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ORIGINAL ARTICLE

The relationship of complete blood parameters, high-density lipoprotein cholesterol, and bilirubin values with disease severity in obstructive sleep apnea syndrome

Obstrüktif uyku apne sendromunda tam kan parametreleri, yüksek yoğunluklu lipoprotein kolesterol ve bilirubin değerlerinin hastalık şiddeti ile ilişkisi

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ABSTRACT

Objectives: This study aimed to compare total bilirubin levels with monocyte-to-high-density lipoprotein ratio (MHR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in patients diagnosed with obstructive sleep apnea syndrome (OSAS) according to the apnea-hypopnea index (AHI) values.

Patients and methods: The files of patients who underwent polysomnography and had total bilirubin and complete blood count values were retrospectively reviewed. Patients were divided into three groups: AHI <5, AHI =5-29.99, and AHI ≥30. All blood parameters and calculated ratios were compared between the groups, and the relationship between these parameters and OSAS severity was investigated.

Results: The study included 240 patients (149 males, 91 females; mean age: 47.4±11.9 years; range, 21 to 82 years). High-density lipoprotein values were significantly lower and MHR was significantly higher in the group with AHI ≥30 compared to the other two groups (p<0.001 and p=0.001, respectively). Apnea-hypopnea index was correlated with MHR (r=0.270, p<0.001). The groups were similar in terms of MLR, NLR, PLR, and total bilirubin levels.

Conclusion: Considering that these easily accessible blood parameters are affected by many factors, they can only be used as auxiliary parameters in assessing the severity and follow-up of diseases such as OSAS.

Keywords: Apnea hypopnea index, monocyte to HDL ratio, obstructive sleep apnea syndrome, total bilirubin.

ÖZ

Amaç: Bu çalışmada obstrüktif uyku apne sendromu (OUAS) tanısı konmuş olan hastaların, apne hipopne indeksi (AHİ) değerlerine göre total bilirubin düzeyleri ile monosit yüksek yoğunluklu lipoprotein oranı (MHO), monosit lenfosit oranı (MLO), nötrofil lenfosit oranı (NLO) ve platelet lenfosit oranının (PLO) karşılaştırılması amaçlandı.

Hastalar ve yöntemler: Çalışmada polisomnografi yapılmış ve total bilirubin ve tam kan değerleri olan hastaların dosyaları retrospektif olarak incelendi. Hastalar AHİ <5, AHİ =5-29,99 ve AHİ ≥30 olmak üzere üç gruba ayrıldı. Gruplar arasında tüm kan parametreleri ve hesaplanan oranlar karşılaştırıldı ve bu paramatrelerin OUAS şiddeti ile ilişkisi araştırıldı.

Bulgular: Çalışmaya 240 hasta (149 erkek, 91 kadın; ort. yaş: 47,4±11,9 yıl; dağılım, 21-82 yıl) dahil edildi. Apne hipopne indeksi ≥30 olan grupta diğer iki gruba kıyasla yüksek yoğunluklu lipoprotein değerleri istatistiksel olarak anlamlı düşük, MHO anlamlı yüksek bulundu (sırasıyla, p<0,001, p=0,001). Apne hipopne indeksi ile MHO arasında korelasyon izlendi (r=0,270, p<0,001). Gruplar MLO, NLO, PLO ve total bilirubin düzeyleri açısından benzerdi.

Sonuç: Kolay ulaşılabilir bu kan parametrelerinin birçok faktörden etkilendiği düşünülürse OUAS gibi hastalıkların şiddet ve takibinde ancak yardımcı parametreler olarak kullanılabilirler.

Anahtar sözcükler: Apne hipopne indeksi, monosit HDL oranı, obstrüktif uyku apne sendromu, total bilirubin.

