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Factors Determining the Need For Bilevel Therapy in Obstructive Sleep Apnea Patients

Obstrüktif Uyku Apnesi Hastalarında Bilevel Terapi İhtiyacını Belirleyen Faktörler

Nevra Güllü Arslan

University of Health Sciences Turkey, Samsun Training and Research Hospital, Clinic of Pulmonary Disease, Samsun, Turkey

Abstract

Objective: Except for continuous positive airway pressure (CPAP), which is the first choice in the standard treatment of Obstructive Sleep Apnea Syndrome (OSAS), it is recommended to continue treatment with bilevel PAP (BPAP) in patients, who cannot tolerate constant pressure or no success was achieved with this treatment. However, there is a group of patients without complicated OSAS and do not have BPAP indication at the first hospitalization, but for which adequate titration cannot be performed with CPAP. The purpose of this study was to investigate which characteristics of these patients or which data in their polysomnography (PSG) may be indicative of BPAP need.

Materials and Methods: Comorbid diseases [diabetes mellitus (DM), cardiac diseases, pulmonary diseases], body mass index, neck/core/hip circumference measurements the patients evaluated with total sleep time, apnea-hypopnea index (AHI), hourly obstructive/central apnea and hypopnea numbers, mean desaturation index (ODI), rapid eye movement (REM) sleep latency, REM time, AHI in REM and non-REM (REM/non-REM index), average overnight saturation (SaO2), lowest saturation value (min O2%), time when saturation is below 90% overnight (T90), a position dependency in PSG.

Results: Presence of DM, hypertension and cardiac disease, elevation of neck/core/hip circumference measurements, ODI, REM index, T90 values and ODI/SaO2 ratios were found to be statistically significant in the BPAP group, elevation in min O2% and SaO2 levels were found to be statistically significant in the CPAP group ($p<0.05$). It was determined that the probability of BPAP increased with the presence of DM 0.214 times, the presence of heart disease 0.205 times, a one-unit increase in the REM index 1.018 times, and a one-unit increase in T90 1.030 times. The REM index and T90, which were found to be significant in the receiver operating characteristic analysis, were determined as 70.850 and 56.150 cut-off values, respectively.

Conclusion: In this study; it was determined that the probability of CPAP being insufficient and switching to BPAP increases with the presence of DM and heart disease; and that T90 and REM index, and their cutoff values can be used for this purpose. It was also thought that regional adiposity may affect the type of PAP to be used.

Keywords: BPAP, OSAS, CPAP failure, prediction, OSAS treatment

Öz

Amaç: Obstrüktif Uyku Apne Sendromu'nda (OSAS) devamlı pozitif havayolu basıncı (CPAP) ile başarı sağlanamayan ya da sabit basıncı tolere edemeyen hastalarda, bilevel PAP (BPAP) ile tedaviye devam edilmesi önerilmektedir. Bu çalışmanın amacı, ilk yatışta BPAP endikasyonu olmayan ve CPAP ile yeterli titrasyonun yapılamadığı hasta grubunun hangi özellikleri ya da polisomnografilerindeki (PSG) hangi verilerin BPAP ihtiyacı açısından belirteç olabileceğinin belirlenmesidir.

Gereç ve Yöntem: Hastaların komorbid hastalıkları [diabetes mellitus (DM), kardiak hastalık, akciğer hastalığı], vücut kitle indeksi, boyun/göbek/kalça çevresi uzunlukları ile PSG'deki total uyku süresi, apne hipopne indeksi (AHİ), saatlik obstrüktif/santral apne/hipopne sayıları, ortalama desaturasyon indeksi (ODI), hızlı göz hareketi (REM) uyku latansı, REM süresi, REM ve non-REM uykudaki AHİ (REM/non-REM indeksi), gece boyu ortalama saturasyon (SaO2), en düşük saturasyon değeri (min O2%), saturasyonunun gece boyu %90'ın altında kaldığı süre (T90) ve pozisyon bağımlılığı incelendi.

Bulgular: DM, HT ve kardiak hastalık varlığı, boyun, göbek, kalça çevresi uzunluğu, ODI, REM indeksi, T90 ve ODI/SaO2 oranlarının yüksekliği BPAP grubunda; min O2% ve SaO2'nin yüksekliği CPAP grubunda istatiksel olarak anlamlı saptanmıştır ($p<0,05$). DM varlığının 0.214 kat, kalp hastalığı varlığının 0.205 kat, REM indeksinde bir birimlik artışın 1.018 kat, T90'da bir birimlik artışın 1.030 kat BPAP olasılığını artırdığı saptanmıştır. Cut-off değerler REM index ve T90 için sırasıyla 70.850 ve 56.150 olarak belirlenmiştir.

