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Original Research

Evaluation of the Relationship Between Biomarkers and Disease Severity in Patients with Community-Acquired Pneumonia

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ABSTRACT

Objective: Biomarkers in community-acquired pneumonia (CAP) have the potential to facilitate clinical decisions by guiding the prediction of disease severity, treatment and prognosis. In this study, we evaluated the relationship of biomarkers with disease severity in patients with CAP.

Methods: 156 patients diagnosed with CAP were included in the study. Diagnosis of CAP was determined according to the Infectious Diseases Society of America (IDSA)/ American Thoracic Society(ATS) 2019 guidelines along with clinical findings. The CRB-65 scoring system was used to determine outpatient and hospitalized patients. Patient information was obtained retrospectively from their files. In these two patient groups; C-reactive protein (CRP), complete blood count (CBC) parameters, neutrophil/ lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/neutrophil ratio (MNR), lymphocyte/monocyte ratio (LMN), lymphocyte/CRP ratio (LCR), WBC/mean platelet volume ratio (WBC/MPV), CRP/MPV ratio, and MPV/PLT ratio were examined.

Results: Of the 156 patients included in the study, 72 were pneumonia patients receiving inpatient treatment (mean age 66.88±16.29) and 84 patients receiving outpatient treatment (mean age 51.57±16.68). Age was found to be statistically significant between the groups ($p< 0.001$). In the inpatient group; CRP, WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, hematocrit, MPV, NLR, PLR, LMR, NMR, LMR, LCR, WBC/ MPV, and CRP/MPV were found to be significantly high ($p<0.05$). Parameters with diagnostic performance that may be helpful in distinguishing hospitalized patients with pneumonia are CRP/MPV (AUC:0.775, 95% CI:0.701-0.850), NLR (AUC:0.771, 95% CI:0.697-0.846) and CRP (AUC:0.758, 95% Cl:0.679-0.837).

Conclusion: NLR and CRP/MPV values, which can be measured easily and quickly together with CRP, can be used as additional tests to help distinguish patients with pneumonia requiring hospitalization.

Keywords: Biomarkers in Pneumonia, C-reactive protein, Community-acquired pneumonia, Disease Severity Assessment, Mean platelet volume

INTRODUCTION

Despite advancements in diagnostic and treatment methods, community-acquired pneumonia (CAP) continues to be a prevalent infectious disease that can lead to severe health issues and mortality [1,2]. In spite of precautions, the disease's effects and the burden on health systems are anticipated to increase in the upcoming years due to factors such as the nature of the disease and its rate of spread, the inadequacy of existing prevention strategies [3]. Clinical evaluation, pneumonia-specific severity scores, and biomarkers can provide additional information about the severity and etiology of the disease [4,5].

In CAP infections, it is important to determine the causative pathogens in disease management. However, identifying the causative pathogens is quite challenging and sometimes requires invasive methods. Non-invasive diagnostic methods that can identify outpatients and patients requiring hospitalization for CAP infections have been frequently investigated in recent years. Non-invasive diagnostic methods, such as identifying new specific biomarkers, can contribute to the evaluation and management of CAP. At the same time, they can identify CAP subgroups that require closer monitoring and determine patients who may have unfavorable long-term consequences [6–8].

Biomarkers are emerging as critical biological molecules in the evaluation of CAP. Acute phase proteins in the blood begin to increase in response to cytokines secreted by cells (tumor necrosis factor, interleukin-1, and 6). However, the appearance times of acute phase proteins are not specific. In particular, parameters such as WBC, neutrophils, CRP, and procalcitonin are known as inflammatory biomarkers in pneumonia [9,10]. They are assumed to be useful in assessing microbial features and the severity of illness in pneumonia, and in determining the course of antibiotic treatment [11–13].

Main Points:

- The role of biomarkers is important in determining the severity of the disease in patients with community-acquired pneumonia (CAP).
- Traditional biomarkers such as C-reactive protein and new biomarkers such as NLR and CRP/MPV play an important role in distinguishing pneumonia requiring hospitalization.
- The CRP/MPV ratio, as a simple and easily accessible biomarker, can guide the clinical decision-making process in determining the level of CAP.

