Original Research

Development of an Objective Tool for Predicting Obstructive Sleep Apnea among Adults: PAN Apnea Index

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Abstract

Background and Objective: Obstructive sleep apnea (OSA) is an important health problem, which is commonly under-diagnosed especially in workplace settings. We tried to obtain a model with more objective variables due to the greater reliability in occupational settings.

Materials and Methods: A total of 374 suspected patients with OSA who underwent their first polysomnography (PSG) at Baharloo Sleep Clinic in Tehran, Iran, were enrolled in the study. Before PSG, all patients completed a questionnaire including demographic characteristics. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured for all participants. Furthermore, a blood sample was collected for measuring fasting blood sugar (FBS) and hemoglobin A1c (HbA1c). All the patients underwent full PSG. Respiratory Disturbance Index (RDI) was calculated and recorded for all patients. Different multiple adjusted logistic regression models were constructed to find the best model for prediction of OSA.

Results: A total of 271 (72.5%) participants were men. The mean age and body mass index (BMI) were 48.58 ± 13.04 years and 30.4 ± 5.0 kg/m^2, respectively. The prevalence of RDI ≥ 15 was 78.87% (n = 295). Using regression analysis, several models were obtained, where the best one yielded sensitivity and specificity of 77.29% and 67.09%, respectively. Area under the curve (AUC) of this model was 82%. The variables of this model included SBP, age, neck circumference-height ratio (NHR), FBS, BMI, and gender (PAN apnea index) with a cutoff point ≥ 8 for high-risk individuals.

Conclusion: In this study, we considered only objective parameters to predict OSA which enhances reliability for diagnosis especially in occupational settings.

Keywords: Sleep apnea; Obstructive; Polysomnography; Predictive value of tests

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Introduction

An apneic event refers to stopped breathing for more than 10 seconds whereby oxygen desaturation and arousal usually happen. The major symptoms of people with suspected obstructive sleep apnea (OSA) are snoring, witnessed apneic events, and nocturnal gasping or choking. Sleep apnea is categorized in two major groups: obstructive and central. The most common form of sleep apnea is obstructive and the most frequent complaint is snoring. There are several questionnaires such as Berlin questionnaire (BQ) and STOP-BANG questionnaire (SBQ) for diagnosing and screening of OSA (1).

Note that these questionnaires are tested in selected populations and help in diagnosis, but they do not confirm OSA. So, clinicians should not rule out the OSA because of low score in a questionnaire (1). OSA is a common disorder in workplace and has negative consequences for health, safety, and productivity. It is often undiagnosed as employees do not report their symptoms. Thus, clinicians should rely on objective measures and evaluate possible OSA based on several evidence

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such as falling asleep at work as well as occupational accidents, especially in safety-sensitive positions (such as transportation system) (2). It is estimated that 93% of women and 82% of men with moderate to severe degrees of this disease remain under-diagnosed (3).

OSA is associated with co-morbidities such as hypertension (HTN), cardiovascular diseases (CVDs), and diminished quality of life (4-6). Signs, symptoms, and complications of OSA are a direct result of repeating collapse of airways presenting with periods of awakening during sleep, hypoxia, hypercapnia, increased intrathoracic pressure, and intensified sympathetic nervous system activity. Clinically, OSA is diagnosed based on daily sleepiness, snoring, periods of stopped breathing during sleep, and suffocation. People at risk of OSA are obese, have cardiovascular co-morbidities such as congestive heart failure (CHF), atrial fibrillation (AF), HTN, diabetes mellitus type 2 (DM2), cardiac dysrhythmia, pulmonary HTN, and myocardial infarction (MI). They are more likely to experience fatal traffic accidents, making the disease very important for the public health system (7).

The diagnostic gold standard for OSA is polysomnography (PSG), but this method is not cost-beneficial and is not always available. Therefore, we should use other methods for diagnosing and screening this disorder at the initial evaluations of patients (8).