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The most common type of respiratory disorders during sleep is obstructive sleep apnea syndrome (OSAS).[1] Obstructive sleep apnea syndrome is a sleep disorder characterized by recurrent apnea attacks during sleep. The repeated attacks not only deteriorate sleep depth and quality but also lead to continuous periods of hypoxia.[2]

Clinical studies have demonstrated that untreated OSAS patients have an increased risk of developing major vascular pathologies, such as hypertension, left ventricular dysfunction, coronary artery disease, arrhythmia, ischemic cerebrovascular events, and pulmonary hypertension, as well as severe conditions such as increased insulin resistance and metabolic syndrome.[2,3] It is known that these risks decrease in the long-term follow-up of patients under treatment.[4]

Polysomnography (PSG) is used in the diagnosis of OSAS.[5] The apnea-hypopnea index (AHI), a parameter of PSG, is calculated by dividing the number of apneas and hypopneas by the total hours of sleep. The AHI provides the hourly number of apneas and hypopneas and indicates the severity of the disease.[6] An AHI ≥30 is classified as severe OSAS.[6] The AHI is used in daily practice to assess the severity of the disease.

Circulating monocytes contribute to the development of atherosclerotic lesions in the endothelial wall by transforming into macrophages, thereby accelerating the development of cardiovascular diseases.[7] Furthermore, it has been shown that an increase in neutrophils and a decrease in lymphocytes among other circulating leukocyte subtypes can increase the risk of cardiovascular diseases.

High-density lipoprotein (HDL) cholesterol is thought to play a protective role in cardiovascular diseases due to its anti-inflammatory and antioxidant effects.[9]

The antioxidant effects and cardiovascular protective role of serum bilirubin have been demonstrated.[10] The risk of atherosclerosis decreases as the total serum bilirubin level increases.[11,12] The risk of atherosclerosis is known to increase in patients with OSAS.[2,3] There are limited studies in the literature comparing the severity of OSAS with total bilirubin levels.

In OSAS, aside from hypoxemia, systemic inflammation is also reported to play a role.[13] Recently, the monocyte-to-HDL ratio (MHR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) can be used as biomarkers in diseases associated with systemic inflammation. Studies evaluating MHR, NLR, PLR, and MLR in OSAS patients are limited and generally focus on a single parameter. Therefore, it is not known whether multiple parameters are altered in the same patient group. Hence, this study aimed to compare these anti-inflammatory parameters and total bilirubin levels in individuals with severe OSAS (AHI ≥30), those with mild-to-moderate OSAS (AHI =5-29.99), and those without OSAS (AHI <5).

PATIENTS AND METHODS

The retrospective study included patients who underwent PSG at the sleep laboratory between January 2019 and August 2022. The follow-up of patients was conducted at the Dr. Ersin Arslan Training and Research Hospital Sleep Laboratory, Department of Neurology, and SANKO University, Department of Neurology, the patient files were retrospectively scanned. The Embla N7000 PSG device (Embla, Broomfield, CO, USA) was utilized in this study. Patients with available complete blood count and biochemistry results obtained at the time of PSG in their files were included in the study. The sociodemographic data, PSG data, and blood values were added to a separate form. From complete blood parameters, white blood cell, monocyte, lymphocyte, neutrophil, and platelet counts, and from biochemistry values, total bilirubin and HDL cholesterol levels were recorded on the form. The MHR, MLR, NLR, and PLR were calculated by dividing the number of monocytes by HDL, the number of monocytes by lymphocytes, the number of neutrophils by lymphocytes, and the number of platelets by lymphocytes, respectively. Patients were divided into three groups: AHI <5 (normal), AHI =5-29.99 (mild-moderate), and AHI ≥30 (severe). All blood parameters and the calculated ratios were

TABLE 1
Sex and OSAS severity rates

	AHI <5 (normal)	AHI =5-29.99 (mild-moderate)	AHI ≥30 (severe)	
	n	n	n	*p*
Sex				<0.001*
Male	11	48	90	
Female	18	45	28	

OSAS: Obstructive sleep apnea syndrome; AHI: Apnea-hypopnea index; * Statistically significant at p<0.05, chi-square test.

