Asian Journal of Urology 11 (2024) 486–496

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ajur

Original Article

Effect of nocturia in patients with different severity of obstructive sleep apnea on polysomnography: A retrospective observational study

Chin-Heng Lu [a,b,c,1], Hung-Min Chang [d,1], Kuang-Hsi Chang [e,f,g], Yen-Chuan Ou [a,h], Chao-Yu Hsu [a,b,c], Min-Che Tung [a,i], Frank Cheau-Feng Lin [j,k,*], Stella Chin-Shaw Tsai [d,h,*]

[a] *Division of Urology, Department of Surgery, Tungs' Taichung Metroharbor Hospital, Taichung, Taiwan, China*
[b] *Rong Hsing Research Center for Translational Medicine, Chung Hsing University, Taichung, Taiwan, China*
[c] *College of Life Sciences, Chung Hsing University, Taichung, Taiwan, China*
[d] *Department of Otolaryngology, Tungs' Taichung Metroharbor Hospital, Taichung, Taiwan, China*
[e] *Department of Medical Research, Tungs' Taichung Metroharbor Hospital, Taichung, Taiwan, China*
[f] *General Education Center, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, Taiwan, China*
[g] *Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan, China*
[h] *Department of Post-Baccalaureate Medicine, College of Medicine, Chung Hsing University, Taichung, Taiwan, China*
[i] *Department of Nursing, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, Taiwan, China*
[j] *Department of Surgery, Chung Shan Medical University, Taichung, Taiwan, China*
[k] *College of Medicine, Chung Shan Medical University, Taichung, Taiwan, China*

Received 19 July 2022; accepted 20 February 2023
Available online 20 July 2023

KEYWORDS
Nocturia;

Abstract *Objective:* Obstructive sleep apnea (OSA) is one of the etiologies of nocturia. We analyzed polysomnography (PSG) results to determine correlated factors related to nocturia in OSA patients with different severity.

* Corresponding author. Department of Surgery, Chung Shan Medical University, Taichung, Taiwan, China (F. Cheau-Feng Lin); Department of Otolaryngology, Tungs' Taichung Metroharbor Hospital, Taichung, Taiwan, China (S. Chin-Shaw Tsai)
E-mail address: frnklin@gmail.com (F. Cheau-Feng Lin), t5722@ms.sltung.com.tw (S. Chin-Shaw Tsai).
Peer review under responsibility of Tongji University.
[1] Both authors contributed equally.

https://doi.org/10.1016/j.ajur.2023.02.003

Obstructive sleep apnea;
Polysomnography;
Apnea–hypopnea index;
International Prostate Symptom Score

Methods: Patients with suspected OSA were examined using PSG. They were divided into two groups based on the presence of nocturia. Nocturia was defined as a patient who needed to void at least once. Apnea–hypopnea index (AHI) was employed to classify patients according to degrees of severity: AHI<5 events/h, 5 events/h≤AHI<15 events/h, 15 events/h≤AHI<30 events/h, and AHI≥30 events/h, defined as normal, mild OSA, moderate OSA, and severe OSA, respectively. Demographic variables, PSG parameters, International Prostate Symptom Scores (IPSSs), and quality of life scores due to urinary symptoms were analyzed.
Results: In total 140 patients, 114 patients had OSA (48 had mild OSA; 34 had moderate OSA; and 32 had severe OSA) and 107 patients had nocturia. The total IPSS was significantly higher in nocturia patients in all groups except the group of severe OSA patients. With the increasing severity of OSA, more correlated factors related to nocturia were determined. In mild OSA patients, nocturia related to increased age ($p=0.025$), minimum arterial blood oxygenation saturation ($p=0.046$), and decreased AHI of non-rapid eye movement ($p=0.047$), AHI of total sleep time ($p=0.010$), and desaturation index ($p=0.012$). In moderate OSA patients, nocturia related to increased age ($p<0.001$), awake time ($p=0.025$), stage 1 sleep ($p=0.033$), and sleep latency ($p=0.033$), and decreased height ($p=0.044$), weight ($p=0.025$), and sleep efficiency ($p=0.003$). In severe OSA patients, nocturia related to increased weight ($p=0.011$), body mass index ($p=0.009$), awake time ($p=0.008$), stage 1 sleep ($p=0.040$), arousal number ($p=0.030$), arousal index ($p=0.013$), periodic limb movement number ($p=0.013$), and periodic limb movement index ($p=0.004$), and decreased baseline arterial blood oxygenation saturation ($p=0.046$).
Conclusion: Our study revealed that there were more correlated factors related to nocturia with increasing severity of OSA. This study helps in clinical education and treatment for OSA patients with different severity.

1. Introduction

According to the Standardization Subcommittee of the International Continence Society Committee on standardization of terminology in lower urinary tract function, the current definitions of nocturia is the complaint that the individual has to wake at night one or more times to void [1].

Increased nocturnal urine volume and vesical instability are the two main causes of nocturia [2]. Nocturia is one of the most common lower urinary tract symptoms that impairs quality of life, general health, daily productivity, and quality of sleep [3]. The prevalence and severity of nocturia increase with age [4]. More attention is required for elderly patients with deterioration of nocturia because it interferes with life and sleep quality, and increases the risk of falls and fractures [5,6].

There are three categories of nocturia etiologies: nocturnal bladder capacity reduction, 24-h global polyuria, and nocturnal polyuria. These three causes can act independently or in combination to induce nocturia [2]. Obstructive sleep apnea (OSA) is an etiology of nocturnal polyuria [7]. Two theories explain how OSA induces nocturia. First, airway obstruction due to OSA leads to negative thoracic pressure. Venous return to the right atrium of heart is increased, which results in atrial natriuretic peptide (ANP) secretion. Finally, ANP increases urine production and causes nocturia [8]. Second, hypoxia due to OSA increases pulmonary vasoconstriction and right atrial transmural pressure, resulting in increased ANP secretion and subsequently nocturia [9].

OSA severity can be classified into four categories based on the apnea–hypopnea index (AHI): normal, mild OSA, moderate OSA, and OSA. They are defined as AHI<5 events/h, 5 events/h≤AHI<15 events/h, 15 events/h≤AHI<30 events/h, and AHI≥30 events/h, respectively. The AHI is an index used to indicate the severity of sleep apnea. It is represented by the number of apnea and hypopnea events per hour of sleep and is calculated by dividing the number of apnea events by the number of hours of sleep [10,11].

