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ORIGINAL ARTICLE

Hematological Parameters and Inflammatory Markers in Children with Multisystem Inflammatory Syndrome

Multisistemik İnflmatuar Sendrom (MIS-C) Nedeniyle Takip Edilen Çocuk Hastaların Hematolojik ve İnflamatuar Parametrelerin Değerlendirilmesi

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ABSTRACT

Objective: Multisystem inflammatory syndrome in children (MIS-C), is a newly recognised life-threatening complication of coronavirus disease 2019 (COVID-19). Early determination of clinical severity of the disease is important for early decision of treatment regimens. The aim of this study is to investigate the severity classification value of a number of hematological parameters, inflammatory markers and biochemical tests in patients with MIS-C during the acute stage and after anti-inflammatory treatment.
Material and Methods: In this retrospective case-controlled study, 64 children with MIS-C and 95 healthy age and gender matched children were included. Patients were divided into three clinical severity groups; mild, moderate, and severe.
Results: Mean platelet volume (MPV), MPV to lymphocyte ratio (MPVLR), d-dimer, ferritin, interleukin 6 (IL-6) levels were significantly higher, while albumin levels were lower in the severe MIS-C group compared to all the other groups on admission. Neutrophil-to-lymphocyte ratio (NLR) and derived (d) NLR (d-NLR) levels were significantly higher in the moderate group compared to the mild group. In the pre-treatm ent period of MIS-C patients had higher MPV, platelet distribution width (PDW) values while they had lower white blood cell, lymphocyte, monocyte, haemoglobin, mean corpuscular volume (MCV), red cell distribution width (RDW), plateletcrit and platelet values compared to the post-treatment group.
Lymphocyte, platelets, and haemoglobin levels were significantly higher in the control group compared to the pre-treatment group. Acute phase reactants, NLR, NMR, PLR, d-NLR, MPVLR and systemic inflammatory index were significantly higher in all MIS-C patients on admission compared to the control group.
Conclusion: Specific routine laboratory test results may be useful in determining disease severity of MIS-C, possibly predicting the prognosis and early initiation of the appropriate treatment.

Keywords: disease severity; hematological parameters; inflammatory markers; Multisystem inflammatory syndrome in children

ÖZ

Amaç: Çocuklarda multisistem inflamatuar sendrom (MIS-C), coronavirus disease 2019 (COVID-19)'un yeni tanımlanan yaşamı tehdit eden bir komplikasyonudur. Hastalığın klinik şiddetinin erken tespiti, tedavi rejimlerine erken karar verilmesinde önemlidir. Bu çalışmanın amacı, MIS-C'li hastalarda hematolojik parametrelerin, inflamatuar belirteçlerin ve biyokimyasal testlerin hastalığın cidiyetine göre, akut dönemde ve anti-inflamatuar tedavi sonrasındaki değerlerini araştırmaktır.
Gereç ve Yöntem: Retrospektif vaka kontrollü çalışmaya MIS-C tanısı alan 64 çocuk ve yaş ve cinsiyet uyumlu 95 sağlıklı çocuk dahil edildi. Hastalar klinik bulgulara göre; hafif, orta ve şiddetli olarak üç gruba ayrıldı.
Bulgular: Ciddi MIS-C kliniğinde olan hastalarda hastaneye başvuruda ortalama trombosit hacmi (MPV), MPV/lenfosit oranı (MPVLR), d-dimer, ferritin, interlökin 6 (IL-6) seviyeleri anlamlı olarak daha yüksekken, albumin düzeyleri daha düşüktü. Klinik şiddeti orta olan hastalarda hafif olan hastalara göre; nötrofil-lenfosit oranı (NLR) ve derived NLR (d-NLR) seviyeleri anlamlı olarak daha yüksek saptandı. MIS-C hastalarında tedavi öncesinde tedavi sonrasına göre MPV, trombosit dağılım genişliği (PDW) değerleri daha yüksekken; beyaz küre sayısı, lenfosit, monosit, hemoglobin, ortalama korpüsküler hacim (MCV), kırmızı hücre dağılım genişliği (RDW), plateletcrit ve trombosit değerleri daha düşüktü. Kontrol grubunda, tedavi öncesi gruba göre lenfosit, trombosit ve hemoglobin düzeyleri anlamlı derecede yüksekti. Akut faz reaktanları, NLR, nötrofil monosit oranı, platelet lenfosit oranı, d-NLR, MPVLR ve sistemik inflamatuar indeks, kontrol grubuna kıyasla tüm MIS-C hastalarında başvuru sırasında anlamlı derecede yüksekti.
Sonuç: Spesifik rutin laboratuvar test sonuçları, MIS-C'nin hastalık şiddetini belirlemede, prognozu öngörmede ve uygun tedavinin erken başlatılmasında yararlı olabilir.

Anahtar Kelimeler: hastalık şiddeti; hematolojik parametreler; inflamatuar belirteçler; çocuklarda multisistem inflamatuar sendrom

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was officially declared a pandemic in March 2020. In the early stages of the pandemic, it seemed that affected children had a milder disease course than adults (1). As time progressed, it became apparent that SARS-CoV-2 can cause a range of symptoms and clinical manifestations. At the end of April 2020, the post-COVID infectious multisystem inflammatory state in children was reported by several centres worldwide.

It was observed that some children showed clinical and laboratory findings similar to other paediatric inflammatory diseases such as Kawasaki disease, toxic shock syndrome and macrophage activating syndrome. This new life threatening COVID-19 syndrome was termed as multisystem inflammatory syndrome in children (MIS-C) by the Centre for Disease Control and Prevention, United States of America (USA) and by the World Health Organisation (2).

It is suggested that the pathogenesis of MIS-C may involve an autoinflammatory and/or autoimmune hyper inflammatory processes initially triggered by SARS-CoV-2, rather than a direct viral effect (3). In the early stage of infection, the virus triggers macrophage activation followed by stimulation of T-helper cells, resulting in cytokine release, B-cell and plasma cell activation. Massive proinflammatory cytokine release stimulates macrophages, neutrophils, and monocytes along with B-cell and plasma cell activation. Hyperimmune response causes vascular leakage of fluids, activating the coagulation and complement cascades (4,5). Studies suggest that severe MIS-C cases have persistent immunoglobulin G antibodies with enhanced ability to activate monocyte, persistent cytopenias (particularly T cell lymphopenia) and greater activation of CD8+ T cells that differ from findings in acute COVID-19 infection (6,7).

