Original Article

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TANAFFOS

Prevalence of Sleep Apnea and its Associated Factors in Chronic Kidney Disease Patients

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Background: This study aimed to determine the prevalence of sleep apnea and its associated factors in patients with chronic kidney disease (CKD).
Materials and Methods: This population-based cross-sectional study included 47 CKD patients, referred to the dialysis unit of Kosar Hospital in Semnan, Iran, in 2017. Two questionnaires were used for data collection. The first questionnaire included demographic and clinical variables, and the second questionnaire (STOP-BANG questionnaire) was used to measure sleep apnea in CKD patients. Also, the Apnea-Hypopnea Index (AHI) was calculated for all patients and was considered as the gold standard. To determine the factors associated with sleep apnea, univariate and multiple logistic regression models were used. Finally, the area under the receiver operating characteristic curve (ROC) was determined for assessing the discriminative ability of the model, as well as the accuracy of STOP-BANG questionnaire. STATA version 14 was used for data analysis.
Results: The prevalence of sleep apnea in CKD patients was 53.2%. Also, its prevalence in women and men was 52% and 48%, respectively. In the multiple logistic regression model, body mass index (BMI) (OR: 1.21, 95% CI: 1.04-1.31) and blood urea nitrogen (BUN) (OR: 0.94, 95% CI: 0.91-0.98) had significant associations with sleep apnea in CKD patients; the area under the ROC curve was 0.7982 for this model. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the ROC curve of STOP-BANG questionnaire for AHI≥15 were 71.43, 61.54, 60, 72.73, and 0.6932, respectively.
Conclusion: This study showed that the prevalence of sleep apnea in CKD patients was high. Given the acceptable validity of STOP-BANG questionnaire, this scale can be used to screen sleep apnea in CKD patients.

Key words: Prevalence, Sleep apnea, CKD, STOP-BANG questionnaire, AHI

INTRODUCTION

Sleep apnea refers to interrupted breathing in the upper respiratory tract during sleep for more than ten seconds. It may occur due to upper airway obstruction during sleep and increased sympathetic activity, caused by repeated respiratory arousal during sleep and hypoxia (1,2). Sleep apnea can lead to reduced quality of life, respiratory arousal during sleep, oxygen desaturation, daytime sleepiness, and cognitive impairment. This disorder is a common respiratory problem with 5% prevalence in adults. One of the diseases associated with sleep apnea is chronic kidney disease (CKD) (3, 4). Studies have reported the high prevalence of sleep apnea in hemodialysis patients (5-8). Estimates show that the prevalence of sleep apnea in hemodialysis patients is ten times higher than healthy people. According to statistics, 50-70% of hemodialysis patients have sleep apnea (9, 10).

The absence of breathing sounds is an important symptom, suggesting sleep apnea. Nighttime restlessness, interrupted sleep, disturbed nocturnal sleep, daytime sleepiness, headache, and fatigue are the most common complaints of patients with sleep apnea. The importance of sleep apnea in nephrology is related to the fact that hemodialysis patients are prone to cardiovascular comorbidities and mortality, because repeated oxygen saturation drops can lead to increased oxidative stress and stimulate the sympathetic system, which ultimately causes hypertension and cardiovascular diseases (11-15). The association between CKD and sleep apnea and its exact mechanism are still unclear; however, increased sympathetic nervous discharge, increased blood pressure in patients with sleep apnea during attacks, and persistence of high blood pressure can be influential factors in susceptibility to sleep apnea in CKD patients (7).

Moreover, the results of some previous studies have shown that factors, such as excessive fluid accumulation, are important in increased susceptibility to sleep apnea in CKD patients (16). On the other hand, a number of studies have shown that metabolic acidosis, by creating a compensatory flow of respiratory alkalosis, leads to hypercapnia ventilation and ultimately triggers the onset of sleep apnea in CKD patients (9,10). Nevertheless, factors associated with the higher prevalence of sleep apnea in CKD patients are not completely clear, although some studies have examined non-dialysis patients (17,18).

Considering the importance of sleep apnea and the high morbidity and mortality rates of cardiovascular diseases and complications in CKD patients, besides the limitations of previous studies on the prevalence of this disease and its factors in CKD patients in Iran, the present study aimed to determine the prevalence of sleep apnea and its associated factors in CKD patients, referred to Kosar Hospital of Semnan, Iran.

