

# Nocturic obstructive sleep apnea as a clinical phenotype of severe disease

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## ABSTRACT

**Study Objectives:** This study was done to find whether a history of nocturia is associated with severity of obstructive sleep apnea (OSA) and also whether patients with nocturia constitute a separate phenotype of OSA. **Materials and Methods:** Retrospective chart review was done in consecutive OSA patients who were diagnosed in sleep laboratory of our institute. Detailed sleep history, examination, biochemical investigations, and polysomnography reports were taken for the analysis. Nocturia was defined as urine frequency  $\geq 2$ /night. **Results:** Of 172 OSA patients, 87 (50.5%) patients had nocturia. On multivariate analysis, a history of nocturia had 2.429 times (confidence interval 1.086–5.434) more chances of having very severe OSA ( $P = 0.031$ ). Time between bedtime and first time for urination was significantly less in very severe OSA compared to severe OSA and mild-to-moderate OSA ( $2.4 \pm 0.9$ ,  $3.1 \pm 1.3$ , and  $3.0 \pm 1.1$  h, respectively) ( $P = 0.021$ ). Patients with nocturia were older ( $52.3 \pm 11.9$  vs.  $47.6 \pm 12.1$  years;  $P = 0.012$ ), had higher STOP BANG scores ( $P = 0.002$ ), higher apnea–hypopnea index (AHI) ( $64.8 \pm 35.9$  vs.  $43.9 \pm 29.1$ ;  $P < 0.001$ ), and higher Epworth sleepiness scale (ESS) ( $9.2 \pm 5.3$  vs.  $7.7 \pm 4.4$ ;  $P = 0.052$ ) and were more likely to be fatigued during day ( $P = 0.001$ ). Nocturics had higher body mass index (BMI) ( $P = 0.030$ ), higher waist, and hip circumference ( $P = 0.001$  and  $0.023$ , respectively). Nocturic patients had lower awake  $SpO_2$  ( $P = 0.032$ ) and lower nadir  $SpO_2$  during sleep ( $P = 0.002$ ). **Conclusions:** A history of nocturia ( $\geq 2$ /night) predicts very severe OSA (AHI  $> 60$ ). Nocturic OSA is a phenotype of OSA with more severe AHI, lower oxygen levels, higher BMI, and higher ESS. We believe nocturia can be used for screening in OSA questionnaires, which needs to be validated in further community-based studies.

**KEY WORDS:** Continuous positive airway pressure, nocturia, obstructive sleep apnea

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## INTRODUCTION

Among the various symptoms of obstructive sleep apnea (OSA), nocturia is now increasingly recognized as an important symptom.<sup>[1,2]</sup> Nocturia is known to be associated with OSA, and it has been shown to be associated with severe OSA.<sup>[3,4]</sup> Among the various hypothesis linking OSA and nocturia, the theory of atrial natriuretic peptide (ANP) looks most robust.

Recurrent apneic episodes occurring during OSA leads to several diaphragmatic contractions can occur without airflow leading to increased intrathoracic pressure as documented by Guilleminault that esophageal pressures can drop to as low as  $-80$  to  $-90$  cm  $H_2O$  during apneic episode.<sup>[5]</sup> It causes increased venous return which in turn causes the heart to receive a false signal of volume overload leading to increased secretion

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of ANP. This increased ANP inhibits the secretion of aldosterone, vasopressin, anti-diuretic hormone (ADH), and rennin–angiotensin system. It leads to increased sodium and water excretion by 2.5 and 3.5 times normal rate, respectively. Adding to this insult is hypoxemia caused by OSA which leads to increased pulmonary vasoconstriction which further increases load over the heart.<sup>[2]</sup> Furthermore, it has been shown that more severe the OSA, higher the frequency of urination.<sup>[4]</sup> Continuous positive airway pressure (CPAP) has also been shown to be highly effective in improving nocturia and decreasing urine volume among OSA patients in a recent meta-analysis.<sup>[6]</sup> All these studies support that the evidence that nocturia is caused by OSA and when the disease is treated, nocturia also decreases. In spite of all these supporting evidence, nocturia is not considered an important symptom of OSA by many and predictive value of nocturia in diagnosing OSA is not well known unlike loud snoring or history of apnea. In a retrospective analysis, nocturia was found to be comparable with self-reported snoring as a screening question in predicting OSA.<sup>[7]</sup>

