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Do complete blood count parameters predict diagnosis and disease severity in obstructive sleep apnea syndrome?

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Abstract. – OBJECTIVE: Inflammation and platelet activation play a role in the pathogenesis of obstructive sleep apnea syndrome (OSAS). In this study, it was aimed to investigate the effectiveness of the systemic inflammation markers, the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and WMR (white blood cell count (WBC) to mean platelet volume (MPV) ratio), in determining the severity of OSAS.

PATIENTS AND METHODS: The study included 207 patients who visited the pulmonology polyclinic between 1 and 31 January 2020 with complaints of snoring, apnea periods during sleep and sleepiness and were assessed with polysomnography (PSG) with the indication of hospitalization. The patients were grouped based on their apnea-hypopnea index (AHI) scores as 54 patients with AHI<5 as the control group, 41 patients with AHI=5-15 as the mild, 54 patients with AHI=15-30 as the moderate and 58 patients with AHI>30 as the severe OSAS groups. From the complete blood counts of the patients, NLR, PLR and WMR were calculated. The demographic characteristics of the patient and control groups were assessed by comparing PSG and blood parameters.

RESULTS: The mean age of the 207 patients included in the study was 54.56±10.24 years. Among the patients, 58.5% were male, and 41.5% were female. Between the control and OSAS groups, there were significant differences in terms of the WBC and lymphocyte counts (p=0.004 and p=0.035). In terms of the NLR and PLR values, there was no significant difference among the OSAS groups (p=0.723 and p=0.309). WMR had a significant difference in the OSAS groups (p=0.001). It was determined that WMR was valuable especially in distinguishing severe OSAS from the other groups.

CONCLUSIONS: In our study, where OSAS severity and complete blood count parameters assessed as inflammatory markers were examined, it was identified that the NLR and PLR levels were not very determinant in predicting either OSAS or its severity, and among these parameters, WMR was more significant, and it was determinant in distinguishing severe OSAS. Therefore, we believe it is needed to plan new studies without losing time over these markers in the diagnosis of OSAS, determination of its severity and its monitoring.

Key Words:
Obstructive sleep apnea syndrome, Complete blood count, Disease severity.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by recurrent partial or complete upper respiratory airway obstructions resulting in hypoxia/reoxygenation and arousals during sleep[1]. Although its etiology and pathophysiological mechanisms have not been completely understood, it is a complex, polygenic and multifactorial disease that leads to various clinical pathologies accompanied by some predisposing factors such as age, sex, obesity, anatomical and mechanical factors and disrupted neuromuscular function[2,3]. OSAS may lead to some complications such as cardiovascular, malignancy-related and diabetes-related complications, and it has been shown that these complications may be associated with endothelial dysfunction, excessive oxidative stress, increased systemic inflammation and sympathetic stimulation[4,5].

Chronic systematic inflammation in OSAS has a significant role in its prognosis[6]. Clinically determining inflammatory markers is useful in assessing the degree of nocturnal hypoxia and predicting the presence of complications in OSAS

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patients. In general, to measure the inflammatory status at the clinic, new disease-specific biochemical markers are being used. As biomarkers, such as C-reactive protein (CRP) and interleukin-6 are expensive to measure especially in developing countries, in daily clinical practice, hematological parameters in complete blood count (CBC) are a frequently used, simple and inexpensive laboratory method[7].

A recent meta-analysis[7] reported that white blood cell count (WBC), neutrophil, lymphocyte and platelet activation may be a good indicator of inflammation in OSAS patients. While neutrophils mainly mediate the innate immune response which secretes mediators, lymphocytes mediate the adaptive immune response by regulating inflammation[8]. The mean platelet volume (MPV) and platelet distribution width (PDW) are important markers of platelet activity. It was reported that the red cell distribution width (RDW), which indicates erythrocyte variability, increases with inflammation in OSAS[9].