The association of nocturia with OSA has been reported in many studies. A positive correlation exists between the severity of OSA and the incidence of nocturia [12–14]. A nocturia patient can have more than one etiology at a time [2]. Most of these articles focus on how OSA affects nocturia, and the severity of OSA increasing the incidence of nocturia was reported [12,13].

To our knowledge, there are no studies that have focused on how nocturia affects different severity levels of OSA. The goal of our study was to evaluate the association between nocturia and different severity of OSA and to investigate how nocturia affects the polysomnography (PSG) parameters in patients according to the different severity of OSA. Most studies did not classify OSA patients according to the AHI level or analyze the PSG results of patients with different OSA severity. Therefore, the PSG results of male patients with different types of OSA were reviewed in Tungs' Taichung Metroharbor Hospital and parameters were analyzed according to the presence or absence of nocturia of these men.

2. Patients and methods

2.1. Patients

This retrospective study included consecutive patients treated between January 2019 and January 2021 at Tungs' Taichung Metroharbor Hospital. A total of 140 patients who underwent PSG for suspected OSA were enrolled in the study. All patients were over or equal to 19 years of age and without urinary tract infections. Exclusion criteria included patients under 19 years of age, patients under urological medical treatment, and patients with urinary tract infections. Nocturia was defined as a patient who needed to void at least once, and each void was preceded and followed by sleep [1]. Nocturia was recorded in PSG as interruption of sleep.

Baseline characteristics and results of PSG were compared between patients with nocturia (nocturia group) and patients without nocturia (control group). Parameters included age, height, weight, body mass index (BMI), International Prostate Symptom Score (IPSS), rapid eye movement (REM), non-rapid eye movement (NREM), total sleep time (TST), time in bed, sleep period time, awake time, stage 1 sleep cycle, stage 2 sleep cycle, stage 3 sleep cycle, sleep efficiency, sleep latency, arousal number, arousal index, baseline arterial blood oxygenation saturation (SaO_2), mean SaO_2, minimum SaO_2, and desaturation index. In-lab overnight PSG (Allis 5; Respironics, Murrysville, PA, USA) was performed to diagnose the presence of OSA. Briefly, respiratory events were diagnosed as apnea or hypopnea, and the AHI was calculated as the total number of events per hour of sleep. AHI was classified into four categories as normal, mild OSA, moderate OSA, and severe OSA. They are defined as AHI$<$5 events/h, 5 events/h$\leq$AHI$<$15 events/h, 15 events/h$\leq$AHI$<$30 events/h, and AHI$\geq$30 events/h, respectively. All PSG parameters and recordings were measured by trained sleep technologists, according to the criteria of the American Academy of Sleep Medicine manual [15].

2.2. Statistical analysis

In this study, the Student *t*-test was used for continuous variables, the Chi-square test for categorical variables, and PSG values according to presence or absence of nocturia. All data were expressed as means with standard deviations (SDs). To further understand the influence of non-normally distributed data or ordinal scales, which might not meet the assumptions required for parametric testing, we employed the Mann–Whitney *U* test. This nonparametric test was used to compare differences in PSG parameters, IPSS scores, and quality of life indices between OSA patients with and without nocturia. Multivariate logistic regression models were used to determine associations between nocturia and demographic variables, PSG parameters, IPSSs, and quality of life scores due to urinary symptoms, stratified by different OSA severity. SPSS 20.0 for Windows (IBM, Chicago, IL, USA) was used for all the statistical analyses. A *p*-value of less than 0.05 was considered statistically significant.

2.3. Ethics statement

The study was performed in agreement with applicable laws and regulations, good clinical practices, and ethical principles as described in the Declaration of Helsinki. This study was approved by the Institutional Review Board of Tungs' Taichung Metroharbor Hospital (approval number: 109006). The requirement for informed consent was waived due to the retrospective nature of the study.

3. Results

Of the 140 male patients included in this study, 114 patients had OSA and 107 patients had nocturia. According to the PSG results, 48 patients had mild OSA; 34 patients had moderate OSA; and 32 patients had severe OSA. IPSSs were significantly higher for nocturia patients, in all patients ($p<0.001$), normal patients (AHI$<$5 events/h; $p=0.008$), OSA patients (AHI$\geq$5 events/h; $p=0.001$), mild OSA patients ($p=0.019$), moderate OSA patients ($p=0.025$), except severe OSA patients ($p=0.345$). Quality of life was significantly worse for nocturia patients in all patients ($p<0.001$), normal patients ($p=0.006$), OSA patients ($p<0.001$), and severe patients ($p=0.022$), except mild and moderate OSA patients ($p=0.056$ and 0.055, respectively). Residual sensation was significantly higher in severe OSA patients with nocturia ($p=0.030$). In all patients, IPSSs of voiding and storage symptoms including frequency ($p=0.029$), intermittent ($p=0.038$), urgency ($p=0.044$), and weak stream ($p=0.038$) were significantly higher for nocturia patients. In OSA patients, IPSSs of only the storage symptoms including frequency ($p=0.023$) and urgency ($p=0.040$) were significantly higher for nocturia patients. The severity of nocturia has an increasing trend with the severity of OSA, though it was not statistically significantly ($p=0.251$). The mean IPSSs for nocturia patients were 1.58 (SD 0.90), 1.71 (SD 0.77), 1.56 (SD 0.89), 1.41 (SD 0.74), 1.72 (SD 0.80), 1.96 (SD 1.79) in all patients, normal patients, OSA patients, mild OSA patients, moderate OSA patients, and severe OSA patients, respectively.

Correlated factors related to nocturia were analyzed. In Table 1, analysis of all patients revealed that there were ten significant correlated factors. Nocturia patients were significantly older ($p<0.001$), had increased AHI of NREM and TST ($P=0.020$ and 0.021, respectively), awake time ($p=0.023$), stage 1 sleep ($p=0.013$), arousal number ($p=0.011$), arousal index ($p<0.001$), desaturation index ($p=0.019$), and significantly decreased stage 3 sleeping ($p=0.002$) and sleep efficiency ($p=0.019$).

