



# Nicotine Dependence Level and Sleep Quality in Patients Attending the Smoking Cessation Clinic

## Sigara Bırakma Polikliniğine Gelen Hastalarda Nikotin Bağımlılık Düzeyi ve Uyku Kalitesi

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### ABSTRACT

**Objective:** In our study, the aim is to investigate the impact of nicotine dependence level, smoking habits, and the desire to quit smoking on sleep quality, as well as their relationship with anxiety and depression levels.

**Methods:** The study is a prospective case control research. Two hundred twenty-eight individuals who were admitted to family medicine and smoking cessation clinics (SCC) were included in the study, forming three different groups: those who smoked and visited the SCC, those who smoked, and those who did not smoke. Participants were administered Fagerstrom Nicotine Dependence Test, Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale.

**Results:** In our study, the PSQI score of patients who wished to quit smoking and were admitted to the SCC was 5.29, while the PSQI score of other smokers was 4.58, and the PSQI score of non-smokers was 4.54. Although the PSQI scores of patients who were admitted to the SCC were higher, this wasn't statistically significant ( $p=0.479$ ). Statistically significant results were found regarding anxiety and depression levels between those who were admitted to the SCC and the other groups ( $p<0.001$ ,  $p=0.015$ ). The dependence level of the group smoking and visiting the SCC was significantly higher than that of the other group of smokers ( $p<0.001$ ).

**Conclusion:** Anxiety, depression, physical activity, and nocturnal eating are factors associated with sleep quality. Individuals who visit the SCC have higher scores for cigarette addiction, anxiety, depression, and questioning and treating their symptoms in this direction will be beneficial for the patient's sleep pattern.

**Keywords:** Cigarette smoking, sleep quality, smoking cessation

### ÖZ

**Amaç:** Çalışmamızda, nikotin bağımlılık düzeyi, sigara kullanımı ve sigara bırakma isteğinin uyku kalitesine etkisi ve anksiyete depresyon düzeyleri ile ilişkisinin incelenmesi hedeflenmiştir.

**Yöntemler:** Çalışmamız prospektif, olgu kontrol tipte bir araştırmadır. İki yüz yirmi sekiz kişi, Aile Hekimliği ve sigara bırakma polikliniklerine (SBP) başvurmuş ve çalışmaya dahil edilmiştir. Bu kişiler arasında, SBP'ye gelip sigara içenler, sigara içenler ve sigara içmeyenler olmak üzere üç farklı grup oluşturulmuştur. Katılımcılara Fagerstrom Nikotin Bağımlılık Testi (FNBT), Pittsburgh Uyku Kalitesi İndeksi (PUKİ), Hastane Anksiyete ve Depresyon Ölçeği uygulanmıştır.

**Bulgular:** Çalışmamızda sigara bırakma isteği olup SBP'ye başvuran hastaların PUKİ skoru 5,29, diğer sigara içenlerin PUKİ skoru 4,58, sigara içmeyenlerin PUKİ skoru 4,54 idi. SBP'ye başvuran hastaların PUKİ skorları daha yüksek olmasına rağmen istatistiksel olarak anlamlı çıkmamıştır ( $p=0,479$ ). SBP'ye başvuranlar ve diğer gruplar arasında anksiyete ve depresyon düzeyleri açısından istatistiksel açıdan anlamlı sonuçlar çıkmıştır ( $p<0,001$  ve  $p=0,015$ ). SBP'ye gelip sigara içen grubun bağımlılık düzeyi diğer sigara içen gruptan anlamlı yüksektir ( $p<0,001$ ).

**Sonuç:** Anksiyete, depresyon, fiziksel aktivite ve gece yemek yeme uyku kalitesiyle ilişkili faktörlerdir. SBP'ye gelen kişilerin sigara bağımlılığı, anksiyete, depresyon ve PUKİ uyku bozukluğu skorları yüksek olup, bu yönde semptomlarının sorgulanması ve tedavisi hastanın uyku düzeni için yarar sağlayacaktır.

**Anahtar Kelimeler:** Sigara içme, uyku kalitesi, sigara bırakma

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## Introduction

Sleep disorders are directly associated with socioeconomic status, psychiatric diseases, obesity, smoking addiction, stress, and drug use (1).

