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The role of the systemic inflammatory index in determining the need for intensive care in COVID-19 pneumonia

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Abstract:

BACKGROUND AND AIM: Coronavirus Disease 2019 (COVID-19) can affect multiple systems simultaneously, particularly the respiratory system. New inflammatory markers have been used to identify high-risk patients and accelerate the decision-making process for admission to intensive care. One of these markers is the Systemic Inflammatory Index (SII), which is a prognostic index associated with peripheral blood parameters such as neutrophils, platelets, and lymphocytes. This study aimed to determine the effect of SII and other inflammatory markers in assessing the need for intensive care.

METHODS: The study included patients over the age of 18 who were admitted to the hospital and hospitalized with COVID-19 pneumonia. They were divided into two groups: those with and without direct admission to intensive care. Demographic, clinical, and laboratory results were obtained retrospectively from the hospital data system.

RESULTS: A total of 335 patients were included in the study. SII, C-reactive protein (CRP), ferritin, and D-dimer values were significantly higher ($p<0.05$) in the group with direct Intensive Care Unit (ICU) hospitalization. In the multivariate reduced model, a significant independent ($p<0.05$) efficacy of age, SII, CRP, ferritin and D-dimer values was observed in differentiating patients who required direct ICU hospitalization from those who did not. An SII cutoff value of 127 was found to be significant (area under the curve 0.786) in distinguishing between the two groups.

CONCLUSIONS: COVID-19 leads to alterations in peripheral blood parameters. Clinical symptoms and disease severity may be associated with the levels of inflammatory cells. These parameters should also be examined to determine the need for intensive care and enable prompt treatment initiation.

Keywords:

Intensive care, prognosis, systemic inflammatory index

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Introduction

In December 2019, an outbreak with predominantly respiratory-related symptoms was discovered in Wuhan, China, which later escalated into a pandemic.[1] It was determined that the outbreak was caused by a coronavirus, specifically the 2019 novel coronavirus (2019-nCoV virus), belonging to the ribonucleic acid (RNA) virus family.[2] Coronavirus Disease 2019 (COVID-19) exhibits a wide range of clinical presentations, ranging from asymptomatic cases to severe respiratory failure.[3,4]

COVID-19 exerts systemic effect through the activation of inflammatory mediators such as Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-alpha). Pneumonia, Acute Respiratory Distress Syndrome (ARDS), sepsis, and multiple organ failure have been identified as the primary causes of mortality in some cases.[4] The virus affects various systems, predominantly the respiratory system (causing symptoms such as cough, dyspnea, and pneumonia), as well as the cardiovascular (acute coronary syndrome, acute myocardial infarction, myocarditis), neurological (headache, confusion, encephalitis), and gastrointestinal systems (diarrhea, vomiting, abdominal pain).[5] Treatment and management approaches are based on the treatment methods for ARDS, retrospective data analysis of COVID-19 patient outcomes, expert opinions, and lessons learned from previous outbreaks.[6]

To predict mortality in hospitalized COVID-19 patients, various laboratory values and patient characteristics are utilized. Risk factors for ARDS include advanced age (>65), comorbidities (such as hypertension and diabetes), high fever (39°C), neutrophilia, lymphopenia, elevated levels of C-reactive protein (CRP) and serum ferritin, prolonged prothrombin time, and increased D-dimer values.[7] Studies have shown that elevated levels of CRP, procalcitonin, erythrocyte sedimentation rate (ESH), D-dimer, serum ferritin, and decreased neutrophil-lymphocyte ratio (NLR) are associated with severe disease and mortality in both young patients without comorbidities and elderly patients with comorbidities.[8]

Epidemiologists believe that the COVID-19 infection is ongoing and will continue to be present in 2025 and beyond, with annual fluctuations.[9] Consequently, recent publications have discussed the use of inexpensive and easily accessible new inflammatory markers to determine disease prognosis and identify patients at risk for intensive care admission. One such marker is the Systemic Inflammatory Index (SII), which is a prognostic index associated with neutrophils, platelets, and lymphocytes derived from peripheral blood parameters. SII has been used to predict the prognosis of sepsis and certain types of carcinomas.[10] It has been found to be a good prognostic factor for COVID-19 patients, with 74.9% sensitivity and 68.9% specificity.[11] COVID-19 patients admitted to the Intensive Care Unit (ICU) face twice the risk of thrombotic complications.[3] Therefore, recent studies have aimed to develop inexpensive and rapid diagnostic methods to identify the at-risk population that may require ICU admission.

