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Evaluation of Inflammatory Markers in COVID-19 Disease in Children

Çocuklarda COVID-19 Hastalığında Enflamatuvar Belirteçlerin Değerlendirilmesi

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Abstract

Objective: This study aims to determine the prognostic values of biomarkers obtained from complete blood count in the diagnosis of the coronavirus disease of 2019 (COVID-19) patients who came to the pediatric emergency department of Diyarbakır Pediatric Hospital.

Material and Methods: A total of 190 child patients with COVID-19 with definite diagnosis and 41 healthy children as a control group were included in this study. The lymphocyte count, platelet count, mean platelet volume (MPV), plateletcrit (PCT), C-reactive protein (CRP), neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) obtained from the patients' complete blood count were evaluated.

Results: A statistically significant difference was found between the patient and control groups in the lymphocyte, platelet, NLR, PLR, SII, PCT, and CRP values (p= 0.001, p< 0.0001, p< 0.0001, p= 0.007, p= 0.001, p< 0.0001, and p= 0.002, respectively). A very good positive correlation was found between SII and NLR (r= 0.919, p< 0.0001). There was a good level of positive correlation between PLR and NLR and between SII and PLR (r= 0.746, p< 0.0001; r= 0.787, p< 0.0001, respectively), a moderate positive correlation was found between SII and CRP, between WBC and PLR, and between WBC and PLT (r= 0.432, p< 0.0001; r= 0.408, p< 0.0001; r= 0.538, p< 0.0001 respectively). The relationship between CRP and NLR and between PCT and SII was determined to be a weak positive correlation. The area under the curve for NLR, platelet, lymphocyte was graded as moderate and for PCT very good. Cut-off points were found for the platelet count (≤285.00; AUC= 0.740; 95% CI= 0.644-0.836; p< 0.0001), lymphocyte count (≤2.665; AUC= 0.727; 95% CI= 0.633-0.821; p< 0.0001), NLR (≥0.28; AUC= 0.707; 95% CI= 0.611-0.803; p< 0.0001), and PCT (≥0.83; AUC= 0.979; 95% CI= 0.950-1.000; p< 0.0001).

Öz

Giriş: Bu çalışma, Diyarbakır Çocuk Hastanesi çocuk acil servisine başvuran COVID-19 hastalarının tanısında tam kan sayımından elde edilen biyobelirteçlerin prognostik değerlerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu çalışmaya COVID-19 tanısı kesinleşmiş toplam 190 çocuk hasta ve kontrol grubu olarak 41 sağlıklı çocuk dahil edildi. Hastaların tam kan sayımlarından elde edilen lenfosit sayısı, trombosit sayısı, ortalama trombosit hacmi (MPV), trombosit krit (PCT), C-reaktif protein (CRP), nötrofil-lenfosit oranı (NLO), trombosit-lenfosit oranı (TLO) ve sistemik immün enflamasyon indeksi (SII) değerlendirildi.

Bulgular: Lenfosit, trombosit, NLO, TLO, SII, PCT ve CRP değerlerinde hasta ve kontrol grupları arasında istatistiksel olarak anlamlı fark bulundu (p= 0.001, p< 0.0001, p< 0.0001, p= 0.007, p= 0.001, p< 0.0001 ve p= 0.002 sırasıyla). SII ve NLO arasında çok iyi bir pozitif korelasyon bulundu (r= 0.919, p< 0.0001). TLO ile NLO arasında ve SII ile TLO arasında iyi düzeyde bir pozitif korelasyon vardı (r= 0.746, p< 0.0001; r= 0.787, p< 0.0001 sırasıyla). NLO, trombosit, lenfosit için eğri altında kalan alan orta ve PCT için çok iyi olarak değerlendirildi. Trombosit sayısı (≤285.00; AUC= 0.740; %95 CI= 0.644-0.836; p< 0.0001), lenfosit sayısı (≤2.665; AUC= 0.727; %95 CI= 0.633-0.821; p< 0.0001), NLO (≥1.28; AUC= 0.707; %95 CI= 0.611-0.803; p< 0.0001) ve PCT (≥0.83; AUC= 0.979; %95 CI= 0.950-1.000; p< 0.0001).

Sonuç: Trombosit sayısı, lenfosit sayısı, NLO ve PCT, çocuklarda COVID-19 enfeksiyonunda prognozu öngörebilecek enflamatuvar biyobelirteçler olarak kullanılabilir.