The effects of nicotine and nicotine deprivation on sleep and the tendency of nonsmokers to be more awake in the morning indicate a relationship between smoking and sleep disorders (2). Also, because of the nicotine it contains, smoking is among the factors that might affect sleep quality negatively by stimulating the central nervous system (3). It was reported in previous studies that smokers had sleep problems such as difficulty falling asleep, falling asleep, waking up early, and daytime sleepiness (4). Nicotine stimulates the release of neurotransmitters such as dopamine, which cause sleep disorders. For this reason, smokers can stay awake longer than non-smokers, wake up frequently at night, and experience insomnia (5). Although there are studies in the literature conducted on the relationship between smoking and sleep quality, no study was detected that included smokers who wanted to quit smoking.

Individuals who have psychiatric problems tend to start smoking at an earlier age, smoke more heavily, and be more addicted to cigarettes than the general population (6). It has been confirmed that smoking is highly comorbid with anxiety and depression and that this relationship is moderated by factors such as the smoker's age, type of disorder, and level of nicotine dependence (7). Previous studies reported an association between smoking and increased anxiety symptoms or disorders. In this context, early life exposure predisposes to anxiety in later life (8). The anxiolytic and antidepressant effects of smoking are often described by smokers. Depression causes people to smoke to treat their symptoms, but later smoking increases the risk of depression through changes in neurotransmitter pathways after chronic exposure. Acute or occasional tobacco use might reduce the negative effects, but chronic use exacerbates anxiety and depression (9).

The present study aimed to examine the relationship between nicotine addiction levels, smoking, and desire to quit smoking on sleep quality and anxiety and depression levels.

## Methods

The study had a prospective cross-sectional design and the participants were included in the study with the simple random sampling method among those who were admitted to family medicine and smoking cessation clinics (SCC) of family medicine between 27.07.2022 and 27.09.2022. When the 562 people who were admitted to the clinics were accepted as the study population, the confidence interval was calculated as 95%, the deviation amount was calculated as 0.05, and the minimum number of people required was calculated as 228. The patients were divided into three different groups as smokers who were admitted to SCC, smokers who were not admitted to SCC, and non-smokers, (76 participants in each group). Patients between the ages of 18-65 who volunteered for the study were included, and those with mental retardation, communication

limitations, active psychiatric disease, body mass index (BMI)  $\geq 35$ , asthma and chronic obstructive pulmonary disease, and pregnant women were not included in the study. Also, those who had known sleep disorder diagnosis, substance abuse other than smoking, shift work that would disrupt sleep patterns or long-distance travel requirements, or acute or chronic diseases that would disrupt sleep patterns were not included in the study. Face-to-face interview technique and survey design were used in the study.

After the informed consent forms were approved, a participant information collection form was used, including sociodemographic data, chronic disease, and medication use status, and the results were recorded. This form consisted of questions on the sociodemographic characteristics, height-weight status, chronic diseases, regular medication, and smoking status, physical activity, and general health status of the individuals. Fagerstrom Test for Nicotine Dependence (FTND), Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale (HADS) were admitted to the participants.

The Turkish validity and reliability study of FTND was conducted by Uysal et al. (10) to be used as a measurement tool in the evaluation of nicotine addiction. The score range that can be obtained from the test, which consists of a total of 6 questions, is between "0" and "10". A higher score indicates an increase in addiction.

The PSQI is a self-report scale used to evaluate sleep quality and sleep disturbance over one month. The PSQI was developed by Buysse et al. (11) and was shown to have adequate internal consistency, test-retest reliability, and validity. The Turkish validity and reliability study of the scale was conducted by Ağargün et al. (12) and it was determined that it was suitable for the Turkish population. It consists of a total of 11 questions and 7 subcomponents. These components consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction. The total score on the scale ranges from 0 to 21. The scores of the 7 components are added together, and values  $>5$  indicate poor sleep quality.

The HADS consists of 14 questions, where single-digit questions measure anxiety (HADS-A) level and double-digit questions measure depression (HADS-D) level, each question consisting of 4 options. Participants' anxiety and depression levels are considered normal between 0-7 points, borderline between 8-10 points, and abnormal if 11 and above. The Turkish validity and reliability study was conducted by Aydemir and Güvenir (13).