The objective of this study was to observe how rapid, reliable, and accessible biomarkers, such as leukocyte count, NLR, Platelet/Lymphocyte Ratio (PLR), SII, CRP, D-dimer, and serum ferritin levels measured during hospitalization, influenced the need for intensive care.

Materials and Methods

Study design

Our study was designed as a single-center, retrospective observational cohort study, and patients between March 2020 and March 2021 were selected from the hospital's electronic data system. The study protocol was approved by the Republic of Türkiye Ministry of Health and the local Clinical Research Ethics Committee of the tertiary hospital (Decision no: 08.07.2020-05). The study adhered to the criteria set forth in the Declaration of Helsinki throughout.

Study sample

The study included patients over the age of 18 who presented to the emergency department or the COVID-19 outpatient clinic and were hospitalized with a positive result on reverse transcription-polymerase chain reaction (RT-PCR) test. Pregnant patients, as well as those with chronic liver disease, nephrotic syndrome, hematological disease, and malignancy, were excluded from the study. As per the Ministry of Health guidelines, patients were categorized as mild, moderate, severe, or requiring intensive care. Patients with symptoms such as fever, muscle and joint pains, cough, and sore throat, with a respiratory rate below 30 per minute and oxygen saturation above 90% in room air, and exhibiting mild to moderate pneumonia findings on chest X-ray or tomography, were classified accordingly. In addition to clinical findings, individuals with a respiratory rate above 30 and a

room air oxygen saturation below 90 were classified as severe cases. Patients who experienced respiratory distress in addition to severe pneumonia findings, had a Partial Pressure of Oxygen/Fraction of Inspired Oxygen (PaO_2/FiO_2< 300) ratio below 300, increased oxygen demand during follow-up, and exhibited hypotension and arrhythmia were directly admitted to the ICU.[12]

Study protocol

Patient data was obtained through retrospective scans conducted on the hospital information management system. The case data forms recorded age, sex, other demographic information, comorbidities, laboratory parameters, and the outcomes of these cases. The patients' symptoms including cough, dyspnea, fever, and other relevant factors, as well as vital signs at the time of admission and saturation values, were examined.

During hospitalization, patients were admitted to either the ward or the intensive care unit based on the case definitions provided in the Ministry of Health General Directorate of Public Health COVID-19 (Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2)) Infection Adult Patient Treatment Guidelines. According to the guidelines, patients with symptoms such as fever, muscle and joint pains, cough, and sore throat, with a respiratory rate below 30 per minute and oxygen saturation above 90% in room air, and exhibiting mild to moderate pneumonia findings on chest X-ray or tomography, were categorized accordingly. In addition to clinical findings, individuals with a respiratory rate above 30 and a room air oxygen saturation below 90 were considered as severe cases. Patients who developed respiratory distress in addition to severe pneumonia findings, with PaO_2/FiO_2< 300, increased oxygen demand during follow-up, and experienced hypotension and arrhythmia, constituted the patient group that was directly admitted to the intensive care unit.

The first complete blood count, complete biochemistry, D-dimer, CRP, ferritin, and saturation values were obtained from the hospital data system during hospitalization. NLR, PLR, and SII were calculated based on hemogram parameters, and SII was derived from the Neutrophil x Platelet/Lymphocyte formula. Thorax computed tomography (CT) images were evaluated using the hospital system. Patients with typical findings for COVID-19 on thorax CT were diagnosed as CT(+) COVID-19 pneumonia. Typical CT manifestations of COVID-19 pneumonia include ground glass opacities, consolidation, reticular pattern, and crazy paving pattern.[13] The study aimed to examine the effects of laboratory findings obtained at the time of hospitalization on disease progression, the prediction of the need for intensive care, prognosis, and mortality.

