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Correlation between serum uric acid and pulmonary arterial hypertension based on echo probability in patients with obstructive sleep apnea syndrome

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Abstract

Background Obstructive sleep apnea–hypopnea syndrome is the most common form of SRBDs. Recurrent hypoxia, which accompanies OSAHS, increases the degradation of ATP, which in turn increase uric acid concentration that can be used as a biomarker of tissue hypoxia in OSAHS. There is still debate about whether OSAHS is an independent contributor to pulmonary arterial hypertension.

Aim of the work This study aimed to correlate serum uric acid levels and PAH in OSAHS patients.

Methods We enrolled 100 patients diagnosed with OSAHS using polysomnography. Patients were divided into three severity groups: mild OSA ($5 \le AHI < 15$), moderate OSA ($15 \le AHI < 30$), and severe ($30 \le AHI < 60$). Serum uric acid was measured the morning after polysomnography. All patients underwent standard echocardiograms, and pulmonary artery systolic pressure calculation was done.

Results Among our studied patients (66% males, 34% females), the mean age was 53.04 ± 8.45 years. Six percent, 38%, and 56% were diagnosed as mild, moderate, and severe OSAHS, respectively. The mean AHI was 31.93 ± 11.78 event. Pulmonary HTN was detected in 78% of patients. Those with elevated uric acid levels represented 92.3% of patients versus 9.1% of patients without pulmonary HTN, $p < 0.001$. The level of serum uric acid positively correlated with pulmonary HTN level.

Conclusion Pulmonary arterial pressure correlated positively with serum uric acid level. Both serum uric acid level and PAP positively correlated with the severity of OSA. Further confirmation with right heart catheterization is essential.

Trial registration NCT05967754, on July 22, 2023 — retrospectively registered.

Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is the most common form of sleep-related breathing disorder (SRBDs) [1]. It is characterized by a significant decrease or complete cessation of the airflow due to repeated episodes of upper airway collapse during sleep in the presence of breathing efforts [1]. The episodic narrowing of the upper airway throughout sleep results in intermittent hypoxia (IH) [2] frequently associated with oxyhemoglobin desaturation and terminate by sleep arousals which considerably leads to significant sleep fragmentation and chronic excessive daytime sleepiness (EDS) [3].

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The disease is also linked to a lower quality of life (QOL), a high risk of road traffic accidents, and severe cognitive disability. The link between OSAHS and comorbidities, particularly cardiovascular comorbidity, is certainly of greatest concern [4].

The final product of adenosine triphosphate (ATP) degradation is uric acid (UA), recurrent hypoxia, which usually accompanies OSAHS, resulting in an increase in the degradation of ATP into xanthine, which in turn results in an increase in uric acid concentration [5].

Pulmonary hypertension (PH) is now defined by a mean pulmonary arterial pressure > 20 mm Hg at rest as assessed by right heart catheterization (RHC) [6]. There is some evidence documented that hypoxia, hypercapnia, and the changes in the intrathoracic pressure usually cause an increase in the pressures of the pulmonary artery during apneic periods during sleep. Daytime pulmonary hypertension in patients with OSAHS was revealed by numerous studies. However, there is still a big debate about whether OSAHS is an independent contributor to pulmonary arterial hypertension [7].

Much evidence suggests that oxidative stress, endothelial dysfunction, increased inflammation, and a procoagulant condition frequently lead to OSA-induced PH. Impaired response to endothelium-dependent vasodilators like as acetylcholine had been screened in systemic vessels of OSAHS patients [8]. Furthermore, the long-acting vasoconstrictor peptide that is synthesized by endothelium, endothelin-1, is usually increased and decreases with the treatment by CPAP [9]. Moreover, vascular endothelial growth factor expression is augmented relatively to the nocturnal oxygen desaturation degree in patients with OSAHS [10]. Also, elevation of the levels of (CRP) C-reactive protein and levels of IL-6, which both decline when CPAP therapy is used [11, 12]. A procoagulant state had been reported in many studies in patients with OSAHS; elevated production of the hypoxia-induced erythropoietin had been documented [9, 13]. Levels of serum fibrinogen are usually increased, and fibrinolytic activity is decreased [14]. In addition to elevation of platelet activation level and aggregation [15].

The diagnosis of PH requires advanced diagnostic testing and invasive hemodynamics leading to delayed diagnosis and increased mortality. Consequently, biomarkers for the presence of PH provide great promise for more early detection or screening [16]. The severity and mortality in patients with PH had been correlated with biomarkers like uric acid (UA) [17, 18]. Hasday and Grum were the first to document the overnight change in the secretion of uric acid in urine and to document that it might be a helpful index of tissue hypoxia [19]. We aimed in our study to understand the possible role of serum uric acid as a biomarker of tissue hypoxia and its relation with the level of pulmonary hypertension in those patients.

Aim of the work

This study aimed to correlate serum uric acid level and pulmonary arterial hypertension in obstructive sleep apnea syndrome patients.

Subjects

The study enrolled 100 consecutive patients attending the Alexandria Main University Hospital, Sleep Lab, Chest Department. We enrolled 100 OSAHS patients who matched all inclusion criteria. Patients were diagnosed with OSAHS using polysomnography (PSG), and scoring was done according to "The American Academy of Sleep Medicine (AASM) Guidelines" 2012 [20]. Patients were divided into three groups according to severity of OSAHS as assessed by AHI: group 1: patients with mild OSA ($5 \leq AHI < 15$), group 2: patients with moderate OSA ($15 \leq AHI < 30$), and group 3: patients with severe ($30 \leq AHI < 60$). Inclusion criteria were patients diagnosed with OSAHS by overnight polysomnography ($AHI \geq 5/h$), ≥ 18 years old.

Patients with other sleep disorders as narcolepsy or hypersomnia were excluded as well as patients with neuropsychiatric disorders, hemodynamically unstable, patients with other chronic respiratory or cardiac diseases, patients with other known causes of pulmonary hypertension, and patients with any disease or on medication that could alter the excretion or urinary metabolism of uric acid such as excessive uric acid production: gout, decreased uric acid excretion: renal failure, and drugs: salicylic acid with a dose of more than 2 g/day), nitroglycerin (intravenous), theophylline, and allopurinol.

