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Original Article

The Role of Hematological Parameters in Children with COVID-19, MIS-C, and Other Viral Infections

COVID-19, MIS-C ve Diğer Viral Enfeksiyon Tanılarıyla İzlenen Çocuk Hastalarda Hematolojik Parametrelerin Rolü

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ABSTRACT

Objective: It is known that coronavirus disease-2019 (COVID-19) showed a clinical course with milder symptoms in children than in adults. However, a multisystem inflammatory syndrome in children (MIS-C), which developed 2-4 weeks after COVID-19 infection, emerged in April 2021. Other respiratory viruses such as influenza, respiratory syncytial virus, and parainfluenza spread worldwide after loosening pandemic restrictions. Pediatricians were challenged to distinguish COVID-19, MIS-C, and other viral infections from each other. Herein, we have aimed to determine basic, simple hematological parameters that can predict the prognosis and outcomes of the patients with COVID-19 and MIS-C.

Method: In this study, 300 pediatric inpatients including those with MIS-C, COVID-19, and other respiratory virus infections admitted to Ege University Faculty of Medicine between January 2018 and September 2021, were retrospectively evaluated.

Results: The neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-monocyte ratio (NMR), derived NLR, and the systemic inflammatory index were higher in the MIS-C patients compared to others. The lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) were lower in children with COVID-19 disease than those with MIS-C ($p<0.05$).

Conclusions: In this study, we have shown that commonly used hematological tests, especially higher values of NLR, NMR for children with MIS-C, and lower levels of LMR for children with COVID-19, are significant and can help to determine the possible disease course of children at an early stage.

Keywords: COVID-19, lymphocyte-to-monocyte ratio, multisystem inflammatory syndrome in children (MIS-C), neutrophil-to-lymphocyte ratio, other viruses

ÖZ

Amaç: Koronavirüs hastalığı-2019'un (COVID-19), çocuklarda yetişkinlere göre daha hafif semptomlarla seyrettiği bilinmektedir. Bununla birlikte Nisan 2021'de COVID-19 enfeksiyonundan 2-4 hafta sonra gelişen çocuklarda multisistem enflamatuvar sendrom (MIS-C) görülmeye başlandı. İnfluenza, respiratuvar sinsitiyal virüs ve parainfluenza gibi diğer solunum yolu virüsleri, pandemik kısıtlamaların gevşetilmesinin ardından dünya çapında yayıldı. Çocuk doktorları COVID-19, MIS-C ve diğer viral enfeksiyonları ayırt etmekte zorlandı. Bu çalışmada, COVID-19 ve MIS-C hastalarının prognozunu ve sonuçlarını öngörebilecek temel ve basit hematolojik parametreleri belirlemeyi amaçladık.

Yöntem: Bu çalışmada Ocak 2018-Eylül 2021 tarihleri arasında Ege Üniversitesi Tıp Fakültesi'ne başvuran MIS-C, COVID-19 ve diğer solunum yolu virüs enfeksiyonları ile hastanede yatan 300 çocuk hasta geriye dönük olarak değerlendirildi.

Bulgular: Nötrofil-lenfosit oranı (NLR), nötrofil-monosit oranı (NMR), derived NLR ve sistemik enflamatuvar indeks MIS-C'de diğerlerine göre daha yüksekti. Lenfosit-monosit oranı (LMR) ve trombosit-lenfosit oranı (PLR), COVID-19'lu çocuklarda MIS-C'ye göre daha düşüktü ($p<0,05$).

Sonuç: Bu çalışmada, yaygın olarak kullanılan hematolojik testlerin, özellikle MIS-C'li çocuklar için yüksek NLR, NMR değerlerinin ve COVID-19'lu çocuklar için daha düşük LMR değerlerinin anlamlı olduğunu ve olası erken evrede hastalığı belirlemeye yardımcı olabileceğini gösterdik.

Anahtar kelimeler: COVID-19, lenfosit-monosit oranı, çocuklarda multisistem enflamatuvar sendrom (MIS-C), nötrofil-lenfosit oranı, diğer virüsler

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INTRODUCTION

Pediatric coronavirus disease-2019 (COVID-19) patients showed milder symptoms with a better prognosis than adults. However, it should not be forgotten that severe COVID-19 disease can occur in infants under one year of age and children with chronic diseases[1,2]. In April 2020, pediatricians from the United Kingdom and Italy reported a cluster of patients admitted to pediatric intensive care unit (PICU) with toxic shock syndrome and Kawasaki-like disease. Meanwhile, an epidemiological line with COVID-19 was defined in these patients. The condition characterized by fever and multi-organ involvement seen after COVID-19 has been termed as multisystem inflammatory syndrome in children (MIS-C) and its clinical and laboratory diagnostic criteria have been defined by the Royal College of Paediatrics and Child Health, World Health Organization (WHO), and Centers for Disease Control and Prevention (CDC)[3-5].

