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Relationship Between Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio and Obstructive Sleep Apnea Syndrome

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Abstract

Background. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) give information about many diseases. An increase in inflammation markers occurs in patients with obstructive sleep apnea syndrome (OSAS).

Objectives. The aim of this study is to determine the relationship between OSAS and NLR and PLR values.

Material and Methods. Two hundred eighty four patients with complaints of snoring and excessive daytime sleepiness were included in the study. Polysomnography had been performed on all patients and the control group. Forty eight of these patients with apnea-hypopnea index (AHI) less than 5 (pure snoring) were included in the control group, 67 patients with AHI between 5 and 14.9 in the mild OSAS group, 61 patients with AHI between 15 and 29.9 in the moderate OSAS group and 108 patients with AHI more than 30 in the severe OSAS group. NLR and PLR values were calculated from the complete blood count (CBC) analysis of the patients and control group. The OSAS and control groups were compared by age, gender, body mass index (BMI) and PSG parameters as well as NLR and PLR values.

Results. The PLR value in the OSAS group was found to be less than in the control group ($p = 0.006$). As the non-REM AHI increased, the value of PLR decreased. As the nocturnal time spent with arterial oxygen saturation $< 90\%$ increased, the value of NLR was determined to increase.

Conclusions. NLR and PLR values can give valuable information in OSAS (*Adv Clin Exp Med* 2015, 24, 4, 623–627).

Key words: obstructive sleep apnea, neutrophil, lymphocyte, inflammation.

Obstructive sleep apnea syndrome (OSAS) is a disease characterized by recurrent periods of complete or partial collapse of the upper airway during sleep [1–3]. OSAS has been the subject of many studies due to its close association with cardiovascular metabolic, neurological and urogenital diseases such as hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, panic attacks, depression, erectile dysfunction and stroke [4–10]. The gold standard diagnostic method for the diagnosis of OSAS is polysomnography (PSG) [11].

The neutrophil to lymphocyte ratio and platelet to lymphocyte ratio can be determined by a simple complete blood count (CBC) analysis of peripheral blood. The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) increase in systemic inflammation, certain

gynecological and gastrointestinal cancers and cardiovascular diseases [12–14].

When the role of inflammation in the pathogenesis of OSAS is considered, in our opinion, changes in NLR and PLR values, which increase in systemic inflammation, can be used as appropriate parameters in the evaluation of OSAS. In this article, the relationship between the diagnosis and severity of the illness and NLR and PLR values are investigated in patients with OSAS and a control group.

Material and Methods

Three hundred patients who were admitted to Ankara Numune Education and Research Hospital Sleep Disorders Center between May 2010 and

July 2013 and received polysomnography were retrospectively included in this study. Sleep efficiency below 60% or TST below 240 min. was determined as ineffective sleep. Seven of these patients with sleep efficiency less than 60% were excluded. We also excluded patients with an active infection or fever. Ten patients with White Blood Cell (WBC) more than 12000/ μL and 6 patients less than 4,000/ μL were also excluded. Also patients with congestive heart failure, ischemic heart disease, chronic obstructive pulmonary disease, restrictive lung disease, hematologic, gastrointestinal or gynecological malignancies were excluded from the study. Two hundred eighty four patients were included in the study.

Venous blood samples were taken from the patients admitted to the sleep laboratory for polysomnography, and were collected in ethylene diamine tetraacetic acid (EDTA)-containing tubes. Neutrophil, lymphocyte and platelet counts were analyzed by hematology analyzer machine. NLR was calculated from the differential count by dividing the neutrophil measurement by the lymphocyte measurement. PLR was evaluated as platelet count divided by lymphocyte count.

All-night sleep PSG was performed in our laboratory for patients with symptoms such as excessive daytime sleepiness, snoring and witnessed apneas. The hematological parameters of these patients were evaluated from the blood samples before the examination. PSG was done under technician guidance and during the patients' spontaneous sleep. Electroencephalogram (EEG), electromyogram (EMG-submental and right-left tibialis anterior), electrooculogram (EOG, left-right), nasal airflow, thoracic and abdominal respiratory movements, blood oxygen saturation (pulse oximetry) and body position were recorded during the night. This data was scored manually by the same certificated otolaryngologist using the Alice 5 PSG system.

Of the patients included in the study, 48 patients with apnea-hypopnea index (AHI) less than 5 were included in the control group, 67 patients with AHI between 5 and 14.9 in the mild OSAS group, 61 patients with AHI between 15 and 29.9 in the moderate OSAS group and 108 patients with AHI more than 30 in the severe OSAS group. Age, gender and body mass index (BMI) values were recorded. According to the results of the PSG, total sleep time (TST), sleep efficiencies, AHI, rapid eye movement (REM) period AHI, non-REM AHI, desaturation index, minimum oxygen saturation and nocturnal time spent with arterial oxygen saturation < 90% values were determined. Neutrophil (unit) to lymphocyte (unit) ratio (NLR) and platelet (unit) to lymphocyte (unit) ratio (PLR) were

identified according to the CBC results obtained from the patients' blood samples before PSG testing on the same day.