One of the commonly utilized tools is SBQ. However, this questionnaire and other similar self-reported tools could have different results partially due to the cultural and native characteristics of communities. Subjective components of this questionnaire are not reliable, especially in occupational settings and high sensitive jobs in which apnea screening is important. Self-reports in workplace settings may have false negative results due to dishonest report of symptoms in fear of losing job. Thus, screening tools which are fully objective would be more accurate in such settings (9).

Fasting blood sugar (FBS), neck circumference (NC), neck circumference-height ratio (NHR), hemoglobin A1c (HbA1c), blood pressure (BP), body mass index (BMI), age, and Mallampati classification are among the objective parameters that are indicated in different studies to have strong association with OSA and its severity (10-12). It has previously been observed that tools such as SBQ and Epworth Sleepiness Scale (ESS) could be a source of bias when we screen patients in a workplace setting such as drivers (9)

Thus, we intended to obtain one model with objective variables to enhance the sensitivity and specificity of prediction of OSA.

Materials and Methods

Participants

In this cross-sectional study, patients who were suspicious to have OSA and underwent PSG for the first time in Baharloo Sleep Clinic in Tehran, Iran, from March 2017 to June 2018, were enrolled.

All of the subjects had the chief complaint of snoring, and PSG was performed for all. Written consent was obtained from all of the participants. The study was approved by Ethics Committee of Tehran University of Medical Sciences, Tehran (code: 9511308010).

Study measurements

BP, NC, weight, and height were measured by a trained technician. A blood sample was taken from all patients for measuring the level of FBS and HbA1c. BMI was calculated by dividing the weight (kg) to height squared (m^2). NHR was calculated through dividing the NC (cm) by the height (cm).

HTN was defined as systolic BP (SBP) $\geq$ 140 mmHg or diastolic BP (DBP) $\geq$ 90 mmHg (13). DM was defined as HbA1C $\geq$ 6.5 mg/dl or FBS $\geq$ 126 mg/ml in two different blood tests (14).

PSG was performed for all patients. PSG is used for diagnosing OSA and recording the physiologic signals such as electroencephalogram (EEG): F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1, electrooculogram (EOG), chin electromyogram (EMG), airflow, oxygen saturation, respiratory effort, and electrocardiogram (ECG).

OSA was categorized according to Respiratory Disturbance Index (RDI) based on PSG. $5 \leq$ RDI < 15, $15 \leq$ RDI < 30, and RDI ≥ 30 were defined as mild, moderate, and severe OSA, respectively. We entered PSG $\geq$ 15 in logistic model as the study outcome (15).

Statistical analysis

The mean and standard deviation (SD) were reported for continuous variables while frequency and percentage were studied for categorical variables. The differences in patients’ characteristics were examined using Student's independent t-test for numerical variables and chi-square test for categorical variables.

Different multiple adjusted logistic regression models were constructed to find the best model for prediction of OSA (optimal combination of variables with the best classification). Objective variables that had a significant correlation with RDI such as age, sex, NC, NHR, BMI, SBP, DBP, FBS, and HbA1c were introduced into the regression model.

Candidate variables were selected based on both scientific and statistical evidence. We examined all the objective variables validated from pervious literature as the predictors of sleep apnea.

First, we used continuous variables in logistic models to capture maximum information and also statistical power. Next, we categorized the selected continuous variables using different accepted cut-points.

The discriminative ability of different models was compared against PSG diagnostic test (as gold standard test) using receiver operating characteristic (ROC) curve in logistic regression models. For all of the models, area under the curve (AUC) was also calculated and the final model was selected as the one with the maximum AUC.

To assess the clinical performance of the final model for screening OSA, cutoffs were evaluated using ROC curves. AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratio (LR+ and LR-) were determined. Yuden Index was used for determining the appropriate cutoff points. All statistical analyses were performed using Stata statistical software (version 12 SE, Stata Corporation, College Station, TX, USA). P-values < 0.05 were considered statistically significant.

As sensitivity analyses, the above-mentioned models were repeated only in patients with available data for HbA1c (169 patients), and the results did not change with inclusion of HbA1c.

