

ORIGINAL RESEARCH ARTICLE

Predictors of chronic kidney disease in obstructive sleep apnea patients

Phunphai Somkearti, Paiboon Chattakul, Sittichai Khamsai, Panita Limpawattana, Jarin Chindaprasirt, Verajit Chotmongkol, Kittisak Sawanyawisuth

Department of Medicine, Faculty of Medicine, Sleep Apnea Research Group, Research Center in Back, Neck and Other Joint Pain and Human Performance, Khon Kaen University, Khon Kaen, Thailand

ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is a common condition in patients with chronic kidney disease (CKD). It may worsen renal function in CKD patients and is associated with uncontrolled blood pressure. Although OSA is found in up to 80% of CKD patients, there are limited data available on its clinical features in patients with and without CKD.

Objective: This study aimed to identifying the differences in the clinical characteristics of OSA between CKD and non-CKD OSA patients and determine the clinical predictors for CKD in OSA patients.

Methods: This was a retrospective study conducted at Khon Kaen University's Srinagarind Hospital in Thailand between July and December 2018. The inclusion criteria were diagnosis with OSA *via* polysomnography and having undergone laboratory tests for CKD. Obstructive sleep apnea is diagnosed according to the apnea-hypopnea index (AHI) as experiencing ≥ 5 events/hour, while CKD diagnosed based on the KDOQI guidelines. Eligible patients were divided into two groups: OSA with CKD and OSA without CKD. Predictors of CKD in OSA patients were analyzed using multivariate logistic regression analysis.

Results: During the study period, there were 178 OSA patients who met the study criteria, 88 (49.44%) of whom were in the OSA with CKD group. Both age and body mass index were comparable between OSA patients with CKD and those without (age: 59 and 57 years, respectively; body mass index: 30 and 29 kg/m², respectively). There were three significant factors that differed between those with and without CKD group including systolic blood pressure (147 *vs* 135 mmHg), proportion of patients with diabetes (55% *vs* 34%), and proportion of patients with Mallampati scores of 3-4 (73% *vs* 39%). There were three independent predictors for OSA in patients with CKD: female sex, high systolic blood pressure, and Mallampati score of 3 or 4, with adjusted odds ratios (95% confidence interval) of 4.624 (1.554, 13.750), 1.060 (1.020, 1.101), and 2.816 (1.356, 5.849), respectively. The Hosmer-Lemeshow chi-square statistic of the predictive model was 6.06 (p 0.640). Systolic blood pressure of more than 130 and 150 mmHg resulted in sensitivity of 84.21% and specificity of 81.40%, respectively.

Conclusions: Female sex, high systolic blood pressure, and Mallampati score of 3-4 were suggestive of OSA with CKD. Obstructive sleep apnea patients with one or more of these predictors may have a high risk of CKD.

Key words: Predictors, systolic blood pressure, sex.

Correspondence: Kittisak Sawanyawisuth, MD, PhD, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand. Tel: +66.43.363664 - Fax: +66.43.348399. E-mail: kittisak@kku.ac.th

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Introduction

Obstructive sleep apnea (OSA) is categorized by cyclic obstruction of the upper airway during sleep. It has various clinical manifestations, from loud snoring, excessive daytime somnolence, and apneas. The condition is diagnosed *via* polysomnography according to the apnea-hypopnea index (AHI) as experiencing ≥ 5 events/hour [1]. Obstructive sleep apnea can exacerbate various other conditions such as hypertension, heart failure, stroke, gastroesophageal reflux disease, and chronic kidney disease (CKD) [2]. There is evidence of a bidirectional relationship between OSA and CKD. Chronic kidney disease may potentiate sleep apnea due to fluid redistribution and unstable chemosensitivity of the respiratory control system, while hypoxemia and sympathetic surges associated with arousals and systemic inflammation in OSA may lead to kidney injury [3]. Obstructive sleep apnea is found in nearly 80% in CKD patients [4] and some studies have suggested that OSA is a risk factor for CKD [5-7]. A study from Japan, for example, found that 30.5% of OSA patients had CKD, a rate three times greater than that in the general population (9.1%) [8]. It is difficult to draw the conclusion that worsening kidney function in these patients is solely a result of OSA as they usually have other comorbidities including diabetes mellitus, obesity, and hypertension. However, a cohort study from Taiwan showed that even those OSA patients without hypertension or diabetes were at higher risk of developing CKD and experienced earlier onset of CKD compared to a control group [9]. Although OSA and CKD are related, there are limited data available regarding the factors that predict CKD in OSA patients. This study thus aimed to determine the clinical predictors for CKD in those patients.