In the patient and control groups, the body mass index (BMI), age, gender, NLR and PLR values were compared statistically. With the evaluation of patient and control groups together, the AHI values were compared with the NLR and PLR. In the OSAS and control groups, we investigated the association between AHI and NLR and PLR values. Furthermore, the AHI values of the patients were re-evaluated separately as non-REM AHI and REM AHI. Desaturation index, minimum oxygen saturation, nocturnal time spent with arterial oxygen saturation < 90% and NLR and PLR were analyzed in the patient and control groups.

Statistical Analysis

All statistical analyses of the data were carried out using SPSS 20 statistical software (IBM, CA, USA). When evaluating the data, in addition to descriptive statistical methods (mean, standard deviation), to determine the significance of the differences between the two groups, independent *t*-tests and the Mann-Whitney *U* test were used, and to determine the significance of multiple groups, one-way ANOVA and Kruskal-Wallis tests were used. Spearman and Pearson correlation analysis were used for correlation analysis conducted to test the relationship of continuous data. Differences were considered significant at $p < 0.05$.

Results

Two hundred eighty four patients were included in the study. One hundred ninety six (69%) patients were male and 88 (31%) were female. The mean age of the patients was 47 (75–23). The mean age of the female patients was 49 and male patients was 46. The characteristics of the patients and polysomnographic findings are summarized in Table 1. Patients included in this study were generally middle-aged and obese. The BMI of the patients varied from 50.1 to 18.3 kg/m^2 (mean 30.67 ± 4.6). BMI values according to the patient and control groups are provided in Table 1.

The mean NLR value of the OSAS group was 1.88 ± 0.85 . The mean NLR value of the control group was 2.01 ± 0.85 . The NLR values according to the groups are provided in Table 2.

The mean PLR value of the OSAS group was 109.50 ± 35.72 . The mean PLR value of the control group was 123.97 ± 35.34 . The PLR values according to the groups are provided in Table 2.

Table 1. Patient characteristics and polysomnographic findings in the OSAS group and control group

	Control group	OSAS group
Age	43.08 ± 8.88 (mean ± SD)	47.25 ± 10.14 (mean ± SD)
Male	29 (60.4%)	167 (70.7%)
Female	19 (39.6%)	69 (29.3%)
BMI (kg/m ²)	27.06 ± 3.76 (mean ± SD)	30.67 ± 4.6 (mean ± SD)
Polysomnographic findings	(mean ± SD)	(mean ± SD)
TST (total sleep time) (min)	352.41 ± 38.96	363.18 ± 41.08
Sleep efficiency (%)	80.59 ± 9.99	83.74 ± 9.32
Minimum O ₂ saturation (%)	87.38 ± 3.13	74.79 ± 14.69
Desaturation index	1.02 ± 2.32	33.37 ± 28.79
Time spent < 90% (min)	1.12 ± 3.28	53.52 ± 84.15

BMI – body mass index.
REM – rapid eye movement.

The REM sleep mean AHI score was determined to be 7.3 in the control group, 22.8 in the mild OSAS group, 31.1 in the moderate OSAS group, and 56.2 in the severe OSAS group. Non-REM sleep mean AHI scores were respectively identified as 2.3, 8.5, 20.2 and 59.2.

While mean minimum oxygen saturation was 83.0% in the mild OSAS group, 81.6% in the

moderate OSAS group and 66.5% in the severe OSAS group, in the control group the same value was determined as 89.1%. Nocturnal time spent with arterial oxygen saturation < 90% values was evaluated as 13.7 min in the mild OSAS group, 13.4 min in the moderate OSAS group, 100.7 min in the severe OSAS group and 4.8 min in the control group.

Desaturation index was respectively considered as 9.3, 17.5, 57.0 and 1.0 in the mild, moderate and severe OSAS groups and the control group, respectively.

There was no statistically significant correlation between the age of the patients and the NLR (p = 0.675, CC = 0.051) or PLR (p = 0.065, CC = 0.074) values. Also, no correlation was found between the BMI of the patients and the NLR (p = 0.854, CC = 0.002) or PLR (p = 0.636, CC = -0.046) values.

The patients were compared in terms of gender and the female patients had a higher rate of NLR than the male patients, but this was not statistically significant (p = 0.670, CC = -0.049). Male and female patients had similar PLR rates and this was not statistically significant (p = 0.690, CC = 0.180).