OSA patients with nocturia have been shown to have more severe disease compared to nonnocturic OSA patients. Pływaczewski *et al.* in their study showed that nocturic OSA patients had higher apnea–hypopnea index (AHI) and higher Epworth Sleepiness Scale (ESS) compared to OSA patients without nocturia.<sup>[8]</sup> Raheem *et al.* also found age >70 and higher AHI to be predictors of nocturia, although they had defined nocturia as nocturnal urinary frequency one or more.<sup>[9]</sup>

We hypothesized that the amount of urine produced during night depends on the severity of OSA. Thus, the number of washroom trips during the night will increase as the severity of OSA increases. We also hypothesized that severe OSA will lead to increased urine production and thus patient will arise early from his sleep for first urination.

This study was done with following objectives in mind: (1) To find whether nocturia and frequency of micturition is associated with OSA severity, (2) Whether time to go for first urination after sleep is associated with the severity of OSA, (3) To evaluate clinical predictors of nocturia in patients with OSA, and (4) To determine whether nocturics OSA patients are different from nonnocturics OSA patients.

Although nocturia is defined as the need to void one or more time after sleep, epidemiological studies have shown nocturia to be clinically significant only when patients void two or more times.<sup>[10]</sup> Tikkinen *et al.* showed that voiding only once per night is not a suitable criterion for clinically relevant nocturia.<sup>[10]</sup> Hence, for this study, we defined nocturia as when a patient goes to urination for two or more times after sleep onset.

## MATERIALS AND METHODS

### Design and settings

This retrospective medical record review study was done in OSA patients who were diagnosed in sleep laboratory of AIIMS Bhopal hospital. Records of consecutive patients diagnosed between June 2015 and October 2016 were extracted from our sleep registry.

### Data Abstraction Process

We maintain an electronic record for every patient undergoing polysomnography (PSG). This record consists of clinical history (including questions in the presence of nocturia, its timings, and frequency) and examination, STOP-BANG assessment, and ESS assessment done by sleep physician. It also has information on routine investigations including pulmonary function tests and results PSG. Data abstraction plan consisting of variables described in following section was developed after review of literature. Data were retrieved from the electronic database by sleep physician.

### Exclusion criteria

1. Patients already on diuretics
2. Deranged liver function tests or renal function tests
3. History suggested of Urinary tract infection
4. History suggested of neurological problems.

### Study variables

Detailed history for sleep symptoms, clinical examination for anthropometry and craniofacial abnormalities, and biochemical investigations were taken for the analysis. Hypertension was defined, if the patient was already on antihypertensive or if the patient's blood pressure (BP) was >140/90. Hyperglycemia was defined if patient's fasting blood sugar (FBS) was >126 or if the patient was a known diabetic. The frequency of micturition and also time between sleep onset and first micturition were noted. Nocturia was defined as when a patient goes to urination for two or more times after sleep onset.

Level I PSG was done with Alice 6 PSG laboratory (Philips respironics). Electroencephalography, chin electromyography, Leg electromyography, electrooculography, SpO<sub>2</sub>, chest and abdominal movements with zRIP belts, and body sensor were used in all patients. Sleep data were manually scored by technicians first, then by sleep resident and finally by the lead author of this study (AG) who was blinded for the status of nocturia of that patient. The American Academy of Sleep Medicine criteria for scoring were used. Apnea was defined as the cessation of airflow through the nose  $\geq 10$  s, and hypopnea was defined as the reduction in airflow  $\geq 30\%$  associated with a decrease in the pulse oximetry reading (desaturation)  $\geq 3\%$ . The severity of OSA was described by number of apneas and hypopneas per hour of sleep (AHI). OSA was defined as an AHI  $\geq 5$ . Since we had lesser number of mild OSA patients, we divided OSA into three categories on the

basis of AHI as follows: mild-to-moderate (AHI 5–29.9), severe (AHI 30–59.9), and very severe OSA (AHI >60).