Methods

We conducted a retrospective, cross-sectional, analytic study at Khon Kaen University's Srinagarind Hospital in Thailand. The study period was between July and December 2018. The inclusion criteria were i) age ≥ 18 years; ii) having been diagnosed with OSA *via* polysomnography; and iii) having undergone laboratory tests for CKD. Obstructive sleep apnea is diagnosed according to the apnea-hypopnea index (AHI) as experiencing ≥ 5 events/hour, while CKD is diagnosed based on the KDOQI guidelines. The polysomnography used in this study was Alice PDX[®] as a home sleep study (Type 3 polysomnography) which had agreement of 96.4% with reference polysomnography. The scoring criteria for apnea and hypopnea are as follows: apnea: at least a 90% reduction of airflow for at least 10 seconds with at least 90% of the event's duration meets the amplitude reduction criteria for apnea, hypopnea: either $\geq 30\%$ reduction in airflow for at least 10s with $\geq 4\%$ desaturation or $\geq 50\%$ reduction in airflow for at least 10s with $\geq 3\%$ desaturation [10].

Baseline characteristics, comorbidities, OSA symptoms/signs/complications, and laboratory results of all eligible patients were examined and recorded. All data were recorded at the time of OSA diagnosis. Excessive daytime sleepiness or other OSA symptoms were evaluated by subjective evaluation or self-reported questionnaire by using the STOP Bang questionnaire.

Sample size calculation: the prevalence of CKD in cases of OSA is 30%. Based on a 95% confidence interval, the required sample size was determined to be 82 according to the infinite population proportion described by Ngamjarus *et al.* [11].

Statistical analysis: baseline and clinical characteristics of OSA patients with and without CKD were compared using descriptive statistics. When appropriate, a Wilcoxon rank sum/Student's *t*-test and Fisher's exact tests/chi-square test were

applied to compare the differences between the two groups in terms of numbers and proportions, respectively. Univariate logistic regression analysis was applied to calculate the crude odds ratio (OR) of individual variables for OSA associated with CKD. Those factors with a *p* of less than 0.20 by univariate logistic regression analysis and clinically significant variables were included in subsequent multivariate logistic regression analysis. Analytical results were presented as crude OR, adjusted OR, and 95% confidence intervals. The goodness of fit of the multivariate logistic regression model was tested using the Hosmer-Lemeshow method. Numerical independent factors for OSA associated with CKD were analyzed for appropriate cutoff points. Sensitivities and specificities for various cutoff points for CKD were also computed. All data analysis was performed using STATA software (StataCorp LP, College Station, TX, USA). The study was reviewed and approved by the Khon Kaen University Ethics Committee of Human Research (no. HE611131).

Results

There were 178 OSA patients included into the study, 88 (49.44%) of whom had CKD. The baseline characteristics, physical signs, and laboratory results of OSA patients with and without CKD are shown in Tables 1-3. For the CKD group, were 45 patients (51.13%) with identified causes of CKD as follows: 31 patients with albuminuria, 10 patients with proteinuria >1 gm, 2 patients with obstructive uropathy, 1 patient with IgA nephropathy, and 1 patient with focal segmental glomerulosclerosis (FSGS). Additionally, 10 patients were on dialysis.

Baseline characteristics of the two groups were comparable. For example, median age was 59 *vs* 57, and body mass index was 30 *vs* 29 kg/m² in the CKD and non-CKD group, respectively. However, the proportion of patients with hypertension and dia-

Table 1. Baseline characteristic of obstructive sleep apnea patients with and without chronic kidney disease.

Factor	CKD (n=88)	Non-CKD (n=90)	<i>p</i>
Male sex	51 (57.95)	56 (62.2)	0.646
Median (1 st -3 rd quartile) age, years	59 (44-66)	57 (47-66)	0.831
Excessive daytime sleepiness	39 (68)	39 (58.21)	0.336
Tiredness or fatigue	14 (70.00)	38 (80.85)	0.352
STOP-BANG questionnaire score	5(4-5)	5(4-6)	0.780
Diabetes mellitus	47 (55.29)	27(34.62)	0.012
Coronary artery disease	6 (7.06)	0 (0.0)	0.029
Heart failure	12(14.12)	9 (11.54)	0.648
Atrial fibrillation	15(17.05)	16 (17.78)	0.995
Hypertension	81(95.29)	58(74.36)	<0.001
Stroke	7(8.24)	6(7.69)	0.99
Gastroesophageal reflux disease	14(16.47)	12(15.38)	0.99
Gout	13(15.29)	5(6.41)	0.083
Allergic rhinitis	22(25.88)	13(16.67)	0.183
Previous smoking	10(25.00)	12(20.69)	0.631
Previous alcohol consumption	11(28.95)	9(16.07)	0.199
Current smoking	1(2.50)	5(8.93)	0.396
Current alcohol consumption	1(3.33)	4(7.02)	0.656

