



Monocyte/HDL Cholesterol Ratio and Matrix Metalloproteinase-2 in Obstructive Sleep Apnea Syndrome Without Heart Disease

Kardiyak Hastalık Öyküsü Olmayan Obstrüktif Uyku Apne Sendromu Hastalarında Serum Monosit/HDL Kolesterol Oranı ve Matriks Metalloproteinaz-2

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Abstract

Objective: Long waiting periods for polysomnography (PSG) may delay the diagnosis of obstructive sleep apnea syndrome. We aimed to assess the value of the serum monocyte/high-density lipoprotein (HDL) cholesterol ratio and matrix metalloproteinase-2 (MMP-2) levels in the early diagnosis and determination of disease severity.

Materials and Methods: This cross-sectional analytical study enrolled 162 adult participants-31 with mild, 38 with moderate, and 47 with severe disease and 46 non-affected controls. The clinical and demographic data and the ratio and MMP-2 levels were recorded and compared.

Results: A ratio >8.78 discriminated between cases with and without the condition, with a 73.3% sensitivity and 60.9% specificity ($p=0.004$). A serum MMP-2 level ≤ 4.01 ng/mL was also effective, with a 75% sensitivity and 50% specificity ($p=0.012$). There was a significant positive correlation between the serum monocyte/HDL cholesterol ratio and disease severity, with a 38% sensitivity and 92% specificity ($p=0.025$), but an insignificant negative correlation with (MMP-2) level. The ratio, but not MMP-2 level, was significantly higher in affected subgroups than in the controls. Reanalysis of risk factors using a multivariate model revealed that higher HDL and metalloproteinase-2 levels were associated with a decreased likelihood of developing the condition.

Conclusion: Assessment of the serum monocyte/HDL cholesterol ratio and MMP-2 levels may be useful as rapid and low-cost methods for identifying the condition, and the former may help predict disease severity. Evaluation of these parameters may help plan PSG when obstructive sleep apnea is suspected.

Keywords: Cholesterol, matrix metalloproteinase-2, monocytes, obstructive sleep apnea syndrome

Öz

Amaç: Obstrüktif uyku apne sendromu tanısı (OUAS), polisomnografi için uzun bekleme süreleri nedeniyle gecikebilmektedir. Bu çalışmada serum monosit/yüksek dansiteli lipoprotein kolesterol oranı (MHR) ve matriks metalloproteinaz-2 (MMP-2) düzeylerinin erken tanı koyma ve hastalık şiddetini belirlemedeki değerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışma kesitsel analitik bir çalışma olarak tasarlanmıştır. Çalışmaya 31 hafif, 38 orta ve 47 ağır OUAS hastası ve 46 OUAS olmayan kontrol olmak üzere 162 yetişkin katılımcı dahil edildi. Klinik ve demografik veriler ile MHR ve MMP-2 düzeyleri kaydedildi ve karşılaştırıldı.

Bulgular: MHR $>8,78$, OUAS ve OUAS olmayan olguları %73,3 duyarlılık ve %60,9 özgüllük ile ayırt etmektedir ($p=0,004$). Serum MMP-2 düzeyinin $\leq 4,01$ olması OUAS ve OUAS olmayan olguları %75 duyarlılık ve %50 özgüllük ile ayırt etmektedir ($p=0,012$). Serum MHR ile %38 duyarlılık ve %92 özgüllük ($p=0,025$) arasında anlamlı bir pozitif korelasyon, serum MMP-2 ile OSAS şiddeti arasında ise anlamsız bir negatif korelasyon ($p=0,291$) tespit edilmiştir. Medyan MMP-2 seviyeleri OSAS alt grupları ve kontroller arasında benzer olsa da, MHR OSAS alt gruplarında anlamlı derecede yüksektir. Risk faktörlerinin çok değişkenli bir model kullanılarak yeniden analizi, daha yüksek HDL ve MMP-2 düzeylerinin OSAS gelişme olasılığının azalmasıyla ilişkili olduğunu ortaya koymuştur.

Sonuç: MHR ve MMP-2 değerlerinin OSAS hastalarının belirlenmesinde hızlı ve düşük maliyetli yöntemler olarak yararlı olabileceği sonucuna vardık. Ayrıca, MHR hastalığın şiddetini öngörmeye yardımcı olabilir. Bu testlerin değerlendirilmesi, OUAS olduğundan şüphelenilen bir hastada PSG testinin planlanmasına yardımcı olabilir.