### Statistical analysis

We have used IBM SPSS statistics for windows, version 21.0 Armonk, NY, USA, IBM corporation software for analysis. Nominal variables were summarized using count and proportion. Numerical variables were summarized as the mean and standard deviation when their distribution was nonskewed and as median and interquartile range for skewed distribution. Univariate analysis for finding association between severe OSA and various factors was done using Chi-square test when independent variables were nominal and using *t*-test or Mann–Whitney test for numerical variables. Odds ratio (OR) and their 95% confidence interval (CI) were also calculated. Then, we have performed data-driven multinomial logistic regression analysis to identify independent predictors of severe and very severe OSA; wherein, variables with  $P < 0.2$  on univariate analysis were selected. To determine whether nocturnal and nonnocturnal OSA are different phenotypes, we have used Chi-square and *t*-test/Mann–Whitney test for nominal and numerical variables appropriately.

## RESULTS

Of 172 OSA patients, 87 (50.5%) patients had nocturia. Only 20% of OSA patients did not wake up for urination, and around 30% of patients went only once for urination during the night [Table 1]. There was no difference in nocturia frequency or presence of nocturia in males or females.

On the basis of AHI, three groups were formed; and 60, 42, and 70 patients constituted mild-to-moderate, severe, and very severe OSA [Table 2]; there was no difference regarding baseline characteristics such as age, history of fatigability, or snoring in these three groups of OSA. A history of apnea if present had OR of 3.452 (CI 1.55–7.66) ( $P = 0.002$ ) for developing very severe OSA as compared to mild-to-moderate OSA.

Very severe OSA patients had significantly higher frequency of micturition compared to severe and mild-to-moderate group ( $P < 0.001$ ). On multivariate analysis, a history of

**Table 1: Distribution of obstructive sleep apnea patients by frequency of nocturnal urination**

Number of times patient goes for urination during night	Number of patients (%)
0	35 (20.3)
1	50 (29.1)
2	36 (20.9)
3	28 (16.3)
4	16 (9.3)
5	3 (1.7)
7	1 (0.6)
8	1 (0.6)
10	2 (1.2)
Total	172 (100.0)

nocturia had 2.429 times (CI 1.086–5.434) more chances of having very severe OSA ( $P = 0.031$ ). Time between bedtime and first time for urination was significantly less in very severe OSA compared to severe OSA and mild-to-moderate OSA ( $2.4 \pm 0.9$ ,  $3.1 \pm 1.3$ , and  $3.0 \pm 1.1$  h, respectively) ( $P = 0.021$ ).

Patients with body mass index (BMI) >35 kg/m<sup>2</sup> had higher chances of having severe and very severe OSA compared to patients with BMI < 35 kg/m<sup>2</sup> ( $P = 0.003$ ). Neck, waist, and hip circumferences were significantly higher in very severe OSA compared to other two groups ( $P = 0.003$ , <0.001, and 0.001, respectively). When modified Mallampati was clubbed into 1–2 and 3–4; higher Mallampati grades had higher chances of having severe and very severe OSA ( $P = 0.024$ ). There was no difference seen in any of the other craniofacial abnormalities such as micrognathia, retrognathia, macroglossia, large uvula, high-arched palate, nasal valve dehiscence, crossbite, or tonsil grades.

STOP-BANG score was significantly higher in very severe OSA versus severe OSA and mild-to-moderate OSA;  $4.8 \pm 1.3$ ,  $4.6 \pm 1.2$ , and  $3.9 \pm 1.2$ , respectively ( $P < 0.001$ ). Patients with very severe OSA had higher diastolic pressures ( $P = 0.006$ ); however, the difference in systolic pressure did not meet statistical significance.

Patients with very mild-to-moderate OSA had higher awake SpO<sub>2</sub> compared to other two groups ( $96.3\% \pm 1.6\%$ ,  $94.6\% \pm 3.8\%$ , and  $95.7\% \pm 2.7\%$ ) ( $P = 0.011$ ). Furthermore, nadir oxygen saturation during sleep was much lower in very severe OSA compared to mild-to-moderate and severe OSA ( $71.5\% \pm 16.7\%$ ,  $88.2\% \pm 8.3\%$ , and  $82.3\% \pm 10.5\%$ ) ( $P < 0.001$ ).