CKD, chronic kidney disease. Data are presented as number (percentage) unless indicated otherwise.

betes mellitus differed significantly between the two groups (81% vs 58% for hypertension with a p of <0.001 and 55.29% vs 34.62% for diabetes mellitus with a p of 0.012). As shown in Table 2, OSA patients with CKD had significantly higher systolic blood pressure than those without (147 vs 135 mmHg; p <0.001). The proportions of patients with Mallampati scores of 3-4 were also significantly different between the two groups (73% vs 39%; p <0.001). In addition, apnea-hypopnea index (AHI) scores were significantly higher in the CKD group than in the non-CKD group (23.5 vs 14 events/h; p =0.006), as shown in Table 3. Other laboratory results in which there were significant differences between the two groups include UACR, uric acid, and neutrophil and lymphocyte percentages (Table 3).

There were three independent predictors for CKD in OSA patients according to multivariate regression analysis: sex, systolic blood pressure, and Mallampati classification (Table 4), with odds ratios (95% confidence interval) of 4.624 (1.554, 13.757), 1.060 (1.020, 1.101), and 2.816 (1.356, 5.849), respectively. The Hosmer-Lemeshow chi-square of the predictive model was 6.06 (p =0.640). Systolic blood pressure of 130 and 150 mmHg cut points resulted in sensitivity of 84.21% and specificity of 81.40%, respectively.

Discussion

We found that female OSA patients tended to have a five-times higher risk of CKD than their male counterparts. Sex is an important factor that affects prevalence, clinical features, and clinical outcomes [12]. However, the reason for this correlation has yet to be explained. One possible explanation is that OSA symptoms in female patients tend to be less severe, leading these patients to seek medical treatment later and resulting in greater CKD development [13]. Another reason may have to do with endothelial dysfunction

Table 2. Physical signs of obstructive sleep apnea patients with and without chronic kidney disease.

Factor	CKD (n=88)	Non-CKD (n=90)	p
Body mass index, kg/m ²	30.4(26.27-35)	29(25.4-33.1)	0.248
Neck circumference, cm	41(39-45)	41(39-44)	0.911
Median (1 st -3 rd quartile) SBP, mmHg	146.5(134-156)	135(123-146)	<0.001
Median (1 st -3 rd quartile) DBP, mmHg	80(70-86)	79(72-85)	0.929
Median (1 st -3 rd quartile) BMI, kg/m ²	30.4 (26.27-35)	29(25.4-33.1)	0.248
Median (1 st -3 rd quartile) neck circumference, cm	41(39.0-45.0)	41(39.0-44.0)	0.911
Mallampati classification			<0.001
Class I	2(3.85)	10(16.39)	
Class II	12(23.08)	27(44.26)	
Class III	24(46.15)	21(34.43)	
Class IV	14(26.92)	3(4.92)	
Macroglossia	23(34.85)	23(31.08)	0.719
Torus palatinus	1(1.56)	8(11.11)	0.036
Torus mandibularis	2(3.17)	4(5.71)	0.683
Tonsillar enlargement	28(31.82)	36(40.00)	0.277
Microretrognathia	2(3.13)	2(2.74)	0.990
Retrognathia	3(4.92)	5(7.04)	0.725

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index. Data are presented as number (percentage) unless indicated otherwise.

and inflammation [14-16]. Hypoxemia may stimulate the release of cytokine and free radical products in OSA patients, which leads to a reductions in nitric oxide. Previous studies have found that high levels of various inflammatory proteins are significantly correlated with OSA severity. Surprisingly, increases in C-reactive protein (CRP) levels and the Erythrocyte Sedimentation Rate (ESR) in female OSA patients were found to be greater than those in their male counterparts [17]. Endothelial function was also found to be more sensitive and impaired in female OSA patients than in males. The mechanisms behind this difference have yet to

Table 3. Laboratory investigation results of obstructive sleep apnea (OSA) patients with and without chronic kidney disease.