Anahtar Kelimeler: Kolesterol, matriks metalloproteinaz-2, monositler, obstrüktif uyku apne sendromu

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Introduction

The obstructive sleep apnea syndrome (OSAS) is a serious sleep-related disorder characterized by recurrent breathing pauses during sleep. These pauses lead to deterioration in sleep quality and architecture, oxidative stress, hyperinflammation, increased sympathetic activity, and elevated risk of cardio-cerebrovascular disease.^{1,2}

OSAS affects many systems and has negative consequences on the life of the individual.³ Hypertension, heart failure, pulmonary hypertension, cardiac arrhythmias, coronary artery disease, cerebrovascular disease, and sudden cardiac death may occur.⁴ Studies are ongoing to determine the primary cause of OSAS in patients in whom metabolic syndromes and obesity are at the forefront.⁵ Decreased cognitive function, attention deficits, and depression are observed in patients with OSAS owing to sleep desaturations.⁶ Losses in work-school productivity and an increase in occupational and traffic accidents occur in patients with OSAS.⁷ Although OSAS is a prevalent sleep disorder with serious consequences, the diagnosis may be delayed because of the long waiting periods for polysomnography (PSG). There is a need for alternative diagnostic tools for OSAS that allow for faster screening, early diagnosis, and determination of disease severity.

Previous studies have suggested a potential association between oxidative stress and inflammation with high monocyte counts and low serum high-density lipoprotein (HDL) cholesterol levels, emphasizing the monocyte/HDL cholesterol ratio (MHR) as a novel prognostic marker for various cardiovascular diseases.⁸⁻¹⁰ Both cardiovascular diseases and oxidative stress are linked to matrix metalloproteinases (MMPs), particularly MMP-2. MMP-2, which is involved in long-term processes (days to weeks), becomes more active within minutes, such as in acute ischemia-reperfusion damage in the heart.¹¹

Although the pathogenesis of inflammatory activity in OSAS differs from that in cardiovascular diseases, we suggest that MHR and serum MMP-2 levels may reflect the presence and severity of inflammation regarding upper airway obstruction and oxygen desaturation. In this study, we investigated whether these parameters are associated with the presence and severity of OSAS and, unlike in previous studies, whether they can be helpful in the early diagnosis and determination of disease severity in patients without a history of previously known or detected cardiac disease (all cardiogenic diseases such as valvular diseases, rhythm disorders, inflammatory diseases, or insufficiencies).

Materials and Methods

The study enrolled 162 participants, including 31 patients with mild, 38 with moderate, and 47 with severe OSAS, and 46 non-OSAS controls. The study was approved by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 209, date: 23.06.2022). The study included adult patients referred to the University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital Sleep Laboratory between

November 29, 2022 and May 4, 2023, who were diagnosed with OSAS based on PSG with an apnea-hypopnea index (AHI)¹² greater than 5. The control group consisted of volunteers without OSAS aged 18 to 65 years, without any cardiac disease and who denied complaints of witnessed apnea, snoring, or excessive daytime sleepiness; the diagnosis of OSAS was excluded based on findings from the Epworth Sleepiness Scale, STOP-BANG, and Berlin questionnaires. Studies have been conducted using the Turkish version of these questionnaires and their reliability has been determined.¹³⁻¹⁷ All participants provided voluntary written informed consent. The exclusion criteria included: chronic alcohol use, thyroid dysfunction, malignancy, active infection, history of cardiogenic diseases such as valvular heart disease, history of myocardial ischemia, history of endocarditis-pericarditis, congenital heart disease, heart failure, coronary artery disease, and heart rhythm disorders (atrial fibrillation, history of pacemaker use, and others). Patients on statins and patients with a history of stroke were excluded. PSG could not be performed in the control group owing to the process of PSG examination and load of the currently planned patients. Patients with excessive daytime sleepiness, snoring, or those diagnosed with apnea symptoms were also excluded. Patients with a body mass index (BMI) above 30 were excluded from the study. The ESS, STOP-BANG, and Berlin questionnaires were used, and individuals with a high risk of OSAS were excluded from the study.

Venous blood samples were collected from all groups after 12 h of fasting and analyzed. The samples were analyzed for MMP-2 levels using enzyme-linked immunosorbent assay. The patients with OSAS were classified based on AHI; values between 5 and 15 indicated mild, 16 to 30 indicated moderate, and greater than 30 indicated severe condition.

Statistical Analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as the mean and standard deviation or frequency and percentage, for continuous and categorical data, respectively. For group comparisons, the Mann-Whitney U test was used for two groups and the Kruskal-Wallis H test was used for more than two groups. The Pearson chi-square or Fisher's exact test was used to compare categorical variables. Receiver operating characteristic (ROC) analysis was conducted for parameters that had a discriminative effect on disease diagnosis and severity, and ROC curves were plotted. Logistic regression analysis was used to determine the risk factors affecting the diagnosis of the disease and severe disease. The results were considered statistically significant when the p-value was less than 0.05.