TABLE 2
Blood parameters and rates of the groups according to AHI severity

	AHI <5 (n=29)		AHI =5-29.99 (n=93)		AHI ≥30 (n=118)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
WBC	6.7	3.9-13.4	7.27	3.17-16.3	7.96	3.75-16.44	0.099
Monocyte	0.5	0.36-1.1	0.658	0.21-1.2	0.6	0.2-1.3	0.229
Lymphocyte	2.3	1-4.2	2.64	1.1-4.63	2.59	0.6-6.79	0.079
Platelet	260	147-393	255	103-477	257	128-535	0.854
Neutrophil	4.05	1.7-11.2	3.7	1.74-12.3	4.345	1.38-7.8	0.129
HDL cholesterol	46.8[b]	25-75.5	45.2[b]	18-96.9	40[a]	18.2-68.6	<0.001*
Total bilirubin	0.46	0.16-1.9	0.47	0.09-1.53	0.555	0.18-4.2	0.053
Monocyte/HDL ratio	0.012[b]	0.01-0.03	0.012[b]	0-0.03	0.016[a]	0-0.04	0.001*
Monocyte/lymphocyte ratio	0.26	0.13-0.71	0.21	0.11-0.65	0.23	0.06-0.83	0.107
Neutrophil/lymphocyte ratio	1.52	0.77-8	1.48	0.5-4.76	1.64	0.47-8.14	0.248
Platelet/lymphocyte ratio	114.4	58.1-203.63	100.9	49.39-232.3	100.665	31.5-462	0.076

AHI: Apnea-hypopnea index; WBC: White blood count; HDL: High-density lipoprotein; a-b: There are no differences between groups with the same letter; * Statistically significant at p<0.05, Kruskal-Wallis test.

compared between the three groups, and whether these parameters had a relationship with the severity of OSAS was investigated.

Statistical analysis

Data were analyzed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The suitability of numerical variables to normal distribution was tested with the Kolmogorov-Smirnov test. Student's t-test was used to compare normally distributed variables between two groups, whereas the Mann-Whitney U test was used to compare nonnormally distributed numerical variables between two groups, and the Kruskal-Wallis H test was utilized for comparisons between three groups. The relationships between nonnormally distributed numerical variables were tested with the Spearman rank correlation coefficient. The chi-square test of independence was used to determine whether the relationship between two nominal variables was statistically significant. A p-value <0.05 was considered statistically significant.

TABLE 3
The correlation between AHI and blood parameters

	AHI	
	r	*p*
Monocyte	0.135*	0.036
HDL cholesterol	–0.275*	<0.001
Monocyte/HDL ratio	0.270*	<0.001
Total bilirubin	0.135*	0.049

AHI: Apnea-hypopnea index; HDL: High-density lipoprotein; * Statistically significant at p<0.05, r: Spearman rank correlation coefficient.

RESULTS

The study included 240 patients (149 males, 91 females; mean age: 47.4±11.9 years; range, 21 to 82 years). Twenty-nine patients had an AHI <5, 93 patients had an AHI between 5-29.99, and 118 patients had an AHI ≥30 (Table 1).

The number of males with an AHI of 30 and above was found to be statistically significantly higher.

The comparison of blood parameters and calculated ratios for groups with AHI below 5, between 5-29.99, and 30 and above is shown in Table 2. In the group with an AHI of 30 and above, HDL cholesterol values were significantly lower and the MHR ratio was significantly higher compared to the other two groups (p<0.001 and p=0.001, respectively; Table 2).

The correlation between AHI and monocytes, HDL, MHR, and total bilirubin is displayed in Table 3. No significant relationship was found between other blood parameters and AHI.

