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Evaluation of Sleep Quality, Restless Legs Syndrome, Anxiety and Depression in Polycystic Ovary Syndrome

Polikistik Over Sendromunda Uyku Kalitesi, Huzursuz Bacaklar Sendromu, Anksiyete ve Depresyonun Değerlendirilmesi

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Abstract

Objective: The objective of the study is to investigate sleep disorders in patients with polycystic ovary syndrome (PCOS) and determine the relationship of sleep disorders with the metabolic and psychogenic aspects of PCOS.

Materials and Methods: This case-control study was conducted between October 1, 2019, and March 1, 2020, at the gynaecology and neurology outpatient clinics of a tertiary hospital. The study included 73 patients diagnosed with PCOS and 63 healthy women volunteers. Testosterone, fasting glucose and fasting insulin levels of all the participants were measured. All study participants completed Beck's depression inventory (BDI), Beck's anxiety inventory (BAI), Epworth Sleepiness scale (ESS), Berlin questionnaire (BQ), insomnia severity index (ISI), and Pittsburgh sleep quality index (PSQI). The presence of restless legs syndrome (RLS) was assessed according to the international RLS study group criteria.

Results: According to PSQI scores, 61.6% of patients with PCOS and 34.9% of healthy controls had a poor sleep quality (p=0.003). The PCOS group had significantly higher PSQI, ESS, ISI, BAI, BDI, and BQ scores than the control group (p=0.002, p=0.001, p<0.001, p<0.001, p<0.001, p<0.001, respectively). Although 23.3% of patients with PCOS met the RLS criteria, this rate was only 6.3% in the control group (p=0.013). There was a positive correlation between insulin resistance and PSQI (r=0.320, p=0.006).

Conclusion: This study's results indicate that PCOS may be a risk factor for several sleep disorders. In addition, the cumulative impact of both the organic and psychogenic changes caused by PCOS may lead to sleep disorders.

Keywords: Anxiety, depression, polycystic ovary syndrome, insomnia, insulin resistance, restless legs syndrome

Öz

Amaç: Çalışmanın amacı, polikistik over sendromlu (PKOS) hastalarda uyku bozukluklarını araştırmak ve uyku bozuklukları ile PKOS'un metabolik ve psikojenik yönleri arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntem: Bu olgu kontrol çalışması 1 Ekim 2019-1 Mart 2020 tarihleri arasında bir üçüncü basamak hastanenin jinekoloji ve nöroloji polikliniklerinde yapıldı. Çalışmaya PKOS tanısı almış 73 hasta ve 63 sağlıklı gönüllü kadın dahil edildi. Tüm katılımcıların testosteron, açlık glikozu ve açlık insülin seviyeleri ölçüldü. Tüm çalışma katılımcıları Beck depresyon ölçeği (BDÖ), Beck anksiyete ölçeği (BAÖ), Epworth uykululuk ölçeği (EUÖ), Berlin anketi (BA), uykusuzluk şiddet indeksi (UŞİ) ve Pittsburgh uyku kalitesi indeksini (PUKİ) tamamladı. Huzursuz bacaklar sendromu (HBS) varlığı uluslararası HBS çalışma grubu kriterlerine göre değerlendirildi.

Bulgular: PUKİ skorlarına göre, PKOS hastalarının %61,6'sı ve sağlıklı kontrollerin %34.9'u kötü uyku kalitesine sahipti (p=0.003). PKOS grubu kontrol grubuna göre anlamlı olarak daha yüksek PUKİ, EUÖ, UŞİ, BAÖ, BDÖ ve BA skorlarına sahipti (sırasıyla; p=0.002, p=0.001, p<0.001, p<0.001, p<0.001, p<0.001) PKOS hastalarının %23.3'ü HBS kriterlerini karşılarken bu oran kontrol grubunda sadece %6.3 idi (p=0.013). İnsülin direnci ile PSQI arasında pozitif korelasyon vardı (r=0.320, p=0.006).

Sonuç: Bu çalışmanın sonuçları, PKOS'nin birçok uyku bozukluğu için bir risk faktörü olabileceğini göstermektedir. Ayrıca PKOS'un neden olduğu hem organik hem de psikojenik değişikliklerin kümülatif etkisi uyku bozukluklarına neden olabilir.