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Conclusion: Platelet count, lymphocyte count, NLR and PCT can be used as inflammatory biomarkers that can predict prognosis in COVID-19 infection in children.

Keywords: COVID-19, child, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, systemic immune-inflammation index

Anahtar Kelimeler: COVID-19, çocuk, nötrofil-lenfosit oranı, platelet-lenfosit oranı, sistemik immün-enflamasyon indeksi

Introduction

The coronavirus disease of 2019 (COVID-19) is an urgent public health problem around the world. Children are less affected by COVID-19 than adults (1). Since the first case was reported by Chan et al. on January 20, 2020, the number of cases has been gradually increasing (2). The incidence of infection in children is 1% to 2% (3). The China Center for Disease Control (CDC) and prevention reported that 1% of total cases in February 2020 were individuals under the age of 18 years; likewise, the USA stated that 1.7% of its total cases are younger than 18 years (4,5).

Early diagnosis is important for addressing COVID-19, and laboratory tests determine the severity of the disease. Complete blood count (CBC) is inexpensive and easily performed on patients, and CBC data can be used as biomarkers. These markers include leukocytes, platelets, neutrophils, and lymphocytes (6). The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are inexpensive and easily calculable indexes that correlate with the prognosis of systemic inflammatory diseases. They play an important role in immunological and inflammatory events. In addition, the systemic immune-inflammation index (SII) is useful in many conditions, particularly in cancer and inflammatory and cardiovascular diseases (7).

This study aims to determine the prognostic values of biomarkers such as cell count, NLR, PLR, SII, CRP in peripheral whole blood tests in children with COVID-19 disease at the time of first admission.

Materials and Methods

Research Design

In this study, the files of COVID-19-positive pediatric patients and healthy children between March 11, 2020 and September 6, 2020 in Diyarbakır Pediatric Hospital were analyzed retrospectively.

Research Population

One hundred ninety pediatric patients and 41 children as a control group were included in the study. According to the inclusion criteria, patients under 18 years of age with positive PCR test were included in the study. As exclusion criteria, patients with chronic disease, chronic diarrhea, heart disease, malnutrition, central nervous system infection, respiratory system infection, using antibiotics in the last month and receiving treatment in any center before admission were determined. There was no statistically significant difference between the gender ratio and the average age of the study and control groups. As the control group, 41 children between the same age (2-211 months) and gender (21 girls 51.2% and 20 boys 48.8%) who did not have a chronic disease, who were followed up in a healthy pediatric outpatient clinic and requested routine examination were included in the study.

Research Design and Laboratory Studies

The age, gender, contact history, and laboratory and chest radiography results of the patients were obtained from the patient files. Scores were calculated based on peripheral complete blood counts. SII= platelet count × neutrophil count/lymphocyte count; NLR= neutrophil count/lymphocyte count; and PLR= platelet count/lymphocyte count were calculated using the given formulas. The first-day data of clinical application, namely, real-time polymerase chain reaction (PCR) and laboratory results were included in this study. The pharynx and nasal swabs of all the patients were studied with a Bio Rad (USA) device. Serum urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose and electrolytes, and C-reactive protein (CRP) were studied using an Abbott Architect (USA) c16000. Spectrophotometric and complete blood count were studied with a Beckman Coulter (USA) device. Electronic impedance + optical scatter and blood gas tests were performed on an ABL80 FLEX BASIC analyzer using the electrochemical biosensor method in the Diyarbakır Pediatric Disease Hospital laboratory.

Statistical Analysis

The collected patient data were analyzed IBM Statistical Package for the Social Sciences (SPSS) for Windows 23.0 (IBM Corp., Armonk, NY) the frequency and percentage of the categorical data and the mean ± standard deviation and median (span) of the continuous data are given as descriptive values. For comparisons between groups, the Mann-Whitney U test was used to compare two groups, and the Kruskal-Wallis test was used for comparing more than two groups. Spearman correlation analysis was used to compare the continuous variables, whereas Chi-square test was used to compare the

categorical variables. The cut-off value for diagnosis was evaluated by receiver operating characteristic (ROC) analysis. Results were considered statistically significant when p< 0.05.