Methods

All subjects enrolled in the study signed informed consent before participation. The study was accepted by the local ethical committee of Alexandria Faculty of Medicine (available from www.med.alex.edu.eg/wp-consent/uploads/2012/04/الموافقة-على-الخضوع-لبحث-طبي.pdf).

Each subject underwent the following: Detailed history taking including symptoms related to sleep breathing disorders such as snoring, choking, or gasping attacks at night; EDS, unrefreshing sleep, witnessed apneas, recurrent arousals, nocturia, morning laziness, and fatigue; and morning headaches, morning dry mouth, and memory and personality changes. History of other comorbidities such as (DM., HTN, IHD, and stroke), History of any drugs taken by the patient, Complete physical examination. Routine laboratory investigations as Complete blood count, renal and liver functions, in addition to serum uric acid (A

single blood sample was collected in the morning after overnight polysomnography was done). The reference value used for men and women was 3.5–7.2 mg/dl and 2.5–6 mg/dl, respectively. In Epworth Sleepiness Scale, patients were asked to rate their chance of dozing in each situation on a scale of 0 to 3, with zero indicating no chance of dozing and 3 a high chance of dozing. The possible total score is 24. The normal upper limit is generally considered to be 10 points [21]. Anthropometric data were measured including body mass index (BMI):(Quetelet's index = weight (kg)/height $(m)^2$). Neck circumference was measured at the cricothyroid level [22]. Full overnight PSG had been performed using SOMNOscreen™ plus, SOMNOmedics GmbH, D-97236, and Germany to assess sleep stages and respiratory events. Manual scoring of respiratory events had been calculated according to AASM guidelines [20]. Apnea events were defined, based on PSG, as a ≥ 90% drop of respiratory amplitude, lasting at least 10 s. Hypopneas were defined as > 30% drop of respiratory amplitude, lasting ≥ 10 s, associated with oxygen saturation drops of ≥ 3% [23]. The AHI was defined as an index of the number of apnea and hypopnea events per hour of sleep. Time of oxygen saturation (SpO_2) below 90% (T90) during total sleep and average and lowest nocturnal SpO_2 values were recorded [23].

All patients underwent standard echocardiogram as screening tool for pulmonary hypertension using a Philips HD7 ultrasound system (Philips Healthcare, Amsterdam, the Netherlands), and a 1–3 MHz Philips S3-1 cardiac sector transducer was used (Philips Healthcare, Amsterdam, the Netherlands) to assess the probability of pulmonary hypertension (PH). M-mode, two-dimensional, and Doppler echocardiography were performed using the standard parasternal and apical views in the resting state, in the supine or left lateral position [24]. In pulmonary artery systolic pressure (PASP) calculation by tricuspid regurgitation peak velocity, to measure the difference in pressures between the right ventricle and right atrium, continuous wave (CW) Doppler of the tricuspid regurgitation (TR) trace had been used. To calculate this pressure difference using peak TR velocity, the simplified Bernoulli equation ($P = 4[TRmax]^2$) had been used [25]. This technique is well correlated with PASP on right heart catheterization [26]. A peak TR velocity value of ≤ 2.8 m/s was considered normal [25, 26].

The peak velocity was then measured (TRmax), and according to it, PH had been suggested [27], although this raises the probability of pulmonary hypertension and not a definite diagnosis. A value of ≤ 2.8 m/s suggested low probability. Mean PAP can be approximated from the systolic PAP (SPAP) using the following formula: $mPAP = 0.61\ SPAP + 2$ mmHg [28].

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY, USA: IBM Corp.). Qualitative data were described using numbers and percentages. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level.

The used tests were as follows:

- *Chi-square test*: For categorical variables, to compare between different groups
- *Fisher's exact or Monte Carlo correction*: Correction for chi-square when more than 20% of the cells have expected count less than 5
- *Student t-test*: For normally distributed quantitative variables, to compare between two studied groups
- *Mann–Whitney test*: For abnormally distributed quantitative variables, to compare between two studied groups
- *F-test (ANOVA)*: For normally distributed quantitative variables, to compare between more than two groups
- Post hoc *test (Tukey)*: For pairwise comparisons
- *Kruskal–Wallis test*: For abnormally distributed quantitative variables, to compare between more than two studied groups
- Post hoc *(Dunn's multiple comparisons test)*: For pairwise comparisons
- *Pearson coefficient*: Correlate between two normally distributed quantitative variables

Results

During the period from June 2019 to February 2021, we enrolled 100 patients with OSAHS of different severities: group 1: patients with mild OSAHS (5 ≤ AHI < 15), group 2: patients with moderate OSAHS (15 ≤ AHI < 30), and group 3: patients with severe OSAHS(30 ≤ AHI < 60).

Among our studied patients, 66 (66%) were males. Their mean age was 53.04 ± 8.45 (mean ± SD) years (range 33–70 years). Regarding BMI, 6 patients (6%) were overweight, 90 patients (90%) were obese, and 4 patients (4%) were morbidly obese. All the mild severity group, 84.2% of the moderate group, and 50% of the severe group were males. As for age, there was a statistically significant difference between severity groups I and II and severity groups I and III, $p_1 = 0.038$, $p_2 = 0.004$. The mean values for age were 43.33 ± 8.59, 52.16 ± 6.95, and 54.68 ± 8.70 for severity groups I, II, and III, respectively. Regarding BMI, there was a statistically significant difference between severity groups II and III, $p_3 = 0.024$. The mean values of

BMI were 32.83 ± 2.13, 33.94 ± 3.74, and 35.39 ± 2.48 for severity groups I, II, and III, respectively.

