OBSTRUKTİF UYKU APNE SENDROMU'NDA NÖTROFİL LENFOSİT ORANI

Neutrophil To Lymphocyte Ratio In Obstructive Sleep Apnea Syndrome

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ÖZET

Amaç: Nötrofil ve lenfosit oranı (NLO)'nın inflamatuar belirteç olarak inflamatuar hastalıklarda rolü keşfedilmiştir. Obstruktif uyku apne sendromu (OSAS)'da komorbiditeler ile OSAS'da artan NLO arasındaki ilişki değerlendirildi.

Yöntem: Toplam 232 OSAS hastası çalışmaya alındı. 50 OSAS olmayan olgu kontrol grubunu oluşturdu. NLO her hasta ve kontrol olgusu için hesaplandı ve kaydedildi. Nötrofil lenfosit oranıyla hipertansiyon arasındaki ilişki hipertansiyonu olan ve olmayan iki alt hasta grubunda değerlendirildi.

Bulgular: Çalışmada 100 kadın (%43.1), 132 erkek (%56.9) hasta mevcuttu. OSAS hastalarında ortalama NLO (1.76±0.77), kontrol grubunda ortalama NLO (1.31±0.74) ile karşılaştırıldığında anlamlı olarak daha yüksekti (p= 0.000). Hipertansiyon (HT) olan (3.59±14.92) ve olmayan (1.72±0.69) OSAS'lı hastalarda NLO'da anlamlı farklılık saptandı (p= 0.014).

Sonuç: OSAS'da NLO inflamatuar belirteç olarak değerli olabilir. OSAS'da artan NLO, bu hastalardaki HT gibi komorbid durumlardan kaynaklanabilir. Bu ucuz ve pratik method, günlük klinik pratikte, OSAS hastalarında komorbiditeyi öngörmek için kullanılabilir.

Anahtar Sözcükler: İnflamasyon; Nötrofil ve lenfosit orani; Obstruktif uyku apne sendromu

ABSTRACT

Objective: The role of neutrophil to lymphocyte ratio as an inflammatory marker in inflammatory conditions has been explored. The association between neutrophil to lymphocyte ratio, which is elevated in patients with obstructive sleep apnea syndrome, and hypertension in obstructive sleep apnea syndrome has been examined.

Methods: A total of 232 obstructive sleep apnea syndrome patients were included in this study. A total of 50 subjects without obstructive sleep apnea syndrome comprised the control group. The neutrophil to lymphocyte ratio was calculated and recorded for each patient and control subject. The association of neutrophil to lymphocyte ratio to hypertension was investigated in two sub-groups of patients defined on the basis of the presence or absence of hypertension.

Results: There were 100 (43.1%) female and 132 (56.9%) male patients in the study. Obstructive sleep apnea syndrome patients had significantly higher average neutrophil to lymphocyte ratio (1.76 ± 0.77) as compared to controls (1.31 ± 0.74) (p=0.000). A significant difference in neutrophil to lymphocyte ratio between obstructive sleep apnea syndrome patients with (3.59 ± 14.92) or without (1.72 ± 0.69) hypertension was found (p=0.014).

Conclusion: Neutrophil to lymphocyte ratio may find some value as an inflammatory marker in obstructive sleep apnea syndrome. Elevated neutrophil to lymphocyte ratio in obstructive sleep apnea syndrome may arise from comorbid conditions such as hypertension in these patients. This cheap and practical method may be used in daily clinical practice to predict comorbidity in OSAS patients.

Keywords: *Inflammation; Neutrophil to lymphocyte ratio; OSAS; Obstructive sleep apnea syndrome; Sleep apnea*

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a condition characterized by the recurrent obstruction in the upper respiratory airways with associated excessive daytime sleepiness and cardiopulmonary dysfunction. Hypoxia resulting from apnea, hypopnea, and recurrent interruption of sleep may lead to asphyxia, respiratory acidosis, hypercapnia, as well as local and systemic inflammation. Elevation in inflammatory markers has been associated with an increased risk of hypertension and cardiovascular diseases. Also, in OSAS patients, an increase in systemic inflammatory markers including C-reactive protein (CRP), leptin, tumor necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), reactive oxygen radicals, intracellular adhesion molecule 1 (ICAM-1), and vascular cellular adhesion molecule 1 (VCAM-1) has been reported previously (1-4).