Anahtar Kelimeler: Anksiyete, depresyon, polikistik over sendromu, uykusuzluk, insülin direnci, huzursuz bacaklar sendromu

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy and affects approximately 10% of women of reproductive age (1). The syndrome is characterized by metabolic disorders such as hyperandrogenism, ovulatory dysfunction, dyslipidemia, insulin resistance (IR), and obesity (2,3). While genetic and environmental factors are held responsible, there is evidence that IR plays a major role in the etiology of PCOS (3). When women with PCOS are compared to healthy women of similar age, they have been shown to be at greater risk of obesity and IR (4). Therefore, in the long term, women with PCOS have increased risk of developing metabolic syndrome, type 2 diabetes mellitus, and hypertension. Adverse effects in appearance such as hyperandrogenism-related hirsutism, acne, and androgenic alopecia and anovulation-induced infertility may cause low self-esteem in women with PCOS, causing frequent stress and mood disorders (5). For these reasons, women with PCOS are recommended screening for depression and anxiety (6). It is also known that depression and anxiety lead to sleep disorders. Recent studies have shown a close relationship between PCOS and sleep disorders (7). Hyperandrogenemia, increased adiposity in the abdomen, and changes in the physiology of the upper respiratory tract in PCOS can cause obstructive sleep apnea syndrome (OSAS) (8). On the other hand, obesity, anxiety, and depression, which are frequently encountered in PCOS, are also among the risk factors for restless legs syndrome (RLS), another sleep disorder. Despite studies which have shown increased rates of RLS during pregnancy and menopause (9,10), there is no study assessing the presence and frequency of RLS in PCOS, which is very common in the reproductive period.

In this study, we aim to investigate the relationship between PCOS and sleep quality, sleepiness, insomnia, anxiety, depression, and RLS and the role of IR and testosterone in this relationship.

Materials and Methods

This case control study was conducted at the gynecology and neurology outpatient clinics of a tertiary hospital between October 1, 2019-March 1, 2020. The study adhered to the principles of the Declaration of Helsinki and informed written consent was obtained from all participants. The study received approval from the local ethics committee (protocol no. 2017-KAEK-189_2019.08.07_01).

Study Population

The study included 73 gynecology outpatients between ages 18-40 who were diagnosed with PCOS according to the Rotterdam criteria and 63 healthy women without PCOS as the control group.

Voluntary participants with the mental capabilities to complete the questionnaires and comprehend the scope of the study, who were not using any antidepressants, anxiolytic medications or hormones for PCOS were included in the study. Women with alcohol-substance or caffeine addiction, shift workers or who were pregnant/breastfeeding were excluded from the study. Patients with history of neurological and/or psychiatric disorders were excluded from the study. Patients who were diagnosed with Cushing syndrome, adrenal hyperplasia, and androgen secreting tumor were excluded from the study.

Heights and weights of the participants were measured and body mass indexes (BMI) were calculated. PCOS diagnoses were made according to Rotterdam criteria (11) (those who met two out of three criteria were diagnosed as PCOS): oligo-ovulation or anovulation (>35 days or <8 spontaneous menstruation/year); clinical or biochemical signs of hyperandrogenism (Ferriman-Gallwey score >8); polycystic ovaries on ultrasound (>12 antral follicles in one ovary and/or ovarian volume >10 cm^3). To evaluate IR and the role of testosterone, fasting insulin, fasting blood sugar, and total testosterone levels were measured in all participants. Homeostatic model assessment for insulin resistance (HOMA-IR: fasting glucose mg/dL x fasting insulin mIU/L/405) was used to assess IR. Morphologic features of ovaries were examined using transabdominal/transvaginal ultrasound (GE Voluson E8, USA) in all participants. All study participants completed Beck's depression inventory (BDI), Beck's anxiety inventory (BAI), Epworth sleepiness scale (ESS), Berlin questionnaire (BQ), insomnia severity index, and Pittsburgh sleep quality index (PSQI). Presence of RLS was assessed according to the international restless legs syndrome study group criteria. Questionnaires were completed in face-to-face interviews with the participants.

Assessment Tools

Data Collection Form

This form, which was applied at initial admittance, was used to collect information regarding age, marital status, education level, smoking, medications used, and history of additional illnesses.