MATERIALS AND METHODS

Study design and population

This population-based cross-sectional study aimed to evaluate the prevalence of sleep apnea and its associated factors in CKD patients, referred to Kosar Hospital in Semnan, Iran. The study population included all CKD patients, referred to the dialysis unit of Kosar Hospital of Semnan in 2017. The inclusion criteria were as follows: CKD patients aged ≥18 years; glomerular filtration rate (GFR) <15 ml/min/1.73 m^2; and at least three dialysis sessions per week. The exclusion criteria were neurological defects (acquired or congenital); psychiatric disorders; craniofacial abnormalities (CFA); congestive heart failure (CHF), and opium dependence.

Data collection

In the present study, two questionnaires were used for data collection. The first one included demographic and clinical variables, such as age, sex, body mass index (BMI), systolic and diastolic blood pressure, medical history (e.g., diabetes mellitus, hypertension, and ischemic heart disease), duration of CKD (months), duration of dialysis (months), hours of dialysis per week, and laboratory criteria, including serum creatinine, blood urea nitrogen (BUN), GFR, phosphorus, albumin, calcium, and hemoglobin. The GFR was calculated based on Equation 1 (19):

$$\mathrm{GFR} = \frac{(140-\mathrm{Age}).weight\ (Kg)}{\mathrm{Plasma\ Creatinine\ (mg/dl).72}} \qquad \text{Equation 1}$$

It is worth mentioning that Equation 1 was multiplied by 0.85 for women. The second questionnaire was the STOP-BANG questionnaire, which was used to measure sleep apnea in CKD patients. This questionnaire consisted of eight items, including snoring, tiredness, observed sleep apnea, hypertension, BMI ≥35 kg/m^2, age ≥50 years, neck circumference >40 cm, and male gender. For “Yes” and “No” items, scores of one and zero were assigned, respectively. Finally, scores of 0-2 and ≥3 were considered as low- and high-risk groups for sleep apnea, respectively

(8, 20). Previously, Sadeghniiat-Haghighi et al. examined the reliability and validity of the Persian version of STOP-BANG questionnaire in a sleep clinic population (21). It should be noted that the risk group consisted of patients with sleep apnea.

In the present study, for all patients, a polygraph test was taken by an experienced pulmonologist. To perform the test, the patient was hospitalized for one night in the room designed for the test. During sleep, some electrodes and related devices were attached to the patient for recording the essential information. The apnea-hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of recording. AHI was then classified as follows: 5/h≤ mild <15/h; 15/h≤ moderate <30/h; severe, ≥30/h (20, 22). In the present study, the polygraph test was considered as the gold standard and used to determine the validity of STOP-BANG questionnaire.

Statistical analysis

After obtaining informed consent and explaining the research objectives to the participants, data collection was conducted. Relevant data were entered in STATA version 14 for analysis. In descriptive analyses, mean (standard deviation) and number (percentage) were measured for quantitative and qualitative variables, respectively. Then, univariate and multiple logistic regression models were employed to determine the factors associated with sleep apnea in CKD patients. Finally, the crude and adjusted odds ratios (ORs) with 95% confidence interval (CI) were calculated. Also, the area under the receiver operating characteristic (ROC) curve (AUC) was calculated for assessing the discriminative ability of the multiple logistic regression model and examining the accuracy of STOP-BANG questionnaire in comparison with AHI (gold standard). P-value <0.05 was considered statistically significant.

This research was conducted according to the principles of the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Semnan University of Medical Sciences (Semnan, Iran) (code: IR.SEMUMS.REC.1396.125).

RESULTS

A total of 47 CKD patients, who were referred to the dialysis unit of Kosar Hospital of Semnan during 2017, were included. Overall, 22 (46.8%) and 25 (53.2%) patients had low (score <3) and high (score ≥3) risks of sleep apnea, respectively. Table 1 presents the mean, standard deviation (SD), minimum, and maximum of STOP-BANG score for central apnea, obstructive sleep apnea (OSA), and overnight desaturation index (ODI) in patients. As can be seen, the mean (SD) scores of STOP-BANG questionnaire in the general, low-risk (score <3) and high-risk (score ≥3) groups were 2.96 (1.78), 1.45 (0.74), and 4.28 (1.31), respectively.