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, clinicians have challenged the differential diagnosis of COVID-19 with other respiratory tract viruses and influenza[6]. Symptoms of COVID-19 have significantly overlapped with those of influenza. Therefore, many parameters have been used to differentiate among these infections. However, application of some of these parameters are burdensome and expensive. Simple and more accessible hematological parameters can be used to predict prognosis. The neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-monocyte ratio (NMR), neutrophil-to platelet ratio (NPR), and platelet-to-lymphocyte ratio (PLR) are new biomarkers that provide important data on systemic inflammation and can be easily estimated from routine laboratory studies. NLR, lymphocyte-to-monocyte ratio (LMR), and PLR are thought to reflect physiological stress. Stress causes an increase in circulating cortisol levels which can lead to an increase in circulating neutrophil and a decrease in lymphocyte counts. Higher NLR, LMR, and PLR values are commonly observed in critically ill patients. These indices have not diagnostic value and they are not disease -specific but may guide the prediction of the severity of an inflammatory disease[7]. Increased NLR and PLR values are significantly associated with the mortality of the patients with infectious diseases[8-11]. Therefore, recent studies have suggested that NLR is a good predictor of mortality in COVID-19 patients[12-14].

We have aimed to evaluate the hematological parameters to predict requirement for hospital and PICU admissions of children among COVID-19 patients and compare the hematological parameters in patients with COVID-19 disease, other viral infections and MIS-C.

MATERIALS and METHODS

This retrospective single-center study included COVID-19-associated MIS-C patients, children with COVID-19 disease, and other viral infections admitted to the İzmir Ege University Faculty of Medicine Department of Pediatric Infectious Disease in Turkey, between January 2018 and September 2021. A total of 300 hospitalized children aged ≤18 years were evaluated, including 49 patients with MIS-C, and 147 children with COVID-19. A total of 104 children whose respiratory tract swab samples tested positive for adenovirus, influenza A/B, rhinovirus, parainfluenza, human metapneumonia virus A/B, human bocavirus, or respiratory syncytial virus (RSV) during influenza outbreak period between January 2018 and March 2019 were included in the study.

Demographic characteristics, comorbid conditions, and duration of hospital stay were recorded on a standardized form. Laboratory analysis on admission, including complete blood count (CBC), NLR, LMR, NMR, PLR, NPR, monocyte-to-platelet ratio (MPR), ferritin, D-dimer, C-reactive protein (CRP), and procalcitonin values were recorded. Thrombocytopenia was defined as a blood platelet count less than $150x10^9$/L, neutropenia as absolute neutrophil count (ANC) less than 1500/mm^3, and lymphopenia as an absolute lymphocyte count (ALC) less than 1500/mm^3. For analysis, inflammatory hematological indexes including NLR (NLR: ANC/ALC); LMR [LMR: ALC/absolute monocyte count (AMC)]; NMR (NMR: ANC/AMC); NPR (NPR: ANC/platelet count); MPR (MPR: AMC/platelet count), derived-NLR [ANC/(total white blood cell (WBC) count-ANC)]; and PLR (platelet count/ALC). Were calculated with values obtained from CBCs,

Systemic inflammatory index (SII) was calculated as follows: (SII) = platelet count × neutrophil count/ lymphocyte count.

According to the COVID-19 Guideline released by Turkish Ministry of Health, confirmed cases with COVID-19 disease were defined as those in whom SARS-CoV-2 virus was demonstrated in their nasal and throat swabs by molecular methods[15]. Diagnostic criteria of MIS-C have been defined by the WHO and the CDC in May 2020[3,5].

The ethics committees of Ege University Faculty of Medicine Medical Research Ethics Committee approved

the conduction of this study (approval no: 21-6T/66, date: 11.06.2021).