When evaluated with the Kruskal-Wallis test, the PLR values in patients decreased gradually from the control group to the severe OSAS group (except for moderate OSAS) and were statistically significant (p = 0.019, CC = -0.167). While in the control group, the average value of PLR was 123.97 ± 35.34, the same ratio was found to be 105.40 ± 32.98 in patients with severe OSAS and with evaluation by the Mann-Whitney U test, it was statistically significant (p = 0.002, CC = -0.248).

When the OSAS groups and the control group were compared for NLR value, no significant differences were found (p = 0.611, CC = -0.037) (Table 2).

Table 2. NLR and PLR values and comparisons of patients and control group. NLR and PLR values compared statistically from the control group to the severe OSAS group with Kruskal-Wallis tests

	Group	Mean ± SD	Min–Max	P
NLR	control	2.017 ± 0.85	0.96–4.97	0.611
	mild OSAS	1.97 ± 1.25	0.77–10.88	
	moderate OSAS	1.87 ± 0.66	0.96–4.6	
	severe OSAS	1.85 ± 0.64	0.78–3.91	
PLR	control	123.97 ± 35.34	7.55–210.13	0.019
	mild OSAS	112.40 ± 38.35	55.24–279.17	
	moderate OSAS	113.59 ± 35.16	60.94–230.13	
	severe OSAS	105.40 ± 32.98	48.01–211.24	

NLR – neutrophil to lymphocyte ratio.
PLR – platelet to lymphocyte ratio.
OSAS – obstructive sleep apnea syndrome.

The minimum oxygen saturation and desaturation indexes obtained from the patients' PSGs were evaluated separately and no relationship was determined with NLR or PLR values. However, nocturnal time spent with arterial oxygen saturation < 90% value in the control group was 4.8 min, and respectively evaluated in the mild, moderate and severe OSAS groups as 13.7, 13.4, and 100.7 min. Using the Pearson correlation analysis, while time spent with arterial oxygen saturation < 90% increased, the NLR value also increased and this was statistically significant ($p = 0.016$, $CC = 0.015$).

Discussion

The pathogenesis of OSAS is not clear. In patients with OSAS, elevated levels of inflammatory markers have been found [15].

The pathogenesis of inflammation is not clearly explained and it is thought to be responsible for the cardiovascular complications of OSAS [16]. Chronic intermittent hypoxia increases sympathetic activity and causes systemic inflammation. The best-known indicators of inflammation, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen, were shown to increase in patients with OSAS [17]. It was also reported that inflammatory cytokines such as CRP, tumor necrosis factor- α (TNF- α) and interleukin-6 (IL 6) declined with positive airway pressure (PAP) therapy, which is the gold standard treatment for OSAS [18].

In a prospective study with 24 volunteers and 32 patients, serum CRP and salivary myeloperoxidase (MPO) levels were determined to be statistically significantly higher in OSAS patients [19]. This shows persistent local inflammation in OSAS.

PLR value increases in peripheral artery disease, some malignancies and poor prognostic myocardial infarction patients [12, 20–22]. In the literature, a study of the relationship between PLR and OSAS has not been reported yet. In our study, the PLR value in patients with OSAS was determined

to be lower than the control group. PLR value compared to the control group was significantly reduced in patients with severe OSAS. PLR values were found to decrease with the increasing values of AHI. Using the division of AHI as non-REM and REM, a negative correlation was determined between non-REM AHI and PLR.

In some studies based on platelets, the mean platelet volume (MPV) value is shown to be increased in patients with severe OSAS [23, 24]. It is reported that large volume thrombocytes may have much more thrombotic effects and they cause cardiovascular diseases [25]. In a study by Varol et al. there was shown to be a negative correlation between platelet counts and the value of MPV [24]. In our study, the PLR rate was shown to be reduced in the OSAS patients compared to the control group.

Inflammation is thought to play a role in the etiopathogenesis of sudden idiopathic hearing loss and a significant increase was shown in NLR value in patients with sudden idiopathic hearing loss [26]. NLR was also described as a potential marker for the diagnosis of cardiovascular diseases [27, 28]. In our study, especially nocturnal time spent with arterial oxygen saturation < 90% was found to increase with increasing NLR. In the literature, any study investigating the association between OSAS and NLR has not been revealed yet. Although we found no statistically significant correlation between AHI and NLR values, nocturnal time spent with arterial oxygen saturation < 90% was identified to increase with increasing NLR. NLR can be used as a marker that shows chronic intermittent hypoxia in OSAS.

To date, although many studies were carried out to find a diagnostic method other than PSG in OSAS, a marker with predictive value has not been reported yet. This study investigated the role of NLR and PLR values in OSAS for the first time. As OSAS severity increased, PLR value decreased and, independently from AHI, NLR value was found to be associated with oxygen desaturation. In order to understand the role of NLR and PLR values in OSAS, there is a need for further studies with larger patient series.

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