Table 1: Demographic and clinical results of the patients

	Min-max	Median	Mean±SD	n	%
Age	19.0–95.0	57.0	56.5±18.5		
Sex					
Female				121	36.1
Male				214	63.9
Comorbidities					
(–)				151	45.1
(+)				184	54.9
HT				115	34.3
DM				59	17.6
COPD				10	3.0
Asthma				28	8.4
CVD				37	11.0
Obesity				6	1.8
Others				25	7.5

SD: Standard deviation, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CVD: Cardiovascular disease

Statistical analysis

Descriptive statistics of the data included mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was utilized for analyzing quantitative independent data. The Chi-square test was employed for analyzing qualitative independent data, and the Fisher's exact test was used when the conditions for the Chi-square test were not met. The effect levels and cut-off values were investigated using the Receiver Operating Characteristic (ROC) curve. The effect level was examined through univariate and multivariate logistic regression. The selection of variables for comparison was based on literature reviews and clinical experience. The Statistical Package for the Social Sciences (SPSS) 28.0 (IBM, NY, USA) program was used for the analyses.

Results

A total of 335 patients were included in the study. The median age was 57 (range 19–95). Among the patients, 121 (36.1%) were female and 214 (63.9%) were male. Comorbidities were present in 54.9% of the patients. The three most common comorbidities were hypertension (HT), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) (Table 1). Fever was present

Table 2: Clinical results of the patients

	n	%
CT findings		
(-)	78	23.3
(+)	257	76.7
Fever		
(-)	147	43.9
(+)	188	56.1
Symptoms		
(-)	34	10.1
(+)	301	89.9
Cough	137	40.9
Dyspnea	111	33.1
Malaise	76	22.7
Myalgia	34	10.1
Sore throat	17	5.1
Headache	25	7.5
Anosmia	11	3.3
Loss of taste	9	2.7
Diarrhea-vomiting	8	2.4
Chest pain	4	1.2
Runny nose	3	0.9
Somnolence	5	1.5
Others	7	2.1
Case classification		
Mild	175	52.2
Moderate	73	21.8
Severe	87	26.0

CT: Computed tomography

in 56.1% of the cases. The most common symptom reported was cough (40.9%), followed by dyspnea (33.1%) and fatigue (22.7%). Thoracic CT findings consistent with COVID-19 pneumonia were observed in 76.7% of the cases. Among the cases, 26% were classified as severe upon initial admission. In total, 77 (23%) patients required ICU care at the time of admission and thereafter. Of the patients, 86.3% were discharged and 13.7% died (Table 2). The ages of patients who were directly admitted to the ICU were significantly higher ($p<0.05$) compared to those in the group without ICU admission. There was no significant difference ($p>0.05$) in terms of sex distribution between the two groups. Comorbidities were significantly more prevalent ($p<0.05$) in patients admitted directly to the ICU. The rates of HT and cardiovascular disease (CVD) were found to be significantly higher in the group with ICU hospitalization compared to the other group ($p<0.05$). However, the rates of DM, COPD, asthma, and obesity did not differ significantly between the two groups ($p>0.05$). Thoracic CT findings were significantly more frequent in the group with direct ICU admission ($p<0.05$). In terms of symptoms, there was no significant difference ($p>0.05$) in fever rates between the two groups. However, the presence of dyspnea and somnolence at the time of admission was significantly higher in the ICU group ($p<0.05$), while the rates of cough, fatigue, and myalgia were significantly lower ($p<0.05$) (Table 3). White Blood Cell (WBC), neutrophil count, NLR, PLR, SII, CRP, ferritin, and D-dimer levels were significantly higher ($p<0.05$) in the group with direct ICU admission, while hemoglobin, lymphocyte count, and oxygen saturation levels were significantly lower ($p<0.05$). There was no significant difference in platelet count between the two groups (Table 4). In the univariate model, age, hemoglobin, WBC, neutrophil count, lymphocyte count, NLO, PLR, SII, CRP, ferritin, D-dimer, oxygen saturation, presence of comorbidities (HT, CVD), CT findings, cough, weakness, and myalgia were found to have significant effects in distinguishing patients with and without direct ICU admission ($p<0.05$). In the multivariate reduced model, age, SII, CRP, ferritin, and D-dimer values were found to have significant independent efficacy in separating patients who required and did not require direct ICU admission ($p<0.05$) (Table 5). SII demonstrated significant efficiency (area under the curve = 0.77) in distinguishing between patients who needed and did not need direct ICU admission. The SII cut-off value of 127 was found to be significant in separating both groups (area under the curve = 0.786). The sensitivity was 75.0%, the positive estimate was 30.8%, the specificity was 82.2%, and the negative estimate was 96.9% [Fig. 1].