In Table 2, analysis of normal patients revealed that there were only two significant correlated factors. Nocturia patients were older ($p=0.045$) and had significantly decreased BMI ($p=0.025$). In OSA patients, there were nine significant correlated factors. Nocturia patients were older ($p<0.001$), had longer awake time ($p=0.005$), stage 1 sleep ($p=0.003$), arousal number ($p=0.006$), arousal index ($p=0.002$), periodic limb movement (PLM) number ($p=0.016$), and PLM index ($p=0.011$), and significantly decreased stage 3 sleeping ($p=0.014$), and sleep efficiency

Table 1 Analysis of variables for patients with and without nocturia in all patients.

Variable	With nocturia ($n=107$)	Without nocturia ($n=33$)	p-Value[a]
Age, year	45.82±13.46	34.00±9.08	<0.001*
Height, cm	170.37±8.09	172.41±6.39	0.187
Weight, kg	82.22±15.91	85.45±16.26	0.312
BMI, kg/m^2	28.16±4.43	28.66±4.58	0.577
AHI, events/h			
REM	27.60±21.82	22.12±16.36	0.186
NREM	21.96±24.08	13.66±15.09	0.020*
TST	22.86±23.16	15.01±14.23	0.021*
Sleep time, min			
Time in bed	450.86±51.47	455.39±36.57	0.639
Sleep period	416.47±60.25	427.83±39.67	0.311
TST	372.88±65.84	395.86±41.83	0.061
Sleep cycle, %			
Awake time	11.06±8.58	7.40±5.55	0.023*
Stage 1 sleep	17.74±8.03	13.85±6.81	0.013*
Stage 2 sleep	48.24±10.73	47.50±9.61	0.724
Stage 3 sleep	16.96±8.23	20.93±5.31	0.002*
REM	16.91±6.43	17.73±6.54	0.525
Sleep efficiency, %	82.02±11.40	86.95±6.07	0.019*
Sleep latency, min	15.80±15.84	16.30±9.70	0.863
Arousal			
Total events in sleep	94.09±73.67	59.36±41.10	0.011*
Index, events/h	16.62±13.60	9.54±7.16	<0.001*
SaO_2, %			
Baseline	96.10±1.87	96.52±1.89	0.271
Mean	90.19±3.87	91.27±2.70	0.135
Minimum	79.44±11.44	81.82±7.49	0.264
Desaturation index, events/h	23.00±23.41	14.99±14.24	0.019*
Snore			
Total events in sleep	796.36±567.47	773.97±529.01	0.841
Index, events/h	125.27±84.36	118.68±82.88	0.694
PLM[b]			
Total events in sleep	20.71±25.63	14.86±15.93	0.321
Index, events/h	3.36±4.64	2.34±2.75	0.336
IPSS			
Residual sensation	1.21±1.34	1.09±1.26	0.664
Urinary frequency	1.45±1.15	0.94±1.20	0.029*
Intermittent	0.75±1.18	0.30±0.53	0.038*
Urinary urgency	0.52±1.11	0.12±0.42	0.044*
Weak stream	0.70±1.20	0.24±0.66	0.038*
Straining	0.40±0.90	0.21±0.65	0.253
Nocturia	1.58±0.90	0.00±0.00	<0.001*
Total	6.61±4.62	2.91±2.28	<0.001*
Quality-of-life score due to urinary symptoms	2.05±1.68	0.61±0.10	<0.001*

BMI, body mass index; AHI, apnea–hypopnea index; IPSS, International Prostate Symptom Score; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; PLM, periodic limb movement; PSG, polysomnography; REM, rapid eye movement; SaO_2, arterial blood oxygenation saturation; TST, total sleep time.

Note: values are presented as mean±standard deviation.

[a] p-Value for independent samples t-test.

[b] $n=83$ for patients with nocturia and $n=21$ for patients without nocturia.

* Significant risk factor: $p<0.05$.

($p=0.010$). In addition, multivariate analysis was performed on the age, BMI, and significant risk factors of normal patients including IPSS and quality-of-life score; there was no significant correlation. For OSA patients with AHI of 5 or greater, results from multivariate analysis showed that significant factors included age and quality-of-life score (data not shown).

Table 3 showed that in the mild OSA patients, there were five significant correlated factors. Nocturia patients were older ($p<0.001$), and had higher minimum SaO_2 ($p=0.046$) and significantly decreased AHI of NREM ($p=0.047$), AHI of TST ($p=0.010$), and desaturation index ($p=0.012$).

Table 4 revealed that in the moderate OSA patients, there were seven significant correlated factors. Nocturia patients

Table 2 Analysis of normal and OSA patients with and without nocturia.