There are studies which have shown that NLR and PLR are associated with disease severity in OSAS, and NLR values decrease when the disease is treated with CPAP (continuous positive airway pressure) or oral apparatuses. While some studies found that the NLR value predicted the risk of cardiovascular disease in OSAS, some others determined that it did not, and it was not associated with the severity of the disease[10]. It was determined that the PLR value was lower in OSAS than that in the control group, the PLR value decreased as the AHI value increased, and the NLR value increased as the time spent desaturated in sleep (saturation O2 < 90%) increased[11]. A study conducted to determine the diagnosis and severity of sleep apnea in obese children found a correlation between an increase in NLR and PLR values and an increase in AHI[12].

To the best of our knowledge, there is only one study in the literature which examined the relationship between OSAS and WMR[13]. In the study that was retrospectively conducted at a single center, it was shown that there was a positive correlation between the severity of OSAS and WMR (WBC/MPV).

In our study, the effectiveness and predictive value of the systemic inflammation markers of the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and white blood cell count/mean platelet volume ratio (WBC/MPV=WMR) in determining the severity of OSAS were investigated.

Patients and Method

Ethical Approval

The ethical approval of the study was obtained with the decision No. 2019-23/219 from the Ahi Evran University School of Medicine Clinical Research Ethics Board.

Written consent was obtained from the voluntary participants.

Population

Our study which was conducted at three centers consisted of 207 patients who received polysomnographic (PSG) examination at sleep laboratories throughout January 2020. At all three centers, all mild and moderate OSAS patients were included, and as the number of the patients in the severe OSAS group was high, the population of the study was completed by selecting patients with the method of random non-probability sequential sampling.

Patients with psychiatric causes of sleep disorders, central sleep apnea, use of sedatives and muscle relaxants, narcolepsy, age<18 years, liver or kidney disease, chronic alcoholism, malignancy, hyperthyroidism or hypothyroidism, active infection presence, inflammatory bowel disease, inflammatory connective tissue disorders, asthma and COPD (Chronic Obstructive Pulmonary Disease) diagnosis, history of recent blood transfusion (within 2 weeks) and hematological disorders such as leukemia, anemia or myelodysplastic syndrome were excluded from the study.

Polysomnography (PSG)

In the examination made all night, at all three centers, using a Philips Respironics Polysomnography device (1001 Murry Ridge Lane Murrysville, PA, USA; Respironics Deutschland Gewerbestrasse 17 82211 Herrsching, Germany), four-channel electroencephalogram (EEG) and two-channel electrooculography (EOG), submental electromyography (EMG), pulse-oximetry, thoracic and abdominal movements, electrocardiogram (ECG), tracheal sounds and oronasal air flow were recorded. Interruption of air flow for more than 10 seconds was defined as apnea, whereas a 4% reduction in oxygen saturation and >30% reduction in air flow for more than 10 seconds were defined as hypopnea. OSAS severity was calculated with the apnea-hypopnea index (AHI) scores based on the numbers of apnea and hypopnea occurrences determined per hour during sleep. All patients were grouped based on

their AHI scores as mild (AHI: 5-15), moderate (AHI: 15-30) and severe (AHI> 30) OSAS. Those with AHI values of <5 were included as the control group.

Among the patients who were examined by PSG, at the end of the procedure, at all three centers, hemogram parameters were analyzed with an automated device (Beckman Coulter LH 750, Brea, CA, USA) within two hours from venous blood samples collected in the morning upon fasting. NLR, PLR and WMR were separately calculated by proportioning the relevant values.