Discussion

COVID-19 is a disease caused by SARS-CoV-2 that affects multiple systems, with the lungs being the primary target organ. In severe cases, it can lead to acute respiratory distress syndrome, which can be fatal.[14] Recent studies have shown that the virus binds to receptors, enters alveolar cells, and activates macrophages, leading to the release of inflammatory factors.[15] As a result of inflammation, chemokines and cytokines, which are factors that utilize mononuclear cells, are released. This leads to increased immune activation, resulting in a cytokine storm and subsequent tissue damage.[8] Studies have demonstrated that the worsening of clinical symptoms and prognosis in COVID-19 is directly associated with the immune system and an elevated inflammatory response.[16] Consequently, researchers have investigated the role of specific ratios, such as neutrophil/lympho-

Table 3: Distribution of demographic data by groups

	Direct ICU hospitalization (–)				Direct ICU hospitalization (+)				p	
	n	Mean±SD	%	Median	n	Mean±SD	%	Median		
Age		54.5±17.9		55.0		74.8±12.8		76.5	0.000	m
Sex										
Female	107		35.3		14		43.8		0.345	X²
Male	196		64.7		18		56.3			
Comorbidities										
(–)	148		48.8		3		9.4		0.000	X²
(+)	155		51.2		29		90.6			
HT	96		31.7		19		59.4		0.002	X²
DM	51		16.8		8		25.0		0.249	X²
COPD	10		3.3		0		0.0		0.607	X²
Asthma	27		8.9		1		3.1		0.261	X²
CVD	27		8.9		10		31.3		0.000	X²
Obesity	6		2.0		0		0.0		1.000	X²
Others	19		6.3		6		18.8		0.011	X²
CT findings										
(–)	76		25.1		2		6.3		0.017	X²
(+)	227		74.9		30		93.8			
Symptoms										
(–)	34		11.2		0		0.0		0.046	X²
(+)	269		88.8		32		100.0			
Dyspnea	82		27.1		29		90.6		0.000	X²
Cough	133		43.9		4		12.5		0.001	X²
Malaise	74		24.4		2		6.3		0.020	X²
Myalgia	34		11.2		0		0.0		0.046	X²
Sore throat	17		5.6		0		0.0		0.388	X²
Headache	25		8.3		0		0.0		0.091	X²
Anosmia	11		3.6		0		0.0		0.609	X²
Loss of taste	9		3.0		0		0.0		1.000	X²
Diarrhea-vomiting	8		2.6		0		0.0		1.000	X²
Chest pain	4		1.3		0		0.0		1.000	X²
Runny nose	3		1.0		0		0.0		1.000	X²
Somnolence	2		0.7		3		9.4		0.007	X²
Others	7		2.3		0		0.0		1.000	X²
Case classification										
Mild	175		57.8		0		0.0		0.000	X²
Moderate	73		24.1		0		0.0			
Severe	55		18.2		32		100.0			
Result										
Died	20		6.6		26		81.3		0.000	X²
Discharged	283		93.4		6		18.8			

m: Mann-Whitney U test, X^2: Chi-square test (Fisher test). ICU: Intensive care unit, SD: Standard deviation, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CVD: Cardiovascular disease, CT: Computed tomography

cyte, thrombocyte/lymphocyte, and monocyte/lymphocyte ratios in the diagnosis of various inflammatory conditions and prognoses.[17,18] Building upon these findings, our aim was to evaluate the role of inflammatory parameters measured in peripheral blood in COVID-19 patients, particularly in identifying and predicting the prognosis of patients requiring ICU admission.

Given the presence of comorbidities and weakened immunity, it is expected that elderly patients would have a higher risk of ICU hospitalization. Similar to our study, numerous studies have demonstrated the relationship between COVID-19 severity and advanced age.[14,19,20] However, a large study with over 5,000 cases did not find a significant age difference between patients in the ICU and those out-