Methods of scoring the variables

An apnea risk score was computed for each participant based on their total scores of selected objective variables (age ≥ 50 years, sex = men, BMI ≥ 35 kg/m^2, SBP ≥ 120 mmHg, FBS ≥ 100 mg.ml, NHR ≥ 0.23).

People who had SBP ≥ 120 mmHg received a score of one while the rest received a score of zero (13).

People who had age ≥ 50 years received a score of one and the rest received a score of zero (15).

People who had male sex received a score of one and the rest received a score of zero (15).

People who had BMI ≥ 35 kg/m^2 received a score of one and the rest received a score of zero (15).

People who had FBS ≥ 100 mg/ml received a score of one and the rest received a score of zero (14).

People who had NHR ≥ 0.23 received a score of one and the rest received a score of zero based on the statistical analysis run for proper cutoff of this item.

The apnea risk score of every individual was calculated through summing up the total scores of the mentioned factors, and the cutoff point was selected by ROC. The formula for the apnea risk score was calculated based on final model (below formula):

The apnea risk score = 4 * age + 3 * sex + 2.5 * BMI + 2.5 * SBP + 2.5 * FBS + 2.5 * NHR

Results

As mentioned earlier, 374 subjects were included in this study. In our sample, 271 (72.5%) were men. The mean age of them was 48.58 ± 13.04 years. The prevalence of RDI ≥ 15 was 78.87% (n = 295), and the mean BMI was 30.4 ± 5.8 kg/m^2. The mean NC was 40.34 ± 3.97 cm and the mean SBP was 128.0 ± 18.3 mmHg. Further, the mean HbA1c was 5.88 ± 1.08 mmol/mol. Other demographic and clinical characteristics of the patients are presented in table 1.

Table 1. Demographic and clinical characteristics of study participants

Characteristic	Total (n = 374)	RDI ≥ 15 (n = 295)	RDI < 15 (n = 79)	P-value
Age (year)	48.58 ± 13.04	50.51 ± 12.54	41.35 ± 12.40	< 0.001
Sex (men)	271 (72.45)	224 (75.93)	47 (59.49)	0.003
NC (cm)	40.34 ± 3.97	40.91 ± 3.77	38.21 ± 4.00	< 0.001
Height (cm)	170.08 ± 10.12	169.87 ± 10.04	170.88 ± 10.45	0.431
NHR	0.23 ± 0.02	0.24 ± 0.02	0.22 ± 0.20	< 0.001
BMI (kg/m^2)	30.44 ± 5.81	31.17 ± 5.87	27.73 ± 4.71	< 0.001
SBP (mmHg)	128.02 ± 18.33	130.78 ± 18.06	117.70 ± 15.48	< 0.001
DBP (mmHg)	84.77 ± 12.28	86.00 ± 12.04	80.19 ± 12.15	< 0.001
FBS (mg/ml)	107.65 ± 33.70	110.84 ± 36.47	95.73 ± 16.00	< 0.001
HbA1c* (mmol/mol)	5.88 ± 1.08	5.99 ± 1.14	1.14 ± 5.28	0.001
RDI	44.13 ± 31.01	53.68 ± 28.00	8.45 ± 3.90	< 0.001
Smoking**	90 (24.06)	71 (24.06)	19 (24.05)	0.563

Data are presented as mean ± standard deviation (SD) or number and percentage
NC: Neck circumference; NHR: Neck circumference-height ratio; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HbA1c: Hemoglobin A1c; RDI: Respiratory Disturbance Index
*HbA1c data for 205 patients was not available, **Smoking status was defined as patients who had current usage of any kind of tobacco. Comparison was done using t-test analysis

Relationships between the objective parameters and RDI predicting RDI ≥ 15 are presented in table 2.