The clinical presentation of MIS-C includes fever, severe illness, and the involvement of two or more organ systems (mucocutaneous reminiscent of Kawasaki disease, gastrointestinal symptoms, cardiac involvement, hematological features, or other organ dysfunctions) in combination with laboratory evidence of inflammation and laboratory or epidemiological evidence of SARS-CoV-2 infection (4).

The majority of patients with MIS-C appear to have a hyperinflammatory state that manifests as neutrophilic leucocytosis, lymphopenia, thrombocytopenia, elevated levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, d-dimer, serum ferritin, lactate dehydrogenase (LDH), interleukin 6 (IL-6); not associated with bacterial infection. Other common findings include hyponatremia, or hypoalbuminemia (2,8).

Similar to other severe inflammatory conditions, MIS-C is expected to exhibit suggestive, hematological, biochemical abnormalities and changes in the levels of inflammatory markers. The demonstration of such hematological and biochemical changes may carry considerable diagnostic and prognostic significance. Peripheral white blood cell (WBC) count, neutrophil (NEU), lymphocyte (LYM), platelet counts (PLT), NEU to LYM ratio (NLR), NEU to monocyte ratio (NMR), derivate neutrophil lymphocyte ratio (d-NLR), LYM to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and, LYM counts to CRP (L/CRP) ratio, mean corpuscular volume (MPV) ratio to LYM (MPVL), systemic inflammatory index (SII) are indicators of the systematic inflammatory response (9). Furthermore, hematological parameters include red cell distribution width (RDW), plateletcrit (PCT), platelet distribution width (PDW) and MPV values can be affected by inflammatory conditions. Abnormalities in biochemical parameters may occur due to organ damage.

Recommended first line treatment for MIS-C is the use of intravenous immunoglobulins (IVIG) as an immunomodulatory agent or high dose glucocorticoids or both. Biologic immunomodulators should be considered in severe cases refractory to IVIG and steroids (10,11).

As the patient's clinical condition may suddenly deteriorate even during the course of active treatment, patients should be closely monitored during the treatment process. Therefore, clinicians need some parameters to predict disease severity in order to optimise management. We aimed to determine the severity of the disease at the time of diagnosis by routine laboratory markers and thus to tailor the most appropriate treatment.

Methods

In this retrospective study, 64 children with MIS-C hospitalized at the Department of Paediatric Infectious Diseases, Selcuk University, Faculty of Medicine, Konya, Turkiye, between 1 September 2020–1 June 2021, were included. The study protocols were approved by the hospital's ethics committee (approval number: 2021/366).

Patients were divided into three groups: mild MIS-C patient group (MiPG), with no inotropic support or respiratory support requirements and minimal organ injury; moderate MIS-C patient group (MoPG), with mild or isolated organ injury; and severe MIS-C patient group (SePG), with moderate or severe organ injury, including moderate to severe ventricular dysfunction (12). We categorized the ventricular dysfunction in patient as, mild ventricular dysfunction (EF:41-50%), and moderate severe ventricular dysfunction (EF:<40%). All patients were treated by administrating IVIG (2 g/kg/dose), and methylprednisolone. The dose of methylprednisolone was adjusted according to the clinical severity of the disease. The patients had no previous history of COVID-19 vaccination.

In mild cases (MiPG), methylprednisolone was given in a dose of 2 mg/kg/day for 5 days, then gradually tapered over a period of 2–3 weeks. In moderate cases (MoPG), methylprednisolone was given as a single loading dose of 10 mg/kg, then continued in a dose of 2 mg/kg/day for 7 days followed by gradual dose tapering over a period of 4–6 weeks. Severe cases (SePG) received methylprednisolone 20–30 mg/kg/day (max. 1 g/day) for 1–3 days, then the dose was reduced to 2 mg/kg/day for 14 days followed by gradual dose tapering over a period of 6–8 weeks. Any refractory to standard treatment, requiring further intervention with biologic agents were excluded from this study.

The demographic and clinical characteristics were compared between the three patient groups.

The hematological and the biochemical laboratory markers were also compared between the three patient groups during the acute stage of the disease and after treatment together with similar comparison with the 95 healthy age-matched children included as a control group (CG). Post-treatment laboratory markers belong to three days after steroid discontinuation.

The data on demographic characteristics and results of the laboratory tests were obtained from patient records.

The complete blood count (CBC), WBC, NEU, LYM, monocytes, eosinophil, haemoglobin (Hb), mean corpuscular volume (MCV), RDW, PLT, PDW, MPV, PCT were analysed on a Beckman Coulter DXI 800 automated autoanalyzer (Beckman, CA, USA).

Serological biomarkers were derived from a combination of two or more of the above indicators, including NLR, NMR, LMR, PLR, d-NLR, L/CRP, NMR, PVLR, SII was calculated. d-NLR was calculated by neutrophil count divided by the result of WBC count minus neutrophil count. The SII was calculated as thrombocyte count x neutrophil count/lymphocyte count.

Laboratory data on admission and after treatment were collected, including routine biochemical tests (urea, creatinine, albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], LDH, acute phase reactants [CRP, erythrocyte sedimentation (ESR), IL-6, procalcitonin, ferritin, fibrinogen], d-dimer, troponin, pro-brain-type natriuretic peptide (pro-BNP), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). The biochemical parameters analyses were performed on a Beckman Coulter 5800 automated autoanalyzer (Beckman, CA, USA).

Statistical analysis

Categorical variables were tabulated as number and percentage. Shapiro-Wilk test and Kolmogorov-Smirnov test were applied to check the distribution of parameters. Since all parameters were not normally distributed, these were presented as median with interquartile range (IQR). Mann–Whitney U test was used to compare groups, and the associations between parameters were assessed using Spearman's correlation test. The chi-square test was used to compare categorical variables between groups. Paired samples t-test or Wilcoxon signed rank test was used to compare pre- and post-treatment values of the study groups. The Kruskal–Wallis's analysis of variance test was used to compare groups, and the Bonferroni-corrected Mann–Whitney U-test was used as a more conservative measure of significance for multiple comparisons. Results were considered significant if $p<0.05$ or, in case of k comparisons, when $p<0.05/k$. Statistical analysis was performed using a computer software package (SPSS for Windows, version 21.0).