Results

A total of 162 individuals [105 (64.8%) men and 57 (35.2%) women], were included in the study. The median age was 45 (25-62) years. One hundred sixteen of the 162 (71.6%) participants were diagnosed with OSAS. In our cohort, 73.3% (n=85) in the OSAS group and 43.5% (n=20) in the control

group were men ($p<0.001$). The median age was 47 (25-62) years in the OSAS group and 35 (26-59) years in the control group ($p<0.001$). Among the patients with OSAS, 29% ($n=47$) were classified with severe, 23.5% ($n=38$) with moderate, and 19.1% ($n=31$) with mild disease.

The distribution of demographic characteristics in the control and patient groups is presented in Table 1. Examination of the data revealed statistically significant differences between the two groups in terms of age, sex, weight, BMI, and presence of comorbidities ($p<0.05$). The proportion of men was higher in the patient group, while the proportion of women was higher in the control group. In addition, the age, weight, and BMI of the patient group were higher than those of the control group. Comorbidities were more common in the patient group. Statistically significant differences were determined between the participants who were

included in the control group and who were identified using the ESS, STOP-BANG, and Berlin questionnaires and the patients with OSAS who were identified using PSG.

The median MMP-2 level was significantly lower in the OSAS group [3.4 ng/mL (min.-max., 0.3-14.2) vs. 4 ng/mL (2.3-15.3), $p=0.013$]. The median MHR was higher in the OSAS group than in the controls [11.7 (4.4-32.1) vs. 8.3 (4.1-29.6), $p=0.003$] (Table 2).

The median MMP-2 levels were similar between the OSAS subgroups and controls [mild OSAS: 3.4 ng/mL (0.5-9.3), moderate OSAS: 3.5 ng/mL (0.3-14.2), and severe OSAS: 3.3 ng/mL (2.2-13.2); $p=0.063$]. The MHR was significantly higher in the OSAS subgroups than in the controls [mild OSAS: 10.5 (4.4-16.9), moderate OSAS: 12 (5.1-18), and severe OSAS: 12.4 (6.3-32.1), $p=0.002$] (Table 3).

Table 1. Distribution of demographic characteristics of the OSAS and control groups

	Control group (n=46) n (%) or median (min.-max.)	OSAS group (n=116) n (%) or median (min.-max.)	p
Age (years)	35 (26-59)	47 (25-62)	<0.001
Sex			<0.001
Men	20 (43.5)	85 (73.3)	
Women	26 (56.5)	31 (26.7)	
Height (cm)	167 (150-187)	170 (140-189)	0.513
Weight (kg)	70 (50-98)	90 (57-155)	<0.001
BMI	24.7 (18.3-33.6)	31.2 (20.7-58.4)	<0.001
Smoker	7 (15.2)	36 (31)	0.063
Family history	0 (0)	2 (1.7)	1.000
Comorbidity	3 (6.5)	32 (27.6)	0.006
Diabetes mellitus	2 (4.3)	18 (15.5)	0.092
Hypertension	1 (2.2)	23 (19.8)	0.009
Epworth Sleepiness Scale			<0.001
Low risk	40 (87)	44 (37.9)	
High risk	6 (13)	72 (62.1)	
STOP-BANG questionnaire			<0.001
Low risk	38 (82.6)	16 (13.8)	
High risk	8 (17.4)	100 (86.2)	
Berlin questionnaire			<0.001
Low risk	33 (71.7)	18 (15.5)	
High risk	13 (28.3)	98 (84.5)	

BMI: Body mass index, OSAS: Obstructive sleep apnea syndrome, min.-max.: minimum-maximum

Table 2. Comparison of laboratory data between the OSAS and control groups

	Entire group (n=162) median (min.-max.)	OSAS group (n=116) median (min.-max.)	Control group (n=46) median (min.-max.)	p
Monocyte count (/ μ L)	440 (210-1,030)	440 (210-1,030)	420 (260-850)	0.359
HDL level (mg/dL)	41.5 (20-83)	40 (20-68)	47 (23-83)	<0.001
MHR	10.7 (4.1-32.1)	11.7 (4.4-2.1)	8.3 (4.1-29.6)	0.003
MMP-2 level (ng/mL)	3.4 (0.3-15.3)	3.4 (0.3-14.2)	4 (2.3-15.3)	0.013

OSAS: Obstructive sleep apnea syndrome, MMP-2: Matrix metalloproteinase-2, HDL: High-density lipoprotein cholesterol, MHR: Monocyte/HDL cholesterol ratio, min.-max.: minimum-maximum

Table 3. Comparison of the laboratory data between the OSAS subgroups and controls