Sonuç: Bu çalışmada; CPAP'ın yetersiz kalıp BPAP'a geçilme olasılığının DM ve kalp hastalığı varlığı ile arttığı, T90 ve REM indeksinin bu amaçla kullanılabileceği belirlenmiş ve bölgesel yağlanmanın kullanılacak PAP tipine etki edebileceği ön görülmüştür.

Anahtar Kelimeler: BPAP, OSAS, CPAP başarısızlığı, tahmin, OSAS tedavisi

Address for Correspondence/Yazışma Adresi: Nevra Güllü Arslan MD, University of Health Sciences Turkey, Samsun Training and Research Hospital, Clinic of Pulmonary Disease, Samsun, Turkey

Phone: +90 362 440 00 44 **E-mail:** nevragullu@hotmail.com **ORCID-ID:** orcid.org/0000-0002-1643-1978

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a disease setting that progresses with repetitive interruptions or slowdowns of the respiratory period, reduces sleep quality and causes frequent desaturation. According to the current guide of the American Academy of Sleep Medicine (AASM) (1); continuous positive airway pressure (CPAP) is the first choice of standard treatment in uncomplicated OSAS cases. It is recommended to continue treatment with bilevel PAP (BPAP) in patients in those no success could be achieved with CPAP treatment (continuing low saturation in the routine control at the 3rd month under treatment) or in patients who cannot tolerate constant pressure. BPAP as a first choice, can be used in the presence of a disease that causes difficulty in exhaling against high pressure or alveolar hypoventilation (such as obesity hypoventilation syndrome) (1,2).

In some randomized studies performed, BPAP treatment was similar to CPAP in terms of effectiveness, adaptation, and some endpoints (3,4). In studies in which treatments started with BPAP instead of CPAP were evaluated in order to increase adaptation with uncomplicated patients, no results in favor of BPAP could be achieved (5,6). Among the recommendations for manual titration in the guideline of the AASM, it is stated that switching to BPAP could be performed in cases where CPAP could not be tolerated or is insufficient. However, there is a group of patients who do not have complicated OSAS and do not have BPAP indication at the first hospitalization, but for which adequate titration cannot be performed with CPAP. Repeated hospitalizations of this group and the prolonged access to definitive treatment create problems both in terms of patient health and comfort and the faster and more economical functioning of the health system. There is limited data on which characteristics of such patients or which data in their polysomnography (PSG) may be indicative of BPAP need (7,8).

In this study, it was planned to investigate which characteristics of the patient group who did not benefit from CPAP treatment and were switched to BPAP treatment, and which variables in PSGs could be similar and directing. By this way, pre-recognition of this patient group, providing an advantage in terms of recurrent hospitalizations, cost and time loss were determined as a secondary target.

Materials and Methods

Study Design and Participants

This study was designed as an observational study in which patients hospitalized in the sleep disorders unit of Samsun Training and Research Hospital were retrospectively examined. Patients over the age of 18 who had an apnea-hypopnea index (AHI) >15/h as a result of all-night PSG and were diagnosed with sleep apnea and were deemed suitable for PAP treatment were randomly included in the study.

After the titration study, the data of the patients for whom CPAP treatment was approved and the patients whose CPAP device was insufficient and switched to BPAP titration, were evaluated. Patients with known chronic respiratory failure or sleep-related hypoventilation/hypoxemic syndromes, who started treatment with BPAP or BPAP/ST titration, and who meet the criteria of obesity hypoventilation syndrome [combination of obesity (body mass index (BMI) ≥30 $kg \cdot m^{-2}$), sleep disordered breathing after ruling out other disorders that may cause alveolar hypoventilation and confirmed daytime hypercapnia] were not included in the study.

Study Data

Ethical approval was taken from Samsun University Clinical Trials Ethic Committee (protocol no: SUKAEK-2022/1/5, date no: 18/05/2022).

Demographic data and first hospitalization all-night PSG results of the patients who met the criteria and were hospitalized for titration between January 2019 and March 2022 in the sleep laboratory were examined.

