ORIGINAL ARTICLE

A retrospective study of age-defined hematologic inflammatory markers related to pediatric COVID-19 diagnosis

Yasemin Üstündağ[1] | Elif G. Kazanci[2] | Rahime F. Koloğlu[1] | Hatice A. Çağlak[1] | Fatih Yildirim[1] | Elif Y. Arikan[1] | Kağan Huysal[1]

[1]Department of Clinical Biochemistry, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

[2]Department of Pediatric Hemato-Oncology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

Correspondence
Elif Y. Arikan, Department of Clinical Biochemistry, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey.
Email: drelifyalcin@gmail.com

Abstract

Background: The aim of this study was to examine age-related differences in hemogram parameters and hematologic inflammatory markers in pediatric patients with COVID-19.

Methods: This retrospective study included children aged 2 months to 18 years ($n = 208$) who have a confirmed diagnosis of COVID-19 and a control group comprising 117 healthy children between February 2021 and July 2021. The analysis of subgroup hematological values were performed according to the children's age cutoffs.

Results: The most significant difference between pediatric patients with COVID-19 and controls were peripheral blood eosinophil counts and eosinophil-to-monocyte ratio (EMR) levels on admission. The levels of monocyte-to-lymphocyte ratio, aggeregate index of systemic inflammation (neutrophil × platelet × monocyte/lymphocyte), neutrophil-to- lymphocyte × platelet ratio, and systemic inflammation response index (neutrophil × monocyte/ lymphocyte) were higher in patients than in controls. EMR had the highest area under the curve (AUC) value of 0.777, with a cutoff value of 0.26. The sensitivity for EMR was 75% under 2 years of age, and between 78.6–87.5% in the other age groups.

Conclusion: In children younger than 6 months, the discriminative power of hematological indices is low, while the discriminative power of EMR is high at all ages when age appropriate cutoffs are used. Hematological inflammatory parameters may be particularly practical in pediatric clinics to help identify COVID-19 infection.

KEYWORDS
child, COVID-19, eosinophils, leukocytes, lymphocytes

1 | INTRODUCTION

Recently, the COVID-19 pandemic has significantly impacted the lives of millions of people globally.[1] All age groups are susceptible to COVID-19, but children are less likely to have a severe course of disease relative to adults.[2,3] The most common symptoms found in children at admission are fever and cough, followed by sore throat, weakness, muscle pain, difficulty breathing, headache, runny nose, and gastrointestinal symptoms.[4]

Complete blood cell count (CBC) is one of the most common laboratory tests requested in children in clinical practice. CBC parameters have been demonstrated to be useful in the early suspicion of COVID-19 and in predicting prognosis in adults.[5-7] Calculated ratios of CBC parameters have been proposed as biomarkers for diagnosis, classification, and progression in inflammatory diseases.[8,9]

A limited number of studies to date have examined alterations in CBC inflammatory parameters in pediatric patients infected with COVID-19.[10-12] Unlike in adults, a consistent pattern of

hematological alterations has not yet been proven in children with COVID-19.[13] However, since CBC parameters will change with increasing age from birth, age should not be ignored when interpreting test results.[14,15] Therefore, the aim of this study is to discover whether there are age-related differences in hemogram parameters and calculated hematologic markers between healthy controls and pediatric patients with COVID-19 at their first hospital admission as triage test.

2 | MATERIALS AND METHODS

This retrospective study included patients who were admitted between February 2021 and July 2021, to the pediatric emergency department at Saglik Bilimleri University, Bursa Yuksek Ihtisas Training and Research Hospital. Data on demographics, clinical manifestations, and laboratory abnormalities were extracted from hospital records. Given the retrospective observational nature of the study, informed consent was not obtained. The study protocol was approved by the Institutional Ethics committee (2011-KAEK-252021/08-05) and the Turkish Ministry of Health (2021-0812T14_57_53) and carried out according to the Declaration of Helsinki.