Then, these patients were classified into two groups on the basis of the presence or absence of nocturia [Table 3]. There was no difference in distribution of males or females with relation to the presence of nocturia. Patients with nocturia were older ( $52.3 \pm 11.9$  vs.  $47.6 \pm 12.1$  years;  $P = 0.012$ ). Nocturnal patients had higher STOP-BANG scores ( $P = 0.002$ ) and also higher AHI ( $64.8 \pm 35.9$  vs.  $43.9 \pm 29.1$ ;  $P < 0.001$ ) [Figure 1]. There was no difference in the history of apnea or snoring among nocturics and nonnocturics; however, nocturnal patients were more likely to be fatigued during the day ( $P = 0.001$ ), and they were more sleepy as evident by higher ESS ( $9.2 \pm 5.3$  vs.  $7.7 \pm 4.4$ ;  $P = 0.052$ ).

Nocturics had higher BMI ( $P = 0.030$ ), and also they were more likely to have BMI >35 ( $P = 0.007$ ) compared to nonnocturics. Furthermore, nocturics had significantly higher waist and hip circumference ( $P = 0.001$  and  $0.023$ , respectively). However, a statistical difference was not observed in neck circumference or other craniofacial abnormalities among nocturics and nonnocturics. Furthermore, there was no difference in blood pressure in two groups.

Nocturnal patients had lower awake SpO<sub>2</sub> ( $P = 0.032$ ) and lower nadir SpO<sub>2</sub> during sleep ( $P = 0.002$ ) compared

**Table 2: Baseline characteristics of patients according to severity of obstructive sleep apnea**

Variables	Mild to moderate	Severe	Very severe	P
Gender, n (%)				
Females	15 (38.5)	7 (17.9)	17 (43.6)	0.562
Males	45 (33.8)	35 (26.3)	53 (39.8)	
Fatigability, n (%)				
No	14 (31.1)	10 (22.2)	21 (46.7)	0.637
Yes	46 (36.2)	32 (25.2)	49 (38.6)	
Snore, n (%)				
No	3 (50.0)	1 (16.7)	2 (33.3)	0.725
Yes	57 (34.3)	41 (24.7)	68 (41.0)	
History of Apnoea, n (%)				
No	38 (47.5)	20 (25.0)	22 (27.5)	0.001
Yes	22 (23.9)	22 (23.9)	48 (52.2)	
BMI >35, n (%)				
No	55 (40.7)	33 (24.4)	47 (34.8)	0.003
Yes	5 (13.5)	9 (24.3)	23 (62.2)	
Hypertension (BP>140/90) or patient on antihypertensive, n (%)				
No	37 (42.0)	19 (21.6)	32 (36.4)	0.131
Yes	23 (27.4)	23 (27.4)	38 (45.2)	
Neck circumference >17 inches in males or >16 inch in females, n (%)				
No	52 (39.7)	35 (26.7)	44 (33.6)	0.003
Yes	8 (19.5)	7 (17.1)	26 (63.4)	
Retrognathia, n (%)				
No	53 (34.4)	40 (26.0)	61 (39.6)	0.372
Yes	7 (38.9)	2 (11.1)	9 (50.0)	
Micrognathia, n (%)				
No	49 (36.6)	34 (25.4)	51 (38.1)	0.416
Yes	11 (28.9)	8 (21.1)	19 (50.0)	
Macroglossia, n (%)				
No	20 (39.2)	10 (19.6)	21 (41.2)	0.582
Yes	40 (33.1)	32 (26.4)	49 (40.5)	
Large uvula, n (%)				
No	42 (37.5)	26 (23.2)	44 (39.3)	0.613
Yes	18 (30.0)	16 (26.7)	26 (43.3)	
High arched palate, n (%)				
No	42 (35.0)	26 (21.7)	52 (43.3)	0.385
Yes	18 (34.6)	16 (30.8)	18 (34.6)	
Nasal valve dehiscence, n (%)				
No	36 (35.0)	23 (22.3)	44 (42.7)	0.699
Yes	24 (34.8)	19 (27.5)	26 (37.7)	
Crossbite, n (%)				
No	48 (33.8)	34 (23.9)	60 (42.3)	0.660
Yes	12 (40.0)	8 (26.7)	10 (33.3)	
Mallampatti score, n (%)				
1-2	16 (53.3)	8 (26.7)	6 (20.0)	0.024
3-4	44 (31.0)	34 (23.9)	64 (45.1)	
Tonsil grades, n (%)				
0-2	54 (34.4)	40 (25.5)	63 (40.1)	0.579
3-4	6 (40.0)	2 (13.3)	7 (46.7)	
Hyperglycemia, n (%)				
<126	50 (34.5)	35 (24.1)	60 (41.4)	0.972
126+	8 (34.8)	6 (26.1)	9 (39.1)	
Nocturia, n (%)				
No	37 (43.5)	26 (30.6)	22 (25.9)	<0.001
Yes	23 (26.4)	16 (18.4)	48 (55.2)	
FBS, n (%)	106.0 (35.5)	112.3 (36.0)	110.5 (39.3)	0.672
Age, n (%)	49.5 (14.0)	51.8 (9.9)	49.3 (11.9)	0.539
Nocturia frequency	1.3 (1.2)	1.5 (1.7)	2.5 (1.8)	<0.001
Nocturia first episode duration (h), n (%)	3.0 (1.1)	3.1 (1.3)	2.4 (0.9)	0.021
ESS, n (%)	7.6 (4.9)	8.0 (4.9)	9.5 (4.9)	0.065
BMI, n (%)	31.4 (26.7)	29.8 (6.1)	32.9 (6.7)	0.622
Systolic blood pressure, n (%)	130.3 (16.6)	139.4 (19.0)	137.0 (24.2)	0.059
Diastolic blood pressure, n (%)	79.5 (10.3)	87.3 (12.5)	84.8 (14.0)	0.006
Waist circumference (inch), n (%)	38.4 (5.9)	40.1 (4.7)	42.5 (5.7)	<0.001
Hip circumference (inch), n (%)	40.6 (3.8)	40.7 (4.9)	43.4 (5.1)	0.001