Results

1.Characteristic of demographic features, clinical findings, and laboratory tests result in MIS-C patients according to clinical severity

The demographic, clinical features, hematological parameters, and inflammatory markers on hospital admission were compared between MIS-C groups. The percentage of MIS-C patients in MiPG, MoPG, and SePG were 34.4% (n=22), 32.8% (n=21), 32.8% (n=21), respectively.

The median age of the 64 MIS-C patients was 82 months (range; 5-213 month). The sample included 31 females (48.5%) and 33 males (51.5%). The median age of the 95 healthy children was 110 months (range; 3-213 month). The sample included 52 females (54.8%) and 43 males (45. 2%).There were no significant differences in the median ages (p=0.138) and gender distribution (p=0.435) between MIS-C patients and the CG. The median age of the SePG was 133 months (IQR; 128 months). This was statistically significantly higher than all the other groups (p=0.04).

The most common presenting clinical manifestations of MIS-C patients were fever (n=64;100%), mucocutaneous symptoms (n=44; 68.7%), myocarditis (n=29; 47.5%), gastrointestinal symptoms (n=27; 42.1%), and respiratory symptoms (n=7, 10.9%). Rarely features of aseptic meningitis (n=3; 4.6%), and renal insufficiency (n=1; 1%) were detected. There was no statistically significant difference in the frequency of mucocutaneous, gastrointestinal, renal and neurological involvement between the three patient groups. Myocarditis and hypertransaminasemia was more commonly observed in the SePG. Fever duration (1-8 days) before hospital admission and the length of hospitalization (3-32 day) were longer in the SePG compared to the other groups.

Examination of hematological parameters on admission to the hospital were evaluated. There were no significant differences of WBC, NEU, LYM, eosinophil, Hb, MCV, PCT, and PDW values between all the patient groups. The SePG had the lowest monocyte count. RDW was significantly higher in the MoPG compared to the MiPG. Although MPV levels were significantly higher in the SePG, PLT was significantly lower in the SePG compared to the MoPG. There was no significant difference in levels of ESR, CRP, procalcitonin, fibrinogen, LDH, troponin, pro-BNP), coagulation values, liver, and renal function test between the three patient groups. The SePG showed the highest levels of d-dimer, ferritin, IL-6 and lower albumin values.

Inflammatory markers, such as NLR, NMR, LMR, PLR, d-NLR, L/CRP, MPVLR, and SII in the patient groups were assessed. There was no statistically significant

difference between the three patient groups in terms of LMR, L/CRP and SII variable. The levels of NLR and d-NLR were significantly higher in the MoPG compared to the MiPG. Although SePG showed significantly lower NMR values, PLR value was lower in MiPG (p=0.014). MPVLR levels were statistically significantly higher in the SePG than other groups. Demographical features, clinical findings and laboratory results according to severity of patient with MIS-C are summarized in table 1.

2.Comparison of hematological parameters, inflammatory markers, and biochemical tests of control group subjects with MIS-C patients before and after treatment

Hematological parameters were compared between CG subjects, pre-treatment (PrePG) and post-treatment (PostPG) patient groups. All patients' pre-treatment and post-treatment laboratory values were recorded on hospital admission and at the end of the steroid treatment (4-8 weeks).

WBC count was higher in both pre- and post-treatment patient groups compared to CG. Although neutrophil counts were lower in the CG, there was no statistically significant difference with the PrePG and the PostPG. Lymphocyte count and haemoglobin levels were lower in the PrePG compared to the CG and the PostPG. Monocyte count were higher in the PostPG compared to the CG and the PrePG. MVC was higher in the PostPG compared to the PrePG. The PostPG had higher RDW levels compared to the PrePG while the CG had the lowest RDW levels.

While the highest PLT and PCT levels were observed in the PostPG, the lowest values were observed in the PDW values were higher in the PrePG compared to the CG and the PostPG. While the highest MPV levels were observed in the PrePG, CG had higher values than PostPG. Figure 1 shows a comparison of the hematological parameters between the CG and the MIS-C patient groups.

Acute phase reactants (ESR, CRP, ferritin, fibrinogen), PCT, d-dimer, LDH, troponin, pro-BNP, AST, creatinine levels and coagulation parameters were statistically significantly higher in the three MIS-C patient groups on hospital admission compared with the post-treatment period. On the other hand, urea and albumin values were higher in the post-treatment period.

The highest NLR, d-NLR, and SII values were observed in the PrePG, although these values were higher in the PostPG compared to the CG. NMR and PLR ratio were higher in the PrePG when compared to the PostPG and CG. LMR was higher in CG than all the patient groups, while L/CRP ratio was higher in PostPG than the PrePG..

The comparison of the hematological parameters, inflammatory markers (NLR, NMR, LMR, PLR, d-NLR, L/CRP, MPVLR, and SII) and biochemical tests between the three patient groups are shown in table 2. Inflammatory markers are compared between the CG and the MIS-C patients in figure 2.

3.Correlation between mean platelet volume and other laboratory parameters with MIS-C

We determined the correlation between the MPV and hematological and inflammatory markers using Spearman's rank correlation coefficient. A significant positive correlation was observed between MPV level and PDW, MPVLR, procalcitonin, d-dimer, ferritin, IL-6, troponin, ALT, urea, creatinine whereas a significant negative correlation was detected between platelet, PCT, L/CRP and albumin levels. Correlation between MPV and inflammatory markers and biochemical tests is shown in table 3.