Neutrophil lymphocyte ration (NLR) is a widely available inflammatory marker, the role of which has been explored in a variety of inflammatory conditions. However, studies examining the association between NLR and OSAS are scarce in number despite observations suggesting the presence of a low grade inflammation in OSAS (5,6). Also, an increasing body of recent evidence points out to an association between OSAS and a variety of comorbid conditions, and the underlying inflammation may have a causative role in this association.

The association of OSAS with cardiovascular conditions has been well established, in addition to studies linking OSAS with treatment resistant hypertension (HT) (7).
In the present study, our objective was to determine an increase in NLR as a potential inflammatory marker in OSAS patients and to investigate its role in identifying the severity of OSAS. Also examined was the association between NLR and HT in OSAS, as a means for predicting comorbidities such as HT in subjects with OSAS.

MATERIALS AND METHODS

A total of 232 patients with polysomnographically diagnosed OSAS within the past 2 year period in our unit were included in this study. Fifty individuals, in whom a diagnosis of OSAS was excluded, served as controls. After the study protocol was approved by the Institutional Ethics Committee, the data were retrieved from patient files. Patients with a history of infectious conditions within the past 2 months were excluded from the study. Demographic data, neck circumference, body mass index (BMI), apnea-hypopnea index (AHI), and laboratory data were retrospectively assessed and recorded. Venous blood sampling was performed 8 to 12 hours prior to polysomnography (PSG), which was performed in our 3-bed polysomnography unit using a digital PSG device with a video recorder. Electroencephalography, electrooculography, and submental and bilateral tibial electromyography recordings were performed. Snoring was assessed with a tracheal microphone, while nasal cannula was used for air flow measurements. The respiratory effort was assessed using thoraco-abdominal belts, and the arterial oxygen saturation using pulse oximetry. The stages of the sleep were assessed by the same physician manually with 30 second epochs according to Rechtschaffen-Kales criteria. AHI was calculated based on the hourly number of apneic and hypopneic episodes. A diagnosis of OSAS was made when AHI was ≥ 5/hour, while the severity was classified as mild, moderate or severe when AHI was 5-15/h, 16-30/h, or > 30/h, respectively. NLR was calculated based on the ratio of the neutrophil counts to lymphocyte counts in routine complete blood counts and was recorded for each patient and control. The information on comorbid conditions were retrieved from patient files. The presence or absence of chronic obstructive pulmonary disease (COPD) was ascertained using pulmonary function tests values, in which a FEV1/FVC of less than 70 was considered to denote the presence of COPD.
Statistical Analysis: Constant variables were shown as mean ± standard deviation. Categorical variables were presented as frequency percentages. Statistical differences between the intervention and control groups were investigated with t-test and Mann-Whitney U test for constant variables. Categorical data were evaluated with chi-square test. Data was analyzed using SPSS 16 statistical software, with a p value of less than 0.05 showing statistical significance.

RESULTS

There were 100 female (43.1%) and 132 male (56.9%)

patients in the study, with 52, 50, and 130 cases having mild (AHI: 5-15), moderate (AHI: 15-30) and severe (AHI > 30) OSAS, respectively. The mean age of the overall participants was 49.06 ± 11.161 years, while this figure in mild, moderate, and severe OSAS cases was 42.88 ± 10.10, 47.24 ± 10.10, and 52.24 ± 10.70 years, with a statistically significant difference between severe cases of OSAS and the two other groups (p = 0.013 and 0.000, for moderate and mild OSAS, respectively). The mean neck circumference in the overall group was 41.82 ± 5.90 cm, while it was 39.64±3.96, 40.40±3.42, and 43.17±6.835, in mild, moderate and severe OSAS subjects, respectively. Again, patients with severe OSAS had significantly higher neck circumference measurements than patients with moderate or mild OSAS (p = 0.013 and 0.001, respectively). The overall BMI was 33.9 ± 18.7, while patients with mild, moderate or severe OSAS had a BMI of 33.66 ± 26.48, 31.4300 ± 8.47479, and 34.9123 ± 18.11516, respectively, with no significant BMI difference between the groups (p = 0.532). Triglyceride levels were 164.2 ± 94.8, 199 ± 109, and 221 ± 138 mg/dl, in mild, moderate, or severe cases of OSAS, respectively, with a significant difference between mild and severe cases of OSAS in this parameter (p = 0.038). LDL in these three groups were 100.2 ± 27.4, 118.1 ± 39.6, and 108.3 ± 33.5 mg/dl, with a significant difference between moderate and mild cases of OSAS (p = 0.032). C-reactive protein (CRP) in mild, moderate and severe cases of OSAS was 0.63 ± 1.00, 1.13 ± 2.69, and 0.59 ± 0.71 mg/dL, respectively, with no significant difference (p = 0.088). Leukocyte (WBC) count was 7.13 ± 2.05, 7.00 ± 2.07, and 7.71 ± 1.93 K/mm3, respectively in mild, moderate, and severe OSAS groups, and the difference between the groups was insignificant (p = 0.052). NLO in these three groups was 4.51 ± 18.70, 1.67 ± 0.82, and 1.79 ± 0.82, respectively, without a significant difference (p = 0.157).