Contd...

**Table 2: Contd...**

Variables	Mild to moderate	Severe	Very severe	P
STOPBANG, n (%)	3.9 (1.2)	4.6 (1.2)	4.8 (1.3)	<0.001
Nadir oxygen, n (%)	88.2 (8.3)	82.3 (10.5)	71.5 (16.7)	<0.001
Awake SpO <sub>2</sub> , n (%)	96.3 (1.6)	94.6 (3.8)	95.7 (2.7)	0.011

BMI: Body mass index, BP: Blood pressure, FBS: Fasting blood sugar, ESS: Epworth Sleepiness Scale, SD: Standard deviation

**Table 3: Baseline characteristics of nocturics versus nonnocturics**

Variable	Nocturia		P
	Yes	No	
Gender, n (%)			
Females	23 (59.0)	16 (41.0)	0.233
Males	64 (48.1)	69 (51.9)	
Age (years), mean±SD	52.3±11.9	47.6±12.1	0.012
Age (years), n (%)			
≤50	39 (45.3)	47 (54.7)	0.170
>50	48 (55.8)	38 (44.2)	
History of fatigability, n (%)			
No	13 (28.9)	32 (71.1)	0.001
Yes	74 (58.3)	53 (41.7)	
History of snore, n (%)			
No	2 (33.3)	4 (66.7)	0.390
Yes	85 (51.2)	81 (48.8)	
History of apnoea, n (%)			
No	36 (45.0)	44 (55.0)	0.172
Yes	51 (55.4)	41 (44.6)	
ESS, mean±SD	9.2±5.3	7.7±4.4	0.052
BMI, mean±SD	34.3±22.5	28.9±5.1	0.030
BMI >35 kg/m <sup>2</sup> , n (%)			
No	61 (45.2)	74 (54.8)	0.007
Yes	26 (70.3)	11 (29.7)	
Systolic blood pressure, mean±SD	135.1±23.1	135.4±18.2	0.914
Diastolic blood pressure, mean±SD	83.7±13.7	83.4±11.8	0.873
Hypertension (BP >140/90) or patient on antihypertensive, n (%)			
No	44 (50.0)	44 (50.0)	0.876
Yes	43 (51.2)	41 (48.8)	
SpO <sub>2</sub> , mean±SD	95.2±3.2	96.1±2.1	0.032
Neck circumference inch, mean±SD	17.0±10.7	15.6±1.3	0.244
Neck circumference >17 inches in males or >16 inch in females, n (%)			
No	64 (48.9)	67 (51.1)	0.418
Yes	23 (56.1)	18 (43.9)	
Waist circumference (inch), mean±SD	42.0±5.6	39.0±5.6	0.001
Hip circumference (inch), mean±SD	42.6±5.1	40.9±4.3	0.023
Retrognathia, n (%)			
No	76 (49.4)	78 (50.6)	0.345
Yes	11 (61.1)	7 (38.9)	
Micrognathia, n (%)			
No	64 (47.8)	70 (52.2)	0.165
Yes	23 (60.5)	15 (39.5)	
Macroglossia, n(%)			
No	25 (49.0)	26 (51.0)	0.790
Yes	62 (51.2)	59 (48.8)	