During the study period, both nasopharyngeal and oropharyngeal swabs were collected from a total of 6218 suspected pediatric COVID-19 cases, as recommended by Turkish COVID-19 guidelines.[16] The swab samples were subjected to reverse transcription-polymerase chain reaction (RT-PCR) testing with SARS-CoV-2 (2019-nCoV) RT-qPCR Detection Kit (Bio-Speedy®, Bioeksen R&D Technologies, İstanbul, Turkey) according to the manufacturer's instructions.[5,16]

All children aged 2 months to 18 years ($n = 208$) with a laboratory-confirmed diagnosis of COVID-19 were included in the subsequent analysis. The control group comprised 117 healthy children selected from those presenting to the General Pediatric Clinic for routine health check-up. Children who had acute or chronic diseases were excluded from the control group.

CBC was performed with Mindray BC-6000 hematology analyzer (Mindray Medical International Ltd, Shenzhen, China) within 2 h of sampling. All the CBC counts and differentials showed satisfactory analytical performance, and the repeatability results for eosinophils were between 3.99 and 5.94%.[17]

The hematologic inflammatory markers were calculated as follows: Neutrophil-to-lymphocyte ratio (NLR; neutrophil count/lymphocyte count), derived neutrophil-to-lymphocyte ratio (dNLR; neutrophil count/(white blood cell count– neutrophil count)), monocyte-to-lymphocyte ratio (MLR; monocyte count/lymphocyte count), platelet-to-lymphocyte ratio (PLR; platelet count/lymphocyte count), aggregate index of systemic inflammation (AISI; (neutrophil count × platelet count × monocyte count)/lymphocyte count), neutrophil-to-lymphocyte platelet ratio (NLPR; neutrophil count/(lymphocyte count × platelet count)), systemic immune-inflammation index (SII; (neutrophil count × platelet count)/lymphocyte count), systemic inflammation response index (SIRI; (neutrophil

count × monocyte count)/lymphocyte count), and eosinophil-to-monocyte ratio (EMR; eosinophil count/monocyte count).[14-20] The analysis of subgroup hematological values was performed according to the children's age cutoffs.

2.1 | Statistical analyses

Data were statistically analyzed using SPSS version 21 (IBM, Chicago, IL, USA). Conformity of variables to normal distribution was assessed using the Shapiro–Wilk test. Descriptive statistics were stated as mean ± standard deviation, median values, or number and percentage. In the comparisons between groups, the Student's t-test was applied to variables that were normally distributed and the Mann–Whitney U test to variables that were not normally distributed. Differences between age-defined markers were analyzed using the Kruskal–Wallis test, and receiver operating characteristic (ROC) analysis was used to determine cutoff points. The area under the curves (AUC) were compared using the Z test using MedCalc statistical software (MedCalc, Mariakerke, Belgium). A value of $p < .05$ was considered statistically significant.

3 | RESULTS

A total of 208 COVID-19 patients were evaluated, 108 (51.9%) of whom were girls and 100 (48.1%) of whom were boys, with a median age of 9.0 years (IQR:11; range: 0–18 years) (Table 1). A control group of 117 healthy children was also included, comprising 62 (53%) girls and 55 (47%) boys, with a median age of 8.0 years (IQR:11; range: 0–18 years).

The most common symptoms at the first visit were fever (52%) and cough (45%). Less frequent symptoms were sore throat, myalgia, dyspnea, and diarrhea. Fourteen children with COVID-19 were admitted to general pediatric services or the pediatric intensive care unit (PICU) ($n = 2$), according to the first emergency physician's assessment. Hospitalized children ranged from newborns to 12-year-olds, with a median age of 4.5 years. The children who required admission to the PICU were both 2 years old.