Standard 16-channel PSG (Embla; Medcare Flaga, Reykjavik, Iceland) was applied to all patients. The system consists of four electroencephalography channels, two electrooculography channels, tibial/submental electromyography, and electrocardiography, as well as monitoring of oronasal airflow, thoracic movements, abdominal movements, average overnight saturation (SaO2), and body position. PSGs were scored in accordance with the 2013 AASM guidelines. Manual titration attended to moderate or severe OSAS patients. PAP titration was switched to BPAP, if a patient was uncomfortable or intolerant of CPAP or CPAP was ineffective at controlling respiratory events.

Gender, age, comorbid diseases [diabetes mellitus (DM), hypertension (HT), cardiac diseases, pulmonary diseases], BMI, neck/core/hip circumference lengths of the patients were recorded. In PSG; total sleep time, AHI, hourly obstructive/central apnea and hypopnea numbers, mean desaturation index (ODI), rapid eye movement (REM) sleep latency, REM time, REM and non-REM index, SaO2, lowest saturation value (min O2%), time when saturation is below 90% overnight (T90), whether it is position dependent were evaluated.

Statistical Analysis

In the statistical analysis phase of the study, frequency analysis, descriptive statistics, chi-square relationship tests, mean comparison tests, multiple logistic regression analysis and receiver operating characteristic (ROC) curves were shown. The conformity of numerical measurements to normal distribution was examined with the Shapiro-Wilk test and the independent samples were examined with t-test. Sensitivity, 1-selectivity (solid-phase extraction), positive class prediction rate, cut-off and area under the curve values are provided along with the graph of ROC curves. The entire application was performed with the R-Project program (R Core Team, 2020).

Results

A total of 111 patients, 31 (27.9%) of whom BPAP and 80 (72.1%) of whom CPAP titration was applied, were included in the study. The gender distribution and comorbidity status of the patients are shown in Table 1, and the mean values of the numerical data are shown in Table 2.

When the relationship between gender, positional OSAS, pulmonary disease, DM, HT, presence of coronary artery disease (CAD) or heart failure (HF) and receiving CPAP and BPAP treatment of the patients was compared (Table 3); the presence of DM, HT and cardiac disease was found to be statistically significantly higher in patients in the BPAP group ($p<0.05$).

Table 1. Demographic characteristics		
Variable	**n**	**%**
Gender		
Female	27	24.3
Male	84	75.7
Lung disease	30	27.3
DM	16	14.5
HT	39	35.5
Cardiac disease	16	14.5
Positive airway pressure		
CPAP	80	72.1
BPAP	31	27.9
DM: Diabetes mellitus, HT: Hypertension, CPAP: Continous positive airway pressure, BPAP: Bilevel positive airway pressure		

Table 2. Descriptive statistics		
Variable	**Mean**	**SD**
Age	50.89	10.91
Neck circumference (cm)	42.77	3.90
Core circumference (cm)	118.06	14.26
Hip circumference (cm)	119.79	13.07
BMI (kg/m^2)	38.23	32.48
TST (min)	306.99	69.42
AHI (/h)	53.17	24.49
AI (/h)	19.46	22.08
HI (/h)	31.99	20.76
CI (/h)	0.90	3.74
ODI (/h)	55.88	26.91
REM latency	126.66	104.72
REM period (min)	24.10	21.95
REM index	38.60	35.33
NREM index	53.92	25.98
SaO2%	90.45	4.16
Min O2%	75.52	9.69
T90%	30.75	27.05
Apnea/hypopnea ratio	2.38	7.68
REM index/NREM index	0.79	0.83
ODI/SaO2	0.63	0.33
BMI: Body mass index, TST: Total sleep time, AHI: Apnea-hypopnea index, AI: Obstructive apnea index per hour, HI: Hypopnea index per hour, CI: Central apnea index per hour, ODI: Oxygen distress index per hour, REM latency: Rapid eye movement sleep starting time, REM index: AHI index in REM period, NREM index: AHI in NREM period, SaO2: Average oxygen saturation over the duration of sleep, Min O2%: Lowest oxygen saturation during sleep, T90: Percentage of sleep time in less than 90% oxygen saturation, SD: Standard deviation		

The comparison of the mean values between the variables is provided in Table 4. Accordingly, neck/core/hip circumference measurements, ODI, REM index, T90 and ODI/SaO2 ratio were found to be statistically significantly higher in the BPAP group and, min O2% and SaO2 were found to be statistically significantly higher in the CPAP group ($p<0.05$).