Statistical Analysis

The statistical analyses of the study were conducted using the SPSS (IBM SPSS version 21.0, Armonk, NY, USA) software. The normality assumption of the continuous variables was tested by using Kolmogorov-Smirnov and Shapiro-Wilk tests. According to the satisfaction status of the normality assumption, the descriptive statistics of the variables are presented as mean±standard deviation, median (25^{th} percentile-75^{th} percentile), frequencies (n) and percentages (%). For the univariate analyses of the variables in the study, based on the type of the variable and satisfaction status of the assumptions, chi-squared test, one-way analysis of variance (ANOVA) and Kruskal-Wallis H test were used. To compare the groups with significant differences found as a result of the ANOVA, Duncan's multiple comparison test was used. For the pairwise comparisons of the groups with significant differences found as a result of the Kruskal-Wallis H test, Mann-Whitney U test was used with Bonferroni correction (0.05/4=0.0125). The relationships between the AHI scores and the variables were assessed by Spearman's rho correlation analysis. The variables that revealed significant differences between groups as a result of the univariate analyses were subjected to backward stepwise multinomial logistic regression analysis. To determine whether or not the variables that significantly contributed to the model as a result of the multinomial logistic regression analysis had diagnostic value, ROC curve analysis was used. In all analyses, $p<0.05$ was accepted as statistically significant.

Results

The mean age of the 207 patients who were included in the study was 54.56±10.24 years. Among the patients, 58.5% (n=121) were male, and 41.5% (n=86) were female. According to the PSG results, the AHI value of 54 patients was found to be smaller than 5, OSAS was excluded, and these patients were included in the control group. The patients diagnosed with OSAS were divided into groups as: AHI: 5-15 (mild) including 41 patients, AHI: 15-30 (moderate) including 54 patients and AHI>30 (severe) including 58 patients.

The descriptive statistics of the variables included in the study are summarized in Table I. As seen in Table I, there was no significant difference in the OSAS groups in terms of their mean age, sex, MCV and RBC values ($p>0.05$). The difference among the OSAS groups based on the hemoglobin (HGB) and MPV values was significant ($p<0.05$). The mean MPV value of the control group was determined to be higher than those of the OSAS groups. The HGB values of the control group were found to be higher than those of the OSAS groups ($p=0.000$).

In terms of the platelet (PLT) values, the difference among the OSAS groups was not significant ($p>0.05$). However, the difference among the OSAS groups was significant in terms of the WBC variable ($p=0.004$). As the severity of OSAS changed from mild to severe, the WBC values decreased. The WBC values of the control group were lower than those of the OSAS groups. Although the neutrophil values of the OSAS groups were higher in comparison to the control group, the difference was not significant ($p>0.05$). The difference among the OSAS groups in terms of the lymphocyte values was significant ($p=0.035$). The lymphocyte values of the control group were lower than those of the OSAS groups. The difference among the mild, moderate and severe OSAS groups in terms of the lymphocyte values was insignificant ($p>0.05$). The difference in terms of the WBC/MPV, namely WMR, values among the OSAS groups was significant ($p=0.01$). The WBC/MPV=WMR values in the mild and moderate OSAS groups were higher than those of the control and severe OSAS groups.

The relationships between the AHI scores and the variables included in the study are presented in Table II. There was a negative and significant relationship between the AHI scores and the WBC, MPV and WMR values ($p<0.01$). As the AHI score increased, the WBC, MPV and WMR values decreased. There was a positive and significant relationship between the AHI scores and

Table I. Explanatory statistics of variables and group comparisons.