Table1. Mean, Standard Deviation, min and max of STOP-BANG score, Central, OSA and ODI in Patients under Study

STOP-BANG Score	Number	Mean	S.D	Minimum	Maximum
General	47	2.96	1.78	0	8
Low Risk (Score <3)	22	1.45	0.74	0	2
High Risk (Score ≥3)	25	4.28	1.31	3	8
AHI	**Number**	**Mean**	**S.D**	**Minimum**	Maximum
Central	47	2.63	9.45	0	63.60
OSA	47	8.28	13.14	0	70.50
ODI	47	19.40	19.85	0	89.40

Also, the mean (SD) scores of central apnea, OSA, and ODI were 2.63 (9.45), 8.28 (13.14), and 19.40 (19.85), respectively. Since the high-risk group (score≥3) included patients with sleep apnea, the overall prevalence of sleep apnea was 53.2% in CKD patients; it was also 52% and 48% in women and men, respectively. Table 2 presents the details of STOP-BANG questionnaire in patients under study. The mean (SD) age of low-risk and high-risk groups was 58.54 (14.32) and 64.92 (11.98) years, respectively. Also, the mean (SD) BMI of low-risk and high-risk groups was 24.12 (4.85) and 27.33 (5.11) kg/m^2, respectively. Other demographic and clinical characteristics of CKD patients, as well as the results of univariate logistic regression analysis, are presented in Table 3.

Table 2. The Various Dimensions of STOP-Bang Questionnaire in patients under Study

STOP-Bang		Number	%
S :Snoring	Yes	20	42.55
	No	27	53.45
T :Tiredness	Yes	18	38.30
	No	29	61.70
O :Observed	Yes	14	29.80
	No	33	70.20
P :Pressure	Yes	6	12.80
	No	41	87.20
> 35m2/kg : B BMI	Yes	5	10.60
	No	42	89.40
A:> 50 year Age	Yes	35	74.50
	No	12	25.50
N :Neck >40 cm	Yes	11	23.40
	No	36	76.60
G:- male Gender	Yes	20	42.60
	No	27	57.40

The results of univariate logistic regression model showed that only BMI and BUN had significant associations with the occurrence of sleep apnea in CKD patients (P<0.05). In other words, for every unit increase in BMI, the odds of sleep apnea in the high-risk group was 1.45 times higher than the low-risk group (OR: 1.45, 95% CI: 1.01-1.30). Similarly, for every unit of BUN increase, the odds of sleep apnea in the high-risk group was 4% lower than the low-risk group (OR: 0.96, 95% CI: 0.92-0.99). Other variables had no significant association with the occurrence of sleep apnea in CKD patients (P>0.05) (Table 3).

To eliminate potential confounding factors, variables with P≤0.20 in the univariate logistic regression model were included in the multiple logistic regression model simultaneously. After adjusting for the confounding variables in the multiple logistic regression model, the occurrence of sleep apnea in CKD patients showed significant associations with BMI (adjusted OR: 1.21, 95% CI: 1.04-1.31) and BUN (adjusted OR: 0.94, 95% CI: 0.91-0.98) (P<0.05). Table 4 shows the results of multiple logistic regression analysis.

Figure 1 shows the AUC for significant variables in the multiple logistic regression model. As can be seen, the AUC was 0.7982 (95% CI: 0.6720-0.9250, P<0.001), which indicated the high discriminative power of this model in distinguishing high-risk and low-risk CKD patients for sleep apnea. Also, Table 5 shows the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of STOP-BANG questionnaire at different cut-off points as compared to AHI (gold standard). The highest sensitivity, specificity, PPV, and NPV of STOP-BANG questionnaire for AHI≥15 were 71.43, 61.54, 60, and 72.73, respectively. Also, the AUC for the accuracy assessment of STOP-BANG questionnaire relative to AHI was 0.6932 (95% CI: 0.5510-0.8266; P=0.024), which indicates the adequate validity of STOP-BANG questionnaire in the diagnosis of sleep apnea in CKD patients (Figure 2).

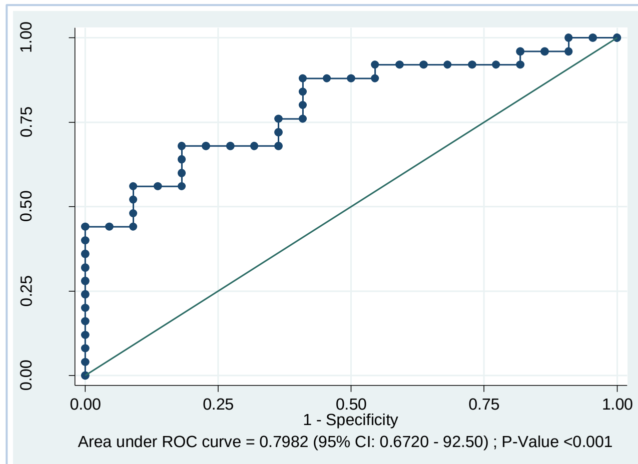

Figure 1. ROC curve for the significant variables in multiple logistic regression model