The mean NLR value in OSAS patients (1.76 ± 0.77) was significantly higher than that among the controls (1.31 ± 0.74) (p = 0.000).

Hypertension (HT), obstructive pulmonary disease, diabetes mellitus (DM), congestive heart failure (CHF), and goiter were present in 75 (32.3%), 36 (15.5), 36 (15.5%), 1 (4%), and 21 (9.1%) patients. Table 1 depicts the distribution comorbid conditions in study groups. As shown, HT was significantly more frequent among patients with severe OSAS (p = 0.04). Obstructive pulmonary disease was more common among OSAS patients, although the difference was not significant (p = 0.79). DM occurred at a higher incidence in subjects with OSAS than in controls (p = 0.017). CHF was present in a single patient with severe OSAS, and the number of patients was inadequate for statistical comparison, as was the case for goiter.

Table 1: Comorbid conditions in obstructive sleep apnea syndrome patients

Comorbidity		Mild OSAS*	Moderate OSAS*	Severe OSAS*	Total
Hypertension	(n)	12	12	51	75
	%	23.1%	24.0%	39.2%	32.3%
Diabetes Mellitus	(n)	4	4	28	36
	%	7.7%	8.0%	21.5%	15.5%
Asthma	(n)	7	7	22	36
	%	13.5%	14.0%	16.9%	15.5%
Congestive heart failure	(n)	0	0	1	1
	%	0%	0%	8%	4%
Goitre	(n)	6	5	10	21
	%	11.5%	10.0%	7.8%	9.1%

*: Obstructive sleep apnea syndrome

Table 2 shows the results of laboratory parameters in patients with or without HT. Other comorbidities were not evaluated for NLR association due to the number of patients was inadequate for statistical comparison. OSAS patients without HT had an average CRP of 0.57 ± 1.06 mg/dL, while the corresponding value was 1.02 ± 2.04 mg/dL among those with HT, with a statistically significant difference between the two groups (p = 0.05). Also, there was a statistically significant difference in ESR values in OSAS patients with (21.55 ± 19.73) or without (9.77 ± 10.99) HT (p = 0.008). Again, a significant difference in NLR between OSAS patients with (3.59 ± 14.92) or without (1.72 ± 0.69) HT was found (p = 0.014).

Table 2: Characteristics of obstructive sleep apnea syndrome patients with or without hypertension.

	OSAS* without hypertension	OSAS* with hypertension	p value
Age	45±10	55±11	0.98
Body mass index (kg/m2)	30.55±6.74	40.66±30.29	0.06
Neck circumference (cm)	41.50±6.63	42.49±3.94	0.62
Apnea Hypopnea Index (/h)	34.40±24.85	39.53±23.34	0.38
Glucose (mg/dl)	111.27±36.042	128.95±57.34	0.06
C reactive protein (mg/dl)	0.57±1.07	1.02±2.05	0.05
White blood cells (X103/mm3)	7.24±1.92	7.78±2.12	0.33
Neutrophils (X103/mm3)	4.09±1.34	4.51±1.59	0.16
Lymphocytes (X103/mm3)	2.48±0.71	2.51±0.79	0.33
Neutrophil to Lymphocyte Ratio	1.72±0.69	3.59±14.92	0.01
Sedimentation (mm/sa)	9.77±10.99	21.55±19.73	0.00

*: Obstructive sleep apnea syndrome

DISCUSSION

This study revealed that the NLR value in OSAS patients was higher than the controls. Furthermore, NLR in OSAS patients with HT was higher than NLR in OSAS patients without HT. These were the main findings of the study.