Variables	Control, n = 54 $\bar{x}$ ± SD	Mild, n = 41 $\bar{x}$ ± SD	Moderate, n = 54 $\bar{x}$ ± SD	Severe, n = 58 $\bar{x}$ ± SD	p
Sex, n (%)					**0.048**
Female	28 (32.6)	20 (23.3)	22 (25.6)	16 (18.6)	
Male	26 (21.5)	21 (17.4)	32 (26.4)	42 (34.7)	
Age, years	53.1 ± 11.2	53.4 ± 11.0	54.5 ± 10.3	55.2 ± 14.5	0.680
HGB	**10.8 ± 1.38[a]**	**14.5 ± 1.2[b]**	**14.5 ± 1.3[b]**	**16.0 ± 1.6[b]**	**0.000**
MCV	83.9 ± 3.7	86.7 ± 4.1	86.0 ± 4.2	86.4 ± 4.4	0.803
RBC	5.0 ± 0.2	5.0 ± 0.4	5.0 ± 0.2	5.1 ± 0.5	0.368
MPV	**10.4 ± 0.9[a]**	**9.7 ± 0.9[b]**	**9.8 ± 1.1[b]**	**10.3 ± 0.9[b]**	**0.001**
PLT, $\times 10^3/\mu L$	245.7 ± 78.3	276.2 ± 88.5	245.2 ± 45.7	257.7 ± 56.1	0.384
WBC	**8260 (7370-10250)[a]**	**7800 (5500-8750)[a]**	**7660 (5700-8750)[a]**	**6170 (11.44-8180)[b]**	**0.004**
Neutrophil	3890 (1682-6250)	4400 (3300-5505)	4390 (3095-5750)	4330 (3400-5920)	0.870
Lymphocyte	**3200 (2725-3475)[a]**	**2480 (2000-3015)[b]**	**2500 (1915-2910)[b]**	**2480 (1970-3320)[b]**	**0.035**
Eosinophil	200 (1.37-210)	200 (100-310)	160 (100-240)	180 (110-340)	0.512
EOS%	1.6 (1.25-2.2)	2.6 (1.35-3.70)	2 (1.20-3.00)	2.4 (1.40-4.00)	0.495
MCH	27.6 (27.45-29.75)	29.30 (28.05-29.90)	29.60 (28.05-30.30)	29.10 (27.60-30.0)	0.253
RDW	13.40 (12.70-13.50)	13.30 (12.90-14.25)	13.10 (12.70-13.80)	13.30 (12.70-14.00)	0.448
NLR	1.26 (0.55-2.08)	1.69 (1.22-2.25)	1.65 (1.29-2.27)	1.67 (1.22-2.13)	0.723
PLR	84.25 (65.18-105.84)	108.07 (86.69-124.03)	100 (82.21-127.29)	103.29 (76.94-125.60)	0.309
WBC/MPV (WMR)	**723.21 (649.09-1177.59)[a]**	**764.22 (539.30-884.61)[a]**	**775.63 (629.46-865.92)[a]**	**566.64 (1.04-792.22)[b]**	**0.001**

The difference between the means shown with the same letter on the same row is not statistically significant (p>0.05). n: Number of patients; X: Mean; SD: Standard deviation; Significant p-values are shown as bold. Abbreviations: AHI: Apnea-Hypopnea Index; WBC: White Blood Cell; MPV: Mean Platelet Volume; RDW: Red Cell Distribution Width; NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, WMR: White Blood Cell to Mean Platelet Volume Ratio.

the HGB and RBC values (p=0.006). As the AHI score increased, there was an increase in the HGB and RBC values.

Table II. Correlation between AHI score and laboratory parameters.

	AHI	
Variables	Coefficient	p
WBC	-0.208**	0.009
Neutrophil	0.107	0.182
Lymphocytes	-0.084	0.298
Platelets	-0.075	0.353
MPV	-0.177*	0.027
RDW	-0.018	0.828
EOS	-0.018	0.828
HGB	0.178*	0.028
RBC	0.218**	0.006
MCV	0.039	0.628
NLR	0.141	0.184
PLR	-0.007	0.929
WMR	-0.269**	0.001

AHI: Apnea-Hypopnea Index; WBC: White Blood Cell; MPV: Mean Platelet Volume; RDW: Red Cell Distribution Width; NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, WMR: White Blood Cell to Mean Platelet Volume Ratio.

Using the variables that revealed significant differences among the four groups as a result of the univariate analyses, a multinomial logistic regression analysis was carried out. To determine the regression model most suitable for the data, backward stepwise multinomial regression analysis was used. The goodness of fit indices for the strongest multinomial logistic regression model that fit the data best found as a result of this analysis are shown in Table III.