Parameter of PSG	AHI<5: normal patients			AHI≥5: OSA patients		
	With nocturia (n=17)	Without nocturia (n=9)	p-Value	With nocturia (n=90)	Without nocturia (n=24)	p-Value[a]
Age, year	40.59±3.29	29.67±4.01	0.045*	46.81±1.40	35.63±1.50	<0.001*
Height, cm	170.94±2.02	171.44±2.53	0.792	170.26±0.85	172.77±1.23	0.209
Weight, kg	73.68±3.40	82.56±4.22	0.051	83.84±1.67	86.54±3.58	0.914
BMI, kg/m^2	25.18±1.01	27.97±0.89	0.025*	28.72±0.45	28.92±1.05	0.684
AHI, events/h						
REM[b]	5.47±0.88	9.86±2.10	0.096	31.29±2.26	26.71±3.40	0.387
NREM	1.99±0.29	1.76±0.33	0.634	25.73±2.58	18.13±3.16	0.357
TST	2.46±0.33	2.84±0.44	0.426	26.71±2.46	19.57±2.90	0.442
Sleep time, min						
Time in bed	425.71±24.82	456.33±14.27	0.263	455.61±3.54	455.04±7.14	0.936
Sleep period	380.09±26.98	421.78±16.37	0.263	423.34±4.47	430.10±7.45	0.449
TST	323.50±25.77	377.94±15.50	0.241	382.21±5.35	402.58±7.93	0.062
Sleep cycle, %						
Awake time	17.70±3.06	10.06±2.74	0.051	9.81±0.74	6.40±0.81	0.005*
Stage 1 sleep	22.18±2.43	19.13±2.02	0.958	16.90±0.78	11.87±1.24	0.003*
Stage 2 sleep	44.69±2.05	41.73±3.34	0.312	48.91±1.16	49.66±1.78	0.569
Stage 3 sleep	19.65±2.10	22.88±1.52	0.396	16.45±0.85	20.20±1.12	0.014*
REM	13.48±1.77	16.26±2.22	0.525	17.56±0.64	18.28±1.34	0.571
Sleep efficiency, %	72.49±4.29	82.96±2.59	0.058	83.82±0.93	88.45±0.95	0.010*
Sleep latency, min	20.82±3.94	21.44±3.53	0.634	14.85±1.65	14.38±1.80	0.426
Arousal						
Total events in sleep	39.00±9.51	48.89±14.45	0.426	104.50±7.82	63.29±8.26	0.006*
Index, events/h	7.94±1.63	8.96±3.02	0.958	18.26±1.47	9.75±1.33	0.002*
SaO_2, %						
Baseline	97.18±0.31	97.22±0.55	0.672	95.90±0.20	96.25±0.40	0.253
Mean	94.47±0.34	93.78±0.52	0.263	89.38±0.38	90.33±0.50	0.321
Minimum	89.47±0.78	88.89±0.73	0.458	77.54±1.21	79.17±1.44	0.772
Desaturation index, events/h	2.46±0.33	2.84±0.44	0.426	26.88±2.49	19.55±2.90	0.430
Snore						
Total events in sleep	387.94±105.49	376.00±134.82	1.000	873.50±58.84	923.21±101.50	0.536
Index, events/h	66.98±15.79	64.29±24.30	0.634	136.29±8.78	139.08±15.96	0.773
PLM						
Total events in sleep[c]	13.90±4.02	27.00±18.18	0.839	21.64±3.14	12.00±1.18	0.016*
Index[c], events/h	2.67±0.68	4.53±3.11	0.839	3.46±0.57	1.82±0.21	0.011*
IPSS						
Residual sensation	1.41±1.58	0.56±0.88	0.148	1.17±1.30	1.29±1.33	0.678
Urinary frequency	1.18±0.88	1.11±1.36	0.883	1.50±1.19	0.88±1.15	0.023*
Intermittent	0.88±1.11	0.22±0.44	0.102	0.72±1.20	0.33±0.57	0.126
Urinary urgency	0.53±1.07	0.33±0.71	0.626	0.52±1.12	0.04±0.20	0.040*
Weak stream	1.06±1.56	0.22±0.67	0.140	0.63±1.12	0.25±0.68	0.112
Straining	0.53±1.01	0.22±0.67	0.420	0.38±0.89	0.21±0.66	0.382
Nocturia	1.71±0.77	0.00±0.00	<0.001*	1.56±0.89	0.00±0.00	<0.001*
Total	7.29±4.44	2.67±2.29	0.008*	6.48±4.66	3.00±2.32	0.001*
Quality-of-life score due to urinary symptoms	2.59±1.62	0.78±1.09	0.006*	1.94±1.68	0.54±0.98	<0.001*

BMI, body mass index; AHI, apnea–hypopnea index; IPSS, International Prostate Symptom Score; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; PLM, periodic limb movement; PSG, polysomnography; REM, rapid eye movement; SaO_2, arterial blood oxygenation saturation; TST, total sleep time.

Note: values are presented as mean±standard deviation.

[a] p-Value for Mann–Whitney test.

[b] n=15 for normal patients (AHI<5 events/h) with nocturia.

[c] n=10 for normal patients (AHI<5 events/h) with nocturia and n=4 without nocturia; n=73 for OSA patients (AHI≥5 events/h) with nocturia and n=17 without nocturia.

* Significant risk factor: p<0.05.

Table 3 Analysis of mild OSA patients (5 events/h≤AHI<15 events/h) with and without nocturia.

Parameter of PSG	With nocturia ($n=34$)	Without nocturia ($n=14$)	p-Value[a]
Age, year	44.85±2.60	35.86±2.32	0.025*
Height, cm	168.44±1.78	172.29±1.90	0.317
Weight, kg	77.65±2.75	84.57±4.66	0.340
BMI, kg/m^2	27.04±0.64	28.44±1.39	0.634
AHI, events/h			
REM	16.88±1.78	18.22±3.19	0.847
NREM	5.86±0.53	8.66±1.26	0.047*
TST	7.91±0.53	10.37±0.87	0.010*
Sleep time, min			
Time in bed	459.41± 5.75	455.29±9.11	0.489
Sleep period	426.07±6.22	425.96±10.15	0.847
TST	386.43±6.92	392.89±10.34	0.634
Sleep cycle, %			
Awake time	9.31±0.93	7.73±1.16	0.401
Stage 1 sleep	16.38±1.08	13.51±1.60	0.156
Stage 2 sleep	43.79±1.56	47.10±2.42	0.204
Stage 3 sleep	21.74±1.14	22.56±1.02	0.329
REM	17.63±1.12	16.84±2.00	0.700
Sleep efficiency, %	84.21±1.30	86.28±1.30	0.540
Sleep latency, min	14.10±1.59	18.25±2.54	0.102
Arousal			
Total events in sleep	68.71±7.19	51.93±10.44	0.192
Index, events/h	11.43±1.27	8.52±1.81	0.200
SaO_2, %			
Baseline	96.59±0.26	96.71±0.38	0.662
Mean	92.00±0.36	91.71±0.42	0.355
Minimum	83.94±0.82	82.64±0.75	0.046*
Desaturation index, events/h	7.98±0.53	10.34±0.88	0.012*
Snore			
Total events in sleep	708.56±96.50	832.14±127.16	0.238
Index, events/h	108.74±14.48	130.40±21.03	0.286
PLM			
Total events in sleep[b]	27.00±9.08	12.60±1.54	0.322
Index[b], events/h	4.43±1.68	2.00±0.29	0.467
IPSS			
Residual sensation	1.32±1.47	1.07±1.07	0.565
Urinary frequency	1.38±0.99	0.79±1.12	0.073
Intermittent	0.62±1.05	0.36±0.63	0.391
Urinary urgency	0.21±0.54	0.00±0.00	0.162
Weak stream	0.38±0.85	0.29±0.73	0.712
Straining	0.35±0.88	0.29±0.83	0.808
Nocturia	1.41±0.74	0.00±0.00	<0.001*
Total	5.68±4.19	2.79±2.16	0.019*
Quality-of-life score due to urinary symptoms	1.41±1.48	0.57±0.94	0.056