When the findings of all children were compared without age discrimination, the absolute lymphocyte and eosinophil counts of the patients on admission were lower than the control group [2.1 (IQR: 1.98) vs. 2.5 (IQR: 1.30); $p < .001$; 1.1 (IQR: 1.6) vs. 2.1 (IQR: 1.9), respectively] (Table 1). Eosinopenia (a reduction of circulating eosinophils $<0.02 \times 10^9$/L) was present in 6.8% of healthy subjects and 15.9% of patients. The positive predictive value (PPV) of eosinopenia for COVID-19 was 80.5. Lymphopenia (lymphocyte count of $<1.1 \times 10^9$/L) was noted 16.8% in the patient group and 0.0% in the control group.

Of the calculated hematological markers, EMR [0.34 (IQR: 0.30) vs. 0.11 (IQR: 0. 20) $p < .001$] was significantly lower in patients than in the control group (Figure 1). Additionally, MLR [0.27 (IQR: 0.27) vs. 0.16 (IQR: 0.10), $p < .001$], AISI [264 (IQR: 444) vs. 155 (IQR: 211), $p < .001$], NLPR (0.0066 vs. 0.0046, $p < .001$), and SIRI (0.99

TABLE 1 Median (interquartile range) of the laboratory findings in pediatric patients with COVID-19 infection on admission to the hospital

	Patient $n = 208$	Control $n = 117$	p
Gender (M/F)	100/108	55/62	
Age, years (IQR)	9 (11)	8 (11)	.680
WBC count, 10^9/L	7.0 (4.3)	7.3 (2.4)	.870
Neutrophile count, 10^9/L	3.7 (3.15)	3.3 (2.80)	.097
Lymphocyte count,10^9/L	2.1 (1.98)	2.5 (1.30)	<.001
Monocyte count,10^9/L	0.61 (0.46)	0.48 (0.23)	<.001
Eosinophil count,10^9/L	0.06 (0.11)	0.15 (0.15)	<.001
PLT count, 10^9/L	253 (123)	284 (85)	.001
NLR	1.7 (3.02)	1.3 (1.06)	.003
PLR	123 (99)	109 (52)	.046
MLR	0.27 (0.27)	0.16 (0.10)	<.001
dNLR	1.3 (1.7)	1.0 (0.80)	.05
AISI	264 (444)	155 (211)	<.001
NLPR	0.0066 (0.013)	0.0046 (0.003)	<.001
SII	404 (637)	365 (338)	.034
SIRI	0.99 (1.91)	0.54 (0.59)	<.001
EMR	0.11 (0.20)	0.34 (0.30)	<.001

Abbreviations: AISI, aggregate index of systemic inflammation (neutrophil * platelet * monocyte-to-lymphocyte ratio); dNLR, (Neutrophil count / (White blood cell count–Neutrophil count)); EMR, (eosinophil-to-monocyte ratio).* Median (interquartile range); F, female; IQR, Inter quartile range; M, male; MLR, (monocyte count / Lymphocyte count); NLPR, (neutrophil-to-lymphocyte * platelet ratio); NLR, (Neutrophil count / Lymphocyte count); PLR, (Platelet count / Lymphocyte count); PLT, platelet; SII, systemic immune–inflammation index (neutrophil * platelet-to-lymphocyte ratio); SIRI, systemic inflammation response index (neutrophil * monocyte-to-lymphocyte ratio); WBC, white blood cell.

vs. 0.54, $p < .001$) levels were higher in patients than in controls (Table 1).

In the ROC curve analysis of children diagnosed with COVID-19, the EMR had the highest AUC value of 0.777 (95% CI 0.723–0. 832, $p < .001$), with a cutoff value of 0.26. At the highest Youden index, EMR had a sensitivity of 77.4% and a specificity of 71.1% [AUC: 0.777, 95% CI 0.723–0.832]. The EMR results a PPV of 83.8% and LR +2.67 (Table 2).