Presence of systemic inflammation associated with sleep disorders may be demonstrated using blood markers of inflammation. The recurrent attacks of hypoxia-reoxygenation have been shown to be associated with elevated levels of pro-inflammatory markers (IL6, CRP, and TNF-alpha etc.). CRP and erythrocyte sedimentation rate (ESR) also represent other inflammatory markers that are frequently utilized in the clinical practice. Newer inflammatory markers such as NLO may also have role in the assessment of systemic inflammation. NLR is a marker that can be readily measured and that is influenced by the neutrophil-mediated innate immune responses as well as the acquired immune response (8).

The prognostic significance of NLR has been demonstrated in a number of conditions including coronary artery disease, hypertension, diabetes, cerebrovascular disease, peripheral arterial disease, chronic renal disease, and in certain malignancies (9). However, studies examining its role in OSAS are limited in number. In a previous study by Korkmaz et al. NLR was compared among 118 patients with OSAS and 29 healthy controls, with no significant difference based on a comparison in AHI defined subgroups. These authors concluded that NLR could represent a diagnostic or prognostic factor in this condition (5). On the other hand, the overall comparison between OSAS patients and controls in our study revealed a significantly higher NLR value in the former group. We believe that in a condition such as OSAS that is characterized by low-grade inflammation, NLR may have a value in demonstrating the presence of inflammation. On the other hand, the absence of a significant difference between mild, moderate, and severe OSAS in our study suggests that NLR may be impractical for identifying the severity of OSAS.

The published data on the association between CRP and the severity of OSAS is controversial, with certain studies reporting an association, while others at odds with this finding (10) Another observation in our study was the absence of a significant difference in CRP, ESR, and WBC in different subgroups of OSAS severity.

Patients with OSAS have been found to have an increased risk of cardiovascular and metabolic morbidities (11-13). Particularly cardiovascular morbidities seem to pose a greater risk for this group of patients. A study by

Khan et al. involving 139 OSAS patients, 46.12%y 37.2%, and 29% of the patients had cardiovascular, metabolic, and pulmonary comorbidities, with no difference in subgroups of OSAS severity (7). Comorbid conditions that were observed in our OSAS group included HT, CHF, pulmonary conditions, DM, and goiter that were identified in 32.3%, 4%, 15%, 15.5%, and 4% of the study subjects, respectively. Although these figures were lower compared to previous reports, they were consistent with published data in terms of a higher incidence of cardiovascular comorbidities among OSAS patients.

Non-treated OSAS was associated with fatal (myocardial infarction, stroke, coronary artery bypass surgery, need for coronary angiography) or non-fatal (myocardial infarction or strokes) cardiovascular events (14). Since the comorbid conditions were identified during the study time period, their eventual fatal or non-fatal outcome is unknown.

The reported prevalence of HT in OSAS patients varies between 35 and 80% (4). Of our OSAS patient 32.3% were found to have HT. Although this figure was lower compared to previous reports, it represented the most common type of comorbidity in our patient group.

Inflammation plays a significant role in the pathophysiology of vascular diseases. In a study by Balta et al. examining the association between NLR and vascular diseases, NLR emerged as an independent prognostic factor in coronary artery disease (15). Liu et al. found an association between increasing values of NLR and risk of HT development (16). In our study, OSAS patients had higher NLR as compared to controls. Similarly, NLR, which may be a marker of inflammation, was higher in OSAS patients with HT than in those without HT. Other inflammatory markers (CRP and ESR) were also higher among OSAS patients with HT.

Limited sample size is one of the major limitations of the study, however; statistical analyses of the findings reveal statistical significance. Issues such as obesity and chronic inflammatory disorders may also have effect on neutrophil to lymphocyte ratio which was not taken into consideration in this analysis. Although these limitations could not be eliminated, the outcome of the study has significant importance on identifying the value of NLR in OSAS, as well as its association with hypertension in some subgroups. These outcomes contribute to the current knowledge on this era which is somehow controversial as explained above.

In conclusion, our results suggest that NLR may be utilized as an inflammatory marker in OSAS based on the adequately sized sample size of our study. However, NLR did not appear to be a useful indicator for the severity of OSAS. A positive correlation between elevated NLR and HT was found as well as between elevated NLR and other inflammatory markers such as CRP and sedimentation rate. A high NLR may represent an inexpensive and practical marker for predicting hypertension in patients with OSAS.

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