Table 4: Distribution of laboratory parameters based on groups

	Direct ICU hospitalization (–)			Direct ICU hospitalization (+)			p
	Mean±SD	1Q3Q	Median	Mean±SD	1Q3Q	Median	
Hemoglobin	13.9±1.8	12.8–15.2	14.1	13.0±2.4	10.9–14.9	13.2	**0.040** [m]
WBC	6.6±2.8	4.8–7.8	6.0	10.5±5.4	6.9–14.9	8.7	**0.000** [m]
Neutrophil (×10³)	4.5±2.7	2.8–5.4	3.9	8.9±5.3	5.3–13.5	7.5	**0.000** [m]
Lymphocyte (×10³)	1.5±1.3	0.9–1.8	1.3	1.0±1.0	0.5–1.2	0.7	**0.000** [m]
Platelets (×10³)	203.5±68.8	161–233	193	222.2±89.8	133.5–258	232	**0.199** [m]
NLR	4.3±4.5	1.8–5	2.7	15.2±14.6	5.1–17.8	10.5	**0.000** [m]
TLR	176.6±119.5	108.4–196.1	141.3	371.6±314.1	173.6–529.3	240.6	**0.000** [m]
SII	88.7±105.3	0.0–0.1	52.3	389.2±439.4	0.1–0.7	224	**0.000** [m]
CRP	42.3±56.5	4.6–58.1	16.7	159.6±93.4	73.3–213.8	159.5	**0.000** [m]
Ferritin	269.5±276.9	88–360	180	785.1±1237.9	291.8–725.8	489.5	**0.000** [m]
D.Dimer	1.3±5.0	0.3–1	0.5	8.1±16.5	0.9–5	1.8	**0.000** [m]
ST O_2 %	93.6±3.6	92–96	95.0	74.1±12.3	65.8–85	76.5	**0.000** [m]

[m]: Mann-Whitney U test. ICU: Intensive care unit, SD: Standard deviation, WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, TLR: Platelet/lymphocyte ratio, SII: Systemic inflammatory index, CRP: C-reactive protein, ST: Saturation

Table 5: Results of logistic regression analysis

	Univariate model			Multivariate model		
	OR	95% CI	p	OR	95% CI	p
Age	1.086	1.053–1.121	**0.000**	1.108	1.055–1.164	**0.000**
Hemoglobin	0.800	0.672–0.952	**0.012**			
WBC	1.281	1.159–1.415	**0.000**			
Neutrophil	1.320	1.195–1.459	**0.000**			
Lymphocyte	0.333	0.163–0.682	**0.003**			
NLR	1.160	1.100–1.222	**0.000**			
TLR	1.005	1.003–1.007	**0.000**			
SII	239.7	31.7–1813.5	**0.000**	1.001	1.000–1.001	**0.043**
CRP	1.017	1.012–1.022	**0.000**	1.013	1.006–1.019	**0.000**
Ferritin	1.002	1.001–1.003	**0.000**	1.001	1.001–1.002	**0.000**
D.Dimer	1.068	1.024–1.114	**0.002**			
ST O_2 %	0.613	0.518–0.726	**0.000**			
Comorbidities	9.230	2.753–30.948	**0.000**			
HT	3.151	1.495–6.644	**0.003**			
CVD	4.646	1.995–10.823	**0.000**			
CT Findings	5.022	1.172–21.511	**0.030**			
Cough	26.053	7.727–87.840	**0.000**			
Malaise	0.183	0.063–0.533	**0.002**			
Myalgia	0.206	0.048–0.884	**0.034**			

OR: Odds ratio, CI: Confidence interval, WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, TLR: Platelet/lymphocyte ratio, SII: Systemic inflammatory index, CRP: C-reactive protein, ST: Saturation, HT: Hypertension, CVD: Cardiovascular disease

side the ICU.[21] Hamad et al.[22] reported in their study that patients admitted to the ICU were older and predominantly male. In our study, age was found to be significantly higher in patients admitted to the ICU, although there was no significant difference in terms of gender. When considering comorbidities such as DM, HT, COPD, and CVD, HT was the most prevalent comorbidity among ICU-hospitalized patients, which aligns with the findings of Akhtar et al.'s[23] study. In our study, unlike other studies, CVD was the second most common comorbidity, not diabetes. This difference could be attributed to variations in the patient populations across the countries where the studies were conducted.