Multiple regression analysis is provided in Table 5. Accordingly, the suitability of BPAP therapy to the patient is increased 0.214 times in the presence of DM and 0.205 times in the presence of CAD. Moreover, it was determined that a one-unit increase in REM index increased the probability of BPAP 1,018 times, and a one-unit increase in T90 increased the probability of BPAP 1.030 times.

REM index and T90% were found to be statistically significant in the ROC evaluation performed on the variables that were significant according to the result of multiple regression analysis (Figures 1 and 2). 70.850 for REM index and 56.150 for T90 were determined as cut-off values.

Discussion

There is a small group of patients with uncomplicated OSAS who did not benefit from CPAP titration and were switched to BPAP. Due to the lack of guiding data in terms of pre-identifying these patients and initiating appropriate treatment quickly, this study was planned and it was concluded that some variables could be used for this purpose. Accordingly, especially after multiple regression analysis, the presence of DM and cardiac disease increased the possibility of transition to BPAP, and T90 and REM index were determined as determinant variables for BPAP, cut-off values were obtained for T90 and REM index.

BPAP is an approach that increases the patient's compliance with PAP treatment by applying different pressures during inspiration and expiration. In studies investigating the reasons for switching to BPAP in OSAS patients, the main reason was often intolerance to CPAP (7,9,10). In the study performed by Schwartz et al. (10), it was reported that treatment with BPAP can be started in OSAS patients with neurological diseases in whom sufficient muscle tone cannot be achieved. However, in

Table 3. Relationship between individuals' gender, comorbidity, and status of being position-related OSAS with BPAP and CPAP treatment					
Variable	**CPAP**		**BPAP**		**p**
	n	**%**	**n**	**%**	
Gender					
Female	18	22.5	9	29.0	0.223^{Y}
Male	62	77.5	22	71.0	
Lung disease	17	21.5	13	41.9	0.054^{Y}
DM	7	8.9	9	29.0	0.014^{F}
HT	22	27.8	17	54.8	0.015^{Y}
Cardiac disease	7	8.9	9	29	0.014^{F}
Positional OSAS	11	86.1	1	3.2	0.173^{F}
^{Y}: Yates correction, ^{F}: Fisher test, DM: Diabetes mellitus, HT: Hypertension, Cardiac disease: Coronary artery disease (CAD) or heart failure (HF), CPAP: Continous positive airway pressure, BPAP: Bilevel positive airway pressure					

Table 4. Comparison of mean values between study groups					
Variable	CPAP		BPAP		p
	Mean	SD	Mean	SD	
Age	50.26	10.66	52.52	11.56	0.331
Neck crcm (cm)	42.01	3.35	44.60	4.54	0.002
Core crcm (cm)	114.61	11.89	126.33	16.17	0.001
Hip crcm (cm)	115.87	9.91	129.07	15.01	<0.001
BMI (kg/m^2)	36.99	37.81	41.44	9.44	0.520
TST (min)	310.63	68.72	297.59	71.48	0.377
AI (/h)	17.49	21.17	24.48	23.87	0.136
HI (/h)	30.50	19.43	35.83	23.75	0.227
CI (/h)	0.59	2.79	1.70	5.46	0.291
ODI (/h)	50.53	24.10	69.69	29.18	0.001
REM latency	125.17	101.02	130.50	115.40	0.811
REM period (min)	23.30	21.55	26.16	23.18	0.540
REM index	32.80	32.86	53.59	37.57	0.005
NREM index	51.06	26.15	61.31	24.41	0.062
SaO2	91.52	2.62	87.68	5.87	0.001
Min O2%	78.00	8.10	69.13	10.62	<0.001
T90	23.74	22.07	48.84	30.51	<0.001
Apnea/hypopnea ratio	1.60	3.96	4.39	12.96	0.248
REM index/NREM index	0.74	0.85	0.91	0.78	0.351
ODI/SaO2	0.56	0.27	0.81	0.39	<0.001

Crcm: Circumference, BMI: Body mass index, TST: Total sleep time, AHI: Apnea-hypopnea index, AI: Obstructive apnea index per hour, HI: Hypopnea index per hour, CI: Central apnea index per hour, ODI: Oxygen distress index per hour, REM latency: Rapid eye movement sleep starting time, REM index: AHI index in REM period, NREM index: AHI in NREM period, SaO2: Average oxygen saturation over the duration of sleep, Min O2%: Lowest oxygen saturation during sleep, T90: Percentage of sleep time in less than 90% oxygen saturation, SD: Standard deviation