Table 2. Candidate parameters for prediction of Respiratory Disturbance Index (RDI) ≥ 15

Variable	Category	RDI Mean ± SD	P-value
Age (year)	≥ 50	50.87 ± 26.15	< 0.001
	< 50	38.07 ± 33.78	
Sex	Men	46.10 ± 21.87	0.024
	Women	38.23 ± 22.91	
BMI (kg/m^2)	≥ 35	62.41 ± 35.40	< 0.001
	< 35	39.84 ± 28.43	
SBP (mmHg)	≥ 120	48.62 ± 30.86	< 0.001
	< 120	33.88 ± 29.06	
FBS (mg/ml)	≥ 100	53.23 ± 31.06	< 0.001
	< 100	35.41 ± 28.47	
NHR	≥ 0.23	53.33 ± 31.63	< 0.001
	< 0.23	28.03 ± 22.24	

BMI: Body mass index; SBP: Systolic blood pressure; FBS: Fasting blood sugar; NHR: Neck circumference-height ratio; SD: Standard deviation; RDI: Respiratory Disturbance Index

All variables that had a significant correlation with RDI were introduced into the regression model. We developed 7 models; using ROC curve, we found that one of these models outperformed the other models (based on the AUC value and Hosmer-Lemeshow test).

Table 3 shows all statistical characteristics of the developed models. With every cut points for age ≥ 50, sex: men, BMI ≥ 35 kg/m^2, SBP ≥ 120 mmHg, FBS ≥ 100 mg/ml, NHR ≥ 0.23, score 1 was considered for the reference level for each item. Then, patients with score ≥ 8 with sensitivity of 77.29, specificity of 67.09, as well as PPV of 89.76, NPV of 44.16, LR+ of 2.34, and LR- of 0.33 were candidate for PSG. This model included the following parameters as reported in table 4 and was compared with other indexes in table 5.

Figure 1 contains ROC curves for the final model.

Discussion

In this study, we aimed to obtain an objective tool for prediction of sleep apnea, which can be especially helpful in occupational settings. We used comprehensive objective parameters possessing a significant correlation with RDI, and we tried to create a model with the highest sensitivity and specificity. Our final model included NHR, FBS, BMI, sex, age, and SBP with sensitivity and specificity of 77.29 and 67.09, respectively.

Table 3. Statistical characteristics of all models developed in logistic model

	AUC (95% CI)	R squared	P-value for Hosmer-Lemeshow test
Model 1	0.79 (0.76-0.87)	0.215	0.012
Model 2	0.79 (0.75-0.82)	0.315	0.306
Model 3	0.80 (0.70-0.87)	0.301	0.297
Model 4	0.80 (0.73-0.87)	0.199	0.002
Model 5	0.78 (0.73-0.84)	0.185	0.287
Model 6	0.79 (0.73-0.85)	0.288	0.047
Model 7	0.82 (0.76-0.85)	0.330	0.330

Model 1: age ≥ 50, sex = men, BMI ≥ 35, SBP ≥ 120, FBS ≥ 100, NHR ≥ 0.23, DBP ≥ 80
Model 2: age ≥ 50, sex = men, BMI ≥ 35, SBP ≥ 120, FBS ≥ 100, NHR ≥ 0.23
Model 3: age ≥ 50, sex = men, BMI ≥ 35, SBP ≥ 120, FBS ≥ 126, NHR ≥ 0.23
Model 4: age ≥ 50, sex = men, BMI ≥ 35, SBP ≥ 120, FBS ≥ 100, NC ≥ 40
Model 5: age ≥ 50, sex = men, BMI ≥ 35, SBP ≥ 120, FBS ≥ 126, NC ≥ 40
Model 6: age ≥ 50, sex = men, BMI ≥ 35, SBP ≥ 120, FBS ≥ 126, NC ≥ 40
Model 7: age ≥ 50, sex = men, BMI ≥ 35, SBP ≥ 120, FBS ≥ 100, NHR ≥ 0.23, DBP ≥ 80
AUC: Area under the curve; NC: Neck circumference; NHR: Neck circumference-height ratio; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; CI: Confidence interval

The scoring of the final model was based on a range of 0 to 17 and the cut point of this model was 8. PAN apnea score ≥ 8 places the screened individual in high-risk group for OSA, indicating a more objective alarm for PSG, especially in high-sensitive jobs such as driving. Further, we included HbA1c instead of FBS with greater sensitivity and specificity in one of the models (75.0 and 70.9, respectively).