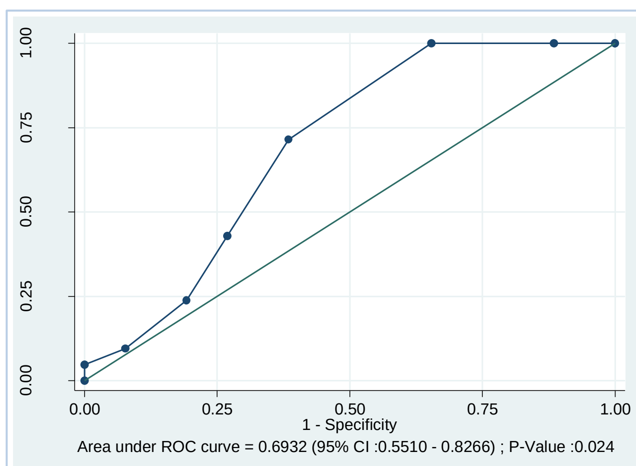

Figure 2. ROC curve of STOP-BANG questionnaire in compared to AHI in the diagnosis of sleep apnea in CKD Patient

Table 3. Demographic and Clinical Characteristics of CKD Patients Under Study and the Association of These Factors with Sleep Apnea Using Univariate Logistic Regression Model

Quantitative Variables (Mean, SD)	Low Risk (<3) (N=22)	High Risk (≥3) (N=25)	Crude OR (95% CI)	P-Value
Age (Year)	58.54 (14.32)	64.92 (11.98)	1.04 (0.99 -1.08)	**0.108**
BMI (Kg/m2)	24.12 (4.85)	27.33 (5.11)	1.45 (1.01 -1.30)	**0.042**
Duration of CKD (Month)	43 (37.02)	61.40 (62.49)	1.007 (0.99 – 1.02)	0.240
Duration of Dialysis (Month)	26.45 (30.75)	22.48 (27.50)	0.99 (0.97 – 1.01)	0.635
Hours of Dialysis per Week	11.41 (2.20)	11.56 (1.87)	1.04 (0.78 – 1.39)	0.705
GFR Before Dialysis	13.85 (5.10)	15.58 (5.09)	1.07 (0.94 – 1.22)	0.290
Hemoglobin (g/dl)	10.61 (1.04)	10.38 (1.46)	0.86 (0.54 – 1.37)	0.536
Hematocrit (%)	33.20 (3.46)	31.91 (4.32)	0.92 (0.78 -1.07)	0.267
Creatinine (mg/dl)	4.70 (1.41)	4.47 (1.67)	0.91 (0.61 – 1.32)	0.610
BUN (mg/dl)	49.90 (14.94)	38.52 (19.41)	0.96 (0.92 – 0.99)	**0.038**
Fasting Blood Glucose (mg/dl)	128.41 (68.95)	134.60 (75.80)	1.001 (0.99 – 1.009)	0.767
Heart Rate (Pulse)	75.72 (13.17)	80 (14.60)	1.02 (0.98 – 1.07)	0.297
Albumin (g/l)	3.68 (0.31)	3.60 (0.50)	0.61 (0.15 – 2.44)	0.482
Phosphorus (mg/dl)	4.67 (0.81)	4.74 (0.88)	1.11 (0.56 – 2.23)	0.310
Calcium (mg/dl)	9.21 (0.62)	9.13 (0.69)	0.84 (0.34 – 2.04)	0.699
Qualitative Variables (Number, %)	**Low Risk (<3) (N=22)**	**High Risk (≥3) (N=25)**	**OR (95% CI)**	**P-Value**
Sex				
Male	8 (36.4)	12 (48)	Reference	0.422
Female	14 (63.6)	13 (52)	0.62 (0.19 – 1.99)	
History of Diabetes				
No	9 (40.9)	9 (36)	Reference	0.730
Yes	13 (59.1)	16 (64)	1.23 (0.38 – 4.01)	
History of Hypertension				
No	8 (36.4)	8 (32)	Reference	0.310
Yes	14 (63.6)	17 (68)	1.21 (0.36 – 4.06)	
History of Ischemic Heart Disease				
No	15 (68.2)	19 (76)	Reference	0.551
Yes	7 (31.8)	6 (24)	0.68 (0.19 -2.44)	
History of Hypothyroidism				
No	21 (95.5)	22 (88)	Reference	0.378
Yes	1 (4.5)	3 (12)	2.86 (0.27 – 29.75)	