As seen in Table III, when the model goodness of fit values (AIC=373.938; BIC=419.877; -2LL=343.938; X2=33.413; p=0.001) and model goodness of fit Pearson's (X2=483.358; p=0.993) and Deviance (X2=413.938; p=0.996) values are checked, it is seen that the model was statistically significant, and it showed a good fit with the data. The results of the likelihood ratio test on the variables included in the created multinomial logistic regression model are shown in Table IV. Considering these results, it may be observed that the WBC/MPV=WMR, MPV and WBC independent variables in the logistic regression model did not have a significant effect on the severity of OSAS (p>0.05). The effect of the lymphocyte variable, on the other hand, was significant (p=0.000).

Table III. Model goodness of fit values of the multinomial logistic regression model.

Model Fitting Criteria						Goodness of Fit		
Model	**AIC**	**BIC**	**-2Log Likelihood**		***p***			***p***
Intercept only	576.601	586.599	570.0601	–	–	Pearson	483.358	0.993
Final	443.481	493.472	413.481	157.120	0.000	Deviance	413.938	0.996

Table IV. Likelihood ratio test results.

Variables	-2Log Likelihood of reduced model	X^2	*p*
WBC/MPV	416.262	2.781	0.427
MPV	418.687	5.206	0.157
WBC	346.264	2.236	0.508
Lymphocytes	470.549	57.068	0.000

AHI: Apnea-Hypopnea Index; WBC: White Blood Cell; MPV: Mean Platelet Volume; RDW: Red Cell Distribution Width; NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, WMR: White Blood Cell to Mean Platelet Volume Ratio.

The results of the multinomial logistic regression analysis used in the study are given in Table V. As seen in Table V, as the severity of OSAS was taken as the dependent variable, four categories as control, mild OSAS, moderate OSAS and severe OSAS were entered into the multinomial logistic regression model. When the control group was taken as the reference category, it was determined that the WBC/MPV=WMR and MPV variables were not significant determinants in the OSAS categories of the patients (p>0.05). These variables were not sufficient in predicting in which OSAS group the examined patient would be included. Among the variables in the model, only the lymphocyte variable was a significant determinant in predicting all OSAS groups (p=0.000). The WBC variable was a significant determinant in predicting the moderate OSAS group (p=0.043).

In order to determine whether or not there was a diagnostic cutoff value in determination of the OSAS groups by the variables that entered the model and showed a significant contribution as a result of the logistic regression analysis, an ROC curve analysis was conducted (Table VI). As a result of the assessment made by the ROC curve analysis, it was determined that the lymphocyte values had a diagnostic value in the diagnosis of the mild OSAS group. When the ROC curve given in Figure 1A is examined, it

Table V. Multinomial logistic regression analysis results.

OSAS Severity	Variables	β	Wald	*p*	Exp(β)	95% CI: LOWER-UPPER
Mild	WBC/MPV	-0.011	1.862	0.172	0.989	0.973-1.005
	MPV	-0.845	2.366	0.124	0.429	0.146-1.261
	WBC	0.001	2.818	0.093	1.001	0.999-1.004
	Lymphocytes	0.001	2.402	0.000	1.001	1.001-1.002
Moderate	WBC/MPV	-0.014	2.738	0.098	0.986	0.970-1.003
	MPV	-0.958	2.863	0.091	0.384	0.127-1.164
	WBC	0.002	4.102	0.043	1.002	1.000-1.003
	Lymphocytes	0.001	22.521	0.000	1.001	1.001-1.002
Severe	WBC/MPV	-0.008	1.291	0.256	0.992	0.978-1.006
	MPV	-0.081	0.037	0.848	0.922	0.402-2.115
	WBC	0.001	1.750	0.186	1.001	1.000-1.002
	Lymphocytes	0.002	29.392	0.000	1.002	1.001-1.002

The reference category is the control group.

Table VI. ROC analysis results.