Largeuvula, n (%)			
No	55 (49.1)	57 (50.9)	0.597
Yes	32 (53.3)	28 (46.7)	
High arched palate, n (%)			
No	61 (50.8)	59 (49.2)	0.920
Yes	26 (50.0)	26 (50.0)	
Nasal valve dehiscence, n (%)			
No	52 (50.5)	51 (49.5)	0.975
Yes	35 (50.7)	34 (49.3)	
Crossbite, n (%)			
No	70 (49.3)	72 (50.7)	0.463
Yes	17 (56.7)	13 (43.3)	
Mallampatti score, n (%)			
1-2	13 (43.3)	17 (56.7)	0.382

Contd...

**Table 3: Contd...**

Variable	Nocturia		P
	Yes	No	
3-4	74 (52.1)	68 (47.9)	
Tonsil grades, n (%)			
0-2	78 (49.7)	79 (50.3)	0.445
3-4	9 (60.0)	6 (40.0)	
STOPBANG, mean±SD	4.8±1.3	4.1±1.3	0.002
Hyperglycemia, n (%)			
<126	69 (47.6)	76 (52.4)	0.050
126+	16 (69.6)	7 (30.4)	
Nadir oxygen, mean±SD	76.6±15.5	83.5±12.9	0.002
FBS, mean±SD	115.3±43.6	103.4±28.0	0.037
AHI, mean±SD	64.8±35.9	43.9±29.1	<0.001

ESS: Epworth Sleepiness Scale, BMI: Body mass index, BP: Blood pressure, FBS: Fasting blood sugar, AHI: Apnea hypopnea index, SD: Standard deviation

**Table 4: Multinomial logistic regression analysis for determinants of severity of obstructive sleep apnea**

OSA severity <sup>a</sup>	B (regression coefficient)	P	Exp(B) (OR)	95% CI for Exp(B) (OR)	
				Lower bound	Upper bound
Severe OSA					
Intercept	18.515	0.085			
ESS total	0.015	0.751	1.015	0.925	1.115
Waist circumference (inch)	0.034	0.439	1.034	0.949	1.127
SpO <sub>2</sub>	-0.217	0.046	0.805	0.650	0.996
Nocturia	-0.419	0.364	0.658	0.267	1.623
History of apnea	0.565	0.192	1.759	0.753	4.108
BMI >35 kg/m <sup>2</sup>	0.628	0.360	1.874	0.489	7.180
Hypertension	0.592	0.169	1.808	0.778	4.205
Very severe OSA					
Intercept	-2.207	0.844			
ESS total	0.036	0.402	1.036	0.953	1.127
Waist circumference (inch)	0.105	0.037	1.110	1.006	1.226
SpO <sub>2</sub>	-0.038	0.732	0.962	0.773	1.198
Nocturia	0.888	0.031	2.429	1.086	5.434
History of apnea	1.239	0.002	3.452	1.555	7.662
BMI >35 kg/m <sup>2</sup>	0.562	0.393	1.754	0.483	6.372
Hypertension	0.596	0.140	1.815	0.823	4.005