Microbiological Methods

After admission, nasopharyngeal swab specimens for polymerase chain reaction (PCR) analysis were obtained by a physician. All nasopharyngeal and oropharyngeal swab specimens were collected in a viral transport medium (vNat® Bioeksen, Turkey). All samples were tested using the Bio-speedy® SARS-CoV-2 Double Gene RT-qPCR kit (Bioeksen, Turkey). This same kit can differentiate among respiratory tract pathogens [influenza A (H3N2 and H1N1), influenza B, human metapneumonia virus A/B, human bocavirus, RSV A/B, adenovirus, enterovirus]. Anti-spike immunoglobulin G (IgG) and IgM antibodies were detected in serum samples using rapid lateral flow immunoassay (Colloidal Gold-Hotgen, Germany).

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences version 25 program. Continuous variables were expressed, if appropriate, as means and standard deviations or medians and interquartile ranges. Categorical variables were summarized as blood cell counts and respective percentages for each category. Categorical variables were compared between MIS-C, COVID-19, and other viral infection groups using the chi-square test. Non-parametric data were compared using the t-test for independent samples or Mann-Whitney U test. The Spearman's rank correlation test was used to analyze the association between laboratory markers. A p-value of less than 0.05 was set as the level of statistical significance, within corresponding 95% confidence intervals (CIs). After binary logistic regression analysis, we displayed the receiver operating characteristic (ROC) curve of statistically significant variables. We calculated the area under the curve (AUC) to evaluate the sensitivity and specificity of each parameter/model to predict PICU admissions and to differentiate COVID-19 from other viruses.

RESULTS

The mean ages of the COVID-19 group (95.7±75 months), MIS-C group (101.5±53.5 months), and other viral infection groups (49.9±55.7 months) were as indicated, while these corresponding groups contained 81 (55.1%), 24 (49%), and 63 (60.6%) male children, respectively. The mean age was significantly lower in the other viral infection group ($p<0.001$). There was no significant difference between the groups regarding gender of the patients ($p>0.05$). The baseline characteristics of all patients are shown in Table 1.

Influenza A/B, RSV, rhinoviruses, parainfluenza viruses, and adenoviruses were detected in 49 (47.1%), 15 (14.4%), 11 (10.6%), 4 (3.8%), and 3 (2.9%) patients, respectively.

Indicated number of patients with COVID-19 (n=77; 52.4%), MIS-C (n=7; 14.3%), and other viral infections (n=53; 51%) had at least one underlying medical condition. As is seen, underlying medical conditions were observed at significantly lower rate in the MIS-C group ($p<0.001$; Table 2).

When laboratory findings were evaluated, MIS-C patients had significantly higher mean values for parameters of WBC and eosinophil counts, ANC, mean platelet volume (MPV), derived NLR, median NLR, NMR, PLR, NPR, SII, and lower mean levels for ALC, monocyte, and platelet counts, median MPR than patients with COVID-19 or other viral infections ($p<0.05$). Median LMR was significantly lower in the COVID-19 group ($p=0.002$) (Table 1). Patients with influenza A/B had significantly lower median eosinophil counts, mean monocyte, and platelet counts than those with COVID-19 disease. The median values of NLR, LMR, NMR, PLR, NPR, MPR, derived NLR, and SII were not significantly different between influenza and COVID-19 groups ($p>0.05$) (Table 3).

The patients with MIS-C required invasive mechanical ventilation at a lower rate, and the duration of mechanical ventilation was shorter relative to the other groups ($p=0.001$). Children with MIS-C were more likely to need intensive care, and the mean length of stay in PICU for COVID-19 patients was more prolonged than in other groups (mean 17.5±19 days for COVID-19, 3.4±2.5 days for MIS-C, and 4.3±2.5 days for groups with other viral infections). Two patients with other viral infections died. No deaths were observed among patients with MIS-C and COVID-19 ($p>0.05$).

The mean age of the group of patients with other viral infections was 60.2±64.3 months, and 11 (50%) male patients from this group were admitted to the PICU. Among patients hospitalized in the PICU, the mean age of the children with other viral infections was significantly lower compared to the children with COVID-19 or MIS-C ($p<0.001$) (Table 4). Mean NMR, derived NLR indices, CRP, D-dimer values, platelet, and eosinophil counts, and median NLR were higher in the

patient group with MIS-C hospitalized in the PICU than in other groups (p<0.05) (Table 4). Mean SII was lower in patients with other viral infections admitted to the PICU without any significant intergroup difference (p>0.05).