The distribution of the most common associated comorbidities was as follows: HTN in 80 patients (80%), DM in 76 patients (76%), and 6 patients (6%) had a history of DVT. As for DM, there was a statistically significant difference between mild and severe groups and between moderate and severe groups, $p_2 < 0.001$, $p_3 < 0.001$, whereas diabetic patients were present in 33.3% of mild severity group, 52.6% of moderate severity group, and 96.4% of severe group patients. Thirty-three percent of the mild severity group, whereas 89.5% of the moderate severity group and 78.6% of severe group patients suffered from HTN. There was a statistically significant difference between mild and moderate patients and between mild and severe patients, $p_1 = 0.007$, $p_2 = 0.034$. History of DVT was reported in 33.3%, 10.5%, and 0% of mild, moderate, and severe groups, respectively.

Chocking attacks at night and snoring were the most frequent presenting symptoms reported by all studied patients. Unrefreshing sleep was reported in 96 patients (96%). Witnessed apnea was reported in 94 patients (94%), fatigue was reported in 90 patients (90%), and dry mouth, EDS, morning headache, and nocturia in 88 (88%), 86 (86%), 78 (78%), and 74 (74%) patients, respectively.

Among the studied patients, 6 (6%), 38 (38%), and 56 (56%) were diagnosed with mild, moderate, and severe OSAHS, respectively. The mean value of AHI was 31.93 ± 11.78 event ranged (7.70–55.0 event). Different parameters were assessed in our study including AHI, respiratory disturbance index (RDI), time of oxygen saturation (SpO_2) below 90% (T90), oxygen desaturation index (ODI), and average SpO2 (Table 1).

Pulmonary HTN has been detected in 78 patients (78%). Comparing groups of patients with or without pulmonary HTN according to different parameters is shown in Tables 2 and 3. Tables 4 and 5 compare patients with normal uric acid levels to patients with elevated uric acid levels regarding demographic data and ESS and associated comorbidities.

Relation between pulmonary HTN and uric acid

Patients with abnormal uric acid levels represented 92.3% of patients with suspected pulmonary HTN versus 9.1% of patients without suspected pulmonary HTN, $p < 0.001$ which was statistically significant (Fig. 1).

Our study showed a significant positive correlation between serum uric acid level and T90% and a significant positive correlation between serum uric acid and ODI, also between uric acid and AHI as shown in Fig. 2. Similarly, our study showed a significant positive correlation between suspected pulmonary HTN and T90% and a significant positive correlation between suspected pulmonary HTN and ODI, also between suspected pulmonary HTN and AHI, $p < 0.001$, < 0.001, and < 0.001, respectively, as shown in Fig. 3. The level of serum uric acid in our studied patients positively correlated with the suspected pulmonary HTN, as shown in Fig. 4.

Discussion

We enrolled 100 patients suffering from different severities of OSAS as diagnosed by full-night PSG according to "AASM Manual for Scoring of Sleep and Associated Events" 2012 [20]. Among these 100 patients, 66% were males, and 44% were females, and this male-to-female ratio reflects the known high prevalence of OSAS among males as reported by the Wisconsin Sleep Cohort [29] and reflects the prevalence of OSA in our population.

Obstructive sleep apnea is accompanied by many comorbidities, and the prevalence of these comorbidities increases with the increase in severity of OSAHS as shown by many studies [30]. In our study, we reported the prevalence of hypertension, DM, and DVT in 80%, 76%, and 6%, respectively, in descending order. This high prevalence of hypertension and DM was reported by previous studies as well [31, 32].

Regarding venous thromboembolism, 6% of our patients reported a history of DVT. Yi-Hao Peng et al. [33] reported a prevalence of DVT in 3% among his studied patients with OSA, and he reported that the prevalence of OSAHS was significantly higher in the patients with VTE than in the patients without VTE (30% vs 9.1%). Sweed, Hassan, ElWahab, Aref, and Mahmoud [34] reported a significantly higher prevalence of DVT among patients with severe, very severe, and extreme OSA in comparison to patients with mild and moderate OSA.

Patients with OSA have a wide range of symptoms. In our study, choking attacks at night and snoring were the most common presenting complaint; they were reported by all patients. Choking or gasping attacks were found to be the most effective finding in identifying patients with OSA in a systematic evaluation of OSA diagnosis matching our study results [35].

The main aim of our study was to correlate uric acid level and and levels of pulmonary hypertension in patients with OSAHS. Many studies addressed questions about levels of serum uric acid [36, 37] and pulmonary hypertension [38] in OSAHS, but no clear data was reported about their correlation in OSAHS patients.

In 2009, sleep apnea was officially documented as a leading cause of pulmonary hypertension when the WHO added OSAHS to the group III classification of pulmonary hypertension [39]. The prevalence of pulmonary arterial hypertension in our studied OSAHS patients was 78%. Wong, Williams, and Mok [40]

Table 1 Polysomnographic data of different severity groups ($n=100$)