<sup>a</sup>The reference category is mild-moderate OSA group. OSA: Obstructive sleep apnea, OR: Odds ratio, ESS: Epworth Sleepiness Scale, BMI: Body mass index, CI: Confidence interval

to nonnocturics. Furthermore, nocturics had higher FBS compared to nonnocturics, ( $115.3 \pm 43.6$  vs.  $103.4 \pm 28.0$ ;  $P = 0.037$ ); however, on multivariate analysis, hyperglycemia was not found to be statistically significant.

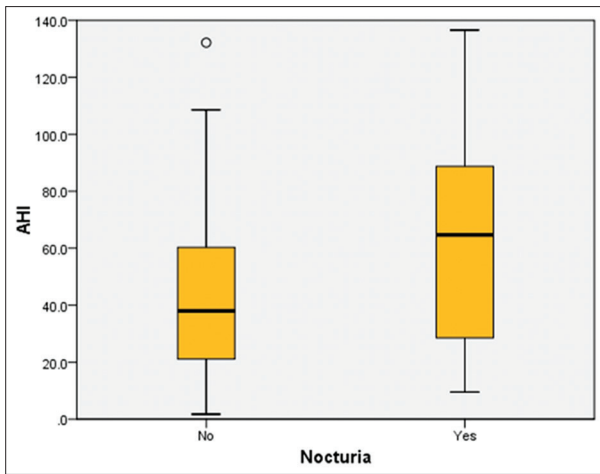
On multivariate analysis (keeping mild-moderate group as a reference), only awake SpO<sub>2</sub> was found to be statistically different in severe OSA ( $P = 0.046$ ); and only waist circumference, nocturia, and history of apnea were significant in very severe OSA group ( $P = 0.037$ ,  $0.031$ , and  $0.002$ , respectively) [Table 4].

## DISCUSSION

OSA is characterized by repetitive collapse of upper airways with airflow limitation. During apnea, several diaphragmatic contractions can occur without airflow leading to increased intrathoracic pressure as documented by Guilleminault that esophageal pressures can drop to as low as  $-80$  to  $-90$  cm H<sub>2</sub>O during apneic episode.<sup>[5]</sup> It

causes increased venous return which causes the heart to receive a false signal of volume overload leading to increased secretion of ANP. This increased ANP inhibits the secretion of aldosterone, vasopressin, anti-diuretic hormone (ADH), and rennin-angiotensin system. It leads to increased sodium and water excretion by 2.5 and 3.5 times normal rate, respectively. Adding to this insult is hypoxemia caused by OSA which leads to increased pulmonary vasoconstriction which further increases load over the heart. Although nocturia has been known to be associated with OSA, its association with severity of OSA has been documented only in few studies. It has been recently documented in a meta-analysis that CPAP treatment effectively reduces nocturia.<sup>[6]</sup>

Tikkinen *et al.* showed that voiding only once per night is not a suitable criterion for clinically relevant nocturia.<sup>[10]</sup> Hence, for this study, we defined nocturia as urination frequency  $>1$ /night. Not all patients of OSA develop nocturia; in our study, around 80% of patients void at least once and around 50% of patients void at least twice per night.



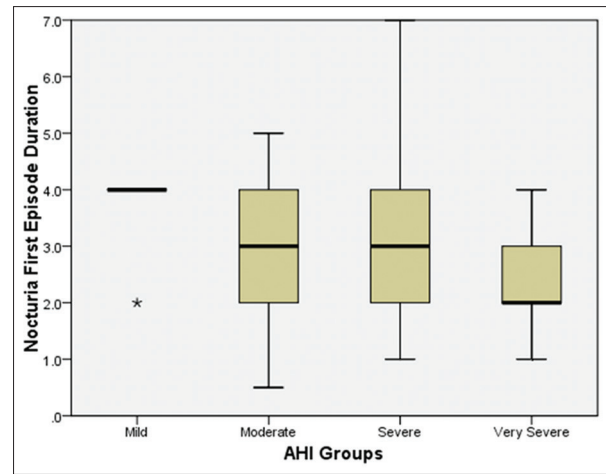
**Figure 1:** Box and whisker plot of apnea–hypopnea index among obstructive sleep apnea patients with and without nocturia