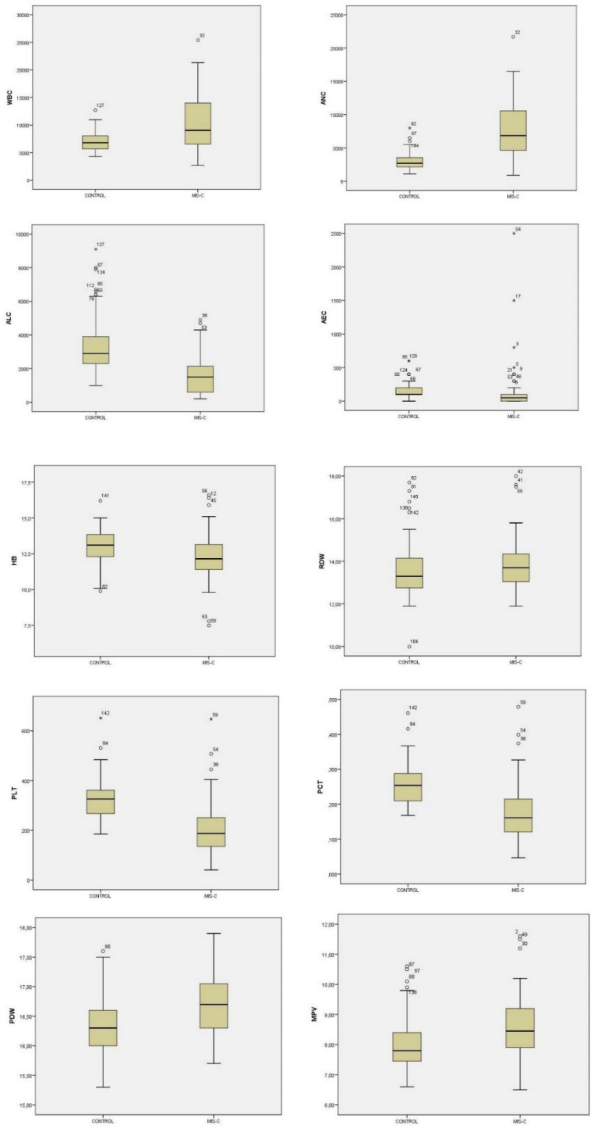

Fig. 1:

Table 1. Comparison of demographic and laboratory characteristics according to severity of patients with MIS-C

Characteristics	*Clinical severity*			*p*-value				
				Chi-square test	Kruskal-Wallis test	Mann-Whitney U test		
	Mild	Moderate	Severe			Mild-Moderate	Mild-Severe	Moderate-Severe
Number of patients	22	21	21					
Age (month)	74 (94)	82 (72)	133 (128)		**0.040**	0.874	**0.029**	**0.028**
Male / Female	12/10	10/11	11/10	0.898				
Fever duration (day)	5 (3)	5 (4)	6 (2)		**0.023**	0.319	**0.005**	0.118
Mucocutaneous involvement	16	12	16	0.364				
Gastrointestinal involvement	9	10	8	0.813				
Myocarditis	0	11	18	**<0.0001**				
Lung involvement	1	1	5	0.070				
Renal insufficiency	0	0	1	0.168				
Neurological involvement	0	2	1	0.336				
Hypertransaminemia	1	0	5	**0.019**				
Inotropic support	0	2	12	**<0.0001**				
Hospital stay (day)	5 (2)	7 (4)	11 (3)		**<0.0001**	0.126	**<0.0001**	**<0.0001**
White blood cell (K/uL)	8900 (7425)	9500 (8650)	9400 (7150)		0.980			
Neutrophil (K/uL)	6700 (5500)	6700 (7450)	7400 (6950)		0.874			
Lymphocyte (K/uL)	1800 (1200)	1400 (1150)	600 (1600)		0.027			
Monocyte (K/uL)	550 (425)	800 (700)	200 (150)		**0.002**	0.386	**0.003**	**0.003**
Eosinophil (K/uL)	0 (100)	0 (150)	100 (150)		0.548			
Hemoglobin (g/dL)	11.85 (2.5)	12.2 (1.5)	12.3 (1.7)		0.906			
MCV (fl)	81 (5.2)	79.6 (4.8)	84.5 (8.3)		0.044			
RDW (%)	13.9 (1.23)	14.1 (1.35)	13 (1.55)		**0.016**	0.415	**0.035**	**0.007**
Platelet (K/uL)	190.5 (96)	218 (212)	158 (82)		**0.010**	0.065	0.109	**0.005**
PCT (%)	0.160 (0.082)	0.194(0.151)	0.1470(0.07)		0.050			
PDW (f/L)	16.7 (0.75)	16.5 (0.75)	16.8 (0.85)		0.285			
MPV (f/L)	8.4 (1.4)	8 (1.3)	9.2 (1.45)		**0.003**	0.258	**0.016**	**0.001**
ESR (mm/h)	30 (28.5)	38 (43)	42 (35.5)		0.684			
CRP (mg/L)	155 (150.3)	134 (173.3)	188 (216.5)		0.605			
Procalcitonin (ug/L)	1.61 (7.16)	1.58 (7.66)	4 (20.83)		0.177			
IL-6 (pg/mL)	65 (100.3)	44.49(59.67)	164.9(617.9)		**0.008**	0.263	**0.025**	**0.004**
Ferritin (ng/ mL)	110 (225)	126.5(288.9)	522(674.8)		**0.001**	0.855	**0.001**	**0.002**
D-dimer (ng/mL)	1402 (2109.3)	1109 (1871)	3262 (3172)		**0.007**	0.395	**0.012**	**0.005**
Fibrinogen (mg/dL)	426.5 (636.3)	535.5 (324)	565 (367)		0.512			
Troponin (ng/L)	4.8 (7.1)	3.4 (8.7)	25 (80.4)		0.001			
Pro-BNP (pg/mL)	1444.5(2442)	902.5(1534)	5722 (8478)		0.169			
LDH (U/L)	311.5 (73.5)	312 (109.3)	360 (104.5)		0.164			
AST (U/L)	31.5 (22)	35 (26)	31 (57)		0.578			
ALT (U/L)	17.5 (16)	24 (30)	34 (52)		0.073			
Urea (mg/dL)	20 (8)	20 (13)	25 (25)		0.090			
Creatinine (mg/ dL)	0.35 (0.19)	0.43 (0.22)	0.51 (0.42)		0.243			
Albumin (g/dL)	3.65 (1.1)	3.7 (1.1)	2.90 (0.6)		**0.001**	0.903	**0.001**	**0.001**
INR	1.14 (0.27)	1.15 (0.19)	1.20 (0.25)		0.446			
aPTT	28.3 (5.8)	29.30 (5.75)	29.4 (3.90)		0.971			
NLR	3.527 (5.355)	4.0 (5.2565)	1.539 (2.2746)		**0.014**	0.356	**0.009**	**0.024**
NMR	11.30 (12.312)	10.400 (15.6319)	6.3642 (4.8000)		**0.004**	0.752	**0.004**	**0.005**
LMR	3.1428 (4.6155)	2.4000 (2.0411)	3.8730 (3.0400)		0.422			
PLR	0.1053 (0.0816)	0.1925 (0.1068)	0.1085 (0.0802)		**0.014**	**0.004**	**0.031**	0.678
d-NLR	2.5897 (2.3963)	3.0769 (2.4587)	1.2055 (1.2623)		**0.006**	0.610	**0.004**	**0.009**
L/CRP	10.1829 (27.4326)	10.6060 (34.3661)	2127.7 (1621.3)		0.063			
MPVLR	0.0046 (0.0024)	0.0054 (0.0112)	0.0056 (0.0048)		**0.009**	0.285	**0.005**	**0.023**
SII	752.5 (780.6)	1084.9 (1423.6)	1118.18 (1521.80)		0.083			