EMR exhibited a significantly higher AUC as compared to other hematological indices. In comparison with the AUCs, statistical differences were observed for EMR vs. PLR ($z = 3.69$, $p < .001$), EMR vs. AISI ($z = 3.42$, $p = .001$), and EMR vs. dNLR ($z = 4.12$, $p < .001$). The AUCs of EMR was greater than that of eosinophil and monocyte counts ($z = 3.748$, and $z = 2.68$, $p < .001$, and $p = .007$, respectively). There was no statistically significant difference between AUCs of EMR and MLR ($z = 1.151$, $p = .294$).

The hematological values of the children were analyzed in 5 age groups (Table 3). When analyzed according to age, a statistical difference is seen between the number of eosinophils, the number of monocytes, SIRI, and EMR between the patient and controls (≥2 years of age).

An EMR of 0.266 was found to be the most appropriate cutoff point. When we separate according to age, the cutoff value for EMR was between 0.26 and 0.28. The sensitivity for EMR was 75% under 2 years of age, and between 78.6 and 87.5 in the other age groups.

4 | DISCUSSION

Lymphocyte count, monocyte count, and some of the calculated hematologic inflammatory markers change significantly along with increasing age. These observations support the idea that clinical decision limits for total and differential leukocytes should be modified as children grow, in efforts to reduce misdiagnosis in clinical practice. In cases of COVID-19, levels of WBCs, neutrophils, lymphocytes, platelets, and hemoglobin were mostly within the pediatric reference ranges or only slightly changed.[13,21]

Eosinopenia was present in 15.9% of COVID-19 patients in our study. Similarly, Du et al.[22] reported that 29.5% of the pediatric COVID-19 patients had eosinopenia on admission. There are a number of reports showing that, eosinopenia enables early identification of adult patients with suspected COVID-19 infection from other patients.[23] This finding may serve as an early diagnostic tool in triage when children with COVID-19 or COVID-19-like symptoms await confirmatory nucleic acid tests and/or radiographic examination.

We observed an increase in monocyte counts in pediatric patients with COVID-19, consistent with the results of a number of recent studies.[24,25] Increased monocyte counts may contribute to the milder disease severity in pediatric patients with COVID-19 by inhibiting SARS-CoV-2 viral replication.[24,25]

The most significant differences between pediatric patients with COVID-19 and controls were MLR and EMR levels on admission. EMR levels with the optimal cutoff value of 0.26 produced a sensitivity of 77.4% and a specificity of 71.1% for separating COVID-19 cases and controls, suggesting its usefulness for preliminary COVID-19 screening in pediatric patients. Cutoff values for EMR change little as the children grow.

When we evaluated according to age specific groups, the discriminative power of EMR (AUC: up to 0.886, sensitivity: 87.5%, specificity: 81.5% at ages 9–13) and MLR (AUC up to 0.760, sensitivity = 75% in ages 9–13 years) changed (Table S1, Figure S1).

WBC and lymphocyte counts were highest in early childhood and progressively decreased until adulthood, consistent with the previous studies.[14,15,26] According to our findings, lymphopenia was observed in 16.8% of the total cases.[27] In a meta-analysis that included 2874 pediatric patients with COVID-19, lymphopenia was found in only 5.5% of cases (95 CI:2.8–8.8%).[27,28]

