77%,[7,16,28,30,32] and mechanical ventilation 4–43%[7,28,32] in patients with MIS-C. Notable findings were the high prevalence of cardiac dysfunction and shock, in contrast with most cases of acute COVID-19 among children in the PICU. Our results are consistent with those of other studies to date, which have been limited to case reports, short reports, and case series.[10,17,25,27,33]

Both NT-proBNP and cardiac troponin levels are extremely high in patients with MIS-C. In our study, the majority of patients had elevated levels of NT-proBNP and troponin. Whittaker et al. found that NT-proBNP levels were elevated in 83% of patients, and troponins were increased in 68% of patients.[7] We have reported 85% of all patients as evidencing of cardiac involvement based on biochemical, electrocardiogram (ECG), and

Table 5. Mortality screening tests and ROC curve results.

	Mortality scan					ROC curve		*p*
	Cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% confidence interval	
Leukocyte on admittance	≥17.6	50.0	82.62	13.11	96.92	0.746	0.619–0.874	0.002**
Lactate on admittance	≥2.34	86.67	61.73	10.92	98.84	0.823	0.731–0.945	0.001**
Lactate max	≥4,6	100.0	80.59	22.05	100.0	0.936	0.894–0.978	0.001**
Ferritin on admittance	≥1082	80.0	79.79	16.90	98.73	0.803	0.660–0.946	0.001**
Ferritin max	≥2790	78.57	92.34	35.48	98.77	0.795	0.604–0.986	0.001**

**$p < 0.01$.

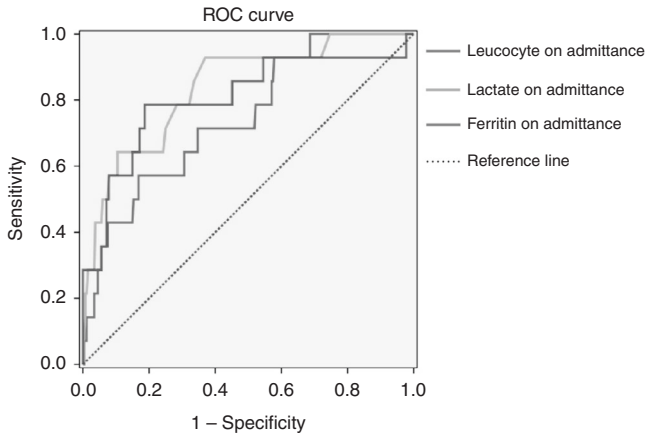

Fig. 1 Leukocyte, lactate and ferritine levels on admission. ROC curves of leukocyte, lactate and ferritin on admission.

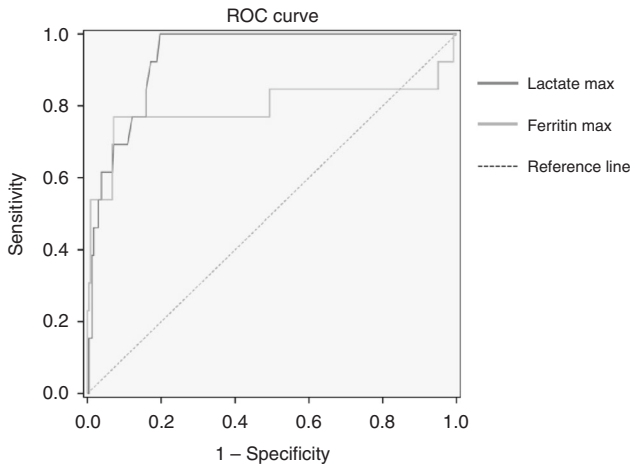

Fig. 2 Max lactate and ferritin levels. ROC curves of max lactate and ferritin levels.

echocardiogram data. This is a significantly high rate when compared with a study from Spain, which reported cardiologic complications in 61% and myocardial dysfunction in 48% of MIS-C patients.[31] A study by Garcia-Salido et al.[30] described cardiac dysfunction in 53.3% of patients, an Italian study reported cardiac involvement with ECG abnormalities in 60%,[6] and Torres et al.[34] found abnormal ECG in 31%. All MIS-C patients should be evaluated through ECG in a sequential protocol because the rate of cardiac involvement is high with myocardial dysfunction and changes in coronary arteries and the long-term prognosis is not definitive.

TPE is a well-known immunomodulatory technique in pediatrics that removes high-molecular-weight substances, including cytokines and autoantibodies. In adult patients with severe COVID-19 infection, good results with TPE have been reported attributed to the control of the hyperinflammatory state, removing cytokines and chemical mediators, decreasing the viral load, and targeting the effects of endothelial dysfunction and coagulopathy with TPE.[35] Although the data are insufficient, there are case series reporting the benefit of TPE as salvage therapy in situations where LV dysfunction, a high vasoactive inotropic score or PELOD or PRISM scores with high levels of laboratory markers (ferritin, CRP, and NT-proBNP) are present.[11] Our study data show that mortality rate was not associated with TPE in high-risk patients (those with high lactate and ferritin levels and high VIS and PRISM scores, presence of shock, LV dysfunction, mechanical ventilation).

The strength of our study lies in its presentation of detailed clinical and laboratory data from multiple centers about MIS-C in a specific patient population (PICU patients). The main limitations are the retrospective design and that the tests and treatments were not made according to a single common protocol but were determined independently in the different centers by the attending physician. Extrapolations of our findings to the current pandemic with viral variants and rising vaccination rates may be challenging because our study ended in March 2021. Lastly, we do not have data following discharge to capture late mortality or delayed complications.

In conclusion, we have defined laboratory and clinical factors that can affect severe disease, PICU stay, and mortality in these 322 patients admitted to the PICUs in Turkey for the new inflammatory phenomenon known as MIS-C. Although long-term results are not known, most of the patients had cardiac involvement. Most (93.2%) of the patients were evaluated using ECG, but echocardiography should be ordered for all the children presenting with MIS-C because the cardiac involvement rate is high. According to our data, high levels of D-dimer and CK-MB are related to longer stay; high leukocyte count and ferritin and lactate levels, and mechanical ventilation are related to mortality. Although there is inadequate evidence to support any specific treatment, most patients received immunomodulatory treatment; some were treated with TPE but we were unable to show any positive effect of this therapy on mortality could be defined. This lack of evidence on useful treatment modalities are useful underlines the need for further clinical studies.

DATA AVAILABILITY

The datasets generated during and/or analyzed in the current study are not publicly available as the patients were in intensive care, but they available from the corresponding author upon reasonable request.

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G.S., A.I., A.C., I.B., and A.A. conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript. N.A., S.K., F.A., T.K., G.A., O.S., F.V., P.Y.O., M.D., A.Z.B., S.O., G.A., M.K., S.B., U.A., A.B.A., M.H., A.F.Y., T.D., N.Z., A.O., H.S.K., F.İ.G., L.T., D.Y., N.Y., U.Y., M.A., M.A.K., M.C., A.D., F.B., F.S., M.O.,

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Scientific Research Platform of the Turkish Republic Ministry of Health and was ethically approved by Acıbadem Mehmet Ali Aydınlar University Medical Research Evaluation board (2021-02/16). Since it was a retrospective study, ethics committee approval was obtained while patient consent was not required.

ADDITIONAL INFORMATION

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