Abbreviations: ALT, Alanine aminotransferase; **AST**, Aspartat aminotransferase; a**PTT,** activated partial thromboplastin time; **CRP**, C-reactive protein; **d-NLR**, derivated Neutrophil to lymphocyte ratio; **ESR**, Erythrocyte sedimentation rate; **IL-6,** Interleukin 6**; INR;** International normalized ratio; **L/CRP**, Lymphocyte to C-reactive protein ratio; **LDH,** Lactate dehydrogenase; **LMR**, Lymphocyte to monocyte ratio; **MCV,** Mean corpuscular volume; **MPV**, Mean platelet volume; **MPVLR**, Mean platelet volume to lymphocyte ratio; **NLR**, Neutrophil to lymphocyte ratio; **NMR**, Neutrophil to monocyte ratio; **PCT,** Plateletcrit; **PDW,** Platelet distribution width; **PLR**, Platelet lymphocyte ratio; **Pro-BNP**, pro-brain-type natriuretic peptide; **RDW**, Red cell distribution width; **SII,** Systemic inflammatory index

Results were compared using the Kruskal–Wallis test followed by the Bonferroni-corrected Mann–Whitney U test. Significance was determined by $p<0.05$ for the Kruskal–Wallis test and $p<0.016$ ($p = 0.05/3$) for the Bonferroni correction.

Table 2. Demographic and laboratory characteristics of patients with MIS-C pre-treatment and post-treatment and controls

				p-value		
Characteristics	**Healthy controls**	**Patients with MIS-C**		**Patients with MIS-C vs. Healthy controls**		**Patients with MIS-C**
		Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**	**Pre and Post-treatment**
Number of patients	95	64				
Age (month)	110 (105)	82 (94)		0.138		
Male / Female	43/52	33/31		0.435		
Fever duration (day)	-	5 (3)				
Hospital stay (day)	-	7 (6)				
White blood cell (K/uL)	6800 (2400)	9050 (7575)	11050 (6200)	**<0.0001**	**<0.0001**	**0.042**
Neutrophil (K/uL)	2700 (1500)	6850 (6075)	6250 (5725)	**<0.0001**	**<0.0001**	0.654
Lymphocyte (K/uL)	2900 (1700)	1500 (1575)	3300 (1600)	**<0.0001**	0.121	**<0.0001**
Monocyte (K/uL)	500 (200)	400 (600)	900 (700)	0.359	**<0.0001**	**<0.0001**
Eosinophil (K/uL)	100 (100)	50 (100)	100 (100)	**<0.0001**	**<0.0001**	0.744
Hemoglobin (g/dl)	13.1 (1.6)	12.15 (1.8)	12.85 (2)	**<0.0001**	0.355	**0.004**
MCV (fl)	82.2 (6.3)	81 (6.1)	83.6 (7.7)	0.232	0.025	**<0.0001**
RDW (%)	13.3 (1.5)	13.7 (1.35)	15.4 (2.9)	**0.033**	**<0.0001**	**<0.0001**
Platelet (K/uL))	326 (95)	187.5 (122)	388.5 (227)	**<0.0001**	**<0.0001**	**<0.0001**
PCT (%)	0.254 (0.079)	0.161 (0.095)	0.2795 (0.153)	**<0.0001**	**0.010**	**<0.0001**
PDW (f/L)	16.3 (0.60)	16.7 (0.78)	16.2 (0.6)	**<0.0001**	0.972	**<0.0001**
MPV (f/L)	7.8 (1)	8.45 (1.3)	7.35 (1.1)	**<0.0001**	**<0.0001**	**<0.0001**
ESR (mm/h)	-	36 (33.3)	10 (15.8)	-	-	**<0.0001**
CRP (mg/L)	-	155.5 (149.8)	1.54 (1.34)	-	-	**<0.0001**
Procalcitonin (ug/L)	-	2.1 (8.21)	0.0950 (0.15)	-	-	**<0.0001**
D-dimer (ng/mL)	-	1682.5 (2540)	271 (309)	-	-	**<0.0001**
Ferritin (ng/ mL)	-	248 (519.2)	137 (160.8)	-	-	**0.001**
Fibrinogen (mg/dL)	-	551 (324)	280.5 (73)	-	-	**0.002**
IL-6 (pg/mL)	-	78.85 (128.24)	-	-	-	-
LDH (U/L)	-	319 (100)	230.5 (69)	-	-	**<0.0001**
Troponin (ng/L)	-	5.4 (21.6)	2.30 (1.7)	-	-	**<0.0001**
Pro-BNP (pg/mL)	-	1495 (4825.5)	86 (60.5)	-	-	**<0.0001**
AST (U/L)	-	32.5 (22)	26 (9)	-	-	**<0.0001**
ALT (U/L)	-	25.5 (33)	29.5 (28)	-	-	0.703
Urea (mg/dL)	-	21 (11)	29.5 (15)	-	-	**0.001**
Creatinine (mg/dL)	-	0.42 (0.33)	0.38 (0.27)	-	-	**0.014**
Albumin (g/dL)	-	3.35 (1.1)	4.10 (0.5)	-	-	**<0.0001**
INR	-	1.15 (0.24)	0.96 (0.12)	-	-	**<0.0001**
APTT	-	29.30 (5.1)	24.3 (5.3)	-	-	**<0.0001**
NLR	0.900 (0.756)	4.7564 (8.1369)	1.5390 (2.2746)	**<0.0001**	**<0.0001**	**<0.0001**
NMR	5.600 (3.523)	12.8409 (28.6310)	6.3642 (4.8000)	**<0.0001**	0.114	**<0.0001**
LMR	6.000 (3.200)	2.6190 (3.2045)	3.8730 (3.0400)	**<0.0001**	**<0.0001**	0.160
PLR	0.1116 (0.0524)	0.1460 (0.1271)	0.1085 (0.0802)	**<0.0001**	0.336	**0.017**
d-NLR	0.7333 (0.5894)	3.2720 (3.6098)	1.2055 (1.2623)	**<0.0001**	**<0.0001**	**<0.0001**
L/CRP	-	9.1651 (24.5663)	2127.7 (1621.3)	-	-	**<0.0001**
MPVLR	0.0027 (0.0019)	0.0054 (0.0112)	0.0021 (0.0012)	**<0.0001**	**0.016**	**<0.0001**
SII	292.95 (256.74)	1084.9 (1423.6)	675.03 (1236.4)	**<0.0001**	**<0.0001**	**0.088**