Complete blood count (CBC) parameters are simple, inexpensive, and accessible measurements. There are studies suggesting that parameters such as red blood cell distribution width (RDW), MPV, and the ratios of CBC parameters (NLR, PLR, LMR, and MPV/PLT etc) are significant indicators of systemic inflammation [14,15]. Platelets play crucial roles in immune and inflammatory processes [16]. An increase in MPV is thought to be a sign of severe inflammation and elevated platelet activity [17]. In recent years, new parameters such as the CRP/MPV and WBC/MPV ratios have been studied to assess inflammation [9,18]. However, studies examining the significance of these ratios in the identification and monitoring of pneumonia and other diseases with acute inflammation are limited.

In this research, we assessed the values of CRP complete blood count parameters, and the biomarkers obtained by their ratios in determining disease severity and identifying patients requiring hospitalization in patients with CAP.

MATERIALS AND METHODS

The study was carried out by retrospectively reviewing the files of 2785 patients who presented to the Pulmonology Clinic of Konya Meram State Hospital between May 2022 and May 2023 and were diagnosed with pneumonia. Exclusion criteria for the study were set as patients under the age of 18, those who were PCR positive for Covid-19, and patients with missing or inaccessible laboratory and radiological data. Based on these criteria, 156 patients were included in the study. Laboratory parameters, radiological and demographic characteristics of the cases included in the study were obtained from the hospital information management system. The diagnosis of pneumonia was based on clinical findings as well as the guidelines of the American Infectious Diseases Society (IDSA)/American Thoracic Society (ATS) 2019. To decide on outpatient treatment or hospitalization, patients were divided into two groups using the CRB-65 scoring system (confusion, respiratory rate >30 breaths·min−1, blood pressure <90 mmHg (systolic) or <60 mmHg (diastolic), age >65 years). 72 patients (CRB-65=0) constituted the outpatient pneumonia group, and 84 patients (CRB-65≥1) constituted the inpatient pneumonia group. In addition, hospitalized patients were grouped within themselves according to their length of stay as 7 days and above and below 7 days. Case groups were evaluated by comparing them in terms of biomarkers and radiological findings. In both groups, complete blood count parameters such as CRP, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin-

Hbg, hematocrit-Htc, platelet-PLT, Platelet Distribution Width-PDW, plateletcrit-PCT, Mean Platelet Volume-MPV, and their ratios (Neutrophil/Lymphocyte ratio-NLR, Neutrophil/Monocyte ratio-LMR, Platelet/Lymphocyte ratio-PLR, Lymphocyte/CRP ratio-LCR, MPV/PLT ratio, and CRP/MPV ratio) were compared.

Statistical Analyses

The software SPSS 22.0 was used to analyze the data. The normal distribution was tested using the Kolmogorov-Smirnov method. For comparing continuous variables, the t-test or Mann-Whitney U test was recommended, while the chi-square test was utilized for categorical variables. The Pearson correlation test was used to look at the correlations between the variables. For diagnostic prediction and performance, ROC analysis and logistic regression were employed. The tests were deemed to have a significance level of $P<0.05$.

RESULTS

Of the 156 patients who met the admission criteria, 72 were treated as inpatients and 84 as outpatients. The average age were involved in the study as outpatients with pneumonia was 51.57 ± 16.68, while it was 66.88 ± 16.29 for those treated as inpatients. The average age of patients with pneumonia receiving treatment in the hospital was significantly higher compared to those treated as outpatients ($p< 0.001$). In the group of pneumonia patients treated in the hospital, CRP, WBC, neutrophils, lymphocytes, monocytes, basophils, hemoglobin, hematocrit, MPV, NLR, PLR, LMR, NMR, LCR, WBC/MPV ratio, and CRP/MPV ratio were considerably higher in comparison with the outpatient pneumonia group ($p< 0.05$) (Table 1).

Table 1. Comparison of Laboratory Parameters Between Patients Treated as Outpatients and Inpatients.