Ethics committee approval was obtained from Health Sciences University Gazi Yaşargil Training and Research Hospital before starting the study (11.09.2020/543). The study was carried out in accordance with the principles of the Declaration of Helsinki.

Results

A total of 190 pediatric patients with positive PCR tests were included in the study. Of these patients, 95 (50.0%) were girls, 95 (50.0%) were boys, and the mean age was 127.5 ± 70.0 (3-216) months. The control groups were 21 (51.2%) girls, 20 (48.8%) boys and the mean age was 93.0 ± 72.2 (2-211) months. While 112 (58.9%) of the patients had a history of contact, 78 (41.1%) had none (p= 0.014). Then, 165 (86.8%) of the patients were followed up at home, 22 (11.6%) in the service, and three (1.6%) in the intensive care unit. The mean hospitalization of the patients in the intensive care unit was 12.0 ± 7.0 days. One patient in the intensive care unit died and other patients were discharged with full recovery. In the comparisons made according to the laboratory results of the patient and control groups during the first examination, a statistically significant difference was found in the lymphocyte, platelet, NLR, PLR, SII, PCT, CRP, calcium, AST, and ALT values (p= 0.001, p< 0.0001, p< 0.0001, p= 0.007, p= 0.001, p< 0.0001, p= 0.002, p= 0.001, p= 0.045, and p= 0.050 respectively) (Table 1). Spearman correlation test results, which examine the relati-

Table 1. Comparison according to laboratory parameter results

	Control (n= 41)		COVID-19 patients (n= 190)		
	Mean	**Standard deviation**	**Mean**	**Standard deviation**	**p**
Sodium, mEq/L	138	2	137	3	0.057
Potassium, mEq/L	4.42	0.44	4.26	0.60	0.124
Chloride, mEq/L	107	2	106	3	0.393
Calcium, mg/dL	9.6	0.6	9.1	0.8	**0.001**
Glucose, mg/dL	90	11	92	17	0.555
AST, IU/L	28	8	35	27	**0.045**
ALT, IU/L	18	8	23	22	**0.050**
BUN, mg/dL	20	7	21	7	0.683
Creatine, mg/dL	0.54	0.14	0.57	0.14	0.297
CRP, mg/L	2.09	0.29	11.50	23.61	**0.002**
WBC, $10^3/mm^3$	9.19	3.57	8.33	3.83	0.250
Neutrophil, $10^3/mm^3$	3.91	1.47	4.69	2.72	0.058
Lymphocyte. $10^3/mm^3$	4.14	2.34	2.74	1.94	**0.001**
Platelet, $10^3/mm^3$	344	127	252	92	**<0.0001**
NLR	1.15	0.58	2.60	2.37	**<0.0001**
PLR	97.42	41.68	130.26	80.80	**0.007**
SII	367.573	174.789	614.110	524.793	**0.001**
Hemoglobin, g/dL	13.2	1.8	12.7	1.9	0.143
Hematocrit, %	39.9	4.8	38.2	5.3	0.090
PCT, μm^3	0.362	0.267	2.290	0.857	**<0.0001**
MPV, fL	9.2	1.1	9.6	1.4	0.154
pH	7.400	0.057	7.363	0.088	0.565
PCO_2, mmHg	38.2	0.6	39.0	9.5	0.904
PO_2, mmHg	36.7	3.9	40.8	17.6	0.744
HCO_3, mmol/L	23.3	3.1	21.5	3.1	0.418
Ca^{++}, mmol/L	1.26	0.09	1.30	0.11	0.547
Lactate, mmol/L	1.5	0.1	2.1	1.5	0.551

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, CRP: C-reactive protein, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune inflammation index, PCT: Plateletcrit, MPV: Mean platelet volume: Ca++: Ionized calcium.

Table 2. Spearman correlation study between laboratory tests

		CRP	NLR	PLR	SII	PLT	PCT	WBC
CRP	Correlation Coefficient	1.000						
	p							
NLR	Correlation Coefficient	**0.386**	1.000					
	p	**<0.0001**						
PLR	Correlation Coefficient	0.141	**0.746**	1.000				
	p	0.149	**<0.0001**					
SII	Correlation Coefficient	**0.432**	**0.907**	**0.787**	1.000			
	p	**<0.0001**	**<0.0001**	**<0.0001**				
PLT	Correlation Coefficient	0.052	**-0.308**	-0.090	-0.002	1.000		
	p	0.596	**0.001**	0.357	0.984			
PCT	Correlation Coefficient	0.112	0.189	0.152	**0.224**	-0.036	1.000	
	p	0.252	0.051	0.117	**0.020**	0.716		
WBC	Correlation Coefficient	**0.297**	-0.039	**-0.408**	0.100	**0.538**	0.074	1.000
	p	**0.002**	0.689	**<0.0001**	0.304	**<0.0001**	0.449	

CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune inflammation index, PCT: Plateletcrit, WBC: White blood cell, PLT: Platelet.