Table 4. Final logistic model for objective risk factors and screening obstructive sleep apnea (OSA) [Respiratory Disturbance Index (RDI) ≥ 15]

	OR	CI (95%)	P-value
Age (≥ 50 years)	4.01	2.03-7.89	< 0.0001
Sex (men)	2.86	1.46-4.61	0.0020
BMI (≥ 35 kg/m^2)	2.41	0.96-4.46	0.0060
SBP (≥ 120 mmHg)	2.64	1.46-4.78	0.0010
FBS (≥ 100 mg/ml)	2.52	1.34-4.68	0.0040
NHR (≥ 0.23)	2.42	1.39-3.42	0.0040
AUC (95% CI)	0.82	0.76-0.85	

BMI: Body mass index; SBP: Systolic blood pressure; FBS: Fasting blood sugar; NHR: Neck circumference-height ratio, AUC: Area under the curve; OR: Odds ratio; CI: Confidence interval

Table 5. Screening questionnaires for obstructive sleep apnea (OSA) in terms of sensitivity and specificity

Questionnaire	Sensitivity	Specificity	PPV	NPV	LR+	OR	AUC
Current study	77.29	67.09	89.76	44.16	2.34	6.94	0.82
STOP (16)	74.30	53.30	51.00	76.00	1.56	3.29	0.72
SBQ (English version) (16)	92.90	43.00	51.60	90.20	1.62	9.80	0.82
SBQ (Persian version) (15)	91.10	37.10	61.50	79.00	1.44	6.04	0.72
BQ (English version) (17)	76.69	39.34	63.17	55.44	NA	1.62	0.60
BQ (Persian version) (18)	72.80	75.00	92.50	32.80	2.91	NA	0.80
ESS (19)	17.80	85.40	83.70	19.80	1.22	NA	0.52
MAP index (20)	83.30	64.30	NA	NA	2.30	NA	0.79

PPV: Positive predictive value; NPV: Negative predictive value; LR: Likelihood ratio; OR: Odds ratio; AUC: Area under the curve; SBQ: STOP-BANG questionnaire; BQ: Berlin questionnaire; ESS: Epworth Sleepiness Scale; MAP: Multivariable Apnea Prediction; NA: Not available

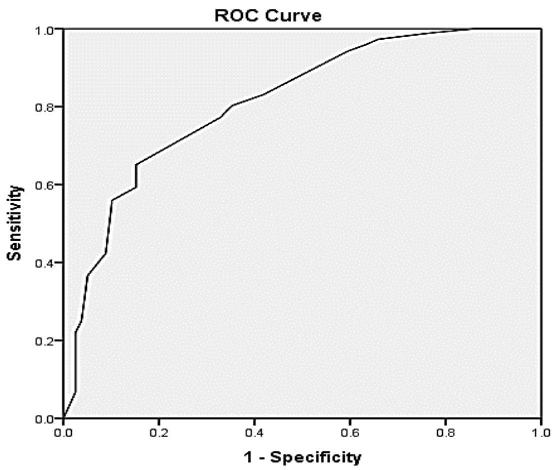

Figure 1. Receiver operating characteristic (ROC) curves for the final model [age ≥ 50 years, sex = men, body mass index (BMI) ≥ 35 kg/m^2, systolic blood pressure (SBP) ≥ 120 mmHg, fasting blood sugar (FBS) ≥ 100 mg/ml, neck circumference-height ratio (NHR) ≥ 0.23, area under the curve (AUC) = 0.82 (0.76-0.85)]

Among the variables of the final model, NHR, FBS, and SBP are important because of their objectivity, which are appropriate for occupational settings where people do not report their problems.

Abnormal glucose metabolism including impaired fasting glucose (IFG) and DM2 were associated with RDI ≥ 10 in patients with OSA. Accordingly, RDI is independently proportional to glucose metabolism (21). Furthermore, Lam et al. have indicated that OSA is associated with metabolic syndrome or FBS, DBP, and waist circumference as its components after statistical adjustment for confounding factors (22).