	Mild OSAS (n=31)	Moderate OSAS (n=38)	Severe OSAS (n=47)	Control (n=46)	p
Monocyte count (/μL)	440 (230-680)	440 (210-830)	450 (280-1,030)	420 (260-850)	0.422
HDL level (mg/dL)	42 (26-65)	40.5 (20-68)	38 (24-54)	47 (23-83)	<0.001
MHR	10.5 (4.4-16.9)	12 (5.1-18)	12.4 (6.3-32.1)	8.3 (4.1-29.6)	0.002
MMP-2 level (ng/mL)	3.4 (0.5-9.3)	3.5 (0.3-14.2)	3.3 (2.2-13.2)	4 (2.3-15.3)	0.063
OSAS: Obstructive sleep apnea syndrome, MMP-2: Matrix metalloproteinase-2, HDL: High-density lipoprotein cholesterol, MHR: Monocyte/HDL cholesterol ratio					

The ROC curve results for the differentiation effect of MHR and MMP-2 levels in the patients with OSAS and control group are presented in Table 4 and Figure 1.

Regarding MHR, the area under curve (AUC) the ROC value was 65.1%, with a cut-off value >8.78 ($p<0.05$). Regarding the MMP-2 level, the AUC and cut-off values were 62.5% and ≤ 4.01 ng/mL, respectively. MHR and MMP-2 were found to have 60-70% accuracy in disease diagnosis.

ROC analysis was further conducted to examine the differential effect of being in the severe OSAS group compared to the moderate or mild group in terms of MHR and MMP-2 measurements. We determined that the cut-off value for MHR was >14.05 ($p=0.025$). The MMP-2 measurement did not discriminate the severe OSAS group from the moderate or mild group ($p=0.025$ and 0.291 , respectively). We determined that MHR had a weak ability (60-70%) to distinguish severe OSAS from mild or moderate cases. The ROC curve for MHR is shown in Figure 2.

The results of the logistic regression analysis examining the risk factors affecting the development of sleep apnea in the study participants are presented in Table 5. Potential risk factors

affecting the development of sleep apnea were first evaluated in the univariate model, and the statistically significant variables were re-evaluated in the multivariate model. In the univariate analysis, all variables included in the model were statistically significant ($p<0.05$). We determined that each increase in HDL and MMP-2 values had a decreasing effect on disease development, while each increase in the value of the other parameters had the opposite effect. The disease was 3.57 times more likely to develop in men and 5.46 times more likely in individuals with, rather than without, comorbidities.

When the variables found to be significant in the univariate model were re-evaluated in the multivariate model using the retrospective method, sex and MHR were found to be the most appropriate parameters. When the variables were analyzed, it was determined that the disease developed 11.4 times more frequently in men than in women, and each increase in BMI and MHR had an increasing effect on disease development.

Discussion

In OSAS, ischemia-reperfusion injury, increased sympathetic activation, oxidative stress, systemic inflammation, and endothelial dysfunction due to periodic episodes of hypoxia

Table 4. ROC analysis results for MHR and MMP-2

	AUC (95% CI)	p	Cut-off value	Sensitivity (%)	Specificity (%)	PPV	NPV
MHR	0.651 (0.548-0.753)	0.004	>8.78	73.3	60.9	82.5	47.5
MMP-2 (ng/mL)	0.625 (0.528-0.723)	0.012	≤ 4.01 ng/mL	75.0	50.0	79.1	44.2
ROC: Receiver operating characteristic curve, AUC: Area under the curve, CI: Confidence interval, NPV: Negative predictive value, PPV: Positive predictive value, MHR: Monocyte/high-density lipoprotein cholesterol ratio, MMP-2: Matrix metalloproteinase-2							

Table 5. Investigation of risk factors affecting disease development

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.11 (1.06-1.16)	<0.001		
Sex				
Men	3.57 (1.75-7.28)	<0.001	11.40 (2.55-50.97)	0.001
BMI	1.50 (1.31-1.72)	<0.001	1.39 (1.17-1.66)	<0.001
Comorbidity	5.46 (1.58-18.85)	0.007		
HDL level (mg/dL)	0.92 (0.89-0.96)	<0.001		
MHR	1.10 (1.01-1.20)	0.026	1.09 (1.05-1.07)	0.007
MMP-2 level (ng/mL)	0.85 (0.76-0.95)	0.005		
BMI: Body mass index, CI: Confidence interval, HDL: High-density lipoprotein, MHR: Monocyte/HDL cholesterol ratio, MMP-2: Matrix metalloproteinase-2, OR: Odds ratio				

increase the risk of atherosclerosis. Both MMP-2 and MHR have the potential to be important biomarkers for the assessment of inflammation and cardiovascular risk associated with OSAS. According to the results of our study, the MHR and MMP-2