Parameters	Outpatient Pneumonia Cases (mean ± SD)	Inpatient Pneumonia Cases (mean ± SD)	p-value
AGE (years)	51.57±16.68	66.88±16.29	<0.001
WBC (/uL)	8.48±0.81	10.38±4.42	<0.001
Neutrophil (x10^3 /µL)	5.35±2.43	7.97±4.36	<0.001
Hbg (g/dL)	14.17±1.68	12.75±2.14	<0.001
Hct (%)	43.74±5.55	39.51±6.19	<0.001
MCV(fL)	86.76±6.05	88.10±5.66	0.158
PLT (x10^3 /µL)	259.97±72.91	271.79±80.288	0.337
PDW (fL)	19.17±2.35	19.02±2.33	0.684
MPV (fL)	8.54±1.44	7.94±1.40	0.010
PCT (ng/mL)	0.21±0.06	0.22±0.07	0.826
Lymphocyte (x10^3/µL)	2.21±0.78	1.57±0.73	0.001
Monocyte (x10^3 /µL)	0.63±0.23	0.66±0.28	0.007
Eosinophil (x10^3 /µL)	0.18±0.20	0.10±0.19	0.085
Basophil (x10^3 /µL	0.08±0.04	0.06±0.05	<0.001
CRP (mg/L)	12.75±14.08	51.18±49.47	<0.001
PLR	132.26±61.49	212.57±126.88	<0.001
NLR	2.72±1.66	6.41±5.2	<0.001
NMR	9.12±5.43	12.65±6.62	<0.001
LMR	3.86±1.76	2.78±1.83	<0.001
LCR	0.36±0.29	0.12±0.20	<0.001
WBC/MPV	1.02±0.40	1.33±0.60	<0.001
CRP/MPV	1.58±2.01	7.41±0.30	<0.001
MPV/PLT	0.03±0.01	0.03±0.01	0.100

WBC: White Blood Cells, Hbg: Hemoglobin, Hct: Hematocrit, MCV: Mean Corpuscular Volume, PLT: Platelets, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume, PCT: Plateletcrit, CRP: C-Reactive Protein, PLR: Platelet to Lymphocyte Ratio, NLR: Neutrophil to Lymphocyte Ratio, NMR: Neutrophil to Monocyte Ratio, LMR: Lymphocyte to Monocyte Ratio, LCR: Lymphocyte to CRP Ratio, WBC/MPV, CRP/MPV, MPV/PLT: Ratios of the respective parameters

No gender difference was observed between the patient groups (p> 0.05). Radiological findings showed substantial variations between the groups (p< 0.001). Bilateral multilobar involvement was more common in the group with pneumonia treated as inpatients, while minimal atypical involvement was more common in the group with pneumonia treated as outpatients (Table 2).

Correlation analysis revealed high levels of positive and negative relationships between laboratory values. The relationship between white blood cells (WBC) and neutrophils is quite strong (r 0.962, p< 0.01). Likewise, there is a strong positive correlations between WBC and the WBC/MPV ratio (r 0.912, p< 0.001). High levels of strong positive correlations were found between neutrophils and WBC (r 0.962, p< 0.001), neutrophils and the Neutrophil/Lymphocyte ratio (NLR) (r 0.749, p< 0.001), and neutrophils and WBC/MPV (r 0.885, p< 0.001). Additionally, strong positive correlations were found between CRP and CRP/MPV (r 0.783, p< 0.001), hemoglobin (Hbg) and hematocrit (Htc) (r 0.926, p<0.01), hemoglobin and red blood cell (RBC) (r 0.811, p<0.01), platelet (PLT) and MPV / PLT (r 0.782, p< 0.01). On the other hand, a strong negative correlation was determined between MPV/PLT and PLT (r 0.782, p< 0.01).

According to logistic regression analysis, factors predicting inpatient treatment of pneumonia patients were determined. Age factor (B: -0.039, Odds Ratio(OR): 0.961, 95% Confidence Interval (CI): 0.935-0.989, p=0.006), C-reactive protein (CRP) level (B: -0.048, OR: 0.954, CI: 0.933-0.975, p< 0.001), Neutrophil/Lymphocyte ratio(NLR) (B: -0.413, OR: 0.661, CI: 0.546-0.802, p< 0.001) and Mean Platelet Volume(MPV) (B: 0.462, OR: 1.587, CI: 1.108-2.274, p=0.012) were identified as s important components in predicting the necessity of hospitalization for pneumonia patients (Table 3).