	Total ($n=100$)	OSAHS severity			Test of sig	p
		Mild ($n=6$)	Moderate ($n=38$)	Severe ($n=56$)		
AHI						
Min.–max	7.70–55.0	7.70–11.30	16.80–29.60	30.0–55.0	$F=143.58^{*}$	$<0.001^{*}$
Mean ± SD	31.93 ± 11.78	9.0 ± 1.79	22.98 ± 4.19	40.45 ± 7.14		
Median (IQR)	32.0 (22.0–39.0)	8.0 (7.70–11.30)	22.0 (18.90–26.70)	38.25 (35.0–47.50)		
Sig. bet. categ		$p_1<0.001^{*}, p_2<0.001^{*}, p_3<0.001^{*}$				
RDI						
Min.–max	7.70–55.0	7.70–11.30	16.80–55.0	15.30–55.0	$F=57.284^{*}$	$<0.001^{*}$
Mean ± SD	32.66 ± 12.26	9.87 ± 1.71	25.50 ± 8.63	39.97 ± 8.58		
Median (IQR)	33.0 (22.20–41.0)	10.60 (7.70–11.30)	23.20 (20.0–29.10)	39.35 (35.0–48.35)		
Sig. bet. categ		$p_1<0.001^{*}, p_2<0.001^{*}, p_3<0.001^{*}$				
t90%						
Min.–max	0.0–38.0	0.0–0.0	0.0–38.0	0.10–38.0	$H=43.917^{*}$	$<0.001^{*}$
Mean ± SD	7.17 ± 8.90	0.0 ± 0.0	3.96 ± 8.56	10.12 ± 8.47		
Median (IQR)	5.30 (0.90–9.80)	0.0 (–)	1.20 (0.40–3.50)	7.65 (5.85–11.85)		
Sig. bet. categ		$p_1=0.033^{*}, p_2<0.001^{*}, p_3<0.001^{*}$				
ODI						
Min.–max	1.70–60.0	1.70–9.30	7.80–60.0	15.0–60.0	$H=44.825^{*}$	$<0.001^{*}$
Mean ± SD	22.21 ± 13.89	4.57 ± 3.69	18.44 ± 10.75	26.65 ± 14.29		
Median (IQR)	18.60 (16.10–20.8)	2.70 (1.70–9.30)	16.1 (15.20–16.90)	19.7 (18.65–26.20)		
Sig. bet. categ		$p_1=0.023^{*}, p_2<0.001^{*}, p_3<0.001^{*}$				
Minimal SpO_2%						
Min.–max	30.0–92.0	91.0–92.0	30.0 – 90.0	30.0–89.0	$F=36.977^{*}$	$<0.001^{*}$
Mean ± SD	57.48 ± 18.98	91.67 ± 0.52	66.47 ± 15.25	47.71 ± 14.54		
Median (IQR)	52.50 (41.0–70.0)	92.0 (91.0–92.0)	64.0 (58.0–85.0)	45.0 (38.0–51.0)		
Sig. bet. categ		$p_1<0.001^{*}, p_2<0.001^{*}, p_3<0.001^{*}$				
Baseline O_2 sat						
Min.–max	90.0–99.0	95.0–97.0	90.0–99.0	91.0–97.0	$F=5.240^{*}$	0.007^{*}
Mean ± SD	93.94 ± 1.90	96.0 ± 0.89	94.16 ± 2.21	93.57 ± 1.58		
Median (IQR)	94.0 (92.0–95.0)	96.0 (95.0–97.0)	94.0 (92.0–96.0)	93.0 (92.0–95.0)		
Sig. bet. categ		$p_1=0.061, p_2=0.007^{*}, p_3=0.282$				

IQR Interquartile range, *SD* Standard deviation, *F* F For ANOVA test, pairwise comparison bet. Each 2 groups was done using post hoc test (Tukey). *H* H for Kruskal–Wallis test, pairwise comparison bet. Each 2 groups was done using post hoc test (Dunn's for multiple comparisons test). *p* *p*-value for comparing between different categories. p_1 *p*-value for comparing between *mild* and *moderate*. p_2 *p*-value for comparing between *mild* and *severe*. p_3 *p*-value for comparing between *moderate* and *severe*

* Statistically significant at $p \leq 0.05$

reported that the prevalence of pulmonary arterial hypertension in OSAHS ranged from 17 to 53% across numerous studies.

According to the presence or absence of pulmonary HTN, among our studied patients, there was no statistically significant difference regarding gender, $p=0.451$, and this does not agree with the findings of Kessler, Chaouat, Weitzenblum, Oswald, Ehrhart, and Apprill [41], who proved that the prevalence of pulmonary hypertension was higher in male patients than females. On the other hand, Minai, Ricaurte, Kaw, Hammel, Mansour, and McCarthy [42] approved that more female than male patients had pulmonary HTN (86% vs 58%; $p=0.01$).

Regarding age, our patients who suffered from pulmonary HTN were older than patients without pulmonary HTN (54.13 ± 8.12 vs 49.18 ± 8.63) years old, $p=0.015$. This might be explained by the fact that the greater the age, the worse the complications as reported by Mokhlesi, Ham, and Gozal [43], who found that the divergence between OSAHS and control subjects was more obvious after the 6th decade of life. Our results also matched those of Alchanatis, Tourkohoriti, Kakouros, Kosmas, Podaras, and Jordanoglou [44]

Table 2 Comparing groups of patients with or without pulmonary HTN regarding demographic data and ESS ($n=100$)

	Total ($n=100$)		Pulmonary HTN				Test of sig	p
			No ($n=22$)		Yes ($n=78$)			
	No	%	No	%	No	%		
Sex								
Male	66	66.0	16	72.7	50	64.1	$\chi^2=0.569$	0.451
Female	34	34.0	6	27.3	28	35.9		
Age (years)								
Min.–max	33.0–70.0		33.0–60.0		36.0–70.0		$t=2.489^*$	0.015^*
Mean ± SD	53.04 ± 8.45		49.18 ± 8.63		54.13 ± 8.12			
Median (IQR)	53.0 (49.0–58.0)		53.0 (42.0–55.0)		53.0 (49.0–60.0)			
BMI								
Overweight	6	6.0	6	27.3	0	0.0	$\chi^2=17.654^*$	$^{MC}p<0.001^*$
Obese	90	90.0	16	72.7	74	94.9		
Morbid obese	4	4.0	0	0.0	4	5.1		
Min.–max	25.50–40.96		25.50–36.70		30.44–40.96		$t=7.350^*$	$<0.001^*$
Mean ± SD	34.69 ± 3.10		31.23 ± 3.07		35.66 ± 2.32			
Median (IQR)	35.4 (32.4–36.8)		31.20 (29.0–32.40)		35.99 (34.2–37.1)			
ESS								
Normal (≤ 10)	6	6.0	2	9.1	4	5.1	$\chi^2=0.478$	$^{FE}p=0.610$
Abnormal (> 10)	94	94.0	20	90.9	74	94.9		
Min.–max	10.0–20.0		10.0–20.0		10.0–20.0		$t=2.241^*$	0.027^*
Mean ± SD	13.90 ± 2.62		12.82 ± 2.79		14.21 ± 2.50			
Median (IQR)	14.0 (12.0–16.0)		12.0 (11.0–13.0)		14.0 (12.0–16.0)			

* means significant

who observed a significant difference between pulmonary HTN and non-pulmonary HTN OSAHS patients regarding age (62 ± 4 vs. 48 ± 15 years; $p<0.05$).