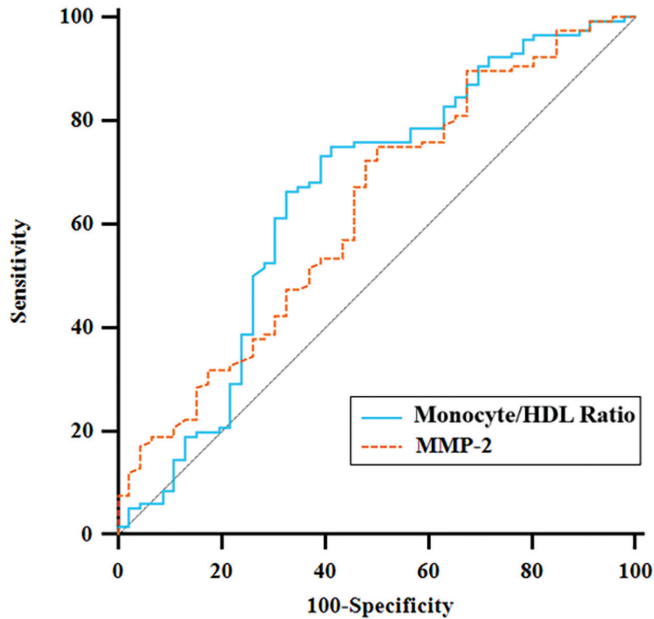


Figure 1. ROC curves for MHR and MMP-2

ROC: Receiver operating characteristic, HDL: High-density lipoprotein, MHR: Monocyte/HDL cholesterol ratio, MMP-2: Matrix metalloproteinase-2

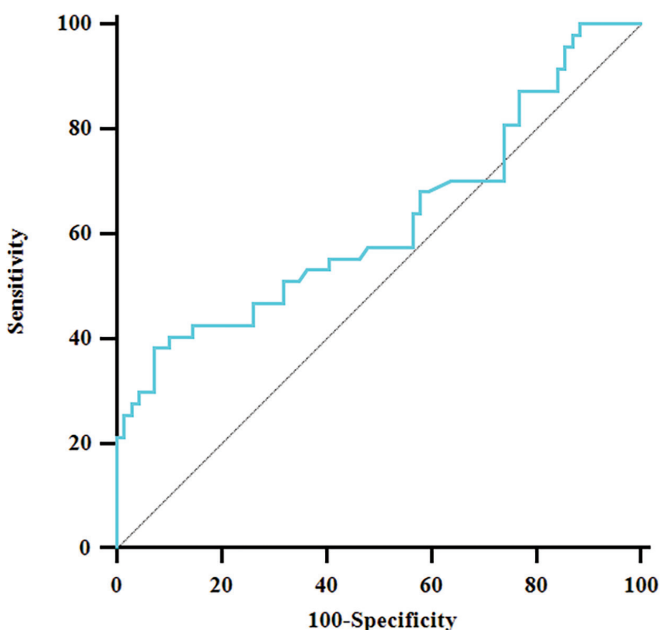


Figure 2. ROC curve for MHR in severe OSAS

ROC: Receiver operating characteristic, MHR: Monocyte/high-density lipoprotein cholesterol ratio, OSAS: Obstructive sleep apnea syndrome

values had a low ability to differentiate between the patient and control groups. Median MMP-2 levels were similar between the OSAS subgroups and controls; in contrast, MHR was significantly higher in the OSAS subgroups (mild, moderate, and severe) than in the controls. The statistically significant variables among the risk factors affecting the development of sleep apnea were re-evaluated in the multivariate model. It was found that as HDL and MMP-2 values increased, the risk of disease development decreased.

Monocytes are vital immune cells involved in oxidative stress and inflammatory processes. Hypoxia has been shown to increase peripheral blood monocyte counts.^{18,19} Sun et al.²⁰ reported that the monocyte count was similar between patients with OSAS and controls but was significantly higher in the severe OSAS subgroup than in the controls. In our study, the median monocyte count was slightly higher in the OSAS group and subgroups than in the controls but the difference was not statistically significant. This lack of significance was attributed to the small size of the study population, suggesting that different results could be obtained with a larger sample size.

Basoglu et al.²¹ reported that the HDL cholesterol levels are lower in patients with OSAS than in those without, and lower in the severe OSAS group than in the other groups. They concluded that non-HDL cholesterol, reflecting atherogenic dyslipidemia, is significantly correlated with the severity of OSAS as well as with parameters reflecting hypoxia. Although our analysis included fewer cases, the results are compatible with those of the earlier study. In addition, since variables such as diet and physical activity affect HDL levels,^{22,23} long-term follow-up of participants should be planned.