The positive correlation between NMR and NLR, LMR, NPR, WBC, CRP, procalcitonin, D-dimer, MPV, use of inotropes, length of PICU stay, and negative correlation between NMR and MPR, lymphocyte count are shown in Figure 1. We detected a positive correlation between NPR and CRP, MPV, length of hospitalization, and PICU stay. This study have shown the presence of positive correlations between NLR, CRP, procalcitonin, and D-dimer, and also between PLR, CRP, MPR, MPV and length of hospitalization.

The ROC analysis was performed to determine the cut-off values of NLR, NMR, NPR, derived NLR, SII to predict the requirement for hospitalization of the patients with the MIS-C in PICU. Respective diagnostic sensitivities, specificities and AUC values of indicated cut-off values of NLR, NMR, NPR, derived NLR, and SII for the MIS-C group of patients were as follows: NLR: >2.62 [87.8%, 66.5%, 0.802 (95% CI 0.752-0.846), p<0.0001];

Table 1. Baseline characteristics, and laboratory data of children presenting with MIS-C, COVID-19, and other viral infections

	Group of patients with other viral infections, n=104	Group of patients with COVID-19 disease, n=147	Group of patients with MIS-C, n=49	p-value
Gender Male (n, %)	63 (60.6)	81 (55.1)	24 (49)	0.384
Age, months, (Mean ± SD)	49.9±55.7	95.7±75	101.5±53.5	<0.001
Underlying disease (n, %)	53 (51)	77 (52.4)	7 (14.3)	<0.001
WBC/(Mean ± SD)/mm^3	9128±5431	9014.6±7375	11884.9±6718.9	0.002
ANC/(Mean ± SD)/mm^3	5115±4217	5523.9.6±6410	9510.6±6298.6	<0.001
ALC/(Mean ± SD)/mm^3	3027±2291	2479.5±2001.1	1638±1344.9	<0.001
Hb (Mean ± SD, g/dL)	10.8±1.9	12.5±6.5	11±1.1	<0.001
PLT/(Mean ± SD)/mm^3	266836±129108	271768±123839	22040±120416	0.017
MPV (Mean ± SD)/FL	9.8±1.71	10±1.04	10.5±1.2	0.001
Eosinophil/(Median-IQR)/mm^3	10 (67.5)	20 (100)	100 (235)	<0.001
Monocytes/(Mean ± SD)/mm^3	817±808	878.8±689.8	516±403	<0.001
Leucopenia (n, %)	13 (12.5)	21 (14.3)	4 (8.2)	0.535
Neutropenia, (n, %) (<1,500/µL)	13 (12.5)	23 (15.6)	5 (10.2)	0.575
Lymphopenia (n, %) (<1,500/µL)	25 (24)	57 (38.8)	33 (67.3)	<0.001
Thrombocytopenia (n, %) (<150,000 µL)	21 (20.2)	22 (15)	16 (32.7)	0.026
NLR (Median, IQR)	1.4 (2.67)	1.8 (3.46)	6.3 (9.5)	<0.001
LMR (Median, IQR)	4.04 (5.12)	2.9 (3.03)	3.54 (5.59)	0.002
NMR (Median, IQR)	6.34 (7.44)	5.43 (6.33)	21.6 (25.8)	<0.001
PLR (Median, IQR)	103.7 (106.05)	127.3 (114.2)	142 (132.6)	0.001
NPR (Median, IQR)	0.016 (0.02)	0.015 (0.018)	0.041 (0.033)	<0.001
MPR (Median, IQR)	0.0024 (0.002)	0.0027 (0.002)	0.0019 (0.002)	0.022
Derived NLR (Mean ± SD)	1.7±2.2	2.1±2.4	5.5±4.9	<0.001
SII (Median, IQR)	347 (566)	433 (933)	1228 (2078)	<0.001
The total hospital length of stay, days, (Mean ± SD)	11.9±9.9	9.3±12.2	10.9±5.4	<0.001
PICU admission, n, (%)	21 (20.2)	22 (15)	25 (51)	<0.001

COVID-19: Coronavirus disease-2019, SD: Standard deviation, IQR: Interquartile range, WBC: White blood cell count, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, Hb: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte rate, LMR: Lymphocyte/monocyte ratio, NMR: Neutrophil/monocyte ratio, PLR: Platelet/lymphocyte ratio, NPR: Neutrophil/platelet ratio, MPR: Monocyte/platelet ratio, SII: Systemic inflammatory index, PICU: Pediatric intensive care unit

NMR: >9.93 [79.6%, 77.2%, 0.812 (95% CI 0.763-0.855), p<0.0001]; NPR; >0.024 [81.6%, 73.7%, 0.797 (95% CI 0.746-0.841), p<0.0001]; derived NLR: >1.63 [91.8%, 63.3%, 0.819 (95% CI 0.771-0.861), p<0.0001]; SII: >570,263 [81.6%, 60.2%, 0.744 (95% CI 0.691-0.793), p<0.0001].