BDI

BDI was developed by Beck et al. (12) to determine the risk of depression and measure the level and change in severity of depressive symptoms in adults. The first 13 items are related to affective symptoms followed by 8 items related to somatic symptoms, for a total of 21 items. Total score ranges between 0-63.

BAI

BAI was developed by Beck et al. (13) to determine the individual's frequency of anxiety symptoms. The 3-point Likert-type scale, consists of 21 items in total. Total score ranges between 0-63.

PSQI

PSQI was developed by Buysse et al (14). The scale consists of 18 items comprising of 7 constructs. These constructs include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A total (global) PSQI score >5 indicates clinically poor sleep quality.

ESS

ESS is an 8-item self-report scale used to assess daytime sleepiness (15). Each item is scored from 0-3 by the patient. An ESS score >10 indicates excessive daytime sleepiness (EDS).

BQ

BQ is a questionnaire developed for population screening for OSAS. The commonly used questionnaire evaluates OSAS risk and includes 10 items divided into three categories to assess snoring behavior (category 1), chronic daytime sleepiness (category 2), and presence of BMI>30 kg/m^2 and/or hypertension (category 3). Each category is evaluated separately; positive results in two or more categories is considered high risk for OSAS (16).

Insomnia Severity Index (ISI)

ISI is a highly valid and reliable assessment tool used to determine the severity of insomnia. The scale consists of seven items scored from 0-4. Maximum score ranges between 0-28 (17).

Assessment of RLS

Presence of RLS was assessed according to the revised 2014 diagnostic criteria by the international restless legs syndrome study group (18).

Statistical Analysis

Statistical analysis was performed using the SPSS® 20.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) package program. Descriptive statistics of the data was assessed. Kolmogorov-Smirnov test was used to test normality distribution of the data. For double comprasion, The Mann-Withney U test was utilized for the non parametric numarical data while the Student t-test was adopted for the parametric numerical data. Relationships between categorical variables were analyzed by chi-square test. Bivariate correlations were investigated by Spearman's correlation analysis. P-value of less than 0.05 was considered statistically significant.

Results

Comparison of demographic data and biochemical parameters of the PCOS group and control group is presented in Table 1. Mean BMI of the PCOS group (n=73) was 25.9±4.37 while mean BMI of the control group (n=63) was 24.6±4.34 (p=0.074).

Comparisons of PSQI total scores and subscale scores is presented in Table 2. According to PSQI scores, 61.6% of PCOS patients and 34.9% of healthy controls had poor sleep quality (p=0.003).

Comparisons of BDI, BAI, ESS, ISI, and BQ scale scores and RLS rates of the two groups are presented in Table 2. PCOS patients had significantly higher depression and anxiety scores (p<0.001, p<0.001, respectively) and also significantly higher ISI and ESS scores (p<0.001, p=0.001, respectively) compared to the control group. While 23.3% of PCOS patients met RLS criteria, this rate was 6.3% among the control group (p=0.013). In addition, 31.5% of PCOS patients were at high risk of OSAS, whereas this rate was 4.8% in the control group (p<0.001).

Correlation of PSQI, ESS, ISI and BDI, BAI, HOMAIR, and testosterone level in the PCOS group is presented in Table 3. Table 4 shows the correlation of BQ (OSAS risk) and RLS presence with HOMAIR and testosterone levels. Table 5 demonstrates the relationship between RLS presence and BMI, PSQI, ESS, ISI, BDI, and BAI scores.

Discussion

In this study, it was observed that the PCOS group was at much greater risk for sleep disorders compared to the control group. Similar to previous studies, women with PCOS had higher rates of anxiety and depression. In addition, the relationship between

Table 1. Demographic data and biochemical parameters of the participants

	PCOS (n=73)	Control (n=63)	p
Age (years)*	26.03 ± 5.02	27.35 ± 5.3	0.124
BMI*	25.9 ± 4.37	24.6 ± 4.34	0.074
Marital status**			
Single	41 (56.2)	27 (42.9)	0.122
Married	32 (43.8)	36 (57.1)	
Smoking**			
Non-smoker	63 (86.3)	48 (76.2)	0.195
Smoker	10 (13.7)	15 (23.8)	
Educational status**			
Primary school	8 (11)	7 (11.1)	0.974
High school	30 (41.1)	27 (42.9)	
University	35 (47.9)	29 (46)	
HOMA index (mg/dl X µU/mL)***	2.77±0.9	1.76±0.76	**<0.001**
Testosterone (ng/mL) *	0.34±0.1	0.25±0.1	**<0.001**