The study was conducted in line with the Declaration of Helsinki and the principles of good clinical practice. Approval was received from the Ethics Committee of a Haydarpaşa Numune Training and Research Hospital on 27.06.2022 (decision no: 2022/141, date: 27.06.2022).

## Statistical Analysis

Statistical analyses were made by using the IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA). Demographic variables

such as sex and PSQI classification were summarized by using frequencies (n) and percentages (%) to illustrate the distribution of the participants. The distribution of the continuous variables including age, BMI, FTND, HADS and PSQI scores was evaluated graphically and with the Shapiro-Wilk test. Descriptive statistics were expressed as mean  $\pm$  standard deviation because these variables did not meet the criteria for normal distribution. For group comparisons, nonparametric tests were applied because of the non-normal distribution of continuous variables. The Mann-Whitney U test was used to compare two independent groups, and the Kruskal-Wallis test was used for comparisons involving more than two independent groups. Post hoc pairwise comparisons were adjusted by using the Bonferroni correction and were then analyzed with the Mann-Whitney U test. The Spearman's rank-order relationship coefficient was made use of to examine the relationships between scale scores. Multivariate logistic regression analysis was conducted to identify predictors of poor sleep quality. The independent variables included in the model were HADS-A score, HADS-D score, FTND score, age, sex, marital status, BMI, regular exercise, nighttime eating, and phone use before sleeping. Statistical significance was set at  $p < 0.05$ .

## Results

The study included 76 individuals who were admitted to SCC and smoked, 76 individuals who were not admitted to SCC and smoked, and 76 individuals who did not smoke and a total of 57.9% of the individuals (n=132) were female, the average sleep duration of the individuals was  $7.16 \pm 1.24$  hours. According to the PSQI scale score classification, 70.2% (n=160) were in the healthy sleep class, and 29.8% (n=68) were in the poor sleep class.

The comparison of the demographic characteristics of the individuals and the PSQI scores of other variables that might affect sleep quality is given in Table 1. No statistically significant differences were detected between the PSQI scores and the other variables except for "do you exercise regularly?", "do you have a habit of eating at night?", "do you actively use your mobile phone, television, or computer in the last hour before going to sleep?" ( $p > 0.05$ ). The sleep quality of those who answered "every day" to the question "do you exercise regularly?" was better than those who said "no" or "occasionally" ( $p = 0.007$  and  $p = 0.012$ ).

Comparisons were made between the groups (smokers who were admitted to SCC, smokers, non-smokers) in terms of total PSQI, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, daytime dysfunction, HADS-A, HADS-D and FTND scores (Table 2). No significant differences were detected between the groups in terms of total PSQI scores ( $p = 0.479$ ). However, when we look at its subcomponents, there was a significant difference between the groups in terms of sleep latency, habitual sleep efficiency, and sleep disturbance scores. Sleep latency scores were significantly higher in the group who were admitted to SCC and smoked compared to non-smokers, and habitual sleep efficiency scores were significantly higher in the group