DISCUSSION

Several inflammatory markers have been evaluated as predictors of severity in hospitalized patients with severe and non-severe COVID-19 disease[16-18]. Circulating cytokine levels and inflammatory biomarkers have been shown to successfully predict disease severity and mortality; however, these are not readily available outside tertiary medical centers[19]. For this reason, cheap and simpler parameters that can be easily accessible have been evaluated in the studies. We have shown the presence of higher NLR, NMR, PLR, NPR, derived NLR, SII values and lower MPR levels in MIS-C group, and lower LMR ln COVID-19 group. We have also demonstrated that higher levels of NLR, NMR, and derived NLR are associated with PICU stay in the MIS-C group.

The parameters of NLR, LMR, and PLR are thought to reflect physiological stress. Stress causes an increase in circulating cortisol levels, which triggers an increase

Table 2. Underlying conditions in patient groups

Underlying conditions	Group of patients with other viral infections n=53	Group of patients with COVID-19 disease n=77	Group of patients with MIS-C n=7
Respiratory conditions (n, %)	5 (4.8)	8 (5.4)	1 (2)
Neurologic conditions (n, %)	6 (5.8)	14 (9.5)	0 (0)
Obesity (n, %)	0 (0)	7 (4.8)	4 (8.2)
Cardiac problems (n, %)	3 (2.9)	6 (4.1)	0 (0)
Hematological problems (n, %)	9 (8.7)	7 (4.8)	0 (0)
Transplantation (n, %)	4 (3.8)	5 (3.4)	0 (0)
Other (n, %)	26 (25)	30 (20.4)	2 (4.1)

COVID-19: Coronavirus disease-2019, MIS-C: Multisystem inflammatory syndrome in children

Table 3. Laboratory data of influenza A/B and COVID-19 groups

	Influenza A/B (n=49)	COVID-19 (n=147)	p-value
Gender Male (n, %)	26 (53.1)	81 (55.1)	0.804
Age, months, (Mean ± SD)	68.3±63.7	95.7±75	0.113
WBC/(Mean ± SD)/mm^3	7405±4292	9014.6±7375	0.351
ANC/(Mean ± SD)/mm^3	4372±3209	5523.9.6±6410	0.848
ALC/(Mean ± SD)/mm^3	2201±1420	2479.5±2001.1	0.724
Hb (Mean ± SD, g/dL)	11.4±1.95	12.5±6.5	0.099
PLT/(Mean ± SD)/mm^3	216708±102627	271768±123839	0.050
MPV (Mean ± SD)/FL	10.4±1.2	10±1.04	0.056
Eosinophil/(Median, IQR)/mm^3	10 (20)	20 (100)	0.004
Monocytes/(Mean ± SD)/mm^3	697±659	878.8±689.8	0.017
NLR (Median, IQR)	1.7 (3.03)	1.8 (3.46)	0.526
LMR (Median, IQR	3.5 (5.97)	2.9 (3.03)	0.062
NMR (Median, IQR)	6.5 (6.87)	5.43 (6.33)	0.189
NPR (Median, IQR)	0.016 (0.024)	0.015 (0.018)	0.472
PLR (Median, IQR)	108.9 (109.2)	127.3 (114.2)	0.127
MPR (Median, IQR)	0.002 (0.003)	0.0027 (0.002)	0.272
Derived NLR (Mean ± SD)	1.75±1.67	2.1±2.4	0.700
SII (Median, IQR)	342 (612)	433 (933)	0.113

COVID-19: Coronavirus disease-2019SD: Standard deviation, IQR: Interquartile range, WBC: White blood cell count, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, Hb: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio, NMR: Neutrophil/monocyte ratio, NPR: Neutrophil/platelet ratio, PLR: Platelet/lymphocyte ratio, MPR: Monocyte/platelet ratio, SII: Systemic inflammatory index