Table 3. ROC Analysis for NLR, PLR, SII, PCT, MPV, Platelet, Lymphocyte, WBC

Risk Factor	AUC (95% CI)	Limits	p	Sensitivite (%)	Spesifite (%)
NLR	**0.707 (0.611-0.803)**	**1.28**	**<0.0001**	**62.1**	**61.0**
PLR	0.597 (0.490-0.704)	97.01	0.093	53.0	48.8
SII	0.596 (0.490-0.703)	340.17	0.094	59.1	41.5
PCT	**0.979 (0.950-1.000)**	**0.83**	**<0.0001**	**97.0**	**97.6**
MPV	0.574 (0.463-0.685)	9.15	0.198	57.6	46.3
Platelet	**0.740 (0.644-0.836)**	**285.00**	**<0.0001**	**74.2**	**65.9**
Lymphocyte	**0.727 (0.633-0.821)**	**2.665**	**<0.0001**	**66.7**	**68.3**
WBC	0.585 (0.477-0.693)	8.19	0.141	59.1	56.1

NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune inflammation index, PCT: Plateletcrit, MPV: Mean platelet volume, WBC: White blood cell, AUC: Area under curve.

onship between inflammatory markers, are shown in Table 2. When the results are analyzed, there was a good level of positive correlation between PLR and NLR and between SII and PLR (r= 0.746, p< 0.0001; r= 0.787, p< 0.0001, respectively), while a very good positive correlation was found between SII and NLR (r= 0.907, p< 0.0001), a moderate positive correlation was found between SII and CRP, between WBC and PLR, and between WBC and PLT (r= 0.432, p< 0.0001; r= 0.408, p< 0.0001; r= 0.538, p< 0.0001). The relationship between CRP and NLR and between PCT and SII was determined to be a weak positive correlation (r= 0.386, p< 0.0001; r= 0.224, p= 0.020 respectively). In order to determine the distinctiveness of the test, the receiver operating characteristic (ROC) curve method graphical approach data were interpreted. ROC analyses were performed because there was a statistically significant difference in lymphocyte, platelet, NLR, PLR, SII, PCT, and CRP values between control and patient groups (Table 3, Figure 1). NLR, PCT platelet, lymphocyte values were found to be significant. The area under the NLR, platelet, lymphocyte ROC curve was graded as moderate and for PCT very good. The cut-off point for platelet values was ≤285.00 (AUC= 0.740; 95% CI= 0.644-0.836; p< 0.0001). The cut-off point for lymphocyte values was ≤2.665 (AUC= 0.727; 95% CI= 0.633-0.821; p< 0.0001). The cut-off point for NLR was ≥1.28 (AUC= 0.707; 95% CI= 0.611-0.803; p< 0.0001). The cut-off point for PCT values was ≥0.83 (AUC= 0.979; 95% CI= 0.950-1.000; p< 0.0001).

Discussion

In this study, the possibility of early detection of COVID-19 in pediatric patients was examined with real-time PCR analysis and simple tests. The mean age of the patients was 121.4 ± 71.4 months. Similarly, Gracia et al. reported that the