Abbreviations: ALT, Alanine aminotransferase; **AST,** Aspartate aminotransferase**; aPTT,** activated partial thromboplastin time; **CRP**, C-reactive protein; **d-NLR**, derivated neutrophil to lymphocyte ratio; **ESR**, Erythrocyte sedimentation rate; **IL-6,** Interleukin 6**; INR;** International normalized ratio; **L/CRP**, Lymphocyte to C-reactive protein ratio; **LDH,** Lactate dehydrogenase; **LMR**, Lymphocyte to monocyte ratio; **MCV,** Mean corpuscular volume; **MPV**, Mean platelet volume; **MPVLR**, Mean platelet volume to lymphocyte ratio; **NLR**, Neutrophil to lymphocyte ratio; **NMR**, Neutrophil to monocyte ratio; **PCT**, Plateletcrit; **PDW,** Platelet distribution width; **PLR**, Platelet lymphocyte ratio; **Pro-BNP**; pro-brain-type natriuretic peptide; **RDW**, Red cell distribution width; **SII,** Systemic inflammatory index

Table 3. Spearman's correlation between mean platelet volume and other laboratory parameters in patients with MIS-C

Variables	r	p
Age	0.159	0.209
White blood cell (K/uL)	0.018	0.889
Neutrophil (K/uL))	0.062	0.627
Lymphocyte (K/uL))	-0.189	0.135
Monocyte (K/uL))	-0.226	0.072
Eosinophil (K/uL))	-0.011	0.934
Hemoglobin (g/dL)	-0.024	0.851
MCV (fl)	0.231	0.066
RDW (%)	-0.027	0.835
Platelet (K/uL))	**-0.628****	**<0.0001**
PCT (%)	**-0.477****	**<0.0001**
PDW (f/L)	**0.576****	**<0.0001**
ESR (mm/h)	0.042	0.741
CRP (mg/L)	0.236	0.061
Procalcitonin (ug/L)	**0.421****	**0.001**
D-dimer (ng/mL)	**0.434****	**<0.0001**
Ferritin (ng/mL)	**0.341****	**0.007**
Fibrinojen (mg/dL)	-0.048	0.838
IL-6 (pg/mL)	**0.353***	**0.010**
LDH (U/L)	0.210	0.111
Troponin (ng/L)	**0.299***	**0.016**
Pro-BNP (pg/mL)	0.207	0.194
AST (U/L)	0.131	0.300
ALT (U/L)	**0.303***	**0.015**
Urea (mg/dL)	**0.469****	**<0.0001**
Creatinine (mg/dL)	**0.361****	**0.003**
Albumin (g/dL)	**-0.370****	**0.003**
INR	0.044	0.730
APTT	-0.206	0.102
NLR	0.196	0.120
NMR	0.245	0.051
LMR	-0.020	0.873
PLR	-0.102	0.424
d-NLR	0.213	0.091
L/CRP	**-0.291***	**0.020**
MPVLR	**0.326****	**0.009**
SII	-0.058	0.647

Abbreviations: ALT, Alanine aminotransferase; **AST,** Aspartate aminotransferase**; aPTT,** activated partial thromboplastin time; **CRP**, C-reactive protein; **d-NLR**, derivated neutrophil to lymphocyte ratio; **ESR**, Erythrocyte sedimentation rate; **IL-6,** Interleukin 6**; INR;** International normalized ratio; **L/CRP**, Lymphocyte to C-reactive protein ratio; **LDH,** Lactate dehydrogenase; **LMR**, Lymphocyte to monocyte ratio; **MCV,** Mean corpuscular volume; **MPV**, Mean platelet volume; **MPVLR**, Mean platelet volume to lymphocyte ratio; **NLR**, Neutrophil to lymphocyte ratio; **NMR**, Neutrophil to monocyte ratio; **PCT**, Plateletcrit; **PDW,** Platelet distribution width; **PLR**, Platelet lymphocyte ratio; **Pro-BNP**; pro-brain-type natriuretic peptide; **RDW**, Red cell distribution width; **SII,** Systemic inflammatory index

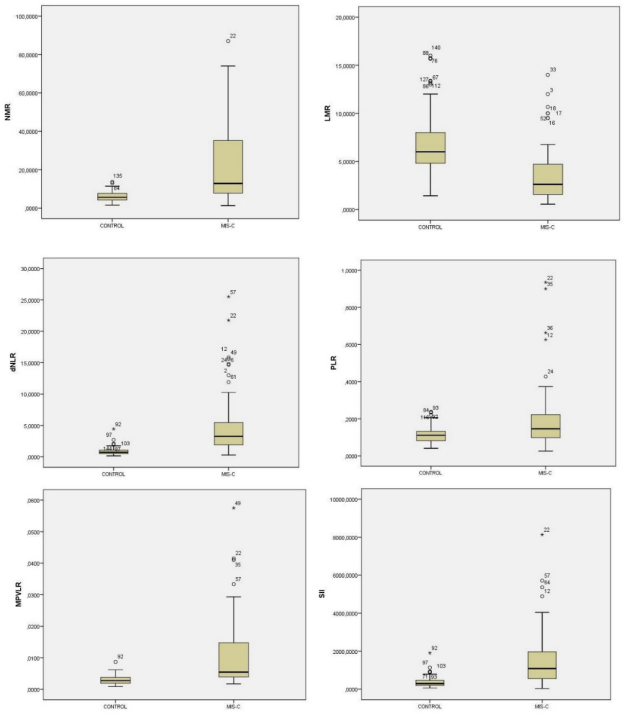

Fig. 2:

Discussion

MIS-C is a life-threatening clinical emergency; therefore, the diagnosis must be confirmed and the appropriate treatment initiated urgently. The clinical spectrum of MIS-C can range from mild to severe. This study is aiming to examine MIS-C severity predictive value of hematological parameters, inflammatory markers and biochemical tests. These tests can be analysed routinely in many health institutions, and inflammatory markers can be easily calculated using these parameters. Data analysis showed that severe cases of MIS-C had lower monocyte, platelets, albumin, NMR counts and had higher MPV, MPVLR, d-dimer, ferritin, IL-6 levels on admission. Hematological parameters and inflammatory markers were affected by immunomodulatory treatment during follow-up of patients. Although detailed hematological parameters and inflammatory markers may be used to predict MIS-C progress in adults, to the best of our knowledge, this has not been investigated in children.

In our study, the demographic and clinical features of the MIS-C patients were similar to previously published reports. In a European multicentre study of 286 children with MIS-C, the median age of participants was 8.4 years, and 67% were males. Common signs and symptoms included persistent fever, gastrointestinal symptoms, mucocutaneous changes and cardiac dysfunction (13).

Although the frequency of MIS-C according to clinical severity (mild-moderate- severe) has not been clearly stated in the literature, the distribution of patients along the severity spectrum in our study was nearly

equal. On the other hand, left ventricular dysfunction and coronary dilatation, features of severe MIS-C in our study are reported to occur in 20-55% and 20% of cases, respectively (10). Age distribution showed that the median age of the severe group (IQR; 10.6 years) was higher than the mild and moderate groups.

There are limited data on hematological parameters and inflammatory markers of MIS-C cases in the literature. Available information about laboratory tests are mostly about adult patients with COVID-19.

The immune response in MIS-C is associated with elevated pro-inflammatory cytokines, CRP, procalcitonin, d-dimer, ferritin, interleukin-10 and IL-6, activated neutrophils, monocytes, and cytopenias (thrombocytopenia and lymphopenia) (14). A meta-analysis indicated that severe MIS-C patients had higher levels of WBC, absolute neutrophil count (ANC), and lower levels of absolute lymphocyte count (ALC) compared to non-severe MIS-C patient (15). In our study, there was no statistically significant difference in WBC, ANC, and ALC levels between severe and non-severe MIS-C cases. The hematological parameters including RDW and monocyte counts were statistically significantly higher in moderate MIS-C cases than in mild cases. RDW reflects the heterogeneity of erythrocyte volume and assess the variation in size and form of circulating erythrocytes. The increase in RDW reflects the increase in other inflammatory markers in the blood (16). Cytokines may directly inhibit erythropoietin-induced erythrocyte maturation which leads to an increase in RDW (17). It is worthy of note that there will be different stages and varying degrees of severity amongst children with COVID-19 related MIS-C at the time of hospital admission.

Various products of the inflammatory process, including cytokines (IL-1,TNF-a) can stimulate megakaryocytes leading to marked elevation of platelets count and is thought to have a parallel correlation with CRP (18,19). Changes in MPV due to platelet activation during the inflammatory process will directly affect PDW. A recent study have reported that severe COVID-19 patients have shown abnormal platelet parameters, including decreased PLT and PCT, increased MPV and PDW (20). In our study, the highest MPV levels were observed in the severe group. A significant positive correlation was observed between MPV levels, acute phase reactants (procalcitonin, d-dimer, ferritin, IL-6), inflammatory markers (PDW, MPVLR) and some biochemical values (troponin, ALT, urea, creatinine). Also, a significant negative correlation was detected between platelet count, PCT, L/CRP and albumin levels. Severe MIS-C cases had lower platelet counts than moderate cases. There was no statistically significant difference in the other hematological parameters (MCV, PTC, PDW) between the groups.

The increase in the levels of proinflammatory cytokines such as IL-1, IL-6, and TNF-a are predictors of disease progression and an impending cytokine storm (21). In our study as predicted, IL-6 levels were higher in the severe MIS-C group.

CRP is an acute-phase reactant which is released from liver cells in response to IL-6 stimulation. CRP is a useful indicator to determine the severity of disease and a reliable predictor of cytokine release syndrome [22]. ESR measures the rate at which red blood cells in anti-coagulated whole blood settles to the bottom of the containing test tube. During inflammation, the ESR is faster than normal because of an increase in the fibrinogen content of the blood (22). The production of procalcitonin from extrathyroidal sources is actively sustained by enhanced concentrations of IL-1, TNF-a and IL-6. Adult studies show that increased procalcitonin values are associated with higher risk of severe SARS-CoV-2 infection (23). In our study, there was no statistically significant difference between the MIS-C groups in ESR, CRP, and procalcitonin values. This may be due to the acute inflammatory response associated with MIS-C, a response expected to be sustained throughout the various stages of disease progress and severity. We believe that it is related to the fact that some patients were admitted with mild symptoms then deteriorated to a more severe state. However, the initial laboratory findings of these patients were evaluated.

D-dimer is released as a product of degeneration of cross linked fibrin, and is directly connected to the activation of the proinflammatory cytokine cascade. The function of serum ferritin as a marker of inflammation and immune dysregulation is well established. Clinical studies suggest that increased ferritin and d-dimer levels are linked to the severity of COVID-19 disease (24,25). Zhao et al. reported in a meta-analysis that severe MIS-C patients had higher levels of CRP, d-dimer, and ferritin levels compared to non-severe MIS-C patient (15). In agreement with Zhao et al, our study shows that; d-dimer and ferritin levels were statistically significantly higher in the SePG. Hypoalbuminemia associated with cytokine storm disorders is thought to reflect hyperinflammation and tissue damage (26). Concordantly, our study shows that albumin levels are statistically significantly lower in severe MIS-C group compared to the other groups. There was no statistically significant difference with regard to the other biochemistry values (LDH, troponin, pro-BNP, AST, ALT, urea, and creatinine) between the patient groups.