Table 4. Laboratory parameters and management of PICU and non-PICU group				
	Requirement for PICU stay in group of patients with other viral infections (n=22)	**Requirement for PICU stay in patients with COVID-19 disease (n=22)**	**Requirement for PICU stay in patients with MIS-C (n=25)**	**p-value**
Age, months, (Mean ± SD)	60.2±64.3	136.3±63.4	115.8±46.2	<0.001
Gender Male (n, %)	11 (50)	8 (36.4)	12 (48)	0.614
Underlying disease (n, %)	12 (54.5)	12 (54.5)	2 (8)	0.001
WBC/(Mean ± SD)/mm^3	8394.5±5363	11254±8993	12272±7406	0.251
ANC/(Mean ± SD)/mm^3	5574±4260.5	9191±8399	10540±7353	0.056
ALC/(Mean ± SD)/mm^3	2036±2328	1415±1008	1158±821	0.354
Hb (Mean ± SD, g/dL)	10.4±1.5	11.9±3.2	10.7±1.2	0.072
PLT/(Mean ± SD)/mm^3	269500±138172	268227±99507	180920±86986	0.008
MPV (Mean ± SD)/FL	9.2±1.93	10.1±1.1	11.3±1.2	<0.001
Eosinophil/(Mean ± SD)/mm^3	18.6±37.5	23±78	154±131	<0.001
Monocytes/(Mean ± SD)/mm^3	616±804	616±460	380±334	0.182
Leucopenia (n, %)	5 (22.7)	3 (13.6)	2 (8)	0.357
Neutropenia, (n, %) (<1,500/µL)	5 (22.7)	4 (18.2)	2 (8)	0.340
Lymphopenia (n, %) (<1,500/µL)	11 (50)	13 (59.1)	20 (80)	0.088
Thrombocytopenia (n, %) (<150,000 µL)	5 (22.7)	3 (13.6)	12 (48)	0.026
NLR (Median, IQR)	2.8 (5.3)	3.7 (10.7)	7.6 (12.9)	0.004
LMR (Median, IQR)	3.5 (8)	2.5 (3.2)	3.6 (5.9)	0.380
NMR (Mean ± SD)	16.3±16.7	17±11.9	40.1±33.8	0.002
PLR (Mean ± SD)	388±626	290.4±256.3	215.5±171	0.421
NPR (Mean ± SD)	0.033±0.045	0.063±0.140	0.062±0.05	0.001
MPR (Mean ± SD)	0.008±0.03	0.002±0.001	0.002±0.001	0.519
Derived NLR (Mean ± SD)	3.6±4.3	4.9±4.1	7.5±5.9	0.001
SII (Median, IQR)	636 (1827)	1478 (1782)	1228 (2789)	0.075
C-reactive protein (Mean ± SD, mg/L)	111.5±138	43±46	195±71	<0.001
D-dimer (Mean ± SD, µG/L FEU)	2357±1562	1968±1407	3152±1283	0.024
Ferritin (Mean ± SD, µG/L)	-	668±1038	653±432	0.076
Procalcitonin (Median, IQR)/µg/L	1.2 (9.07)	0.87 (3.09)	2.39 (7.13)	0.084
Tracheostomy (n, %)	0 (0)	7 (31.8)	0 (0)	<0.001
Use of Inotropes (n, %)	6 (27.3)	9 (40.9)	19 (76)	0.002
Oxygen support (n, %)	21 (95.5)	19 (86.4)	17 (68)	0.034
Nasal oxygen	16 (72.7)	11 (50)	18 (72)	0.192
BIPAP	4 (18.2)	4 (18.2)	5 (20)	0.983
Mechanical ventilation	11 (50)	10 (45.5)	1 (4)	0.001
Duration of using inotropes (Mean ± SD)	1.14±2.1	2.5±4.5	1.7±1.5	0.078
Duration of mechanical ventilation (Mean ± SD)	1.8±2.5	9±12	0.1±0.6	0.001
Duration of BIPAP (Mean ± SD)	0.41±1.1	0.54±1.3	0.3±0.6	0.990
Length of stay in PICU (Mean ± SD)	4.3±2.5	17.5±19	3.4±2.5	0.023
Length of hospital stay (Mean ± SD)	15±12	27±23	13±12	0.099
Mortality (n, %)	2 (9.1)	0 (0)	0 (0)	0.095

SD: Standard deviation, IQR: Interquartile range, WBC: White blood cell, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, Hb: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio, NMR: Neutrophil/monocyte ratio, PLR: Platelet/lymphocyte ratio, NPR: Neutrophil/platelet ratio, MPR: Monocyte/platelet ratio, BIPAP: Bilevel positive airway pressure PICU: Pediatric intensive care unit, MIS-C: Multisystem inflammatory syndrome in children