Regarding BMI, there was a statistically significant difference between patients with pulmonary HTN and patients without regarding their BMI (35.66 ± 2.32 kg/m^2) versus (31.23 ± 3.07 kg/m^2), $p<0.001$, and this agreed with the findings of Alchanatis, Tourkohoriti, Kakouros, Kosmas, Podaras, and Jordanoglou [44], who proved that there was a strong correlation between pulmonary HTN and BMI in OSA patients.

We believe that obesity is the most strong risk factor for OSAHS as demonstrated in the previous studies that there was a 40% prevalence of OSA in obese patients [45, 46]. Friedman and Andrus found a positive relationship between BMI and right ventricular dysfunction (as a sequel of chronic pulmonary arterial hypertension) after adjusting for age, insulin level, and mean arterial pressure [45].

The present study revealed that patients with pulmonary HTN showed statistically higher values for ESS, $p=0.027$, and mean ± SD (14.21 ± 2.50 vs 12.82 ± 2.79) in patients without pulmonary HTN. This might be explained by the concept that pulmonary hypertension leads to several symptoms including excessive fatigue and tiredness during the night that aggravate daytime sleepiness.

Regarding DM, 76.9% of patients with pulmonary HTN suffered from DM versus 72.7% of patients without pulmonary HTN, showing no statistically significant difference, $p=0.684$. On the other hand, the group with pulmonary HTN showed a significantly higher prevalence of systemic hypertension (84.6% versus 63.6%) of patients without pulmonary HTN, $p=0.039$. Similarly, Jen, Orr, Gilbertson, Fine, Li, and Wong [47], reported that OSA patients suffering from pulmonary HTN had a high prevalence of systemic hypertension. A study done by Itelman [48] concluded that pulmonary arterial hypertension was accompanied by systemic arterial hypertension irrespective of left heart disease.

As for AHI, it was significantly higher among patients with pulmonary HTN (mean AHI 33.70 ± 10.71 versus 25.65 ± 13.42) respectively, $p=0.004$. Our study also showed a significant positive correlation between AHI and PAP ($r=0.761$, $p<0.001$). This agrees with Shehata Me, El-Desoky, El-Razek Maaty, Abd-ElMaksoud, and Suliman [49], who reported that there was a significant positive correlation between AHI and mPAP in OSA

Table 3 Comparing groups of patients with or without pulmonary HTN regarding comorbidities and sleep study parameters ($n=100$)

	Total ($n=100$)		Pulmonary HTN				Test of sig	p
			No ($n=22$)		Yes ($n=78$)			
	No	%	No	%	No	%		
DM								
No	24	24.0	6	27.3	18	23.1	$\chi^2=0.166$	0.684
Yes	76	76.0	16	72.7	60	76.9		
HTN								
No	20	20.0	8	36.4	12	15.4	$\chi^2=4.720^*$	$^{FE}p=0.039^*$
Yes	80	80.0	14	63.6	66	84.6		
History of DVT								
No	94	94.0	18	81.8	76	97.4	$\chi^2=7.421^*$	$^{FE}p=0.020^*$
Yes	6	6.0	4	18.2	2	2.6		
Apnea hypopnea index								
Min.–max	7.70–55.0		7.70–51.30		16.80–55.0		$t=2.940^*$	0.004^*
Mean ± SD	31.93 ± 11.78		25.65 ± 13.42		33.70 ± 10.71			
Median (IQR)	32.0 (22.0 – 39.0)		26.70 (11.30–34.0)		35.0 (26.10–41.0)			
ODI								
Min.–max	1.70–60.0		1.70 31.90		13.70–60.0		$U=666.0$	0.110
Mean ± SD	22.21 ± 13.89		16.32 ± 10.72		23.87 ± 14.28			
Median (IQR)	18.60 (16.10–20.80)		15.0 (7.80–27.0)		18.60 (16.30–20.60)			
t90%								
Min.–max	0.0–38.0		0.0–11.90		0.0–38.0		$U=308.0^*$	$<0.001^*$
Mean ± SD	7.17 ± 8.90		1.94 ± 3.66		8.65 ± 9.39			
Median (IQR)	5.30 (0.90–9.80)		0.10 (0.0–1.30)		6.40 (2.50–11.20)			

IQR Interquartile range, *SD* Standard deviation, *t* Student *t*-test, *U* Mann–Whitney test, χ^2 chi-square test, *FE* Fisher exact, *p* *p*-value for comparing between different categories

* Statistically significant at $p \leq 0.05$

patients. Another study reported that the severity of OSAHs correlated with pulmonary artery pressure [50]. Kholdani, Fares, and Mohsenin [50], explained this by stating that severe OSA is accompanied by repetitive nocturnal arterial oxygen desaturation and swings of the negative intrathoracic pressure with an acute increase in the pressure pulmonary artery. Additionally, intermittent hypoxemia for several hours per day enhanced the remodeling of the pulmonary vasculature and sustained pulmonary hypertension. On the other hand, Kessler, Chaouat, Weitzenblum, Oswald, Ehrhart, and Apprill [41] revealed that AHI was identical in two groups of OSA patients with and without pulmonary HTN. Similarly, we also found that our studied patients with pulmonary HTN showed higher values for ODI than those without pulmonary HTN (mean ODI 23.87 ± 14.28 versus 16.32 ± 10.72), respectively, $p=0.110$. Our study also showed a significant positive correlation between ODI and PAP ($r=0.564$, $p<0.001$). This was in agreement with Shehata Me, El-Desoky, El-Razek Maaty, Abd-ElMaksoud, and Suliman [49], who documented significant positive correlations between mPAP and ODI.

Moreover, T90% was significantly higher among patients with pulmonary HTN in comparison to patients without pulmonary hypertension (mean t90% 8.65% ± 9.39 versus 1.94% ± 3.66)), respectively, $p<0.001$. Esnaud, Gagnadoux, Beurnier, Berrehare, Trzepizur, and Humbert [51] found similar results. This might be explained by increased time of hypoxia at night leading to pulmonary hypertension.