Table 5. Analysis of independent variables such as presence of DM/CAD, neck/core circumference, REM index, T90, ODI/SpO2 in case of being in the PAP titration group is the dependent variable			
Variable	**OR**	**95% CI**	**p**
DM	(Ref)	-	-
	0.214	(0.05. 0.917)	**0.038**
Cardiac disease	(Ref)	-	-
	0.205	(0.052. 0.812)	**0.024**
Neck crcm	1.147	(0.936. 1.406)	0.187
Core crcm	1.007	(0.947. 1.07)	0.825
REM index	1.018	(1.001. 1.036)	**0.033**
T90	1.030	(1.005. 1.055)	**0.020**
ODI/SpO$_2$	0.728	(0.081. 6.528)	0.776
Constant	0.001	-	0.049

DM: Diabetes mellitus, Neck crcm Neck circumference, Core crcm Core circumference, REM index: AHI index in REM period, T90 %: Percentage of sleep time in less than 90% oxygen saturation, ODI: Oxygen distress index per hour, OR: Odds ratio, CI: Confidence interval

the guide published by AASM in 2019, it has been suggested that BPAP can be used as an initial treatment or as a subsequent treatment to CPAP on the same night, with the clinician's decision, in suitable patients (11). However, there is a lack of data on which patient should be switched to BPAP using which criteria.

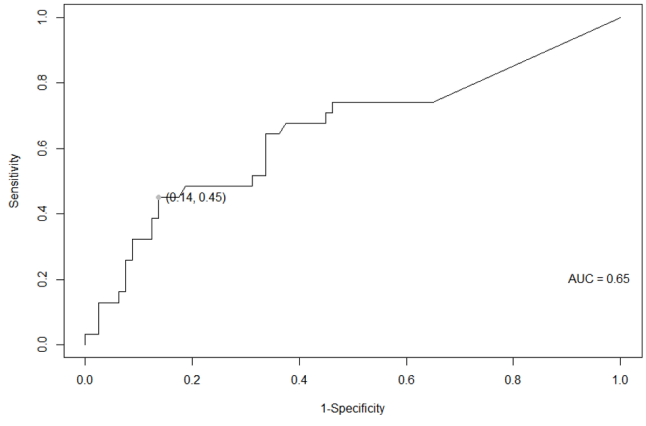

Figure 1. ROC curve performed for the effect of REM index on groups
ROC: Receiver operating characteristic, REM: Rapid eye movement

In this study, in which we investigated BPAP indications, when comorbidities were evaluated with the chi-square relationship test, the presence of DM, HT and heart disease was found to be significantly higher in terms of BPAP treatment (p<0.05). In the multiple regression analysis including other variables, the probability of needing BPAP was found to be 0.214 times higher

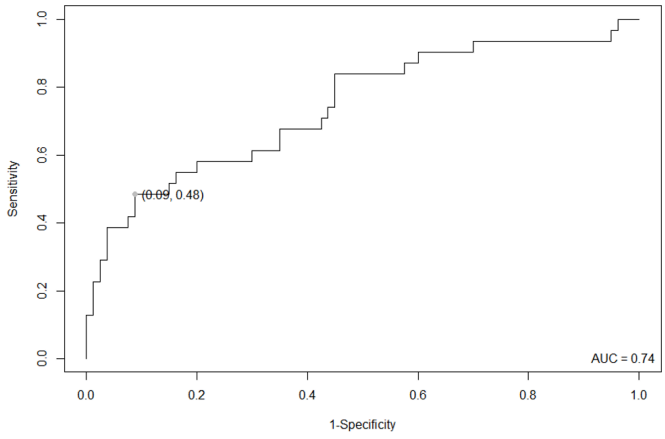

Figure 2. ROC curve performed for the effect of T90% index on groups
ROC: Receiver operating characteristic, AUC: Area under the curve

in the presence of DM and 0.205 times higher in the presence of heart disease. HF is a disease associated with OSAS at a rate of approximately 33%. While CPAP therapy increases the left heart ejection fraction by approximately 5% in patients with systolic dysfunction, no data are available as the use of PAP is contraindicated in the setting of diastolic failure. CPAP therapy reduces major adverse cardiac or cerebrovascular events in CAD patients with OSAS (12). There is no clarity on the effect of CPAP on short- and long-term blood glucose control and diabetes-related complications in DM patients due to inconsistent results (13). If there is no contraindicated condition in this group of patients, randomized controlled studies in which BPAP treatment will be applied after the clinician's evaluation will provide us more data on this subject.