Recently, NLR, dNLR, PLR, MLR, and SII have been shown to be useful for diagnosis and severity assessments in adult COVID-19
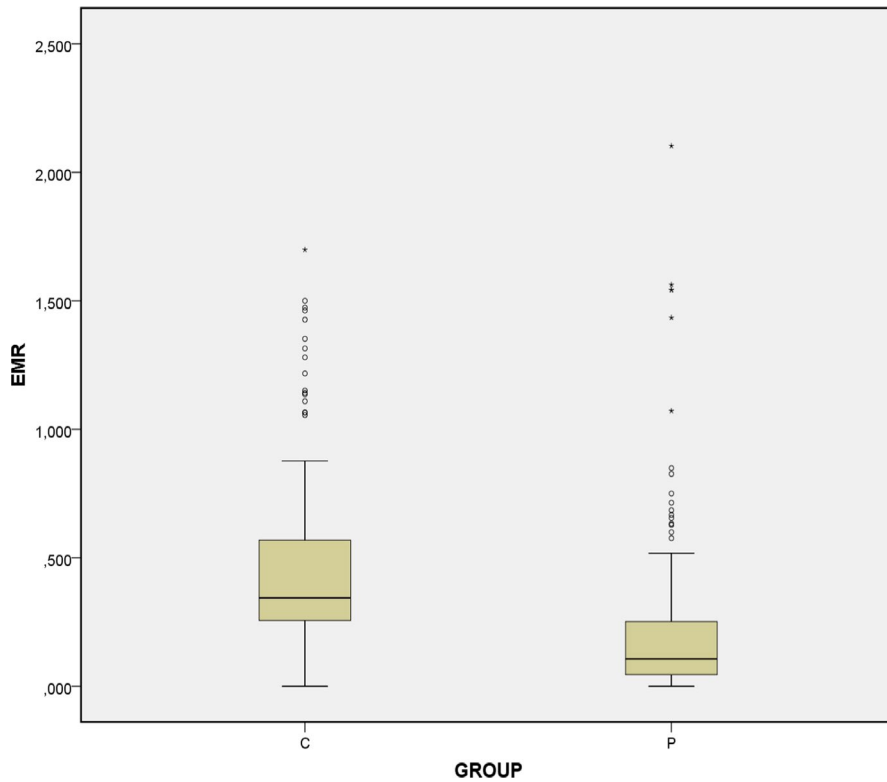
FIGURE 1 Scatter box plot of blood EMR levels of the patients with SARS-CoV-2 test-positive and control groups. EMR; eosinophil count to monocyte count

TABLE 2 ROC curve analysis of hematologic parameters and hematologic inflammatory markers for detecting COVID-19 in pediatric patients

Parameter	AUC(Standard Error)	%95 Confidence interval	p
WBC	0.494 (0.033)	0.429–0.559	.870
Neutrophile count	0.561 (0.034)	0.495–0628	.097
Lympocyte count	0.632 (0.032)	0.570–0695	<.001
Monocyte count	0.664 (0.032)	0.600–0.727	<.001
Eosinophil count	0.733 (0.030)	0.673–0.792	<.001
NLPR	0.635 (0.032)	0.572–0.697	<.001
AISI	0.641 (0.032)	0.578–0.704	<.001
dNLR	0.603 (0.033)	0.539–0.668	.005
SIRI	0.672 (0.031)	0.612–0.733	.001
SII	0.578 (0.034)	0.512–0.644	.034
NLR	0.612 (0.032)	0.548–0.675	.003
PLR	0.574 (0.033)	0.508–0.640	.046
MLR	0.719 (0.029)	0.662–0.775	<.001
EMR	0.777 (0.028)	0.723–0.832	<.001

Abbreviations: AISI, aggregate index of systemic inflammation (neutrophil * platelet * monocyte) /lymphocyte; AUC, Area under curve; dNLR, neutrophil count / (white blood cell count–neutrophil count); EMR, eosinophil count/ monocyte count.; MLR, monocyte count / lymphocyte count; NLPR, neutrophil /(lymphocyte * platelet); NLR, neutrophil count / lymphocyte count; PLR, platelet count / lymphocyte count; SII:systemic immune–inflammation index (neutrophil * platelet)/ lymphocyte ratio; SIRI, systemic inflammation response index (neutrophil * monocyte) / lymphocyte ratio; WBC, white blood cell.

patients.[5,29] These hematologic indices reflect the dynamic response of the immune system.[14-16,30] NLR in adults may be more informative than other commonly used markers,[28,31] but the discriminative power of the NLR in children was not as high as either the EMR or MLR.