Table 3. Predictive Factors for Patients Receiving Inpatient Treatment.

Parameters	B	OR	95%CI	p
Age	-0.039	0.961	0.935-0.989	0.006
CRP	-0.048	0.954	0.933-0.975	<0.001
NLR	-0.413	0.661	0.546-0.802	<0.001
MPV	0.462	1.587	1.108-2.274	0.012

B: Regression Coefficient, C-Reactive Protein (CRP), Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV), B values, Odds Ratios (OR), 95% Confidence Intervals (95% CI).

Table 2. Comparison of Gender and Radiological Findings Between Patients with Pneumonia Treated as Outpatients and Inpatients.

Parameters	Outpatient Pneumonia Patients n (%)	Inpatient Pneumonia Patients n (%)	p-value
GENDER			
Male	41 (48.8)	42 (58.3)	0.23
Female	43 (51.2)	30 (41.7)	
RADIOLOGY			
Minimal Atypical	54 (64.3)	0 (0.0)	
Unilateral Single Lobe	30 (35.7)	22 (30.6)	
Single Lung Multilober	0 (0.0)	16 (22.2)	<0.001*
Bilateral Multilober	0 (0.0)	34 (47.2)	

Chi-square Test. *Significant at the 0.05 level.

According to the results of the Receiver Operating Characteristic (ROC) analysis, it was observed that the diagnostic performances of CRP/MPV, NLR, and CRP values could be helpful in distinguishing pneumonia cases requiring hospital treatment from those that can be treated on an outpatient basis. The Area Under the Curve(AUC) and 95% confidence intervals(CI) are as follows: For CRP/MPV, AUC= 0.775 (95% CI: 0.701-0.850), for NLR, AUC=0.771 (95% CI: 0.697-0.846), and for CRP, AUC=0.758 (95% CI: 0.679-0.837) (Figure 1). The sensitivity and specificity values for the optimal threshold values of CRP/MPV, NLR, and CRP that can be used in diagnosis are as follows: For CRP/MPV, 1.26 (75.6% sensitivity and 60.0% specificity), for NLR, 2.48 (73.6% sensitivity and 58.3% specificity), and for CRP, 12.1 (73.6% sensitivity and 65.5% specificity) (Table 4).

Figure. ROC curves for the diagnostic performance of biomarkers in distinguishing pneumonia cases requiring hospital treatment.

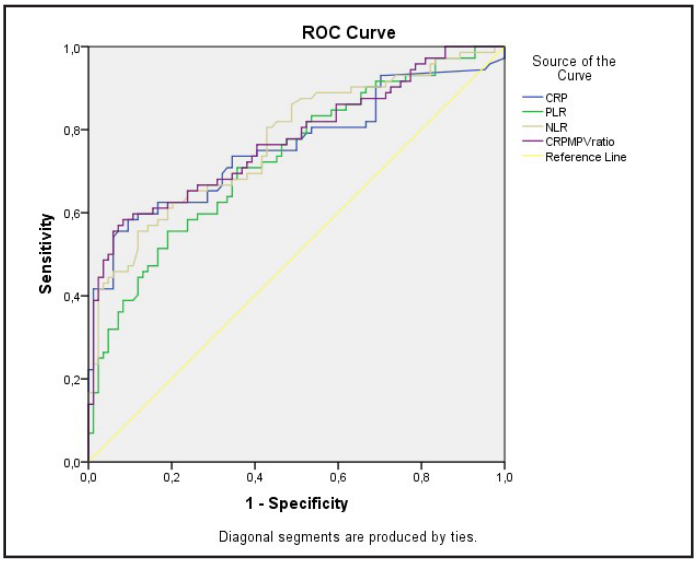

Table 4. Diagnostic Performance of CRP/MPV, NLR, and CRP Threshold Values in Predicting Hospitalized Pneumonia Patients According to ROC Analysis.

Parameters	Cutoff	Sensitivity, %	Specificity, %
CRP/MPV	1.26	75.6	60.0
NLR	2.48	73.6	58.3
CRP	12.1	73.6	65.5

C-Reactive Protein (CRP), Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV).