Our study showed that nocturia (urination frequency  $\geq 2$ ) is strongly associated with very severe OSA (AHI  $>60$ ) and frequency of urination is also associated with the severity of OSA. The patients with very severe OSA were going to washroom earlier than severe and mild-moderate group patients [Figure 2].

Nocturic OSA patients in this study were shown to be more obese, more sleepy, with higher STOP-BANG and more importantly higher AHI and lower nadir SpO<sub>2</sub> during PSG. This suggests that OSA patient with nocturia is a phenotype of OSA and these patients are sicker compared to nonnocturic OSA counterparts.

Similar findings were made by Plywaczewski *et al.* where they found nocturic OSA patients had higher AHI, higher BMI, higher ESS, and lower mean overnight SpO<sub>2</sub> on univariate analysis.<sup>[8]</sup> Although on multivariate analysis, in their study, only AHI, ESS, and coronary heart disease had a positive correlation with nocturia. Similarly, Raheem *et al.* compared OSA with nocturia (nocturnal urinary frequency one or more) versus OSA without nocturics to identify the predictors of nocturia and they found age  $>70$  and higher AHI to be predictors of nocturia.<sup>[9]</sup>

Although the presence of diabetes mellitus is one of the known causes of nocturia, in this study, FBS was not found to be a significant factor in the multivariate analysis. Patients, who were on diuretics, had deranged liver function tests or renal function tests, had history suggested of urinary tract infection, or neurological problems were excluded from the study. Congestive heart failure and prostatomegaly have been associated with nocturia; we did not do echocardiography and ultrasonography kidney, ureter, and bladder in our study, and this is one of the limitations of this study. Another limitation of this study was that we did not ask about consumption of the last meal and timing of urination before going to bed as this can affect micturition at night.



**Figure 2:** Box and whisker plot showing difference in time to first urination after sleep in different categories of obstructive sleep apnea

After multivariate analysis of factors associated with very severe OSA in our study, we found only three factors (waist circumference, history of apnea, and nocturia) to be statistically significant. Among these factors, a history of apnea is already included in the STOP-BANG questionnaire, and elevated waist circumference is also a marker for obesity which is also considered a risk factor for OSA. Nocturia has been a neglected symptom in screening tools of OSA. Romero *et al.* showed that nocturia is comparable with snoring as a screening tool for OSA in population of 1007 subjects.<sup>[7]</sup> In his study, the positive predictive value of snoring and nocturia for OSA was 85% and 81%, respectively. With multinomial logistic regression, patient-reported nocturia frequency predicted AHI above and beyond BMI, sex, age, and self-reported snoring ( $P < 0.0001$ ).

Although our study was done in only OSA patients, since nocturia in this study was significantly associated with very severe OSA, we strongly believe nocturia to be a very specific indicator of severe OSA even among normal population. Other important point, which can have wider implications in screening of OSA, is that since nocturia points toward very severe OSA; inclusion of nocturia in screening questionnaire should increase the specificity of questionnaires in the prediction of OSA.

Therefore, we suggest that all suspected patients of OSA should be screened for nocturia and vice versa; all nocturic patients should be screened for OSA. We believe that the history of nocturia ( $\geq 2$ /night) will help in screening very severe OSA among less severe OSA patients in community setting, however, this needs to be verified in large community-based studies.

## CONCLUSIONS

A history of nocturia ( $\geq 2$ /night) predicts very severe OSA (AHI  $>60$ ). Nocturic OSA is a phenotype of OSA with

more severe AHI, lower oxygen levels, higher BMI, and higher ESS. We believe nocturia can be used for screening in OSA questionnaires, which needs to be validated in further community-based studies.

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### Conflicts of interest

There are no conflicts of interest.

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