4.1 | Strengths and limitations

A limitation of this study is its retrospective design and its small series of cases. More research on hemogram parameters and hematologic inflammatory markers in pediatric patients with COVID-19 as triage test is needed at the national and international levels. Furthermore, available data did not include disease severity, duration of hospital stay, or the treatment methods. Another limitation is that children with symptoms similar to COVID-19 were not used as controls due to the possibility of misclassification. During the coronavirus pandemic, our hospital's testing strategies changed due to the high work load of the laboratories and testing for other respiratory viruses was not available. Additionally, insufficient specificity of the RT-PCR testing and sampling errors may have resulted in increased false negative test results.

5 | CONCLUSION

In children younger than 6 months of age, the discriminative power of hematological indices is low, while the discriminative power of

TABLE 3 Age-specific results for hematological indices

Median (IQR); or Mean ± SD	<6 Mo Patient	<6 Mo Control	≥6Mo-<2 yrs Patient	≥6Mo-<2 yrs Control	≥2-<9 yrs Patient	≥2-<9 yrs Control	≥9-<13 yrs Patient	≥9-<13 yrs Control	≥13-<18 yrs Patient	≥13-<18 yrs Control	p^+	p^{++}
n (M,F)	20 (15 M,5F)	9 (4 M,5F)	36 (20 M,16F)	19 (11 M,8F)	42 (20 M,22F)	31 (16 M,15F)	40 (17 M,23F)	27 (11 M,16F)	70 (29 M,41F)	31 (13 M,18F)		
White blood cell count, ×10⁹/L	8.5 (8.0)	8.6 (4.7)	8.9 (4.6)	8.4 (3.3)	7.6 (4.5)	7.1 (2.4)	7.4 (3.98)	7.1 (2.1)	6.1 (2.9)	6.4 (1.9)	<.001	.010
Lymphocyte count, ×10⁹/L	5.4 ± 3.4	6.1 ± 3.1	4.1 ± 3.4	4.6 ± 1.9	2.4 ± 0.8	2.8 ± 1.8	2.0 ± 0.69	2.5 ± 1.6	1.7 ± 0.6	2.1 ± 0.8	<.001	<.001
Neutrophil count, × 10⁹/L	3.1 ± 3.2	2.5 ± 1.5	4.7 ± 3.2	3.2 ± 1.5	4.2 ± 2.4	3.8 ± 1.5	4.7 ± 2.2	3.8 ± 0.96	4.2 ± 2.5	3.8 ± 1.46	.008	.010
Eosinophil count, ×10⁹/L	0.14 (0.14)	0.34 (0.31)	0.08 (0.19)	0.17 (0.18)	0.06 (0.06)	0.19 (0.10)*	0.03 (0.03)	0.16 (0.09)*	0.06 (0.09)	0.12 (0.11)***	.016	.160
Monocyte count, × 10⁹/L	0.89 ± 0.50	0.82 ± 0.45	0.77 ± 0.36	0.63 ± 0.29	0.78 ± 1.16	0.38 ± 0.21*	0.68 ± 0.33	0.47 ± 0.11*	0.59 ± 0.33	0.41 ± 0.10**	.030	<.001
PLTcount, × 10⁹/L	346 ± 101	325 ± 88	281 ± 120	332 ± 79	259 ± 77	312 ± 54	252 ± 69	293 ± 60	245 ± 62	264 ± 65	.002	.182
MLR	0.18 (0.11)	0.11 (0.11)	0.23 (0.21)	0.12 (0.06)	0.30 (0.34)	0.11 (0.16)*	0.37 (0.37)	0.19 (0.08)*	0.30 (0.46)	0.21 (0.09)	.001	.121
PLR	68 (92)	58 (56)	89 (49)	76 (38)	134 (132)	113 (59)	131 (114)	112 (60)	138 (100)	124 (72)	<.001	<.001
NLR	0.48 (0.5)	0.35 (0.8)	1.26 (1.9)	0.80 (1.0)	1.9 (3.8)	1.3 (1.2)	2.5 (3.1)	1.4 (0.81)	2.0 (2.90)	1.86 (2.03)	<.001	<.001
SII	141 ± 107	177 ± 140	465 ± 440	267 ± 180	404 (837)	389 (341)	591 (551)	440 (290)	516 (744)	300 (417)**	<.001	<.001
SIRI	0.50 (0.74)	0.21 (0.27)	0.93 (1.48)	0.37 (0.63)	1.2 (1.9)	0.48 (0.7)*	1.61 (2.2)	0.37 (0.46)*	1.1 (2.41)	0.76 (0.87)***	<.001	.549
DNLR	0.39 (0.29)	0.29 (0.59)	0.96 (1.20)	0.65 (0.75)	1.6 (2.5)	1.0 (0.97)	1.66 (1.67)	1.0 (0.67)**	1.5 (1.6)	1.4 (1.1)	<.001	<.001
AISI	215 (241)	87 (89)	258 (388)	121 (205)	256 (479)	151 (213)	430 (557)	194 (185)**	300 (534)	180 (217)	.030	.317
NLPR	0.002 (0.002)	0.001 (0.003)	0.004 (0.009)	0.002 (0.003)	0.009 (0.015)	0.004 (0.004)	0.010 (0.001)	0.005 (0.003)	0.007 (0.016)	0.006 (0.004)	<.001	<.001
EMR	0.14 (0.33)	0.39 (0.42)	0.08 (0.28)	0.27 (0.30)	0.11 (0.19)	0.60 (0.19)*	0.07 (0.22)	0.34 (0.14)*	0.14 (0.18)	0.28 (0.18)*	.080	.009