Regarding levels of serum uric acid, the prevalence of hyperuricemia in our studied patients was 74%. It was higher in men 59.5% than in women 40.5% showing a statistically significant difference, $p=0.020$. This agrees with Hirotsu, Tufik, Guindalini, Mazzotti, Bittencourt, and Andersen. The high prevalenceof hyperuricemia (74%) among our patients might be explained by the intermittent state of hypercapnia and hypoxemia caused by OSA. This process results in releasing of purine intermediates which mostly ends with hyper-production of uric acid which is the end product of purine catabolism [52].

According to our studied patients, the group with hyperuricemia was statistically significantly older than the group without hyperuricemia, $p=0.015$. On the other

Table 4 Comparing groups of patients with normal and elevated uric acid levels

	Total ($n=100$)		Uric acid				Test of sig	p
			Normal ($n=26$)		Elevated ($n=74$)			
	No	%	No	%	No	%		
Sex								
Male	66	66.0	22	84.6	44	59.5	$\chi^2=5.426^*$	0.020^*
Female	34	34.0	4	15.4	30	40.5		
Age (years)								
Min.–max	33.0–70.0		33.0–65.0		36.0–70.0		$t=2.464^*$	0.015^*
Mean ± SD	53.04 ± 8.45		49.62 ± 8.66		54.24 ± 8.09			
Median (IQR)	53.0 (49.0–58.0)		53.0 (45.0–55.0)		54.0 (50.0–60.0)			
BMI								
Overweight	6	6.0	6	23.1	0	0.0	$\chi^2=15.601^*$	MC $p<0.001^*$
Obese	90	90.0	20	76.9	70	94.6		
Morbid obese	4	4.0	0	0.0	4	5.4		
Min.–max	25.50–40.96		25.50–38.10		30.44–40.96		$t=4.974^*$	$<0.001^*$
Mean ± SD	34.69 ± 3.10		31.99 ± 3.48		35.64 ± 2.31			
Median (IQR)	35.43 (32.4–36.76)		31.20 (30.60–34.8)		35.99(34.2–36.9)			
ESS								
Normal (≤ 10)	6	6.0	2	7.7	4	5.4	$\chi^2=0.178$	$^{FE}p=0.649$
Abnormal (> 10)	94	94.0	24	92.3	70	94.6		
Min.–max	10.0–20.0		10.0–20.0		10.0–20.0		$t=0.705$	0.485
Mean ± SD	13.90 ± 2.62		13.54 ± 3.24		14.03 ± 2.37			
Median (IQR)	14.0 (12.0–16.0)		12.0 (11.0–15.0)		14.0 (12.0–16.0)			

IQR Interquartile range, *SD* Standard deviation, *t* Student *t*-test, χ^2 chi-square test, *MC* Monte Carlo, *FE* Fisher exact, *p* *p*-value for comparing between different categories

* Statistically significant at $p \leq 0.05$

hand, another study [53] showed no significant difference between both groups regarding their age.

Regarding BMI, it was statistically significantly higher among the group with hyperuricemia than the group with normal uric acid levels, $p<0.001$. In agreement with our results, Hirotsu, Tufik, Guindalini, Mazzotti, Bittencourt, and Andersen [52] also reported significant associations between levels of uric acid and common OSAHS-related risk factors like BMI in their large sample. As for ESS, our studied patients with elevated uric acid levels showed slightly higher values for ESS that were not statistically significant, $p=0.485$.

We found no statistically significant difference between the hyperuricemic group and the normal uric acid level group regarding the presence of DM nor the presence of HTN, $p=0.347$ and 0.648, respectively. Zheng, Song, Wang, Liu, Lin, Du, Xie, Chen, Zheng, Li, Li, and Liu [54] found that OSAHS patients with type 2 diabetes had significantly higher levels of serum uric acid than those without OSAHS, and Hirotsu, Tufik, Guindalini, Mazzotti, Bittencourt, and Andersen [52] also reported significant associations between uric acid level and systemic blood pressure.

Apnea hypopnea index was significantly higher among patients with elevated serum uric acid levels versus patients with normal serum uric acid levels (34.75 ± 11.15) vs (23.90 ± 9.79), respectively, $p<0.001$. Fleming, Ferouz-Colborn, Samoszuk, Azad, Lu, and Riley [55] found that minimum oxygen saturation was an important predictor of levels of uric acid, and oxidative stress was a common pathway link between both OSAHS and the production of uric acid, and AHI showed a significant linear relationship with uric acid.

Similarly, our study showed a significant positive correlation between AHI and serum uric acid level ($r=0.671$, $p<0.001$). Verhulst, Van Hoeck, Schrauwen, Haentjens, Rooman, and Van Gaal [56] also reported that independent of abdominal adiposity, there was an association between the severity of OSAHS and increased levels of serum uric acid.

Regarding ODI, our studied hyperuricemic patients showed higher values for ODI than normouremic patients, but there was no statistically significant difference between the two groups, $p=0.171$.