Table 4. The effective Factors on the Occurrence of Sleep Apnea in CKD Patients under study using multiple logistic regression model

Quantitative Variables	Low Risk (<3) (N=22)	High Risk (≥3) (N=25)	Adjusted OR (95% CI)	P-Value
Age (Year)	58.54 (14.32)	64.92 (11.98)	1.04 (0.99 -1.10)	0.130
BMI (Kg/m2)	24.12 (4.85)	27.33 (5.11)	1.21 (1.04 -1.31)	**0.014**
BUN (mg/dl)	49.90 (14.94)	38.52 (19.41)	0.94 (0.91– 0.98)	**0.014**

Area under the ROC Curve: 0.7982 (CI95%: 0.6720 -0.9250); **P-Value <0.001**

Table 5. Determination of Sensitivity, Specificity, PPV & NPV of STOP-BANG Questionnaire in Different Cut points in Compared to AHI

Cut point	Sensitivity (%)	Specificity (%)	*PPV	**NPV
0	100	0	44.68	0
1	100	11.54	47.73	100.00
2	100	34.62	55.26	100.00
3	**71.43**	**61.54**	**60.00**	**72.73**
4	42.86	73.08	56.25	61.29
5	23.81	80.77	50.00	56.76
6	9.52	92.31	49.99	55.81
7	4.76	100	100.00	56.52
8	0	100	0	55.32

Area under ROC Curve: 0.6932 (CI95%: 0.5510 - 0.8266); **P-Value 0.024**

***PPV:** Positive Predictive Value

****NPV:** Negative Predictive Value

DISCUSSION

The present study was designed to determine the prevalence of sleep apnea in CKD patients and to investigate the effective factors in the occurrence of sleep apnea in these patients. The results showed that the overall prevalence of sleep apnea in CKD patients was 53.2% (52% and 48% for women and men, respectively). The results of multiple logistic regression analysis showed that only BMI and BUN had significant associations with sleep apnea in CKD patients; also, the AUC for this model was 0.7982. In the present study, we found that the sensitivity, specificity, PPV, and NPV of STOP-BANG questionnaire for AHI≥15 were 71.43, 61.54, 60, and 72.73, respectively. Also, the AUC for accuracy assessment of STOP-BANG questionnaire relative to AHI was 0.6932.

The results of the present study indicated that the overall prevalence of sleep apnea in CKD patients was 53.2%; this finding is consistent with similar studies in this area (11, 20, 22). In this regard, a study by Forni Ogna et al., which aimed to determine the prevalence of sleep apnea and introduce a diagnostic approach for hemodialysis patients in Switzerland, showed that the prevalence of moderate to severe sleep apnea in CKD patients was 56% (11). Moreover, a study by Ghanei Geshlagh et al. showed that 41.7% of hemodialysis patients had sleep apnea in Iran (20). Also, a study by Sabry et al. which aimed to determine the prevalence of sleep disorders in hemodialysis patients in Saudi Arabia showed that 31.8% of patients had these abnormalities (22).

In contrast, some other studies reported the very high prevalence of sleep apnea in CKD patients (7-9, 14, 15, 23, 24). For example, a study by Huang et al. showed that 80% of CKD patients had moderate or severe sleep apnea (8). Also, another study investigated the prevalence of sleep disorders in hemodialysis patients in Iran and showed that the total prevalence of sleep disorder was 75% in these patients (10). Overall, the prevalence of sleep apnea is high in CKD patients, and the observed difference in the prevalence rates of different studies may be due to differences in the sample size, screening tools, diagnostic tools for measuring sleep apnea, and also genetics (25).

The main cause of the high prevalence of sleep apnea in CKD patients is unknown. However, some studies have shown that uremic toxins, metabolic acidosis, chronic hypocapnia, amino-acid metabolism abnormalities, and hormone imbalance are associated with the occurrence of sleep apnea in CKD patients (26-28). Given the high prevalence of sleep apnea in CKD patients, its negative impact on the mental health and adaptability of patients, and its role in the increased cardiovascular morbidity and mortality of patients (24,29), it is essential to design and implement regular screening programs for the detection of sleep apnea in CKD patients.