BMI, body mass index; AHI, apnea–hypopnea index; IPSS, International Prostate Symptom Score; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; PLM, periodic limb movement; PSG, polysomnography; REM, rapid eye movement; SaO_2, arterial blood oxygenation saturation; TST, total sleep time.
Note: values are presented as mean±standard deviation.
[a] p-Value for Mann–Whitney test.
[b] $n=24$ for mild OSA patients (5 events/h≤AHI<15 events/h) with nocturia and $n=10$ without nocturia.
* Significant risk factor: $p<0.05$.

had significantly older age ($p=0.000$), and increased awake time ($p=0.025$), stage 1 sleep ($p=0.033$), and sleep latency ($p=0.033$), and decreased height ($p=0.044$), weight ($p=0.025$), and sleep efficiency ($p=0.003$).

In the severe OSA patients shown in Table 5, there were nine significant correlated factors. Nocturia patients had significantly higher weight ($p=0.011$), BMI ($p=0.009$), and increased awake time ($p=0.008$), stage 1 sleep ($p=0.040$), arousal number ($p=0.030$), arousal index ($p=0.013$), PLM number ($p=0.013$) and index ($p=0.004$), and decreased baseline SaO_2 ($p=0.046$).

Table 4 Analysis of moderate OSA patients (15 events/h≤AHI<30 events/h) with and without nocturia.

Parameter of PSG	With nocturia ($n=29$)	Without nocturia ($n=5$)	p-Value[a]
Age, year	51.10±1.93	32.40±2.25	<0.001*
Height, cm	169.40±1.01	174.40±1.81	0.044*
Weight, kg	82.47±2.35	99.60±8.98	0.025*
BMI, kg/m^2	28.72±0.79	32.68±2.61	0.163
AHI, events/h			
REM	28.97±2.51	33.02±8.17	0.603
NREM	20.24±0.86	21.80±1.97	0.539
TST	21.52±0.74	23.70±1.34	0.232
Sleep time, min			
Time in bed	456.59±4.89	436.80±15.96	0.295
Sleep period	422.67±6.40	421.10±15.67	0.962
TST	372.09±10.18	395.40±14.38	0.393
Sleep cycle, %			
Awake time	12.16±1.79	6.06±1.17	0.025*
Stage 1 sleep	19.98±1.54	10.92±3.10	0.033*
Stage 2 sleep	46.21±1.63	51.50±3.82	0.232
Stage 3 sleep	16.14±1.34	19.40±2.32	0.367
REM	17.66±1.05	18.20±1.26	0.925
Sleep efficiency, %	81.38±1.92	90.54±0.94	0.003*
Sleep latency, min	17.00±2.91	6.80±0.92	0.033*
Arousal			
Total events in sleep	95.97±11.35	70.00±17.48	0.420
Index, events/h	17.33±2.45	10.82±3.09	0.318
SaO_2, %			
Baseline	95.86±0.33	94.40±1.17	0.179
Mean	89.62±0.43	89.00±1.26	1.000
Minimum	76.34±2.87	75.40±4.82	0.637
Desaturation index, events/h	21.52±0.74	23.70±1.34	0.232
Snore			
Total events in sleep	901.72±107.58	1025.40±308.09	0.603
Index, events/h	145.45±16.11	153.00±47.46	0.637
PLM			
Total events in sleep[b]	19.00±2.60	14.00±1.00	0.889
Index[b], events/h	3.03±0.40	2.15±0.25	0.889
IPSS			
Residual sensation	1.28±1.28	1.00±1.23	0.657
Urinary frequency	1.79±1.21	1.20±1.30	0.323
Intermittent	1.10±1.37	0.20±0.45	0.159
Urinary urgency	0.83±1.49	0.20±0.45	0.362
Weak stream	0.83±1.23	0.40±0.89	0.464
Straining	0.45±0.91	0.00±0.00	0.285
Nocturia	1.72±0.80	0.00±0.00	<0.001*
Total	8.00±4.59	3.00±2.65	0.025*
Quality-of-life score due to urinary symptoms	2.55±1.64	1.00±1.41	0.055

BMI, body mass index; AHI, apnea–hypopnea index; IPSS, International Prostate Symptom Score; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; PLM, periodic limb movement; PSG, polysomnography; REM, rapid eye movement; SaO_2, arterial blood oxygenation saturation; TST, total sleep time.

Note: values are presented as mean±standard deviation.

[a] p-Value for Mann–Whitney test.

[b] $n=25$ for moderate OSA patients (15 events/h≤AHI<30 events/h) with nocturia and $n=2$ without nocturia.

* Significant risk factor: $p<0.05$.

The total IPSS ($p<0.001$) and quality of life ($p<0.001$) were both significantly higher for nocturia patients in the category of all patients. In severe OSA patients, the total IPSS was not statistically significant ($p=0.345$). Quality of life was significantly worse for nocturia patients, except in mild and moderate OSA patients ($p=0.056$ and 0.055, respectively). The urinary residual sensation was also significant higher in severe OSA patients with nocturia ($p=0.030$).

In summary, baseline SaO_2 decreased significantly in severe OSA patients with nocturia ($p=0.046$). Age was a

Table 5 Analysis of severe OSA patients (AHI≥30 events/h) with and without nocturia.