BMI: Body mass index, HOMA-IR: homeostatic model assessment for insulin resistance data is shown as median (minimum-maximum), n (%) and mean ± standard deviation. Bold values represent significant findings at p<0.05, *Mann-Whitney U test, **chi-square test, ***Independent samples t-test, PCOS: Polycystic ovary syndrome

Table 2. PSQI, BDI, BAI, ESS, ISI, BQ scores and RLS rates of the groups			
	PCOS (n=73)	**Control (n=63)**	**p**
PSQI total*	7 (1-15)	4 (1-13)	**0.002**
Subjective sleep quality*	1 (0-3)	1 (0-2)	**0.022**
Sleep latency*	2 (0-3)	1 (0-3)	**0.025**
Sleep duration*	1 (0-3)	1 (0-2)	**0.065**
Habitual sleep efficacy*	1 (0-3)	0 (0-1)	**0.010**
Sleep disturbance*	1 (0-3)	1 (0-3)	**0.006**
Use of sleep medication*	0 (0-2)	0 (0-0)	**0.020**
Daytime dysfunction*	1 (0-3)	1 (0-3)	**0.040**
Poor sleep quality (PSQI)**			
≤5	28 (38.4)	41 (65.1)	**0.003**
>5	45 (61.6)	22 (34.9)	
BAI*	14 (2-59)	6 (1-28)	**<0.001**
BDI*	15 (5-46)	5 (0-24)	**<0.001**
ESS*	7 (2-24)	5 (0-15)	**0.001**
ISI*	9 (2-22)	6 (0-16)	**<0.001**
ESS**			
≤10	50 (68.5)	54 (85.7)	**0.031**
>10	23 (31.5)	9 (14.3)	
RLS**			
With RLS	17 (23.3)	4 (6.3)	**0.013**
Without RLS	56 (76.7)	59 (93.7)	
BQ, high risk**			
Low	50 (68.5)	60 (95.2)	**<0.001**
High	23 (31.5)	3 (4.8)	

PSQI: Pittsburgh sleep quality index, BDI: Beck depression scale, BAI: Beck anxiety scale, ESS: Epworth sleepiness scale, ISI: Insomnia severity index, PCOS: Polycystic ovary syndrome, RLS: Restless legs syndrome, BQ: Berlin questionnaire, Data is shown as median (minimum-maximum) and n (%). Bold values represent significant findings at p<0.05.

*Mann-Whitney U test, **chi-square test

Table 3. Correlation of PSQI, ESS, ISI and BDI, BAI, HOMAIR, and testosterone level in the PCOS group								
	HOMAIR		**Testosterone**		**BAI**		**BDI**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**
PSQI	0.320	**0.006**	0.051	0.669	0.282	**0.015**	0.311	**0.007**
ESS	-0.033	0.785	0.083	0.486	0.284	**0.015**	0.112	0.347
ISI	0.206	0.081	0.075	0.529	0.363	**0.002**	0.510	**0.000**

PSQI: Pittsburgh sleep quality index, ESS: Epworth sleepiness scale, ISI: Insomnia severity index, BDI: Beck depression scale, BAI: Beck anxiety scale, HOMAIR: Homeostatic model assessment for insulin resistance, r: Spearman's rank correlation,

Bold values represent significant findings at p<0.05

Table 4. Relationship of BQ and RLS with HOMAIR and testosterone level in the PCOS group						
	BQ			**RLS**		
	Low risk	**High risk**	**p**	**Without RLS**	**With RLS**	**p**
HOMA index (mg/dL X µU/mL)	2.5±0.8	3.2±0.9	0.003	2.6±0.91	3.07±0.85	0.117
Testosterone (ng/mL)	0.33±0.08	0.36±0.12	0.370	0.34±0.09	0.34±0.11	0.949

RLS: Restless leg syndrome, BQ: Berlin questionnaire, HOMAIR: Homeostatic model assessment for insulin resistance. Data is presented as mean ± standard deviation. Bold values represent significant findings at p<0.05.