MHR has been proposed as a predictor that reflects the balance between inflammatory and oxidative stress in monocytes and HDL cholesterol. MHR has been investigated extensively in cardiovascular events and many studies have demonstrated that it is a strong index of cardiovascular mortality in patients with specific diseases, especially coronary artery disease.²⁴⁻²⁹

Sun et al.²⁰ reported that MHR is higher in OSAS groups than in controls and increases in relation to disease severity. A multicenter study of 1050 cases conducted by Inonu Koseoglu et al.³⁰ reported that MHR is significantly positively correlated with AHI and the Oxygen Desaturation Index (ODI) and negatively correlated with minimum peripheral oxygen saturation during sleep. Furthermore, MHR is associated with cardiovascular events, and values >14.73 predict the development of a cardiovascular event with 77.9% sensitivity and 59.3% specificity. In a recent study of 172 patients in our country, MHR was positively correlated with the presence of OSAS.³¹ In our study, we evaluated patients with OSAS who had not yet developed cardiac comorbidities, and found that MHR was significantly higher in the OSAS subgroups than in the controls and that it increased with disease severity. An MHR >8.78 discriminated between OSAS and non-OSAS cases with 73.3% sensitivity and 60.9% specificity. The threshold value for discriminating severe from mild and moderate OSAS was >14.05, with a 38.3% sensitivity and 92.8% specificity.

This result suggests that the cut-off value pointing to OSAS in individuals without a known cardiac history is lower than that reported in previous studies and increases with disease severity. MMPs are enzymes that play important roles in various physiological and pathological processes, such as organogenesis, wound healing, tumor invasion, and metastasis, which require extracellular matrix remodeling. Gelatinase A (MMP-2) and B (MMP-9) belong to the group of gelatinases of this family.³² MMP-2 and MMP-9 are involved in extracellular matrix degradation and intimal remodeling after angioplasty and play an important role in the pathogenesis of re-stenosis. Inflammation and oxidative stress contribute to plaque formation and destabilization by increasing MMP activity. MMP-2 is closely associated with cardiovascular events through its rapid activation in both long-term processes and acute ischemia-reperfusion injury. The expression of MMP-2 in cells is unique among the MMPs. Unlike other MMPs, MMP-2 does not appear to be particularly sensitive to stress stimuli.³³ MMP-2 is known to increase in cardiovascular events but the information on MMP-2 in OSAS is limited. Although one study found no association between MMP-2 and OSAS severity, Volná et al.³⁴ found that MMP-2 levels were similar between the OSAS group and controls.

In 2016, Bonanno et al.³⁵ investigated the levels of relaxin-2 (a hormone increased during pregnancy) in 50 men men patients with OSAS without a history of cardiovascular disease, and revealed that although the relaxin level was similar in the two groups, the MMP-2 level-which is controlled by relaxin-2 release-decreased significantly as OSAS severity increased. The effectiveness of this molecule in OSAS will be better understood in future research.

Two studies found elevated MMP-2 levels in OSA. In 2016, Hopps et al.³⁶ conducted a study of 48 patients with OSAS and 31 controls to investigate the relationship between gelatinase levels and OSAS and found a statistically significant increase in MMP-2 values in OSAS. In addition, when grouped according to disease severity, a statistically significant positive correlation was observed between MMP-2 levels and OSAS subgroups. Compared to that study, our study included a larger patient group.

Franczak et al.¹¹ compared the MMP-2 level in 124 patients with OSAS (58% men) and 26 controls (46% men) and reported a positive correlation between MMP-2 level and OSAS severity. However, the authors did not exclude the patients with a history of cardiovascular disease. Unlike that study, we investigated whether MMP-2 was associated with the presence and severity of OSAS in a group of patients without any history or diagnosis of cardiac disease (all cardiogenic diseases, including valvular diseases, rhythm disorders, inflammatory diseases, and insufficiencies) and whether it can help in the early diagnosis and assessment of disease severity. In contrast to the previous results, we revealed a negative correlation, which may be due to the younger age and men predominance in our OSAS group (73.3%) and the exclusion of patients with cardiac diseases. We suggest that, in OSAS, as the intensity of inflammation increases, MMP-2 levels

are suppressed. Increased oxidative stress may also contribute to the modification of MMP-2 levels. The imbalance between MMP-2 and tissue inhibitors in this group can be observed in tissue reshaping and repair.

In our population of patients with OSAS aged 65 years or younger without a history of known cardiovascular system pathology, such as valvular heart disease, cardiomyopathies, or coronary artery disease, the MMP-2 levels were found to be low compared to those in our healthy control group who were thought not to have OSAS based on anamnesis, clinical findings, and questionnaires. In this sense, our study suggests that MMP-2 and monocyte/HDL control levels may be acceptable as early discriminatory criteria in patients younger than 65 years without cardiovascular system pathology in areas where access to PSG is difficult.