Parameter of PSG	With nocturia (n=27)	Without nocturia (n=5)	p-Value[a]
Age, year	44.67±2.48	38.20 ±1.96	0.220
Height, cm	173.48±1.21	172.50±2.21	0.763
Weight, kg	93.10±2.81	79.00±3.96	0.011*
BMI, kg/m^2	30.84±0.79	26.48±0.91	0.009*
AHI, events/h			
REM	51.93±4.37	44.18±4.87	0.418
NREM	56.64±4.20	40.98±7.83	0.098
TST	55.96±4.09	41.18±6.54	0.098
Sleep time, min			
Time in bed	449.78±7.79	472.60±15.36	0.183
Sleep period	420.63±10.87	450.70±14.44	0.310
TST	387.78±11.15	436.90±13.50	0.060
Sleep cycle, %			
Awake time	7.91±0.86	3.04±0.59	0.008*
Stage 1 sleep	14.26±1.26	8.22±1.99	0.040*
Stage 2 sleep	58.25±1.88	55.00±2.57	0.650
Stage 3 sleep	10.13±1.14	14.36±2.62	0.109
REM	17.36±1.19	22.40±2.39	0.122
Sleep efficiency, %	85.93±1.58	92.46±0.61	0.053
Sleep latency, min	13.48±4.12	11.10±1.56	0.545
Arousal			
Total events in sleep	158.74±16.94	88.40±18.07	0.030*
Index, events/h	27.88±3.06	12.14±2.59	0.013*
SaO_2, %			
Baseline	95.07±0.41	96.80±0.73	0.046*
Mean	85.81±0.66	87.80±0.37	0.335
Minimum	70.78±1.50	73.20±2.76	0.687
Desaturation index, events/h	56.43±4.17	41.18±6.54	0.098
Snore			
Total events in sleep	1050.89±93.16	1076.00±167.40	0.841
Index, events/h	161.13±13.46	149.48±25.06	0.841
PLM			
Total events in sleep[b]	19.04±1.50	10.00±2.55	0.013*
Index[b], events/h	2.93±0.24	1.34±0.32	0.004*
IPSS			
Residual sensation	2.20±1.92	0.85±1.06	0.030*
Urinary frequency	1.33±1.39	0.80±1.30	0.432
Intermittent	0.44±1.12	0.40±0.55	0.932
Urinary urgency	0.59±1.15	0.00±0.00	0.265
Weak stream	0.74±1.26	0.00±0.00	0.204
Straining	0.33±0.88	0.20±0.45	0.745
Nocturia	1.96±1.79	0.00±0.00	0.005*
Total	5.85±5.05	3.60±2.88	0.345
Quality-of-life score due to urinary symptoms	1.56±1.12	0.00±0.00	0.022*

BMI, body mass index; AHI, apnea–hypopnea index; IPSS, International Prostate Symptom Score; NREM, non-rapid eye movement; OSA, obstructive sleep apnea; PLM, periodic limb movement; PSG, polysomnography; REM, rapid eye movement; SaO_2, arterial blood oxygenation saturation; TST, total sleep time.

Note: values are presented as mean±standard deviation.

[a] p-Value for Mann–Whitney test.

[b] n=24 for severe OSA patients (AHI≥30 events/h) with nocturia.

* Significant risk factor: $p<0.05$.

significant correlated factor for nocturia patients in all categories of patients, except in severe OSA patients. Awake time and stage 1 sleep increased significantly for nocturia patients, in the categories of all patients, OSA patients, moderate OSA patients, and severe OSA patients. Weight increased significantly for nocturia patients in moderate and severe OSA patients. BMI increased significantly for nocturia patients in normal patients and severe OSA patients. Arousal number and arousal index increased significantly for nocturia patients in the categories of all patients, OSA patients, and severe OSA patients. PLM number and index increased significantly for nocturia

patients in OSA patients and severe OSA patients. AHI of NREM and TST decreased significantly for nocturia patients in mild OSA patients only.

Multivariate analysis between patients with and without nocturia stratified by OSA severity using logistic regression found that older age and worse quality of life significantly correlated to nocturia in OSA patients (AHI≥5 events/h). In addition, there was no significant correlation of factors in other degree stratified groups. This result may be caused by the small number of patient samples after stratification, as well as the high interaction effect and collinearity between independent variables.

4. Discussion

Our study revealed that with increasing severity of OSA, more correlated factors related to nocturia were observed. There were only five significant correlated factors in mild OSA patients. In moderate OSA patients, the correlated factors for nocturia increased to seven. In severe OSA patients, there were nine correlated factors related to nocturia. Hence with increasing severity of OSA, these patients are more vulnerable to correlated factors. Mild OSA patients can overcome these conditions, while moderate or severe OSA patients cannot.

Vrooman et al. [16] reported that more than three quarters of OSA patients suffered from nocturia. Few patients seek medical help for nocturia. Many of them could tolerate it or assume it was normal. The total time from the first symptom of nocturia to first prescribed treatment in their study was approximately 2 years. The importance of the nocturia treatment in OSA patients was underestimated by some patients and physicians. Nocturia has been identified as an independent predictor for severe OSA patients [17]. Our study reported the correlation factors with nocturia was increased with the increase of OSA severity. This finding also highlights the importance of nocturia treatment in OSA patients, especially in severe OSA group.

In our study, baseline SaO_2 decreased significantly in severe OSA patients with nocturia. Mild and moderate OSA patients with nocturia did not show the same results. Pływaczewski et al. [18] reported lower mean overnight SaO_2 and daytime sleepiness. Other study revealed nocturnal hypoxia in OSA patients with nocturia [19]. Our study further analyzed nocturnal hypoxia in different levels of OSA patients. The results alerted special awareness of nocturnal hypoxia in severe OSA patients with nocturia.

Age is a correlated factor for OSA and nocturia [20]. The prevalence of nocturia was 10% in younger patients and 64%—80% in the older population. Aging is also related to OSA, and reportedly, the peaks of newly diagnosed OSA were between the fourth and sixth decades [20]. In our study, age was a significant correlated factor for nocturia in all categories of patients, except in severe OSA patients. It is possible that the impact of other etiologies for severe OSA might have outweighed the impact of age.

Our findings also showed that weight or BMI increased significantly in normal patients, moderate OSA patients, and severe OSA patients with nocturia. Rezaie et al. [21] and Pływaczewski et al. [18] reported that OSA patients with higher AHI scores had more elevated BMI, frequent daytime sleepiness, respiratory disturbance index, and snoring. Hasan et al. [22] revealed that the higher BMI was correlated with metabolic syndrome, nocturia, and OSA. According to these findings, high BMI is positively correlated with nocturia and OSA. In our study, if a patient with severe OSA had a higher weight or BMI, the risk of nocturia was higher. However, this finding could not be identified in mild OSA patients in the present study.