Abbreviations: AISI, aggregate index of systemic inflammation (neutrophil * platelet * monocyte) /lymphocyte; dNLR, neutrophil count / (white blood cell count–neutrophil count); EMR, eosinophil count/ monocyte count.; F, female; IQR, inter quartile range; M, male; MLR, monocyte count /lymphocyte count; Mo, months; NLPR, neutrophil /(lymphocyte * platelet); NLR, neutrophil count / lymphocyte count; PLR, platelet count / lymphocyte count; PLT, platelet; SD, Standard deviation; SII, systemic immune–inflammation index (neutrophil * platelet/lymphocyte ratio; SIRI, systemic inflammation response index (neutrophil * monocyte) / lymphocyte ratio; WBC, white blood cell; yrs,years.

*p < .001 (patients vs. control group; within group); **p < .005 (patients vs. control group; within group); ***p < .05 (patients vs. control group; within group).

+ Statistical differences between (Kruskall–Wallis) age-defined patient groups; ++ Statistical differences between (Kruskall–Wallis) age-defined control groups.

EMR is high in all ages. Hematological inflammatory parameters may be particularly practical in pediatric clinics when age-appropriate cutoffs are used to help identify COVID-19 infection where large volumes of blood from the patients are not preferred.

CONFLICT OF INTEREST

The authors have no conflict of interests.

AUTHOR CONTRIBUTIONS

YU, EGK and KH contributed to the concept and design the work. YU, EGK, EYA and KH drafted the work or revised it critically for important intellectual content. All the authors have acquisited, analyzed, or interpreted of data for the work. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

ORCID

Yasemin Üstündağ https://orcid.org/0000-0003-2415-0372
Elif G. Kazanci https://orcid.org/0000-0003-0910-1142
Rahime F. Koloğlu https://orcid.org/0000-0002-1990-9623
Hatice A. Çağlak https://orcid.org/0000-0002-4358-4339
Fatih Yildirim https://orcid.org/0000-0003-1799-4227
Elif Y. Arikan https://orcid.org/0000-0002-8699-1751
Kağan Huysal https://orcid.org/0000-0003-3142-5944

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SUPPORTING INFORMATION

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