Study Limitations

Our study had a few limitations. A major limitation was the inability to perform PSG in the control group. PSG was not planned for the non-OSAS group to avoid prolonged PSG admission times in the community. Second, as the study was planned in a single center, the sample size was small. Further multicenter studies with more patients may help assess the cut-off levels for discriminating between OSAS and non-OSAS populations.

Conclusion

We conclude that the HDL, MHR, and MMP-2 values may be useful as rapid and low-cost methods for identifying individuals with and without OSAS. HDL and MHR may also be important in determining disease severity. Evaluation of these parameters may help plan PSG in individuals suspected of having OSAS.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 209, date: 23.06.2022).

Informed Consent: All participants provided voluntary written informed consent.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: G.K., B.Ş., Ş.B., T.Ç., Concept: G.K., B.Ş., Ş.B., T.Ç., Design: G.K., B.Ş., Ş.B., T.Ç., Data Collection or Processing: G.K., B.Ş., Ş.B., T.Ç., Analysis or Interpretation: G.K., B.Ş., Ş.B., T.Ç., Literature Search: G.K., B.Ş., Ş.B., T.Ç., Writing: G.K., B.Ş., Ş.B., T.Ç.

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References

1. Martin JL, Rowley JA, Goel N, et al. "Count on Sleep": an OSA awareness project update. *J Clin Sleep Med*. 2024;20(2):303-307.
2. Platon AL, Stelea CG, Boișteanu O, et al. An update on obstructive sleep apnea syndrome-a literature review. *Medicina (Kaunas)*. 2023;59(8):1459.
3. Buysse DJ. Sleep health: can we define it? Does it matter? *Sleep*. 2014;37(1):9-17.
4. Qureshi A, Ballard RD. Obstructive sleep apnea. *J Allergy Clin Immunol*. 2003;112(4):643-651.
5. Muscogiuri G, Barrea L, Annunziata G, et al. Obesity and sleep disturbance: the chicken or the egg? *Crit Rev Food Sci Nutr*. 2019;59(13):2158-2165.
6. Faria A, Allen AH, Fox N, Ayas N, Laher I. The public health burden of obstructive sleep apnea. *Sleep Sci*. 2021;14(3):257-265.
7. Malhotra A, White DP. Obstructive sleep apnoea. *Lancet*. 2002;360(9328):237-245.
8. Ganjali S, Gotto AM Jr, Ruscica M, et al. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. *J Cell Physiol*. 2018;233(12):9237-9246.
9. Açıkgoz SK, Açıkgoz E, Şensoy B, Topal S, Aydoğdu S. Monocyte to high-density lipoprotein cholesterol ratio is predictive of in-hospital and five-year mortality in ST-segment elevation myocardial infarction. *Cardiol J*. 2016;23(5):505-512.
10. Suzuki A, Fukuzawa K, Yamashita T, Sasaki N, Hirata KI. Monocyte-to-HDL-cholesterol ratio and left atrial remodelling in atrial fibrillation: author's reply. *Europace*. 2017;19(8):1409-1410.
11. Franczak A, Skomro R, Sawicka J, et al. Serum matrix metalloproteinase-2 as a predictor of level of hypoxemia and severity of obstructive sleep apnea. *Sleep Breath*. 2021;25(2):877-886.
12. Chang JL, Goldberg AN, Alt JA, et al. International consensus statement on obstructive sleep apnea. *Int Forum Allergy Rhinol*. 2023;13(7):1061-1482.
13. Acar HV, Kaya A, Yücel F, ve ark. Obstrüktif Uyku Apnesi tarama testi olarak kullanılan STOP-Bang testinin türk popülasyonunda geçerliliğinin saptanması. *Türk J Anaesth Reanim*. 2013;41:115-120.
14. Yucege M, Firat H, Sever O, Demir A, Ardic S. The effect of adding gender item to Berlin Questionnaire in determining obstructive sleep apnea in sleep clinics. *Ann Thorac Med*. 2015;10(1):25-28.
15. Ulasli SS, Gunay E, Koyuncu T, et al. Predictive value of Berlin Questionnaire and Epworth Sleepiness Scale for obstructive sleep apnea in a sleep clinic population. *Clin Respir J*. 2014;8(3):292-296.
16. Oktay Arslan B, Ucar ZZ, Batur O, Orman MN. Validation of the NoSAS score for screening sleep-disordered breathing: A sleep clinic-based study in Turkey. *Turk J Med Sci*. 2021;51(1):319-327.
17. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. *Sleep Breath*. 2008;12(2):161-168.