Awake time and stage 1 sleep increased significantly in OSA patients (AH≥5 events/h) with nocturia. In further analysis, moderate and severe OSA patients with nocturia had significantly longer awake time and stage 1 sleep. Mild OSA patients did not show this phenomenon. Parthasarathy et al. [23] reported that NREM stages 1, 2, and 3 showed no statistical difference between the nocturia and non-nocturia groups. Nevertheless, the REM stage decreased significantly in nocturia patients. Our results did not correlate with those of Parthasarathy et al. [23]. The explanation for our finding might be that nocturia decreased the deeper sleep time and increased the awake time and stage 1 sleep time. Our findings also showed that NREM and TST were only significantly decreased in mild OSA patients with nocturia. The result might be a statistical error, and we could not explain this finding.

Arousal number and arousal index increased significantly for nocturia patients, in the categories of all patients, OSA patients (AHI≥5 events/h), and severe OSA patients. This result might be explained by the results reported by Rezaie et al. [21] which showed that higher AHI scores indicated that patients with OSA had a higher respiratory disturbance index. In these patients who suffered from nocturia, the change in respiratory disturbance index should be more significant than in patients with normal and mild OSA.

PLM number and index increased significantly in the categories of OSA patients (AHI≥5 events/h) and severe OSA patients with nocturia. Yoshimura et al. [24] reported that periodic limb movement disorder (PLMD) had a significant correlation with bothersome nocturia. PLMD can induce disturbance in sleep initiation and be potentially associated with nocturia. Urologists rarely survey PLMD in patients with nocturia [24]. Our study highlights the importance of PLM, especially in patients with severe OSA and nocturia.

Our study found that the total IPSS ($p<0.001$) and quality-of-life score ($p<0.001$) were both significantly higher for nocturia patients in the category of all patients, correlated to the results from other studies [19]. Our study further categorized the patients according to the severity of the AHI. In severe OSA patients with nocturia, the total IPSS was not statistically significant ($p=0.345$). The possible explanation was that severe OSA may obscure the impact of nocturia on IPSS. Quality of life was significantly worse for nocturia patients, except in mild and moderate OSA patients ($p=0.056$ and 0.055, respectively). This could be because the severe OSA patients could not tolerate the impact of nocturia and felt poor life quality. Urinary residual sensation was also significantly higher solely in severe OSA patients with nocturia. The reasonable

mechanism for this finding was unknown. In the category of all patients, both voiding and storage symptoms including frequency, intermittent, urgency, and weak stream were significantly higher for nocturia patients. In OSA patients (AHI≥5 events/h), only storage symptoms including frequency and urgency were significantly higher for nocturia patients. Current theories supported that OSA would increase nocturnal urine volume and induce nocturia [8,9]. If nocturia also increases urinary frequency and urgency, further studies should be performed to delineate how OSA increases daytime storage symptoms.

Two theories of how OSA induces nocturia were described before including ANP secretion induced by negative thoracic pressure and increased venous return [8]. Hypoxia increases pulmonary vasoconstriction and right atrial transmural pressure [9].

There are other pathophysiological aspects of nocturia. One of them is about aquaporins (AQPs). Urothelium can regulate both solute and fluid reabsorption and modify the final urine composition. Transurothelial water transport is facilitated by channels called AQPs including several AQP family proteins (AQP1, AQP2, AQP3, AQP4, AQP7, AQP9, and AQP11). AQP expression can be affected by urine composition. AQP3 expression in human urothelial cultures was significantly enhanced in the increased urine osmolality (500 mmol/L NaCl) [25]. AQP was regulated by vasopressin and desmopressin. These receptors expression was increased with age and impacted nocturia especially in the elderly [26,27].

Circadian rhythms is another theory that affects nocturia. The central circadian clock is suprachiasmatic nucleus of the hypothalamus. Light impacting on the retina synchronizes the central circadian clock. Urothelial sensory functions also exhibit circadian rhythms. The possible mechanisms include altered detrusor contractile activity, changes to salt and water transport across the bladder wall, and altered afferent mechanisms according to bladder volume and urine composition. Experimental studies suggest that melatonin administration ameliorates bladder overactivity [26].

We provided a possible pathophysiology reason that there were more factors related to nocturia with increasing severity of OSA. OSA induced nocturia by ANP secretion described before. It is reasonable that more ANP was secreted in severe OSA patients. Nocturia increased awake time and interrupted the circadian rhythms. This also affected secretion of melatonin, vasopressin, and desmopressin. AQP in urothelium was also regulated by vasopressin and desmopressin. The change of AQP might affect bladder function and lead to a vicious cycle [26,27].

This study had some limitations. First, it is a retrospective study from a single hospital, and thus selection bias could not be completely avoided because the patients included in the study came for OSA treatment. Larger scale prospective randomized control trials are therefore needed. Second, the detailed mechanism for the interaction of OSA and nocturia is still unclear. More parameters should be included to analyze the etiology and related factors for OSA and nocturia. Third, the causes of nocturia or relative parameters including the single voided volume, urine production at night, or total urine production per day were not shown in this paper. Forth, the absence of a significant relationship could suggest that the correlation is merely coincidental. Those factors are important to investigate the nocturia and this is a major limitation.

5. Conclusion

With increasing severity of OSA, there are more correlated factors associated with nocturia. The severity of OSA patients should be well evaluated and relative correlated factors should be considered. This study helps in clinical education and treatment for OSA patients with different severity.

Author contributions

Study concept and design: Chin-Heng Lu, Min-Che Tung, Frank Cheau-Feng Lin, Stella Chin-Shaw Tsai.
Data acquisition: Chin-Heng Lu, Stella Chin-Shaw Tsai.
Data analysis: Chin-Heng Lu, Hung-Min Chang, Kuang-Hsi Chang.
Drafting of manuscript: Chin-Heng Lu, Stella Chin-Shaw Tsai.
Critical revision of the manuscript: Chin-Heng Lu, Yen-Chuan Ou, Chao-Yu Hsu, Min-Che Tung, Frank Cheau-Feng Lin, Stella Chin-Shaw Tsai.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This study received a grant support from Tungs' Taichung Metroharbor Hospital (grant number #TTMHH-109R0048 to Stella Chin-Shaw Tsai).