	AUC ± SE	95% CI	Sensitivity	Specificity	*p*	-PV	+PV	Cut-off value
Mild OSAS (ref: control)								
Lymphocytes	0.876 ± 0.04	0.794-0.959	90.7	92.6	**< 0.001**	88.3	94.2	> 737.14
Moderate OSAS (ref: Mild OSAS)								
WBC	0.515 ± 0.06	0.395-0.635	47.5	50.0	> 0.05	41.3	56.2	> 7645.0
Lymphocytes	0.533 ± 0.06	0.413-0.653	50.0	57.4	> 0.05	46.5	60.7	> 2410.0
Severe OSAS (ref: Moderate OSAS)								
Lymphocytes	0.509 ± 0.05	0.400-0.617	61.0	50.0	> 0.05	42.0	46.7	> 2340.0

Abbreviations: AUC: Area under the curve; SE: Standard Error; CI: Confidence Interval; -PV: Negative Predictive Value; +PV: Positive Predictive Value. AHI: Apnea-Hypopnea Index; WBC: White Blood Cell; MPV: Mean Platelet Volume; RDW: Red Cell Distribution Width; NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, WMR: White Blood Cell to Mean Platelet Volume Ratio.

is seen that the area under the curve was statistically significant (AUC:0.876, %CI: 0.794-0.959, $p<0.01$) (Table VI). As seen in the figure, when the value of 737.14 among the lymphocyte values is taken as the cutoff point, the sensitivity (90.7%) and specificity (92.6%) values calculated for this cutoff point also showed that the lymphocyte variable had a diagnostic value on mild OSAS. The area under the ROC curve in the moderate and severe OSAS groups was found to be statistically insignificant ($p>0.05$) (Table VI), and no cutoff point with a significant diagnostic value for these groups could be determined (Figure 1B, C).

Discussion

In our study, an interesting point different from many other studies was showing that the NLR and PLR levels as a proof of increased systemic inflammation in OSAS did not increase in parallel with the severity of OSAS, and they did not predict the severity of OSAS. Likewise, significant results were obtained in the WBC, lymphocyte and WMR parameters, but these parameters were not sufficient to predict the severity of OSAS.

While the underlying mechanism in OSAS is not completely known, hypoxic status, excessive sympathetic activity and chronic inflammation are proposed as the most significant mechanisms[7]. Chronic intermittent hypoxia increases sympathetic activity and causes systemic inflammation[14]. Inflammation starts with secretion of various proinflammatory cytokines (e.g., TNF-a, VEGF, IL-1 and IL-6) from the related blood cells. Various cells like white blood cells, neutrophils, lymphocytes, platelets, monocytes and eosinophils play a specific role in this process. In a study, after CPAP treatment, a reduction was observed in some inflammation markers such as CRP, the tumor necrosis factor-alpha and interleukin-6, and this was reported as an indicator that systemic inflammation plays an active role in

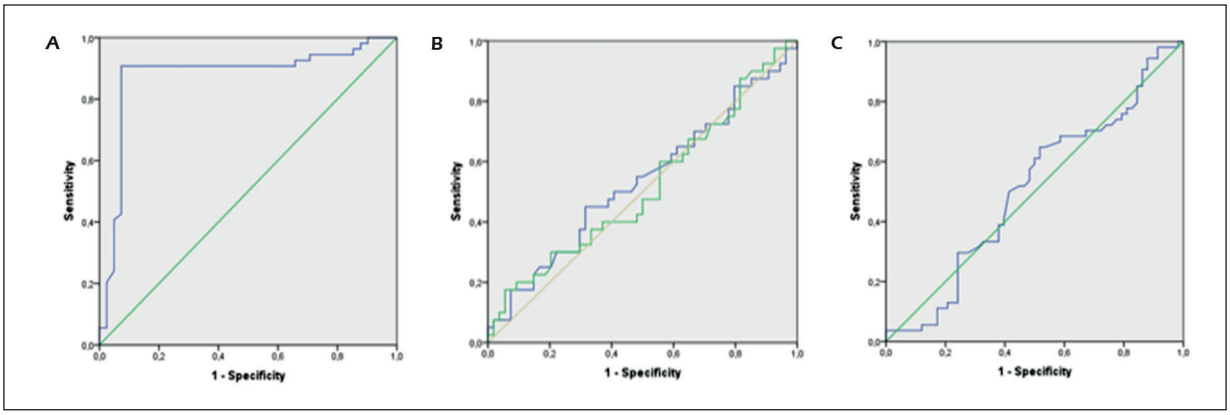

Figure 1. ROC curves.