Factor	CKD (n=88)	Non-CKD (n=90)	p
Blood urea nitrogen, mg/dL	21.1(13.7-38.3)	13.3(11.5-15.7)	<0.001
Serum creatinine, mg/dL	1.4(1.1-2.45)	0.9(0.76-1.1)	<0.001
GFR	47.5(28-66.5)	85.5(73-99.7)	<0.001
Uric, mg/dL	7.2(5.9-8.3)	6.1(5.2-7)	0.002
UACR, mg/g	93.5(29.2-560.2)	4.64(2.4-12.01)	<0.001
HbA1C, %	6.6(5.65-8.25)	6.1(5.5-7)	0.060
Cholesterol, mg/dL	179(152-209)	195(170-220)	0.149
Triglyceride, mg/dL	147(87-188)	148(97-202)	0.448
HDL-c, mg/dL, mg/dL	47(39-56)	48(42-59)	0.149
LDL-c, mg/dL, mg/dL	117(93-159)	130(96-158)	0.288
Neutrophil, %	61.8(53.6-65.6)	53.8(48.4-60.8)	0.002
Lymphocyte, %	26.7(20.4-30.8)	30.9(27-37.2)	0.001
Platelet, mm ³	242x10 ³ (203-282)	233x10 ³ (188-282)	0.311
LVEF, %	66(58-70)	67(62-75)	0.475
RVSP, mmHg	29.59(19.9-51.73)	28.66(21.1-46.97)	0.899
AHI, per hour	23.5(14.7-47)	14(9-30)	0.006
Severity of OSA, %		0.006	
Mild	25%	52%	
Moderate	30%	21%	
Severe	45%	27%	
Lowest O ₂ , %	81(72-88.5)	85(73-90)	0.338

CKD, chronic kidney disease; HDL-c, high density lipoprotein-cholesterol; LDL-c, low density lipoprotein-cholesterol; UACR, urine albumin creatinine ratio; LVEF, Left ventricular ejection fraction; RVSP, right ventricular systolic pressure; AHI, apnea hypopnea index. Data presented as median (1st-3rd percentile) unless indicated otherwise.

Table 4. Factors associated with chronic kidney disease in obstructive sleep apnea patients according to logistic regression analysis.

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Female sex*	1.195(0.655,4.624)	4.624(1.554,13.750)
SBP, mmHg*	1.039(1.019,1.060)	1.060(1.020,1.101)
Mallampati classification*	2.829(1.676,4.776)	2.816(1.356,5.849)
Diabetes mellitus	2.336(1.240,4.398)	0.934(0.312,2.792)
Body mass index, kg/m ²	1.028(0.981,1.076)	0.994(0.911,1.086)

*Independent predictor for chronic kidney disease in obstructive sleep apnea; SBP, systolic blood pressure.

be determined, but menopause may be a factor, as estrogen can promote the production of nitric oxide and slow its degradation [18]. Although the mean age of our patients was over 50 years, we were not able to assess their menopause status. The relationship among OSA, hypertension, and CKD is well-documented [19, 20]. Hypoxia due to OSA leads to increases in sympathetic tone and vascular resistance through the activation of the renin angiotensin aldosterone system (RAAS), which is associated with the fibrosis of kidney [20]. Systolic blood pressure was an important predictor for renal disease progression in this study, which is consistent with the findings of several previous studies [21,22].

Mallampati score (the estimation of tongue size relative to the oral cavity) was also an independent factor for CKD in this study. A score of 3-4 increased the risk of CKD by nearly 3 times. To our knowledge, this is the first study to identify a high Mallampati score as being a risk factor for CKD development in OSA patients. We suspect that the fluid retention process might play role in increasing the tongue size, a phenomenon that has previously been shown in pregnant women [23]. A large tongue may lower oxygen levels during sleep, leading to a higher chance of developing CKD [24]. However, Mallampati scores are subjective and may vary from examination to examination.

We found that if OSA patients had systolic blood pressure over 130 mmHg, sensitivity of having CKD was 84.21%. If the systolic blood pressure was over 150 mmHg, the specificity was 81.40%. These data may imply two points as follows: i) OSA patients with high systolic blood pressure are at risk for CKD. Therefore, the physicians should be aware of CKD in OSA patients with systolic blood pressure over 130 mmHg. ii) OSA patients may need to have a target systolic blood pressure of 130 mmHg to prevent risk of CKD. If the systolic blood pressure was over 150 mmHg, the specificity of having CKD in OSA patients would rise. In other words, the target blood pressure for OSA with hypertension may be appropriate at 130 mmHg. As the target systolic blood pressure has been set for other populations but not in OSA patients [25].

There were some limitations to this study. First, it was conducted in a single-site, referral medical center. Second, the predictive model for CKD included only clinical symptoms and signs and not laboratory results. The benefit of this model, however, is that it can be employed as a simple clinical model for health care facilities with limited resources. Other predictive models that include laboratory results should be developed. No intervention or evaluation of treatment outcomes were studied [26-28]. Due to retrospective data collection, some factors may be missing or not studied such as fluid distribution or menopausal status. Finally, SBP in this study was office blood pressure, and did not take into account home or nighttime blood pressure patterns. Due to the fact that OSA and CKD patients usually have non-dipping blood pressure variations [29], morning blood pressure or home-monitoring blood pressure should be examined further.

Conclusion

Female sex, high systolic blood pressure, and Mallampati classes 3-4 were suggestive of CKD in OSA patients.

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