When patients with pneumonia were evaluated among themselves based on their length of stay, significant relationships were found between some biomarkers and length of stay. CRP, LCR, and CRP/MPV ratio were found substantially greater in patients staying in the hospital for 7 days and above ($p<0.05$) (Table 5).

Table 5. Relationship between Biomarkers and Length of Hospital Stay in Patients with Pneumonia Treated as Inpatients.

Parameters	Length of Hospital Stay <7 days Median (25%-75%)	Length of Hospital Stay ≥7 days Median (25%-75%)	p-value
AGE (years)	75.00 (47.00-79.00)	70.00 (61.25-78.00)	0.684
WBC (/uL)	7.80 (6.20-12.97)	9.30 (7.82-13.55)	0.382
Neutrophil (x103/µL)	5.50 (3.30-10.45)	6.45 (4.95-11.62)	0.364
Hgb (g/dL)	12.60 (10.55-13.95)	12.95 (11.50-14.57)	0.255
Hct (%)	38.80 (32.20-14.50)	40.24 (35.67-44.00)	0.187
MCV (fL)	86.60 (80.75-92.90)	88.35 (85.17-91.30)	0.390
PLT	252.00 (203.00-367.00)	281.00 (220.50-314.00)	0.855
PDW (fL)	19.30 (18.40-19.65)	19.55 (19.00-20.20)	0.145
MPV (fL)	7.40 (6.90-8.60)	7.90 (6.80-18.87)	0.472
PCT (ng/mL)	0.20 (0.10-0.30)	0.20 (0.20-0.30)	0.574
Lymphocyte (x103/µL)	1.40 (1.20-2.15)	1.45 (0.92-2.07)	0.621
Monocyte (x103 /µL)	0.70 (0.40-0.78)	0.70 (0.40-0.80)	0.962
Eosinophil (x103 /µL)	0.01 (0.00-0.15)	0.00 (0.00-0.10)	0.860
Basophil (x103 /µL)	0.10 (0.00-0.10)	0.10 (0.00-0.10)	0.467
CRP (mg/L)	8.54 (3.40-29.20)	48.70 (12.95-104.50)	0.002
RBC	4.40 (3.60-4.75)	4.50 (3.30-10.45)	0.325
PLR	191.66 (113.11-275.98)	192.66 (124.28-272.89)	0.645
NLR	3.43 (0.37-7.22)	4.87 (2.46-8.99)	0.310
NMR	11.00 (6.26-7.07)	11.68 (8.22-15.78)	0.440
LMR	2.55 (1.92-3.75)	2.14 (1.50-3.84)	0.420
LCR	0.18 (0.04-0.37)	0.63 (0.01-0.07)	0.001
WBC/MPV	1.00 (0.92-1.46)	1.14 (0.93-1.51)	0.393
CRP/MPV	1.00 (0.65-3.56)	7.45 (1.60-13.19)	0.001
MPV/PLT	0.03 (0.02-0.04)	0.03 (0.02-0.03)	0.978
Procalcitonin	0.05 (0.02-0.12)	0.05 (0.02-0.09)	0.375

WBC: White Blood Cells, Hbg: Hemoglobin, Hct: Hematocrit, MCV: Mean Corpuscular Volume, PLT: Platelets, PDW: Platelet Distribution Width, MPV: Mean Platelet Volume, PCT: Plateletcrit, CRP: C-Reactive Protein, PLR: Platelet to Lymphocyte Ratio, NLR: Neutrophil to Lymphocyte Ratio, NMR: Neutrophil to Monocyte Ratio, LMR: Lymphocyte to Monocyte Ratio, LCR: Lymphocyte to CRP Ratio, WBC/MPV, CRP/MPV, MPV/PLT: Ratios of the respective parameters

DISCUSSION

This study has examined the function of biomarkers in assessing the necessity of hospital treatment in patients with CAP. The obtained results indicate that CRP, NLR, and CRP/MPV ratios are significant diagnostic biomarkers in patients with pneumonia who were treated in hospital. Parameters such as WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, hematocrit, MPV, LMR, NMR, LMR, LCR, and WBC/MPV were observed to be notably elevated in hospital-treated pneumonia patients compared to those treated as outpatients.