**Table 1.** The comparison of the PSQI scores of the individuals in variable groups

		PSQI score	
		Mean $\pm$ SD	p-value
Sex	Female	4.97 $\pm$ 2.71	0.316
	Male	4.57 $\pm$ 2.33	
Educational status	Not literate	5.67 $\pm$ 4.72	0.441
	Primary school	5.35 $\pm$ 2.43	
	Middle school	5.00 $\pm$ 4.09	
	High school	4.53 $\pm$ 2.54	
	Bachelor's degree and above	4.82 $\pm$ 2.31	
Marital status	Married	4.77 $\pm$ 2.58	0.459
	Single	4.68 $\pm$ 2.32	
	Divorced	5.08 $\pm$ 3.15	
	Spouse passed away	7.00 $\pm$ 3.94	
Living environment	Alone	4.41 $\pm$ 2.00	0.501
	With spouse	4.00 $\pm$ 1.94	
	Nuclear family	4.82 $\pm$ 2.58	
	Extended family	5.21 $\pm$ 3.14	
	Other	5.17 $\pm$ 2.81	
Income status	Less than MW	5.44 $\pm$ 3.03	0.875
	MW	4.80 $\pm$ 2.96	
	More than MW	4.73 $\pm$ 2.51	
	2 times and more than MW	4.78 $\pm$ 2.21	
	3 times and more than MW	4.45 $\pm$ 1.82	
Regular exercise	No	5.16 $\pm$ 2.68	0.023
	Every day	3.60 $\pm$ 1.27	
	At least three days a week	4.18 $\pm$ 2.16	
	At least five days a week	4.63 $\pm$ 2.27	
	Once in a while	5.26 $\pm$ 2.98	
Smoking	Yes	4.93 $\pm$ 2.54	0.369
	No	4.54 $\pm$ 2.59	
Consuming tea one hour before sleep	Yes	4.99 $\pm$ 2.38	0.347
	No	4.53 $\pm$ 2.50	
	Sometimes	5.00 $\pm$ 3.09	
Consuming coffee one hour before sleep	Yes	5.13 $\pm$ 2.14	0.272
	No	4.74 $\pm$ 2.60	
	Sometimes	4.72 $\pm$ 2.79	
Chronic disease	Yes	5.28 $\pm$ 2.99	0.494
	No	4.76 $\pm$ 2.52	
Night eating habit	Yes	5.68 $\pm$ 2.85	0.002
	No	4.51 $\pm$ 2.39	
Screen before sleep*	Yes	5.03 $\pm$ 2.59	0.001
	No	3.78 $\pm$ 2.10	

\*Screen exposure in the last hour before sleep, SD: Standard deviation, MW: Minimum wage, PSQI: Pittsburgh sleep quality index

who were admitted to SCC and smoked compared to non-smokers ( $p=0.013$  and  $p=0.030$ ). Sleep disturbance scores were significantly higher in the group who were admitted to SCC and smoked compared to smokers and non-smokers ( $p=0.029$  and  $p=0.037$ ). HADS-A, HADS-D, and FTND scores of the group that were admitted to SCC and smoked were significantly higher than the group that did not smoke ( $p<0.001$ ,  $p=0.015$  and  $p<0.001$ ).

A statistically significant and positive relationship was detected between FTND score and sleep disturbance ( $\rho: 0.189$ ,  $p=0.019$ ). No statistically significant relationship was found between FTND score and subjective sleep quality, sleep latency, sleep duration, and habitual sleep efficiency ( $\rho: 0.033$ ,

$p=0.683$ ;  $\rho: 0.147$ ,  $p=0.071$ ;  $\rho: -0.003$ ,  $p=0.970$ ;  $\rho: -0.037$ ;  $p=0.654$ , respectively).

The results of the multivariate logistic regression model, which included variables such as HADS-A score, HADS-D score, FTND score, age, sex, marital status, BMI, regular exercise, eating at night, using the phone before going to sleep, etc., whose effects on poor sleep status were investigated, are given in Table 3.

The explanatory power of the model was evaluated by using the Cox and Snell or Nagelkerke  $R^2$  values. The Nagelkerke  $R^2$  value of 0.523 in the logistic regression model indicated that the multivariate model explained the response variable (poor sleep status) very well.

**Table 2.** Comparison of PSQI (total and subcomponents), HADS-A, HADS-D, and FTND scores between the groups

	Coming to SCC and smoking Mean $\pm$ SD	Smoker Mean $\pm$ SD	Non-smoking Mean $\pm$ SD	Test statistics p-value
Total PSQI	5.29 $\pm$ 2.97	4.58 $\pm$ 1.96	4.54 $\pm$ 2.59	0.479
Subjective sleep quality	1.10 $\pm$ 0.72	1.10 $\pm$ 0.42	0.99 $\pm$ 0.62	0.441
Sleep latency	1.32 $\pm$ 0.91 <sup>a</sup>	1.07 $\pm$ 0.87	0.91 $\pm$ 0.94 <sup>a</sup>	0.017
Sleep duration	0.74 $\pm$ 0.72	0.83 $\pm$ 0.62	0.80 $\pm$ 0.67	0.437
Habitual sleep activity	0.34 $\pm$ 0.77	0.09 $\pm$ 0.33 <sup>a</sup>	0.33 $\pm$ 0.66 <sup>a</sup>	0.024
Sleep disorder	1.24 $\pm$ 0.49 <sup>a,b</sup>	1.00 $\pm$ 0.49 <sup>a</sup>	1.03 $\pm$ 0.63 <sup>b</sup>	0.013
Daytime dysfunction	0.41 $\pm$ 0.66	0.45 $\pm$ 0.79	0.46 $\pm$ 0.72	0.878
HADS-A	7.78 $\pm$ 3.82 <sup>a</sup>	5.37 $\pm$ 3.05 <sup>a</sup>	6.50 $\pm$ 4.14	<0.001
HADS-D	6.67 $\pm$ 3.62 <sup>a</sup>	4.96 $\pm$ 3.05 <sup>a</sup>	5.69 $\pm$ 3.84	0.019
FTND	6.37 $\pm$ 2.28	4.43 $\pm$ 3.07		<0.001