Among the risk factors for OSAS, obesity is the most important one; however, while 70% of OSAS patients are obese, 40% of obese patients have OSAS (14,15), and the reason for this is still unclear (16). It was reported that high BMI worsens the response to treatment due to the patient's general body performance rather than directly affecting CPAP therapy (17). In the study performed by Shah et al. (7), BMI was found to be high in the BPAP group, but this did not make a statistical difference, and it was reported that it was not a factor for CPAP failure. In our study, a significant difference was observed between the groups not in terms of BMI, but in terms of neck/core/hip circumference measurements. We think that the effect of regional adiposity on the absence of OSAS in every patient with high BMI and the lack of similar benefit from CPAP, should be investigated with larger case series.

Slouka et al. (17) reported that AHI, ODI, T90, SpO2 and BMI are significant variables for CPAP failure, but after the ROC analysis, they reported that any one or combinations of those variables were insufficient in modeling and clinical prediction. In another study in which age, AHI, COPD, BMI and min O2% were determined as independent variables for BPAP being the first treatment option (18), there was no significant difference between those who received CPAP treatment in terms of adherence to treatment, AHI under treatment, or symptoms. Schwartz et al. (10) reported that advanced age, high BMI, COPD, increased CO2 level, OSAS severity, and min O2% values could be determinant indicators not only for BPAP use but also for long-term adherence to treatment.

In our study, in terms of PSG variables, significant results were obtained for ODI, REM index, T90, min O2%, SaO2 values and ODI/SaO2 ratios. ODI, T90, min O2% and SaO2 were prominent variables in previous studies in terms of CPAP failure or BPAP indication (10,17,18). In our study, the ODI/SaO2 ratio was used for the first time in terms of BPAP estimation, and it was determined that as this ratio increased, the need for BPAP increased, but a statistically significant numerical ratio could not be obtained.

In the ROC analysis, one of the most determinant variables in terms of the statistical model was T90. A 1-unit increase in this variable increases the probability of BPAP 1,030 times. In another study in which T90 was used for this purpose (7), it was stated that with a 5% increase, the probability of BPAP increases by 28%. We also predict that the value of 56.15 for T90 is considered cut-off, and values above this can be used for BPAP indication.

A commonly used definition for REM-dependent OSAS (REM-OSAS) is AHIREM >5 and AHINREM <5 in the presence of at least 30 minutes of REM sleep (19). However, its prevalence is not clear due to the lack of a standard definition (13). In a study conducted with this patient group (20), it was reported that T90 and min O2% should be included in the definition of REM-OSAS. It was stated in the limited number of studies that they could benefit from CPAP treatment (10,21), but there are no studies conducted with other PAP treatments in this group. The REM index, which indicates the AHI during REM sleep, was another determinant variable in our study. An increase of 1 unit increased the probability of BPAP 1.018 times, and values above 70.85 were found to be significant in terms of BPAP. In our study, which was carried out in accordance with the definition above, there was no patient diagnosed with REM-OSAS.

Not using different criteria for the definition of REM-OSAS was one of the limitations of our study. Because the number of patients diagnosed could have changed, and perhaps data on the use of BPAP in this group would have been available for the first time. In addition, the limited number of BPAP patients and the fact that the study was conducted with data from a single center can be listed as other limitations.

Conclusion

Recurrent hospitalizations in centers where the number of patients who need PSG and the waiting time for the test are high, make it difficult for the patient to access treatment, cause obstruction in the health system and increase costs. The inadequacy of CPAP and the necessity of switching to BPAP is the most important reason for this. In this study, which was designed to predict this group of patients, we determined that especially T90, REM index and the cut-off values obtained for these can be used for BPAP estimation. In addition, we think that there is a need for studies to be performed with more

patients to examine the effect of regional adiposity on the type of PAP to be used.

Ethics

Ethics Committee Approval: Ethical approval was taken from Samsun University Clinical Trials Ethic Committee (protocol no: SUKAEK-2022/1/5, date no: 18/05/2022).
Informed Consent: Retrospective study.
Peer-review: Internally and externally peer-reviewed.
Financial Disclosure: The author declared that this study received no financial support.

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