In the present study, although the prevalence of sleep apnea in women was higher than men (52% vs. 48%), the difference was not statistically significant (P>0.05); this result is in line with the results of some similar studies (22,30,31). In contrast, several studies have shown a significant association between sex and sleep apnea (32-35). Although the exact causes of distinction in the prevalence of sleep apnea between men and women are unknown, some studies have highlighted factors, such as obesity, anatomy of the upper airways, respiratory control, and secretion of sex hormones in the circadian rhythm (36). It should be also noted that the higher prevalence of sleep apnea in women may be due to the larger number of female participants in our study.

Moreover, in the present study, although the mean age of the high-risk group was higher than the low-risk group for sleep apnea (64.92 vs. 58.54), the difference was not significant (P>0.05). This finding is inconsistent with the results of previous studies, as they suggested older age as a risk factor for sleep apnea (20,37,38). This discrepancy may be attributed to the small sample size of our study. However, changes in the quantity and quality of sleep and the increased risk of sleep apnea in the elderly were more observed, which may be due to the poor performance of muscles holding the open airway in the elderly (39).

The findings of the present study showed that BMI (adjusted OR: 1.21, 95% CI: 1.04-1.31) had a significant association with the occurrence of sleep apnea in CKD patients, which is in line with similar studies in this area (21,40-44). A study by Sadeghniiat-Haghighi et al., which aimed to determine the reliability and validity of the Persian version of STOP-BANG questionnaire in a sleep clinic population (n=603), demonstrated a significant association between BMI and sleep apnea (21). Two other studies by Lurie and Moroni et al. showed a linear association between the increase in BMI and AHI (45,46). Also, previous studies have shown that a weight loss of 10% in obese patients could reduce AHI by 27% (47). Considering the important role of BMI and overweight in the development of sleep apnea, attention to this risk factor in the preventive and control programs of sleep apnea seems necessary.

Moreover, the present study showed a significant association between BUN and sleep apnea in CKD patients (OR: 0.94, 95% CI: 0.91-0.98), which is consistent with the results of other studies. For example, a study by Hanly et al. demonstrated a significant association between the reduction in BUN and the severity of sleep apnea (48). Also, two studies by Millman et al. and Tada et al. indicated a significant association between uremia (BUN and Cr) and sleep apnea in CKD patients (27,49). Overall, the mechanism of sleep apnea in CKD patients by uremia is unclear. However, a number of studies have suggested that sleep apnea results from a sharp decline in the airway muscle tone due to the effect of uremic toxins on the central nervous system during sleep, besides the instability of respiratory control due to the dis-coordination of the diaphragm and upper airway muscle activities (28).

In this study, we found that the sensitivity, specificity, PPV, and NPV of STOP-BANG questionnaire for AHI≥15 were 71.43, 61.54, 60, and 72.73, respectively. Also, the AUC for accuracy assessment of STOP-BANG questionnaire as compared to AHI was 0.6932. In a study by Chung et al., the sensitivity, specificity, PPV, NPV, and AUC of STOP questionnaire for AHI≥5 were 65.6, 60, 78.4, 44, and 0.703, respectively (50). Another study by Pecotic et al. reported the sensitivity, specificity, PPV, NPV and AUC of STOP questionnaire for AHI≥5 to be 96, 83, 61, 95, and 0.84, respectively (51). According to this finding, the BANG questionnaire has appropriate validity; therefore, it can be used as a screening tool for the diagnosis of sleep apnea in CKD patients.

One of the limitations of this study is its cross-sectional design, because the assumption of temporality was not taken into consideration (52,53). Also, the small sample size (n=47) and the use of polygraphy rather than polysomnography, as the gold standard, are the other limitations of this study.

CONCLUSION

This study highlighted the high prevalence of sleep apnea in CKD patients. The increased risk of sleep apnea was significantly associated with BMI and BUN of CKD patients. Also, the AUC for accuracy assessment of STOP-BANG questionnaire as compared to AHI was 0.6932; therefore, the STOP-BANG questionnaire can be used to screen sleep apnea in CKD patients. Finally, considering the high prevalence of sleep apnea in CKD patients, we suggest that regular screening programs be designed and implemented for the early detection of this disorder. Also, control of major risk factors associated with this disease is recommended in CKD patients.

Competing interests

The authors declare that they have no competing interests.

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