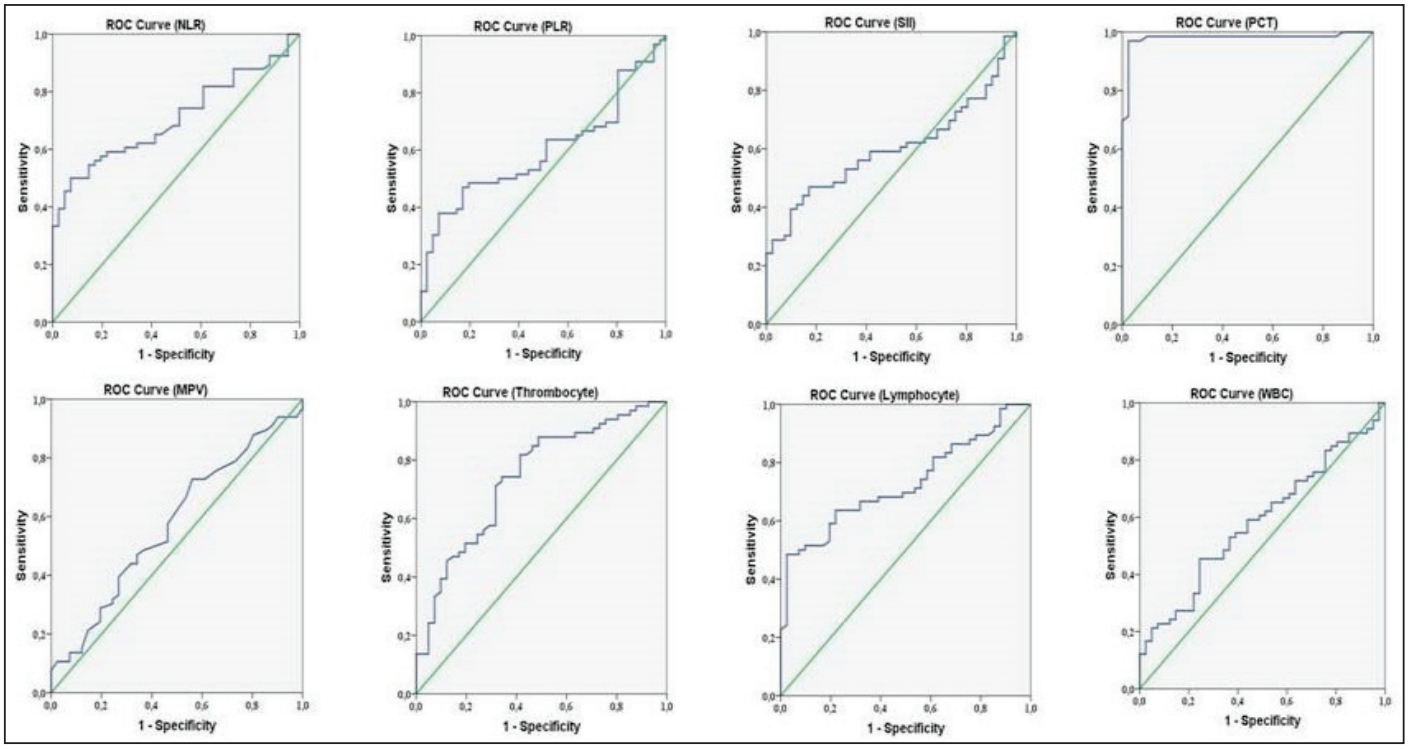

Figure 1. Evaluation of peripheral hematological parameters by ROC analysis.

NLR: Neutrophil-to-lypmhocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune inflammation index, PCT: Plateletcrit, MPV: Mean platelet volume, WBC: White blood cell.

median age was nine years, while according to U.S. data, the median age was 11 years; the average age in Türkiye has been reported to be eight years (3,5,8).

In our study, 58.4% of the patients had a history of indoor contact. Choi et al. reported that 71.2% of infected children had a contact history, while Gracia et al. reported that 69% of infected children had a contact history (3,9). In these studies, the fact that most of the children had a contact history suggests that we should not consider children as index cases.

Pediatric patients were evaluated for diagnosis, clinical findings, and contact history. Laboratory tests included complete blood count, blood gas, biochemistry, and C-reactive protein tests.