OSAS[15]. While inflammation plays a significant role in the progression of atherosclerosis and cardiovascular diseases[16,17], whether this is a cause or result of OSAS is uncertain. There are various reports on the relationship between inflammatory markers and the degree of upper respiratory airway obstruction[18,19]. As systemic inflammation is a significant mechanism in OSAS, investigating new inflammatory markers in OSAS may provide more information for estimating the risk of associated diseases.

With increased platelet adhesion and aggregation as a result of inflammation, platelets are activated[16]. Increased platelet activation leads to an increase in the platelet volume[17]. When platelet production is induced, an increase is also seen in MPV levels[18]. While some studies on platelets reported that the MPV levels of OSAS-diagnosed patients did not show a difference in comparison to the control group[16-18], some others showed that MPV levels increased in severe OSAS patients[18-20]. This assessment was also made among the OSAS groups in our study, and it was seen that MPV decreased as the AHI score increased. Changes in MPV levels may be associated with acute and chronic hypoxia status[19-21] and high oxygen desaturation levels[18].

There are too many internal and external causes that affect platelet indices. Sometimes, not all of these indices may be affected together, or all may show a sudden increase[22]. In this case, it might be needed to assess the question of which of the platelet indices may be associated with OSAS. In our study, a patient group with factors that could lead to these changes was not included, and the WBC/MPV=WMR values were found to be higher in the mild and moderate OSAS groups than the control and severe OSAS groups. The difference among the OSAS groups was statistically significant ($p<0.01$). This finding of ours may be considered as an important result. Additionally, platelet aggregation may show an increase in parallel with the *in vivo* catecholamine levels in circulation. For this reason, in OSAS patients, hematological indices associated with platelet activation (MPV, PLR) may also change based on catecholamine discharge[11]. In our study, as the AHI scores increased, a decrease was observed in the MPV values.

Platelets, neutrophils and lymphocytes interact during infection, inflammation and thrombosis and regulate each other's functions[23]. A high platelet count reflects underlying inflammatory conditions, because platelets are acute phase reactants that are produced as a response to various stimuli including systemic infections, inflammatory conditions, hemorrhage and tumors. Low lymphocyte levels represent an uncontrolled inflammatory pathway. Therefore, increased PLR is a useful inflammatory marker, because it reflects an increase in the number of platelets and a decrease in the number of lymphocytes in an inflammatory condition[24]. Based on this interaction, it was thought that PLR and NLR may play a role in the pathogenesis of OSAS, and several studies have shown that they predict OSAS[11,25-27]. In our study, the NLR and PLR levels did not increase as the severity of OSAS increased, and thus, we believe these could not predict the severity of the disease as inflammatory markers. While changes in the platelet indices may be associated with the aforementioned factor, the apoptosis of neutrophils may show a variance in the OSAS process[28]. It has also been shown that nuclear factor kappa B (NF-kB) activity increases as a result of hypoxia and reoxygenation, and this results in increased numbers of neutrophils in circulation. Both of these situations may lead to an increase in the neutrophil levels in the peripheral blood of OSAS patients. Low lymphocyte counts may be associated with the activation of the hypothalamic-pituitary-adrenal (HPA) axis, and this situation may lead to an increase in the systemic cortisol levels and changes in sleeping habits[29]. In our study, the difference among the OSAS groups in terms of the WBC variable was statistically significant, where the WBC values decreased as the OSAS severity varied from mild to severe. The lymphocyte values were also significantly different among the groups. The lymphocyte variable was found to be a significant determinant in predicting all OSAS groups, while the WBC variable was found to be a significant determinant in predicting the moderate OSAS group.