OSA is significantly more reported in patients with DM compared to subjects with normal glucose metabolism (23). Accordingly, we included FBS in our predictive model for screening sleep apnea. We considered cut point of 100 for FBS (as defined for IFG), with a significant difference found between RDI and FBS. HbA1c was also observed to be associated with RDI. Consistent with the present study, Priou et al., Pillai et al., and Tasali et al. have considered HbA1c as a parameter linked with RDI (24-26). In a most recent study, HbA1c with cut point of 5.8 was associated with RDI. In the current study, we considered cut point of 5.7 for HbA1c (as defined by the IFG) in our calculated predictive model.

BP is also among the parameters with a strong association with RDI, making it a good candidate for predicting OSA. Lavie and Lavie observed a linear correlation between SBP as well as DBP and severity of OSA (27). Similarly, Lavie et al. reported a higher day and night-time DBP and night-time SBP in patients with OSA (28). Likewise, present findings indicated more severe OSA in those with DBP and SBP. The cut point of 120 mmHg was in a significant association with RDI, making it a parameter of interest for PAN apnea index.

The aforementioned parameters are frequently used in available models and tools for screening OSA. However, in occupational settings, more sensitive and specific objective score would be helpful in diagnosing sleep apnea in high-sensitive jobs. NC is widely used in available screening tools of sleep apnea such as SBQ; nevertheless, studies have put this parameter under question. NC depends on visceral fat and can produce false positive results. Ho et al. measured NHR in 100 adults and showed that with cutoff point of 0.25, a significant relationship with Apnea-Hypopnea Index (AHI) can be achieved; therefore, one important objective variable in the final model could be NHR (29).

In the statistical analysis, the best measured cut point was 0.23 with a statistically significant association with RDI, representing it as a good predictor variable for OSA. It is worth to mention that NC reduced the sensitivity and specificity of the model.

As mentioned earlier, there are different tools for predicting and screening OSA [SBQ, BQ, ESS, and Multivariable Apnea Prediction (MAP) index] (Table 5). In the current study, we achieved a comprehensive objective tool for screening sleep apnea, which can be very useful in occupational settings. Different developed models are presented in table 5 with their measured specificity and sensitivity. The complete objective parameters have made our model a robust model for workplace screening of sleep apnea. The sensitivity and specificity reported for SBQ is different among the available reports (16, 30). However, the common point is low specificity of this tool ranging from 43 to 53. ESS is also one of the most utilized available tools in the field of sleep medicine for OSA with high specificity and lower sensitivity. It is also reported to be a good screening tool for OSA in combination with BQ. Persian versions of these questionnaires have also been developed (19). However, subjective questionnaires that are dependent on patients' self-reports could have bias issues when used in occupational settings. In the workplace for highly sensitive jobs, workers may not report their problems honestly, increasing the rate of false negative scores in screening tools such as SBQ, ESS, and BQ. Then, if sleep apnea remains undiagnosed and thus untreated in the workplace, massive accidents will be likely to happen. Therefore, comprehensive objective tools with high sensitivity and specificity would help clinicians to accurately diagnose high-risk patients for sleep apnea, which is the major strength of our current tool. We indicated that using a more accurate tool for impaired glucose metabolism (HbA1c), the specificity of the instrument along with sensitivity could grow to a level higher than that of the instruments presented in table 4.

One of the models obtained here included HbA1c with sensitivity and specificity of 75.0 and 70.9, respectively. However, because of low sample size (169), we did not consider it in our final analysis. Further studies on this subject with a larger sample size are recommended.

Conclusion

We achieved an objective model taking SBP, FBS, BMI, age, NHR, and gender into account. A score ≥ 3 is considered as high risk for OSA and would be a good candidate for one-night PSG as a gold standard tool for OSA diagnosis. This comprehensive tool could be used in occupational settings as it benefits from objective parameters and is not based on patients' self-reports. Further evaluation of this score across different populations is highly recommended. More investigations in different populations are needed to validate this tool.

Conflict of Interests

Authors have no conflict of interests.

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