DISCUSSION

In OSAS patients, increased hypoxia leads to activation of the sympathetic nervous system,

endothelial dysfunction, and increased chronic inflammation.[14] The inflammatory parameters NLR, PLR, and MLR have been examined in patients with OSAS, and the literature presents conflicting results regarding the association of these parameters with the severity of OSAS.[15,16] No relationship is found between these parameters between these parameters and the severity of OSAS in our study, which is consistent with some studies in the literature.[17-19]

In a study, the severity of OSAS was compared with PLR and NLR, and a strong relationship was found between PLR and the severity of OSAS, suggesting that this parameter could be used as a biomarker for the severity of OSAS.[20] The same study argued that platelets contributed to the development of atherosclerosis by initiating the inflammation.[20] Another study found that PLR was lower in patients with OSAS and that PLR further decreased as the severity of the disease increased.[21]

Meta-analyses conducted due to conflicting results in the literature have determined that the NLR and PLR values are higher in OSAS patients and increase in accordance with the severity of the disease, although with heterogeneity.[15,16]

The similarity of the NLR, PLR, and MLR values across control, mild-moderate, and severe OSAS groups in our study did not support the view that these blood parameters could be used as biomarkers to assess disease severity in OSAS.

Monocytes adhere to the endothelial cell surface and stimulate the release of inflammatory cytokines in the formation of chronic inflammation. High-density lipoprotein cholesterol exerts an anti-inflammatory effect by removing monocytes from peripheral cells and increasing the efflux of oxidized cholesterol from macrophages.[22] Due to the inflammatory nature of monocytes and the anti-inflammatory properties of HDL cholesterol, the MHR has been suggested as a marker of systemic inflammation.[23] Furthermore, it has been demontrated that lipid peroxidation is increased and that there is HDL dysfunction in OSAS patients.[23]

The MHR has been considered a potentially more useful parameter for monitoring the severity of the disease in OSAS patients; however, studies on this subject are limited.[14,22,24,25] Consistent with the literature,[14,22,24] the MHR was significantly higher in severe OSAS cases (AHI ≥30) in this study. However, these results may be associated with the lower HDL cholesterol levels in the severe OSAS group. According to data obtained from the European Sleep Apnea Database, it was reported that HDL cholesterol significantly decreased with higher AHI values.[26] The relationship between OSAS and the lipid profile has not been clearly determined by studies. The HDL cholesterol levels may decrease as the severity of OSAS increases, or OSAS may be more severe in patients with lower HDL levels due to the anti-inflammatory protective effect of HDL. We believe that more comprehensive studies are required on this subject.

No statistically significant relationship was found between the severity of OSAS and total bilirubin levels in this study. The antioxidant, anti-inflammatory, and antiadipogenic effects of bilirubin have been demonstrated in the literature.[27] It is known that OSAS paves the way for atherosclerosis.[2,3] Studies investigating the clinical and laboratory findings of OSAS and total bilirubin levels are limited in the literature.[28-30] In one study, the relationship between serum bilirubin levels and carotid intima-media thickness in OSAS patients was evaluated, and it was suggested that low serum levels could be an indicator of subclinical atherosclerosis in these patients.[28] It has been reported that evaluating the NLR and total bilirubin levels together could guide in determining the cardiovascular risk in OSAS patients.[29] The absence of a difference between the control, mild-moderate, and severe OSAS groups in the present study does not support the view that bilirubin levels are associated with the severity of OSAS.

This study has some limitations. First, clinical factors not included in the study due to its retrospective and cross-sectional nature could affect the outcomes. The presence of additional diseases, particularly atherosclerosis, is a significant clinical factor. Second, the study lacks the evaluation of these blood parameters before and after continuous positive airway pressure therapy. Whether these values change over time is important in determining if they are consistent indicators of the severity of OSAS.

In conclusion, these easily accessible blood parameters can only be used as auxiliary parameters in determining the severity and monitoring of diseases such as OSAS since they are influenced by many factors and are not exclusively specific to inflammation. However, we believe that MHR could be a useful parameter. Prospective studies monitoring MHR values after device therapy could provide more insights on this subject.

Ethics Committee Approval: The study protocol was approved by the SANKO University Clinical Research Ethics Committee (date: 27.01.2022, no: 01). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Since the study was retrospective and file review, patient consent was not obtained, but permission for file review was obtained from the head physician's office.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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