*Independent samples t-test

Table 5. PSQI, ESS, ISI, BDI, and BAI scores according to the presence of restless legs syndrome in the PCOS group

	Without RLS (n=50)	With RLS + (n=20)	p
BMI*	25.25±4.34	28.02±3.9	**0.038**
PSQI*	6 (1-15)	9 (2-12)	**0.002**
ESS*	7 (2-20)	11 (3-24)	**0.019**
ISI*	8 (2-20)	12 (2-22)	**0.011**
BAI*	14 (2-45)	20 (7-59)	**0.042**
BDI*	14 (5-37)	21 (11-46)	**0.027**
BQ**	-	-	0.495
Low	40 (71.4%)	10 (58.8%)	
High	15 (28.6%)	7 (41.2%)	

PSQI: Pittsburgh sleep quality index, BDI: Beck depression scale, BAI: Beck anxiety scale, ESS: Epworth sleepiness scale, ISI: Insomnia severity index. Data is presented as median (minimum-maximum), n (%). Bold values represent significant findings at p<0.05. *Mann-Whitney U test, **chi-square test

PCOS and RLS presence was assessed for the first time, and RLS presence was four times more common in the PCOS group compared to the control group. Also, we determined that there was a significant correlation between RLS presence and sleep quality in PCOS group.

PCOS is a common endocrinopathy in women of reproductive age. While it is known for its negative outcomes such as hypertension, diabetes, cardiovascular disease, and infertility, it has also been associated with more complex metabolic and psychiatric conditions such as sexual dysfunction and sleeping and eating disorders. In recent years, the relationship between PCOS and sleep disorders has drawn attention (19). PCOS is an endocrine disorder, and the endocrine system plays an important role in the management of the sleep-wake cycle (20). Therefore, the coexistence of sleep disorders and PCOS is inevitable.

Sleep disorders negatively affect the person's mental, cognitive, and psychomotor state throughout the day. The person is less productive in their daily life due to tiredness and attention deficit, thus creating a serious health problem (21). On the other hand, psychological factors such as anxiety and depression also cause sleep disorders. In our study, anxiety and depression were more common in women with PCOS than the control group, which is consistent with the literature (6). We found that BAI and BDI scores significantly correlated with PSQI and ISI scores. We also observed there was a significant correlation between BAI and ESS scores. One of the reasons why sleep disorders often accompany PCOS may be mood disorders. Other important factors in PCOS include changes in upper respiratory tract physiology and increased abdominal adiposity due to the impact of hyperandrogenemia and IR (8). These changes pose significant risk for OSAS, which is characterized by frequent interruptions in breathing during sleep and cause other sleep disorders (22). OSAS has been the most emphasized sleep disorder in women with PCOS and various studies report prevalence between 17-75%. In our study, 31.5% of PCOS patients were found to have high risk of OSAS, which was significantly higher than the control group. Although obesity plays a major role in the etiologies of both PCOS and OSAS, research has shown significantly increased rates of OSAS in age- and BMI-matched women with PCOS (23). Furthermore, recurrent hypoxia, increases sympathetic tone and oxidative stress, leading to increased IR (24). This consequence causes a vicious cycle between OSAS and IR in PCOS. Therefore, it should not be forgotten that the presence of OSAS should be evaluated in patients with PCOS, and if detected, its treatment will reduce morbidity and mortality, as well as increase the patient's quality of life.

One of the clinical outcomes of OSAS is EDS, which is assessed using the ESS. However, women with PCOS may experience EDS even without OSAS. Vgontzas et al. (23) found that 80% of women with PCOS had EDS, while OSAS was detected in only 17% of these women. In our study, 31.5% of the PCOS group was found to have EDS, which was significantly higher compared to the control group. In addition to the negative effects of EDS on other conditions, the fact that it is a serious risk factor for decreased work performance and in traffic accidents should also be remembered (25).

Poor sleep quality was detected in 61.6% of PCOS patients. Additionally, PCOS patients scored significantly worse than the control group in all PSQI sub-constructs. Azizi Kutenaee et al. (26) conducted a cross-sectional study to investigate the impact of depression, self-worth, and body image in PCOS patients and evaluated sleep quality using PSQI. They concluded that dissatisfaction in body image leads to poor sleep quality, which negative affected the person's mood and daytime function.