Nevertheless, our study showed a positive correlation between serum uric acid level and ODI ($r=0.394$,

Table 5 Comparing groups of patients with normal and elevated uric acid level regarding comorbidities and polysomnographic data ($n=100$)

	Total ($n=100$)		Uric acid				Test of sig	*p*
			Normal ($n=26$)		Abnormal ($n=74$)			
	No	%	No	%	No	%		
DM								
No	24	24.0	8	30.8	16	21.6	$\chi^2=0.883$	0.347
Yes	76	76.0	18	69.2	58	78.4		
HTN								
No	20	20.0	6	23.1	14	18.9	$\chi^2=0.208$	0.648
Yes	80	80.0	20	76.9	60	81.1		
DVT								
No	94	94.0	20	76.9	74	100.0	$\chi^2=18.167^*$	$^{FE}p<0.001^*$
Yes	6	6.0	6	23.1	0	0.0		
Apnea hypopnea index								
Min.–max	7.70–55.0		7.70–39.0		16.80–55.0		$t=4.399^*$	$<0.001^*$
Mean ± SD	31.93 ± 11.78		23.90 ± 9.79		34.75 ± 11.15			
Median (IQR)	32.0 (22.0–39.0)		26.60 (17.8–29.60)		35.0 (26.10–45.0)			
ODI								
Min.–max	1.70–60.0		1.70–60.0		15.0–60.0		$U=788.0$	0.171
Mean ± SD	22.21 ± 13.89		19.48 ± 15.47		23.17 ± 13.27			
Median (IQR)	18.60 (16.10–20.80)		15.0 (8.20–27.0)		18.60 (16.50–19.80)			
t90%								
Min.–max	0.0–38.0		0.0–38.0		0.10–38.0		$U=404.0^*$	$<0.001^*$
Mean ± SD	7.17 ± 8.90		4.55 ± 10.42		8.09 ± 8.19			
Median (IQR)	5.30 (0.90–9.80)		0.10 (0.0–1.30)		6.40 (2.90–9.80)			

IQR Interquartile range, *SD* Standard deviation, *t* Student *t*-test, *U* Mann–Whitney test, χ^2 chi-square test, *FE* Fisher exact, *p p*-value for comparing between different categories

* Statistically significant at $p \leq 0.05$

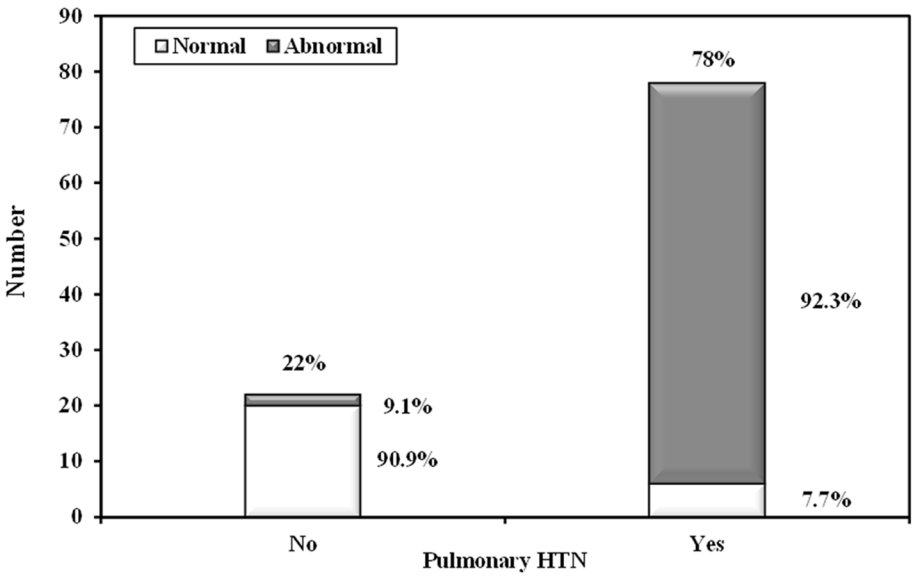

Fig. 1 Comparison between patients with or without pulmonary hypertension regarding uric acid level ($n=100$)

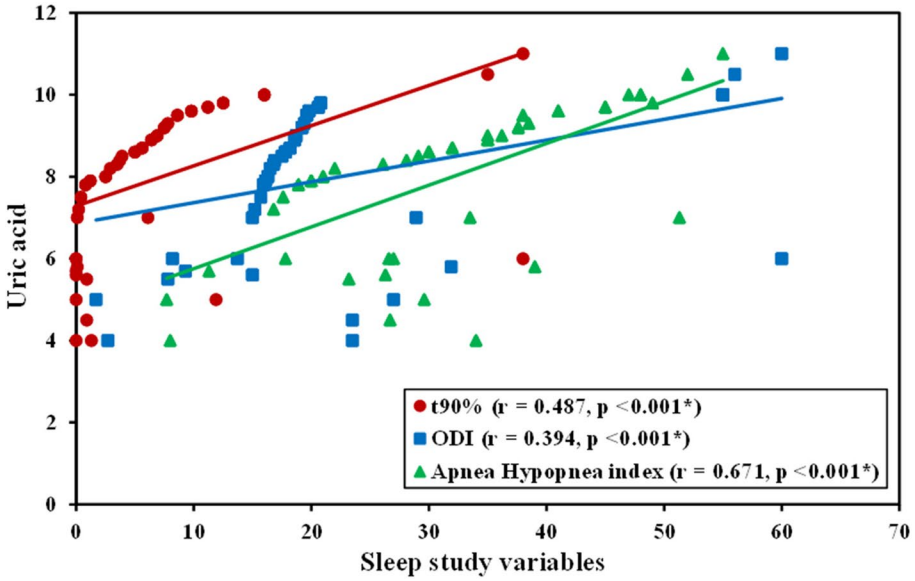

Fig. 2 Correlation between uric acid and sleep study variables ($n = 100$)

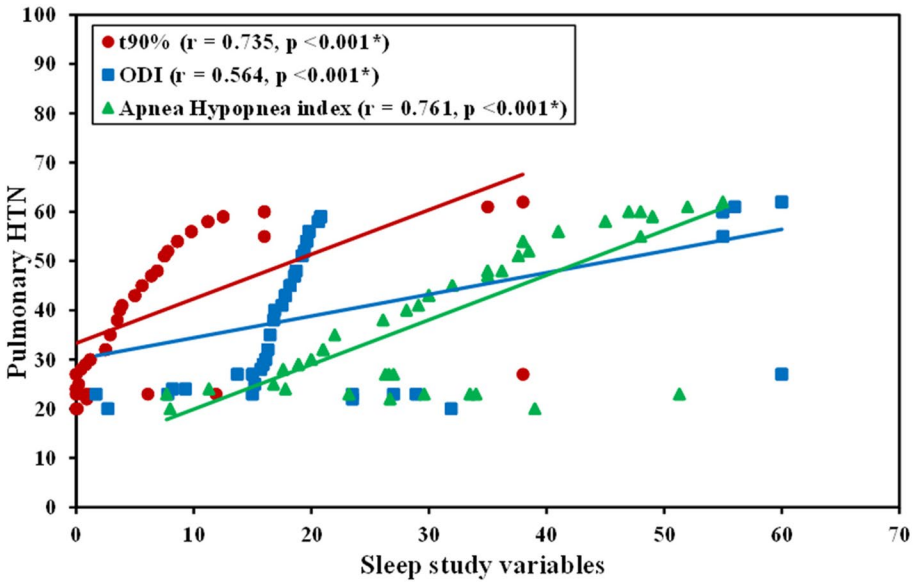

Fig. 3 Correlation between pulmonary HTN and sleep study variables ($n = 100$)