<sup>a,b</sup>: Mann-Whitney U-test statistics, Kruskal-Wallis test statistics, same letters indicate significant difference between groups, PSQI: Pittsburgh sleep quality index, HADS-A: Hospital anxiety and depression scale - anxiety, HADS-D: Hospital anxiety and depression scale - depression, FTND: Fagerstrom test for nicotine dependence

**Table 3.** Potential risk factors predicting poor sleep status in the multivariate logistic regression model

Variables	$\beta$	Standard error	Wald	p-value	Exp (B)	95% Confidence interval for Exp (B)	
						Lower	Upper
Constant	-9.261	2.315	16.005	<0.001	0.001		
HADS-A	0.269	0.088	9.415	0.002	1.309	1.102	1.555
HADS-D	0.223	0.099	5.051	0.025	1.249	1.029	1.517
FTND	0.027	0.094	0.085	0.771	1.028	0.854	1.236
Age	0.010	0.028	0.119	0.730	1.010	0.956	1.066
Sex (male)	0.093	0.513	0.033	0.855	1.098	0.402	2.998
Marital status (married)	-0.784	0.529	2.195	0.138	0.456	0.162	1.288
BMI	0.098	0.059	2.769	0.096	1.103	0.983	1.238
Regular exercise (yes)	-1.066	0.513	4.315	0.038	0.344	0.126	0.942
Eating at night (yes)	1.632	0.536	9.284	0.002	5.113	1.790	14.604
Use of phone etc. before going to sleep (yes)	2.109	1.135	3.450	0.063	8.238	0.890	76.252

$\beta$ : The estimated coefficient for the predictor, SE: Standard error, Wald:  $(\beta/SE)^2$ , Exp (B): Odds ratio, HADS-A: Hospital anxiety and depression scale - anxiety, HADS-D: Hospital anxiety and depression scale - depression, FTND: Fagerstrom test for nicotine dependence, BMI: Body mass index



## Discussion

A total of 29.8% of the participants were in the poor sleep class in terms of PSQI score evaluation in the study. According to the results of the multivariate logistic regression analysis, it was found that the HADS-A score increased the risk of poor sleep by 1.31 times, and the HADS-D score increased by 1.25 times. Individuals who ate at night were more likely to have poor sleep than those who did not. The risk of having poor sleep was found to be 5.11 times higher. The risk of having poor sleep was reduced by 65.6% (1-0.34) in those who exercised regularly compared to those who do not.

In a previous study that was conducted by Dugas et al. (14), higher cigarette consumption, more frequent deprival symptoms, and higher FTND scores were associated with poor sleep quality. In another study conducted by Riedel et al. (15), it was reported that total sleep time was shorter in those who smoked less than 15 cigarettes per day and that heavy smokers did not tend to have insomnia. They attributed this to heavy smokers consuming cigarettes on a more consistent schedule. In the study, the FTND score was not one of the potential risk factors predicting poor sleep status. However, "sleep disturbance", which is one of the subcomponents of PSQI, was higher in SCC patients with high FTND scores and smokers compared to the other groups. Although there were patients with SCC patients with the highest PSQI scores among the three groups in the study and they smoked, it was not statistically significant. In other studies conducted in our country comparing smokers and non-smokers, the relationship between poor sleep and smoking was not significant (16,17,18). In a study conducted by Sujarwoto (19) on approximately 39.000 individuals, the probability of experiencing sleep disturbance was almost 1.5 times higher in current smokers than in non-smokers, and this rate almost doubled among heavy smokers. The finding in the same study that poverty was also associated with poor sleep suggests that differences in socioeconomic levels between the study participant groups may be the cause of this.