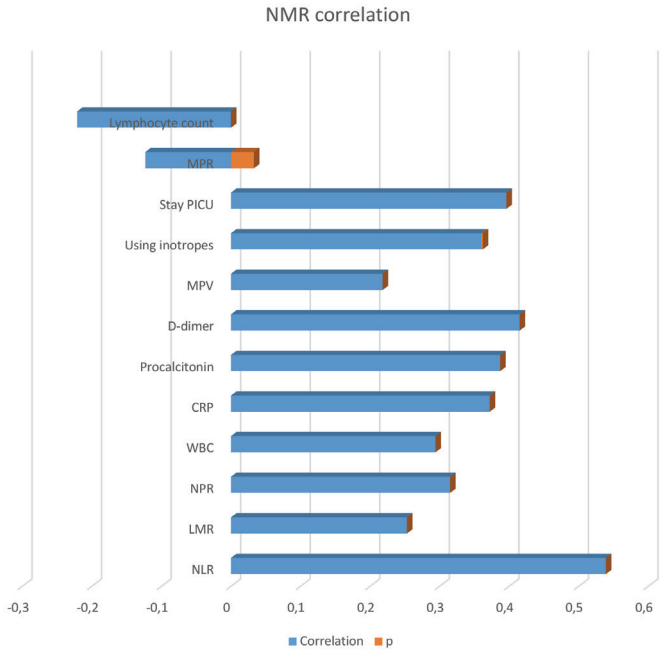

Figure 1. Correlations between NMR and other laboratory markers

MPR: Monocyte/platelet rate, PICU: Pediatric intensive care unit, MPV: Mean platelet volume, CRP: C-reactive protein, WBC: White blood cell, NPR: Neutrophil/platelet ratio, LMR: Lymphocyte/monocyte ratio, NLR: Neutrophil/lymphocyte ratio, Stay PICU: Stay in PICU, Using inotropes: Use of inotropes, NMR: Neutrophil/monocyte ratio

in circulating neutrophil and a decrease in lymphocyte counts. NLR not only reflects the increased number of neutrophils in infection but also indicates the decrease in the number of lymphocytes *in vivo*[20]. Higher NLR, LMR, and PLR values have been shown to associate with the disease severity in critically ill patients. Normal NLR values between 0.78 and 3.53 have been reported in adults excluding the geriatric period[21]. In a study by Zhang et al.[22], on 237 patients from China, NLR was demonstrated as an independent risk factor for mortality of the patients infected with influenza viruses. The same study determined that the H7N9-infected patients with NLR >19.94 had a higher mortality rate than those with lower levels of NLR[23]. Aktürk et al.[24] showed that NLR was significantly higher in patients who were hospitalized for respiratory tract infections than those hospitalized for other indications (mean NLR value 2.05 vs. 3.27). In Liao et al.'s[23] study, NLR showed a certain degree of diagnostic accuracy at optimal cut-off value of 1,478 in children with influenza A and the diagnostic value of NLR was well established in this patient population. Storch-de-Gracia et al.[25] evaluated 39 children with a median age of 9 years who were positive for SARS-CoV-2 PCR and determined that the higher values of NLR were associated with complicated COVID-19 disease. In a study by Yildiz et al.[26] on 79 children, NLR levels were found to be significantly higher in symptomatic children. Yang et al.[27] demonstrated that the increase in NLR values could be used as an independent prognostic biomarker in patients with COVID-19 disease and showed that NLR, LMR, PLR, and CRP levels were significantly higher in severely diseased patients. Feldstein et al.[28] showed higher NLR values were more common in MIS-C patients than in patients with severe COVID-19 disease. Prozan et al.[29] demonstrated lower NRL values in COVID-19 patients than in RSV infection and influenza patients, whereas higher NLR values were associated with poor clinical outcomes only in the COVID-19 group. They suggested that NLR was a more valuable prognostic marker of COVID-19 infection rather than influenza and RSV infection[29]. We have shown that the values of NLR, NMR, and derived NLR were higher in PICU-admitted MIS-C patients. NLR values were not significantly different between influenza and COVID-19 groups.