18. Tamaki S, Yamauchi M, Fukuoka A, et al. Nocturnal hypoxic stress activates invasive ability of monocytes in patients with obstructive sleep apnoea syndrome. *Respirology*. 2009;14(5):689-694.
19. Chuang LP, Wu HP, Lee LA, et al. Elevated monocyte interleukin-8 expression under intermittent hypoxia condition and in obstructive sleep apnea patients. *Int J Mol Sci*. 2021;22(21):11396.
20. Sun M, Liang C, Lin H, et al. Monocyte to HDL cholesterol ratio as a marker of the presence and severity of obstructive sleep apnea in hypertensive patients. *Sci Rep*. 2021;11(1):15821.
21. Basoglu OK, Tasbakan MS, Kayikcioglu M. Could non-HDL-cholesterol be a better marker of atherogenic dyslipidemia in obstructive sleep apnea? *Sleep Med*. 2021;88:29-35.
22. Zachariah G. Management of triglycerides, non-high density lipoprotein cholesterol and high density lipoprotein cholesterol. *Indian Heart J*. 2024;76(Suppl 1):S58-S64.
23. Madan K, Sawhney JPS. Exercise and lipids. *Indian Heart J*. 2024;76(Suppl 1):S73-S74.
24. Cetin MS, Ozcan Cetin EH, Kalender E, et al. Monocyte to HDL cholesterol ratio predicts coronary artery disease severity and future major cardiovascular adverse events in acute coronary syndrome. *Heart Lung Circ*. 2016;25(11):1077-1086.
25. Karataş MB, Çanga Y, Özcan KS, et al. Monocyte to high-density lipoprotein ratio as a new prognostic marker in patients with STEMI undergoing primary percutaneous coronary intervention. *Am J Emerg Med*. 2016;34(2):240-244.
26. Villanueva DLE, Tiongson MD, Ramos JD, Llanes EJ. Monocyte to high-density lipoprotein ratio (MHR) as a predictor of mortality and major adverse cardiovascular events (MACE) among ST elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention: a meta-analysis. *Lipids Health Dis*. 2020;19(1):55.
27. Sercelek A, Besnili AF. Increased monocyte to high-density lipoprotein cholesterol ratio is associated with TIMI risk score in patients with ST-segment elevation myocardial infarction. *Rev Port Cardiol (Engl Ed)*. 2018;37(3):217-223.
28. Zhang DP, Baituola G, Wu TT, et al. An elevated monocyte-to-high-density lipoprotein-cholesterol ratio is associated with mortality in patients with coronary artery disease who have undergone PCI. *Biosci Rep*. 2020;40(8):BSR20201108.
29. Cicek G, Kundi H, Bozbay M, Yayla C, Uyarel H. The relationship between admission monocyte HDL-C ratio with short-term and long-term mortality among STEMI patients treated with successful primary PCI. *Coron Artery Dis*. 2016;27(3):176-184.
30. Inonu Koseoglu H, Pazarli AC, Kanbay A, Demir O. Monocyte count/HDL cholesterol ratio and cardiovascular disease in patients with obstructive sleep apnea syndrome: a multicenter study. *Clin Appl Thromb Hemost*. 2018;24(1):139-144.
31. Ölmez H, Tosun M, Ünver E, et al. Can biomarkers predict the risk of cardiovascular disease in patients with obstructive sleep apnea syndrome? *Journal of Surgery & Medicine (JOSAM)*. 2023;7(2):160-164.
32. Mecham RP, Parks WC. Matrix metalloproteinases: Elsevier; 1998. Available from: https://www.google.com/books?hl=tr&lr=&id=kNsHSAqyU_YC&oi=fnd&pg=PP1&dq=Mecham+RP+Parks+WC.+Matrix+metalloproteinases:+Elsevier%3B+1998.&ots=vqnLye-dAd&sig=QIUrPmXwprFhSi2kY5Qsdb3l6TE
33. Szmitko PE, Wang CH, Weisel RD, Jeffries GA, Anderson TJ, Verma S. Biomarkers of vascular disease linking inflammation to endothelial activation: Part II. *Circulation*. 2003;108(17):2041-2048.
34. Volná J, Kemlink D, Kalousová M, et al. Biochemical oxidative stress-related markers in patients with obstructive sleep apnea. *Med Sci Monit*. 2011;17(9):CR491-CR497.
35. Bonanno A, Riccobono L, Bonsignore MR, et al. Relaxin in obstructive sleep apnea: relationship with blood pressure and inflammatory mediators. *Respiration*. 2016;91(1):56-62.
36. Hopps E, Canino B, Montana M, et al. Gelatinases and their tissue inhibitors in a group of subjects with obstructive sleep apnea syndrome. *Clin Hemorheol Microcirc*. 2016;62(1):27-34.