In COVID-19 pediatric patients, the white blood cell count is generally normal. CRP may be normal or increased (8). A decrease in peripheral lymphocyte count in COVID-19 patients is considered a critical factor associated with disease severity and mortality (10). Therefore, it has been stated that it is related to NLR, PLR and SII sepsis and multiorgan damage, which are accepted as inflammatory indices (11). For COVID-19 patients, NLR has been shown to be an independent risk factor for severe disease (12). In our study, similar to that of Gracia et al. lymphopenia, increased NLR, and CRP were found to be significant in pediatric patients (3). Wu et al. in a study of 148 pediatric patients, found the median (IQR) lymphocytes/µL to be 2.990 (2.360-4.170) (13). However, unlike adult patients, who showed a significant increase, there was no difference in NLR. In our study, high NLR was considered to be a sensitive marker for the diagnosis of COVID-19. Qin et al. stated that it may be helpful in early screening (14). Tjendra et al. observed that systemic inflammation indicators such as the NLR and SII index in COVID-19 infection can be used to predict disease severity, outcome and mortality (15). Paliogiannis et al. found that SII was significantly higher in those who did not survive (16). In our study, although there was a significant difference between the patient and control groups, the sensitivity was found to be 59.1% and the specificity was found to be 41.5%. Ponti et al. found that CRP, a marker of infection associated with IL-6, increases significantly in the early stages of COVID- 19 patients (17). In our study, the accepted serum CRP level was defined as distinctive in patients compared to the control group, and a moderate positive correlation was found between the CRP level and SII. However, as the result of 68% of the CRP levels in the data set was 1 mg/L, it was not included in the ROC analysis.

Platelets play an important role in blood coagulation, angiogenesis, immunity, and inflammation. Fan et al. detected mild thrombocytopenia in some initial admissions who were COVID-19 positive, as in our study (18). Mean platelet volume

(MPV), which correlates with platelet activation, is mainly based on the volume of young platelets compared with the volume of older platelets secreted from the bone marrow in inflammation; this is because platelets shrink in volume as they age. There is a relationship between the platelet index pad and the activation of the coagulation system, severe infection, trauma, systemic inflammatory reaction syndrome, and thrombotic diseases (19). Güçlü et al. specified the parameter of MPV difference between the first and third days of hospitalization in predicting mortality in COVID-19 patients (20). We think that the lack of a significant difference in MPV values in our study may result from spending enough time in the peripheral blood to cause changes as a result of rapid release from the bone marrow or rapid destruction in the periphery.

PCT is another biomarker that can change in infections and in respiratory and cardiovascular pathologies. Data showing a positive correlation between PCT and inflammation is more consistent than that showing a positive correlation between MPV and inflammation (21). Sayed et al. reported that plateletcrit and MPV/PCT in children are readily available, sensitive, prognostic markers that can identify patients with severe sepsis (22). Nam et al. identified PCT as good diagnostic markers in pediatric sepsis patients (23). In accordance with other studies, a significant increase was found in the PCT values of our patients in the early period. We believe that PCT can also be used as an important parameter in the follow-up of pediatric patients diagnosed with COVID-19. However, more clinical studies are needed to better understand the continuation of the increase in PCT values, especially in the late period.

In the comparison of the patient and control groups in our study, as inflammatory biomarkers, high CRP, low platelet count, low lymphocyte count, high NLR, high PLR, high SII ratio, and high PCT were found to be significant.

The strength of our study is that the patient and control groups were evaluated together and there were no previously known chronic diseases that could cause inflammation, no hospital admissions and a history of drug use in the last month. The limitations of our study are that it is a single-center retrospective study, the number of our patients is limited, lack of long-term follow-up of patients, and other inflammatory markers were not evaluated together. Another limiting factor is that only children with a diagnosis of COVID-19 and a healthy control group were compared in our study, and other viral infections were not evaluated in the study. These tests, which are effective in distinguishing between healthy children and children diagnosed with COVID-19, may also change significantly in other infections (for example, during other viral infections). In future studies, we think that comparing children with a diagnosis of COVID-19, a healthy control group, and those diagnosed with other viral infections will contribute to clinical practice.

Conclusion

This is the first study to describe the first changes in inflammatory markers such as CRP, NLR, PLR, SII, PCT, MPV, platelets and lymphocytes in pediatric patients with COVID-19. Platelet count, lymphocyte count, NLR and PCT are sensitive inflammatory biomarkers that can be easily obtained in differentiating healthy and COVID-19 children. These tests can be used as biomarkers to predict disease severity in pediatric patients. However, more prospective studies are needed to determine the severity of inflammation.

Ethics Committe Approval: Ethics committee approval was obtained from Health Sciences University Gazi Yaşargil Training and Research Hospital before starting the study (11.09.2020/543). The study was carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- GY; Design- MA; Supervision- MA; Resource- GY; Data Collection and/or Processing- GY; Analysis and/or Interpretation- MA; Literature Search - GY; Writing- GY; Critical Review- MA.

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