Studies support LMR as a good predictor of inflammatory events. A comparative assessment of LMR values in outpatients diagnosed with H1N1 influenza or pneumonia caused by culture-proven *Streptococcus pneumonia* demonstrated that LMR values below 2 was significantly associated with influenza[30]. Cunha et al.[31] demonstrated that the LMR <2 was more frequently seen in the human parainfluenza virus infections compared to human metapneumovirus, coronaviruses, HRV, human parainfluenza virus, and RSV infections. Temel et al.[32] showed that the mean LMR value was significantly lower, and NLR values were significantly higher in patients with influenza A relative to non-influenza A patients. Fei et al.[33] found that LMR in the influenza A-positive and influenza A-negative patients were significantly lower, while NLR was higher compared to healthy children. We found that LMR value was significantly lower in children with COVID-19 disease. The LMR values were lower in children with COVID-19 disease who were admitted to PICU, without any significant difference in LMR values between those who weren't.

In a recent study, NLR, PLR, SII, and derived NLR were shown to be helpful in the diagnosis and evaluation of disease severity in COVID-19 patients[27]. Bg et al.[34] showed that the derived NLR was not a significant predictor of mortality in adult patients with COVID-19

disease. Núñez et al.[7] demonstrated that the value of derived NLR was higher in COVID-19 patients with primary outcomes (requirement for mechanical ventilation; admission to a critical care unit or death). We have shown that derived NLR was significantly higher in MIS-C patients and higher NLR was significantly associated with PICU admission rate of MIS-C patients.

Several studies have reported that higher NMR values were associated with mortality rates related to COVID-19 disease[35]. A previous study demonstrated that the levels of LNR <0.088 and NMR >17.75 at admission could accurately predict in-hospital mortality rates from severe COVID-19 disease in Mexican adults, and NMR was suggested to be more sensitive and specific than LNR to predict the mortality risk[36]. This is the first study that evaluated NMR in MIS-C patients, and we have shown that NMR was significantly higher in the MIS-C group than in other groups.

PLR is related to immune-inflammatory reactions and indicates the severity of infection[36]. Gong et al.[37] showed higher PLR levels in severely ill patients compared to patients with non-severe COVID-19 disease. Qu et al.[38] reported that the increase in PLR was correlated with the poor prognosis of COVID-19 disease and patients with higher PLR had longer hospital stays. Nalbant et al.[39] showed that PLR values were significantly higher in patients with COVID-19 disease than those without.

Fei et al.[33] reported that patients in influenza A positive group had significantly higher PLR values than the negative group. We have demonstrated that PLR values were higher in the MIS-C group, however, they were not significantly correlated with PICU admissions in MIS-C patients.

SII is an index that describes instability in the inflammatory response, based on platelet, neutrophil, and lymphocyte counts. SII is recommended as a prognostic indicator in the follow-up of patients with sepsis[40]. Usul et al.[41] showed that SII was significantly lower for COVID-19-positive patients. SII was significantly associated with survival in a study including 119 adults with COVID-19 disease[42]. We have shown that SII was lower in children with other viral infections.

Study Limitations

There were several notable limitations to this study. Firstly data were not obtained from multiple centers but from a single center using a retrospective design, Secondly, the experimental data were limited. Our conclusions based on the findings of this study may differ from those of other researchers, and they must be elaborated further in clinical studies.

CONCLUSION

In conclusion, we have shown that higher NLR, NMR, derived NLR values for children with MIS-C and lower LMR values for children with COVID-19 disease could be used to predict the course of the disease. However, predictive diagnostic hematological parameters have not been specified for the COVID-19 disease so far.

Ethics

Ethics Committee Approval: The ethics committees of Ege University Faculty of Medicine Medical Research Ethics Committee approved the conduction of this study (approval no: 21-6T/66, date: 11.06.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Author Contributions

Surgical and Medical Practices: S.Y.A., Z.Ş.B., Concept: S.Y.A., Z.Ş.B., G.G.Ö., N.M.B., P.Y.Ö., F.Ö., B.K., C.Ç., Z.K., Design: S.Y.A., Z.Ş.B., G.G.Ö., N.M.B., P.Y.Ö., F.Ö., B.K., C.Ç., Z.K., Data Collection or Processing: S.Y.A., Z.Ş.B., G.G.Ö., N.M.B., P.Y.Ö., F.Ö., B.K., C.Ç., Z.K., Analysis or Interpretation: S.Y.A., Z.Ş.B., G.G.Ö., N.M.B., P.Y.Ö., F.Ö., B.K., C.Ç., Z.K., Literature Search: S.Y.A., Z.Ş.B., N.M.B., Writing: S.Y.A., Z.Ş.B., F.Ö.

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