In a study that was conducted by Kwan et al. (20), it was found that students with night eating syndrome (NES) had worse sleep quality. In another study conducted by Şen and Kabaran (21), it was found that there were positive relationships between the carbohydrate intake of male participants and night eating, mood, and sleep disorder scores (21). In the study conducted by Basatemür and Güneş

(22), sleep quality was found to be lower in those with night eating habits. Similar to these results in the present study, the PSQI score of individuals with night eating habits was higher than those without. In the regression model created in the present study, it was found that the risk of poor sleep was 5.11 times higher in individuals who ate at night compared to those who did not.

In the study that was conducted by Wu et al. (23), it was found that screen exposure reduced sleep quality. Low physical activity also reduces sleep quality statistically significantly. Rafique et al. (24) concluded that using mobile screens for 8 hours or more per

day and using mobile phones for at least 30 minutes before going to sleep were associated with poor sleep quality. In the present study, those who were exposed to screens in the last hour before going to sleep had higher PSQI scores and lower sleep quality than those who were not exposed to screens.

The study of Brand et al. (25) reported that continuous intense exercise was positively associated with patients' sleep and psychological functioning. It was also found that men with low exercise levels were at risk for increased sleep complaints and poorer psychological functioning. Banno et al. (26) meta-analysis of nine studies concluded that exercise improved sleep quality without significant side effects. Lederman et al. (27) meta-analysis of eight studies reported that exercise significantly improved sleep quality in patients. In the regression model we created, exercise increased sleep quality by 65%. In the present study, similar to the literature data, as exercise level increased, it positively affected sleep quality.

Previous studies show a strong association between nicotine addiction and psychiatric diseases such as stress, anxiety, and depression (1,28). In the meta-analysis conducted by Fluharty et al. (6), half of the studies show that initial depression or anxiety is associated with subsequent smoking behavior in the form of starting to smoke or strong cigarette addiction. In the present study, the HADS-A and HADS-D scores of individuals who were admitted to SCC were found to be significantly higher than those in the smoking group. This may be because individuals who were admitted to SCC were highly dependent or that comorbid conditions caused by smoking increased anxiety and depression. Some of the patients who were admitted to SCC were admitted to our outpatient clinic because of symptoms resulting from smoking. In the study conducted by Esen et al. (29), it was concluded that the health anxiety levels of those who were admitted to SCC because of fear of chronic disease were significantly higher and that the health anxiety levels of these patients were similar to those with chronic diseases.

The smokers who had the worst sleep quality were those who were admitted to SCC among the groups, but the total PSQI scores were not statistically significant. However, there were significant results in sleep latency, habitual sleep efficiency, and sleep disturbance scores between the groups. Anxiety, depression, physical activity, and night eating are factors associated with sleep quality.

## Study Limitations

The fact that the study was conducted in one single center in the provincial borders of İstanbul, was based on volunteering, and the PSQI scale, which provides a subjective assessment of sleep quality, might have affected the results.

## Conclusion

People who are admitted to SCC have high scores for smoking addiction, anxiety, depression, and sleep disorders, and questioning and treating their symptoms will benefit the patient's sleep pattern. Questioning and adjusting lifestyles such as exercise status, eating habits, and screen exposure may be recommended for patients with sleep disorders.

## Ethics

**Ethics Committee Approval:** Approval was received from the Ethics Committee of a Haydarpaşa Numune Training and Research Hospital on 27.06.2022 (decision no: 2022/141, date: 27.06.2022).

**Informed Consent:** Informed consent forms were approved, a participant information collection form was used, including sociodemographic data, chronic disease, and medication use status, and the results were recorded.

## Footnotes

### Authorship Contributions

Concept: Y.O., Ö.B.D., A.D., Design: Y.O., Ö.B.D., A.D., Data Collection or Processing: Y.O., Analysis

or Interpretation: Y.O., Ö.B.D., A.D., Literature Search: Y.O., Ö.B.D., A.D., Writing: Y.O., Ö.B.D., A.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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