The white blood cell count (WBC) is a useful inflammatory marker in clinical applications, whereas WMR that is obtained from the WBC and MPV parameters is a proven inflammatory marker in morbidity and mortality prediction and prognosis definition in cardiovascular diseases. Some studies have shown its superiority in comparison to other CBC ratios (e.g., WBC, MPV, PLR and NLR)[30,31]. Moreover, WMR may represent both inflammatory and thrombotic pathways that could be found together in patients. In a study conducted by Kum et al[13], in determining the severity of OSAS, WMR levels showed a

higher diagnostic performance than PLR and NLR levels, and it was stated that this superiority may be associated with the higher stability of WMR in comparison to other CBC parameters that could be influenced by various pathological and physiological conditions[13]. The data in our study supported their result. In our study, it was also determined that there was a more significant and positive relationship between mild and moderate OSAS and the WMR levels, which may be new information. WMR may be better than other parameters in showing the severity of OSAS in non-homogenous groups and be used in distinguishing severe OSAS.

One limitation of our study may be the small sample size. Although we worked at three centers, only these numbers could be reached. As patient inclusion for PSG was stopped due to the COVID-19 pandemic, our patient numbers stayed on the given levels. Another limitation may be that the complete blood count parameters of the patient group after CPAP were not assessed. In our study, elimination of the patient-related factors on the NLR, PLR and WMR parameters was a strength in comparison to other studies in the literature. However, it may be another limita- tion that the effects of the presence of comorbid diseases, history of corticosteroid treatment and chronic kidney failure on the CBC parameters were not assessed. Another limitation of the study may be the failure to evaluate the relationship be- tween other inflammatory factors, such as WMR with, PCR, ESR and calcitonin.

Consequently, complete blood count parameters have been prevalently studied in many diseases. The number of studies conducted with these parameters in OSAS is also very high. While these parameters have other found significant in many studies, some studies did not find them very predictive as in the case of our study. We summarized our results as follows.

1. For differential diagnosis of OSAS:
- The mean MPV value of the control group was found to be higher than those of the OSAS groups.
- The HGB values of the control group were found to be higher than those of the OSAS groups.
- The WBC values of the control groups were lower than those of the OSAS groups.
- The lymphocyte values of the control group were lower than those of the OSAS groups.

2. For the OSAS groups:
- The WBC value decreased as the OSAS severity varied from mild to severe.
- As the OSAS severity increased, the NLR and PLR levels did not increase. Therefore, we think these cannot be used to distinguish disease severity as inflammatory markers.
- The WBC/MPV=WMR values in the mild and moderate OSAS groups were found to be higher than those in the control and severe OSAS groups. This parameter may be better than the other parameters in determining the severity of OSAS and be used to distinguish severe OSAS.
- As the AHI scores increased, there was a decrease in the WBC, MPV and WMR values.
- The WBC variable was a significant determinant in predicting the moderate OSAS group.
- As the AHI scores increased, there was a decrease in the HGB and RBC values.
- The effect of the lymphocyte variable was significant. The lymphocyte variable was a significant determinant in predicting all OSAS groups. This shows that the lymphocyte variable had a diagnostic value in mild OSAS.

Considering other reports and the results of our study, it may be stated that complete blood count markers cannot predict the diagnosis and severity of OSAS. Despite all studies conducted so far, sufficient data and evidence could not be established to be able to use these markers in daily practice. Therefore, we believe studies need to be planned with new markers without losing time over these markers in determining the diagnosis and severity of OSAS.

Conclusions

The answer to the question "Do Complete Blood Count Parameters Predict the Diagnosis and Severity of Disease in Obstructive Sleep Apnea Syndrome?" is partially yes. In OSAS, MPV and HGB are lower than those without disease, while WBC and lymphocytes are high. As the severity of OSAS increases, the WBC value decreases, and WMR is higher in mild-moderate OSAS. The WBC, MPV and WMR values decrease as the severity of OSAS increases. As the severity of OSAS increases, a decrease in the HGB and RBC values may be seen. The lymphocyte count is a significant predictor of all OSAS groups. It shows that the lymphocyte variable has a diagnostic value in mild OSAS.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Ethics Committee Approval
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