Numerous studies have been reported on CBC parameters and biomarkers in patients with CAP [9,19,20]. While CRP and WBC are frequently used parameters, it is known that CRP and complete blood count parameters can be within normal values at the initial consultation of the patients. In addition, some blood values such as CRP may increase in bacterial infections while they may vary more in viral infections [9]. The fact that CRP and WBC are not specific inflammation biomarkers for CAP has led to studies on many new biomarkers and CBC parameters. In our study, unlike most studies, a number of CBC parameters and their ratios were studied together as biomarkers.

Complete blood count is used as an economical and practical tool in the evaluation of many diseases. In recent years, parameters such as NLR, LMR, PLR, and MPV/PLT based on CBC parameter ratios have been evaluated as bio-indicators of inflammation and their potential uses in community-acquired pneumonia are being investigated [21]. It has been reported in various studies that in systemic inflammation a**s** the number of neutrophils rises, the number of lymphocytes falls and platelets fulfill crucial roles in infection and inflammation [22,23]. It has been determined that platelets, beyond their hemostatic functions such as stopping bleeding, contribute to the accumulation of cells that cause inflammation to the damaged area by stimulating the emission of pro-inflammatory cytokines during inflammation. The decrease in platelet count during infection activates the bone marrow, resulting in the production of young platelets with a wider diameter compared to mature platelets. This situation leads to an increase in MPV values. Studies have revealed that an increase in MPV could be considered as an indicator of illness-related inflammation such as rheumatoid arthritis, cystic fibrosis, and pneumonia [22,24,25]. We observed no significant differences in PLT, and plateletcrit (PCT) values between our pneumonia patient groups.

Recently, biomarkers such as WBC/MPV and CRP/MPV, which use the ratios of traditional acute phase proteins to MPV, have come to the fore in many studies. In particular, they are thought to be new prognostic markers in showing the relationship between inflammation and atherosclerosis in cardiovascular disease risk classification [18,26]. In our study, we determined that WBC/MPV and CRP/MPV ratios were markedly greater in patients with pneumonia requiring hospitalization. These findings indicate that in cases of pneumonia, WBC and CRP levels rise, and the ratios obtained by dividing these values by MPV also increase. This situation may be a useful method in assessing the intensity of the illness. It is critical to determine if a patient with community-acquired pneumonia will receive inpatient or outpatient care. This can be done by accurately assessing the intensity of the illness at the beginning. Depending on the severity of the disease; antimicrobial therapy, the route and length of administration, as well as microbiological investigations vary.

In our study, CRP/MPV, NLR, CRP, and MPV were the prominent parameters in diagnostic adequacy and prediction analyses in pneumonia patients. Among these parameters, the diagnostic performance of CRP/MPV in hospitalized pneumonia cases was found to be higher than the others. The rapid availability of these inflammatory indicators can enable the effective identification of patients requiring hospitalization in pneumonia cases. This provides an opportunity for early and accurate treatment, reducing morbidity and mortality. Based on the data we obtained from our study, we believe that CRP/MPV, in addition to CRP, NLR, and MPV, and especially CRP/MPV as a new marker, will guide clinicians in assessing the level of CAP. In addition, we observed a relationship between the duration of hospitalization and certain biomarkers. The CRP, LCR, and CRP/MPV ratios of patients with a longer than seven-day hospital stay were statistically higher than those with a stay of less than 7 days.

Limitations

There were limitations in our study, such as its retrospective nature and the exclusion of comorbid diseases from the data analysis.

CONCLUSIONS

In conclusion, it is known that traditional inflammatory markers employed in determining the treatment method in pneumonia developed in the community do not always provide precise and clear results. This study demonstrates that, along with standard tests such as CRP and WBC, recent biomarkers such as CRP/

MPV and NLR may also be useful in determining the severity of the disease. In health institutions with limited facilities, these parameters can be used quickly and effectively to determine the indication for hospitalization. However, we believe that more comprehensive investigations are needed to determine the definitive correlation between community-acquired pneumonia and biomarkers.

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Conflict of Interest: There is no conflict of interest in the study.

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Ethics Committee: The study commenced after obtaining approval from the KTO Karatay University Faculty of Medicine Non-Drug and Non-Medical Device Research Ethics Committee on the date of 25.05.2023 with the approval number 2023/019.

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