Insomnia, defined as difficulty falling asleep and staying asleep, has not been shown as great interest in PCOS as other sleep disorders. In our study, ISI was used to evaluate the relationship between PCOS and insomnia; similar to the results of Franik et al.'s (27) study, the PCOS group had significantly higher scores compared to the control group .

RLS, also known as Willis-Ekbom Disease, is also among these sleep disorders. Its prevalence ranges between 3.9-15% and increases with age (28). Prevalence is two times higher in females than males. In our study, RLS prevalence was 23.3% in the PCOS group, and was only 6.3% in the control group. Pregnancy is also a known risk factor of RLS, and while iron and folate metabolism have been emphasized in its etiology, the increase in levels of steroid hormones in pregnancy may also be an effective factor (29). In conclusion, hormonal dysregulation in PCOS may be responsible for the high rate of RLS among PCOS patients in our study.

According to the relationship between RLS and the results of sleep scales in our study, there was a significant correlation with PSQI, ESS, and ISI. The fact that RLS negatively affects sleep quality and that it is frequently seen in PCOS suggests that perhaps one of the reasons for frequent accompaniment of sleep disorders in PCOS may be the presence of RLS. In addition to causing sleep problems such as inability to fall asleep, frequent awakening, and daytime sleepiness, RLS has also been shown to negatively affect the physical, psychological and social aspects of quality of life (30). There is increased incidence of anxiety and depression, and negatively affected

cognitive functions and mental state in individuals with RLS compared to the general population (31). The relationship between OSAS and RLS has drawn interest in recent times. Local recurrent hypoxia in tissue in OSAS has been shown to cause RLS, while CPAP treatment for mild OSAS has a positive effect on RLS morbidity (32). From this standpoint, the high rate of RLS is indicative of underlying OSAS disease. However, we were unable to establish a significant correlation between BQ scores and RLS presence in the PCOS group, and we believe this is because of the young age average, and therefore low number of patients with high OSAS risk, among our study population.

In one meta-analysis, 49% of women with PCOS fell under the obese category, while central obesity was detected in 54% (33). There are studies which demonstrate the relationship between obesity and RLS (34). Therefore, obesity may be considered as another underlying cause of high RLS prevalence in our study.

IR have been held responsible for poor sleep quality and increased OSAS risk in PCOS (23). In addition, the negative effects of testosterone treatment on sleep are known to cause shortening in sleep, exacerbation of sleep apnea, and increased hypoxemia (35). Therefore increase in testosterone has been thought to be responsible for sleep disorders in PCOS, however, studies have been unable to confirm this (23). In our study, we also evaluated the role of IR and increased testosterone level, frequently seen in PCOS, in sleep disorders. While OSAS risk and PSQI significantly correlated with IR, there was no significant correlation with testosterone level. These results seem insufficient to establish a definite cause and effect relationship, and may encourage further studies on this subject.

The main weakness of our study was that sleep scales were used to evaluate sleep disorders, rather than polysomnography. Studies previously investigating the relationship between PCOS and sleep have used mostly only one or two sleep questionnaires. But we used BQ, PSQI, ISI and ESS together, which was the major strength of our study. The main feature that distinguishes our study from other studies is that we investigated the prevalence of RLS in women with PCOS, which has not been assessed before. We also found an association between RLS and other sleep disorders in women with PCOS.

Conclusion

The necessity of examining sleep disorders in PCOS patients within a wide range was demonstrated. It is noteworthy that several metabolic and psychogenic causes, which may or not be detected, may be underlying causes of sleep disorders in PCOS. The fact that RLS prevalence was four times higher in the PCOS group than in the control group may encourage further studies to comprehend the coexistence of PCOS and RLS.

Ethics

Ethics Committee Approval: Yozgat Bozok University Faculty of Medicine Ethics Committee approved the study protocol (protocol no. 2017-KAEK-189_2019.08.07_01).

Informed Consent: Informed written consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.D.Ç., M.H., Design: M.D.Ç., M.H., Data Collection or Processing: M.D.Ç., M.H., T.O., Analysis or Interpretation: M.D.Ç., M.H., T.O., D.A.K., E.B., Literature Search: M.D.Ç., M.H., E.S.Y., Writing: M.D.Ç., M.H.

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