$p < 0.001$). In agreement with our results, Saito, Nishimura, Shibuya, Makita, Tsujino, and Miyamoto [53] found that serum uric acid levels positively correlated with both AHI and ODI in OSAHS patients.

We also found that t90% was significantly higher among our studied hyperuricemic patients than normouricemic patients (mean t90% 8.09 ± 8.19 versus 4.55 ± 10.42), respectively, $p < 0.001$. This matched the result of Hirotsu, Tufik, Guindalini, Mazzotti, Bittencourt, and Andersen [52], Fleming, Ferouz-Colborn, Samoszuk, Azad, Lu, and Riley [55], and Saito, Nishimura, Shibuya, Makita, Tsujino, and Miyamoto [53]. We also found a positive correlation between uric acid level and t90% ($r = 0.487$, $p < 0.001$). This was in agreement with the result of Ozanturk, Ucar, Varol, Koca, Demir, and Kalenci [5], who concluded that T90% was found to be significantly correlated with the excretion of uric acid after adjustments for gender, age,

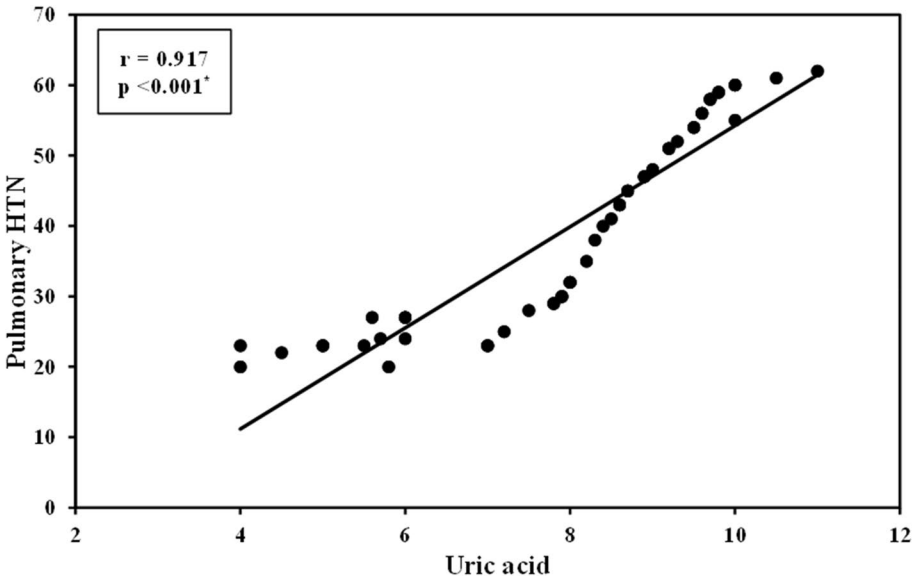

Fig. 4 Correlation between serum uric acid and pulmonary HTN

BMI, and AHI. In our study, there was a positive correlation between the level of uric acid and both pulmonary hypertension ($r=0.917$, $p<0.001$) and AHI ($r=0.671$, $p<0.001$).

The main strength of our study was the fact that all our studied patients underwent full-night polysomnography which is the gold standard diagnostic tool of OSA, and to our knowledge, this is the first study to assess the relationship between OSA, suspected pulmonary HTN, and levels of serum uric acid. Regarding limitations, the small sample size of the study and using echocardiography for screening for pulmonary HTN instead of right heart catheterization are the main limitations.

In conclusion, both serum uric acid level and pulmonary arterial pressure positively correlated with the severity of obstructive sleep apnea. Pulmonary arterial pressure correlated positively with serum uric acid level. Our data suggest that elevated serum uric acid levels in obstructive sleep apnea patients could be used as a predictor of pulmonary hypertension. Both serum uric acid level and pulmonary arterial pressure could be markers of the severity of obstructive sleep apnea. Further studies on a larger scale of patients are recommended. Studies that enroll OSAHS patients free from any other comorbidities could yield more accurate results. The use of standard echocardiogram is only a screening tool for pulmonary hypertension, and further confirmation with right heart catheterization is essential. Furthermore, studies that assess the effect of CPAP treatment on serum uric acid levels in OSAHS with pulmonary arterial hypertension could better confirm the causal association between OSAHS and the studied parameters.

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea hypopnea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
ESS	Epworth Sleepiness Scale
IH	Intermittent hypoxia
mPAP	Mean pulmonary arterial pressure
ODI	Oxygen desaturation index
OSAHS	Obstructive sleep apnea–hypopnea syndrome
PSG	Polysomnogram
SaO2	Arterial oxygen saturation
SRBDs	Sleep-related breathing disorders
T90	Time of oxygen saturation below 90%
UA	Uric acid
WHO	World Health Organization

Authors' contributions

Corresponding author: Dr. RAS, directed the practical part of the research, presenting the results, and writing the manuscript. Prof. Dr. AYS, decided the main idea of the research and the methodology and revised the whole manuscript. GMMB, performed the practical part, statistics, and data collection. Prof. Dr. HAS, guided the practical part and revised the manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was per the ethical standards of the institutional research committee (Alexandria Faculty of Medicine) and with the 1964 Helsinki Declaration. Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interests.

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