The predictive value of inflammatory parameters derived from routine CBC (NLR, NMR, LMR, PLR, d-NLR, L/CRP, MPVLR, SII) have been investigated in many studies. Systemic inflammation can suppress the cellular immunity as a result of decreased CD4+ T lymphocyte counts, and neutrophils can be induced by cytokines such as lymphocyte-derived TNF-a and IL-6. NLR , indicating the inflammatory status of the patient, can be used as a biomarker to assess the disease severity. Various studies suggested that an increase in NLR is a biomarker of poor prognosis (27). d-NLR is an indicator of systemic inflammatory response. Its level is significantly higher in severe cases compared to

non-severe cases of COVID-19 and is considered an independent biomarker of poor prognosis [27]. In our study, NLR and d-NLR levels were significantly higher in the moderate group than the mild group. Rizo-Téllez et al. suggested that raised NMR was an indicator of severe inflammation related immune cell imbalance and was a predictor of poor survival in adult patients with severe COVID-19 (28). Fortunately, none of our patients died, but contrary to the findings of Rizo-Téllez et al, NMR levels were statistically significantly lower in severe MIS-C group. However, the two studies are conducted within opposing age groups.

Low LMR has been shown to correlate with disease severity and as a poor prognostic marker in patients with COVID-19 (29). L/CRP is a newly developed inflammatory score, which reflects the systemic inflammation status. Lower L/CRP levels in severe cases could be the result of fewer lymphocytes leading to immune dysfunction and higher CRP levels reflecting a severe systemic inflammatory response (30). We found no significant difference in LMR and L/CRP values between the MIS-C groups. PLR is an indicator of systemic inflammatory response with severe cases exhibiting significantly higher PLR level than non-severe cases with COVID-19 (27). In our study, PLR levels were statistically significantly lower in the mild group. MPVLR and SII are novel systemic inflammatory indices. SII score was higher in patient with COVID-19 compared with non- severe patients (31). Thrombocytes play a role in the pathogenesis of infectious diseases. Previous studies have suggested that megakaryocytes may be affected by cytokines such as IL-3, IL-6, and lead to more reactive production of thrombocytes (32). Therefore, MPVLR is expected to be higher in severe inflammation. While there was no statistically significant difference in SII values in our study, MPVLR values were statistically significantly higher in the severe MIS-C group.

The main purpose of MIS-C treatment is to control the cytokine storm and suppress systemic inflammation for preventing long-term sequelae. In our study, differences were found in the post-treatment hematological and inflammatory parameters compared to the pre-treatment and control groups.

IVIG inhibit immune cells (B cells, dendritic cells, monocytes/macrophages and basophils) activations, down-regulate pro-inflammatory cytokines (TNF-a, IL-1, IL-6, IL-12) while up-regulate anti-inflammatory cytokines (IL-10 and transforming growth factor) (33). Glucocorticoids induce anti-inflammatory and immunosuppressive effects in both primary and secondary immune cells, thereby decreasing production of proinflammatory cytokines (eg, IL-2, IL-6, and TNF- a) and suppressing activation of T cells, monocytes, and macrophages (34). Cicha et al. reported a decrease in the numbers of leukocytes, neutrophils, lymphocytes, eosinophils, and basophils after IVIG treatment (35). Although the lymphocyte, eosinophil, monocyte, and basophil levels decrease after administration of glucocorticoids, neutrophils increase in blood (36). In contrast, our study showed that WBC, lymphocyte and monocyte counts were statistically significant higher in post-treatment group than pre-treatment group. Also, there was no significant difference in neutrophil counts between the pre- and the post-treatment group, and this may be attributed to discontinuation of steroid therapy over a long period and recovery of the disease.

Glucocorticoids increase haemoglobin and red cell content of blood, possibly by retarding erythrophagocytosis [36]. In our study, haemoglobin, RDW, MCV values were statistically significantly higher in the post-treatment group compared to the pre-treatment group. The PDW and MPV values were higher in the pre-treatment group compared to the post-treatment group. These findings may be due to the suppressing effect of glucocorticoids on the inflammatory process. A recent study showed that the peripheral platelet counts of patients with severe viral infection had significantly increased after receiving IVIG therapy (37). PCT is directly proportional to platelet count. In our study, the PLT and PCT levels were lower in the pre-treatment group compared to the post-treatment group.

As expected, due to suppression of inflammation and clinical improvement, acute phase reactants (ESR, CRP, procalcitonin, ferritin, fibrinogen), d-dimer, LDH, troponin, pro-BNP, AST, creatinine levels, coagulation parameters, and new hematologic parameters (NLR, NMR, PLR d-NLR, L-CRP, MPVL, SII) were statistically significantly lower in the post-treatment group compared to the pre-treatment group. Albumin is exclusively produced in the liver as the main protein in the blood. It is a negative acute phase reactant, the reduced serum level of which is associated with poor prognosis in infectious diseases (38). Glucocorticoids cause protein breakdown and increasing the substrate supply for hepatic urea synthesis (39). In our study, urea and albumin values were higher in post-treatment period of MIS-C patients.

LMR values were statistically significantly lower in post-treatment and pre-treatment patient groups compared to the control group. Despite the recovery of the disease, the lack of difference LMR in the pre-treatment and post-treatment groups suggests the effect of immunomodulatory drugs on the immune cells.

Our study has certain limitations, particularly as a retrospective single-centre study with a small sample size. The laboratory parameters of patients were collected on admission to the hospital and immediately after the completion of the course of glucocorticoid therapy and were examined retrospectively. All patients were treated with standard IVIG and glucocorticoid regimens according to disease severity and, discharged without complications.

In conclusion, routine laboratory tests, including (monocyte count, RDW MPV, MPVLR, d-dimer, ferritin,

IL-6, d-NLR, NMR, NLR,) levels may be helpful predicting the severity of MIS-C. Early recognition of serious cases will provide early initiation of appropriate treatment.

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