In autopsies performed on patients who died due to COVID-19, neutrophil infiltration was detected in the pulmonary capillaries and alveolar spaces, indicating serious inflammation in the airways.[24] Since both lymphopenia and pathological neutrophil infiltration were observed in the peripheral blood and tissues of COVID-19 patients, inflammation indices based on parameter ratios were de-

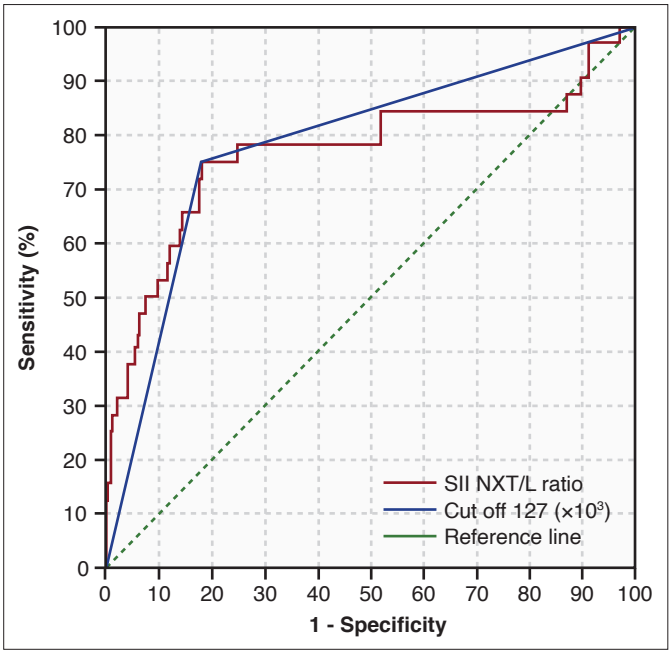

Figure 1: Receiver operating characteristic (ROC) curve of systemic inflammatory index (SII)
NXT/L: Neutrophil×Thrombocyt/lymphocyte

veloped. In the study of Xue et al.,[25] one of these indices, SII, was found to be higher in severe COVID-19 cases compared to mild and moderate cases. Similarly, in our study, SII was significantly higher in the patient group requiring direct ICU admission compared to the other group. Similar to our study, NLR and PLR values were found to be higher in the group of cases with a poor clinical course in the same study. Salman et al.[26] discovered that high SII, high ferritin levels, high NLR, high CRP, and lymphopenia were associated with a more severe disease progression, and the rates of intensive care unit admission, intubation, and mortality were higher in these patients. In our study, SII, NLR, PLR, ferritin, and CRP levels were significantly higher in patients who required direct ICU care, while lymphocyte counts were significantly lower. The effectiveness of age, SII, CRP, ferritin, and D-dimer values in differentiating between patients who required and did not require direct intensive care unit hospitalization was observed in our study's multivariate reduced model. In the study of Fois et al.,[27] it was reported that SII can specifically indicate pulmonary damage.

Furthermore, our study found that the SII value increased with the severity of the disease. In our study, the SII and 127 cut-off values were found to be significantly effective in distinguishing patients who went directly to the ICU. In the study by Karaaslan et al.,[28] the predictive value of SII in determining mortality in COVID-19 was investigated. It was concluded that there is a significant correlation with mortality, and the cut-off value was found to be 619. Similarly, in the study by Nalbant et al.,[29] the cut-off value for SII was found to be 813.6 in predicting the severity of the disease in COVID-19.

A new inflammation index, PLR, reflects the level of systemic inflammation. The causes of low platelet count in COVID-19 infections include a decrease in platelet synthesis by degeneration of bone marrow precursor cells, autoantibody formation, and immune-complex-mediated platelet destruction. Increased PLR levels were found to be correlated with the severity of COVID-19 in the study by Simadibrata et al.[30] Our research yielded similar results.

There are some limitations in the study. Firstly, it was a single-center and retrospective study. Patient data were accessed from the hospital database. Furthermore, because COVID-19 treatment was not standardized during the patients' hospitalization, treatment planning was based on the patient's situation and accumulated experiences.

In conclusion, COVID-19 causes changes in peripheral blood parameters, and the clinical symptoms and severity of the disease may be related to the proportion of inflammatory cells. These parameters should also be examined to determine the disease's prognosis, the need for intensive care, and to quickly initiate treatment. Prospective studies with a larger number of patients and proper design should also be conducted.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the Kahramanmaraş Sütçü İmam University Faculty of Medicine Clinical Research Ethics Committee (No: 05, Date: 08/07/2020).

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Authorship Contributions
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