References

[1] Bosch JL, Everaert K, Weiss JP, Hashim H, Rahnama'i MS, Goessaert AS, et al. Would a new definition and classification of nocturia and nocturnal polyuria improve our management of patients? ICI-RS 2014. Neurourol Urodyn 2016;35:283—7.
[2] van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardisation of terminology in nocturia: report from the standardisation sub-committee of the international continence society. Neurourol Urodyn 2002;21:179—83.
[3] Hetta J. The impact of sleep deprivation caused by nocturia. BJU Int 1999;84(Suppl 1):27—8. https://doi.org/10.1046/j.1464-410x.84.s1.3.x.
[4] Schatzl G, Temml C, Schmidbauer J, Dolezal B, Haidinger G, Madersbacher S. Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project. Urology 2000;56:71—5.
[5] Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1485 males and females aged 50—93: effects of sex and age, and factors related to self-evaluated quality of sleep. J Gerontol A Biol Sci Med Sci 1996;51:M108—15. https://doi.org/10.1093/gerona/51a.3.m108.
[6] Stewart RB, Moore MT, May FE, Marks RG, Hale WE. Nocturia: a risk factor for falls in the elderly. J Am Geriatr Soc 1992;40:1217—20.

[7] Niimi A, Suzuki M, Yamaguchi Y, Ishii M, Fujimura T, Nakagawa T, et al. Sleep apnea and circadian extracellular fluid change as independent factors for nocturnal polyuria. J Urol 2016;196:1183—9.
[8] Hoshiyama F, Hirayama A, Tanaka M, Taniguchi M, Ohi M, Momose H, et al. The impact of obstructive sleep apnea syndrome on nocturnal urine production in older men with nocturia. Urology 2014;84:892—6.
[9] Witthaus MW, Nipa F, Yang JH, Li Y, Lerner LB, Azadzoi KM. Bladder oxidative stress in sleep apnea contributes to detrusor instability and nocturia. J Urol 2015;193:1692—9.
[10] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667—89.
[11] Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. Sleep 2009;32:150—7.
[12] Endeshaw YW, Johnson TM, Kutner MH, Ouslander JG, Bliwise DL. Sleep-disordered breathing and nocturia in older adults. J Am Geriatr Soc 2004;52:957—60.
[13] Oztura I, Kaynak D, Kaynak HC. Nocturia in sleep-disordered breathing. Sleep Med 2006;7:362—7.
[14] Shao C, Jiang JB, Wu HC, Wu SB, Yu BY, Tang YD. Clinical assessment and polysomnographic study of sleep apnea in a Chinese population of snorers. J Zhejiang Univ Sci B 2015;16:215—23.
[15] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of sleep medicine. J Clin Sleep Med 2012;8:597—619.
[16] Vrooman OPJ, van Balken MR, van Koeveringe GA, van Kerrebroeck PVA, Driessen L, Schouten LJ, et al. The effect of continuous positive airway pressure on nocturia in patients with obstructive sleep apnea syndrome. Neurourol Urodyn 2020;39:1124—8.
[17] Chen CY, Hsu CC, Pei YC, Yu CC, Chen YS, Chen CL. Nocturia is an independent predictor of severe obstructive sleep apnea in patients with ischemic stroke. J Neurol 2011;258:189—94.
[18] Pływaczewski R, Stokłosa A, Bednarek M, Czerniawska J, Bieleń P, Górecka D, et al. [Nocturia in obstructive sleep apnoea (OSA)]. Pneumonol Alergol Pol 2007;75:140—6. [Article in Polish].
[19] Chung JH, Moon HS, Park SY, Kim KR, Cho SH, Kim YT. Effect of nocturnal hypoxia on nocturia in patients with obstructive sleep apnea. Int Neurourol J 2019;23:161—8.
[20] Ayik S, Bal K, Akhan G. The association of nocturia with sleep disorders and metabolic and chronic pulmonary conditions: data derived from the polysomnographic evaluations of 730 patients. Turk J Med Sci 2014;44:249—54.
[21] Rezaie L, Maazinezhad S, Fogelberg DJ, Khazaie H, Sadeghi-Bahmani D, Brand S. Compared to individuals with mild to moderate obstructive sleep apnea (OSA), individuals with severe OSA had higher BMI and respiratory-disturbance scores. Life 2021;11:368. https://doi.org/10.3390/life11050368.
[22] Hasan A, Uzma N, Swamy TL, Shoba A, Kumar BS. Correlation of clinical profiles with obstructive sleep apnea and metabolic syndrome. Sleep Breath 2012;16:111—6.
[23] Parthasarathy S, Fitzgerald M, Goodwin JL, Unruh M, Guerra S, Quan SF. Nocturia, sleep-disordered breathing, and cardiovascular morbidity in a community-based cohort. PLoS One 2012;7:e30969. https://doi.org/10.1371/journal.pone.0030969.
[24] Yoshimura K, Oka Y, Kamoto T, Yoshimura K, Ogawa O. Differences and associations between nocturnal voiding/nocturia and sleep disorders. BJU Int 2010;106:232—7.
[25] Rubenwolf PC, Georgopoulos NT, Kirkwood LA, Baker SC, Southgate J. Aquaporin expression contributes to human transurothelial permeability *in vitro* and is modulated by NaCl. PLoS One 2012;7:e45339. https://doi.org/10.1371/journal.pone.0045339.
[26] Vahabi B, Jabr R, Fry C, McCloskey K, Everaert K, Agudelo CW, et al. ICI-RS 2019 nocturia think tank: how can experimental science guide us in understanding the pathophysiology of nocturia? Neurourol Urodyn 2020;39(Suppl 3):S88—95. https://doi.org/10.1002/nau.24274.
[27] Birder LA, Wolf-Johnston AS, Jackson EK, Wein AJ, Dmochowski R. Aging increases the expression of vasopressin receptors in both the kidney and urinary bladder. Neurourol Urodyn 2019;38:393—7.