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Correlation between severity of pulmonary embolism and obstructive sleep apnea using computed tomography pulmonary artery obstruction index and right ventricular to left ventricular diameter ratio as severity indices

Marwa Makboul^{1*}, Doaa M. Magdy², Ahmed Metwally² and Shimaa Farghaly¹

Abstract

Background Recent studies have shown a bidirectional association between pulmonary embolism (PE) and obstructive sleep apnea (OSA), and due to their morbidity and mortality, this contributes significantly to the global health-care burden, so this study aims to assess the relationship between PE and OSA severity using the obstruction index of the pulmonary artery and the ratio of right ventricular to left ventricular (RV/LV) diameter as severity indices.

Results The study comprised 138 patients with a high clinical suspicion of PE that was verified by computed tomography pulmonary angiography. In addition to calculating the RV/LV diameter ratio and pulmonary artery obstruction index (PAOI), the pulmonary embolism severity index was also calculated, and the Epworth Sleepiness Scale and polysomnography (PSG) were used to assess all patients for OSA. Finally, three groups of patients (< 15% vs. 15–50% vs. > 50%) were created based on the PAOI. Age, gender, neck, and waist circumference showed no significant difference between the three groups, but there were significant correlations between higher PAOI and increased BMI, provoked PE, increased rate of thrombolysis, increase in the recurrence of venous thrombosis, a longer length of hospital stay, and a higher ratio of RV/LV diameter (p value was < 0.05). Regarding PSG, a significant positive correlation was observed between the apnea–hypopnea index (AHI) and higher PAOI as well as the ratio of RV/LV diameter ($r=0.957$, p value < 0.001) and ($r=0.825$, p value < 0.001), respectively, with the obstruction index of the pulmonary artery > 40%, and the ratio of RV/LV diameter > 1 being found to be predictors of severe sleep apnea.

Conclusions We deduced from this study that there is a substantial relationship between the severity of PE and the severity of OSA, as patients with higher obstruction of the pulmonary artery had severe OSA, and both the obstruction index of the pulmonary artery > 40% and the ratio of RV/LV diameter > 1 were considered significant predictors for the severity of OSA among the acute PE patients.

Keywords Pulmonary embolism, Obstructive sleep apnea, Computed tomography pulmonary artery obstruction index, Right ventricular to left ventricular diameter ratio, Polysomnography

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Background

Early diagnosis of massive pulmonary embolism (PE) is very important to start thrombolytic therapy, as it is regarded as a frequent and potentially dangerous cardiovascular illness with a mortality rate of about 30% [1]. Obstructive sleep apnea (OSA) is defined as a respiratory disorder that affects sleep in which the patient repeatedly experiences upper airway blockage that results in hypoxia [2].

Growing data from earlier studies show a bidirectional link between OSA and PE, as OSA is considered a risk factor for PE, and patients with PE have an increased risk of moderate-to-severe OSA [3], and this association represents a major contributor to the health-care burden worldwide due to their morbidity and mortality [4].

PE resulted from Virchow's classic triad, which includes impaired vascular endothelial function, blood flow stasis, and enhanced coagulability. These three mechanistic pathways could be potentially impacted by OSA, as intermittent hypoxia increases oxidative stress, and inflammatory response that impairs endothelial function. Also, the intravenous flow may be slowed by OSA-related hemodynamic changes, which may also increase coagulability, platelet activity, and reduce fibrinolytic capacity. These same pathophysiologic derangements are prothrombotic and could promote the development of venous thromboembolic disease. So, the awareness of the impact of sleep apnea on pulmonary embolism is very important, as it might help doctors spot individuals who may be at risk and give advice to patients on how to treat and lower their risk of developing both sleep apnea and PE [3].

Computed tomography pulmonary angiography (CTPA) is considered the first diagnostic method for the identification of PE [5], and the computed tomography pulmonary artery obstructive index (CTPOI) of Qanadli et al. [6] offers an objective method to assess the degree of obstruction of pulmonary arteries in addition to the identification of pulmonary embolism [7].

The right ventricular dilatation is thought to be an indicator of the right ventricular dysfunction based on the right ventricular to left ventricular (RV/LV) diameter ratio measured on computed tomography pulmonary angiography [8]. The right ventricular dysfunction brought on by pulmonary embolism is associated with a poor prognosis.

In this study, we aim to assess the relationship between OSA severity and PE using the obstruction index of the pulmonary artery and the ratio of RV/LV diameter as severity indices due to the paucity of studies on the association between them.

Methods

Between September 2021 and December 2022, 138 patients of different ages were recruited in this prospective cohort study at Assiut University Hospital's Sleep Lab Center and Diagnostic Radiology Department (Fig. 1). The study included all patients with a strong clinical suspicion of PE based on the Wells score [9] and confirmed by CTPA. The Wells' criteria evaluated the patients' clinical data regarding suspected deep venous thrombosis (DVT) (3 points), an altered diagnosis less likely than PE (3 points), heart rate more than 100 beats/min (1.5 points), immobilization or surgery in the previous 4 weeks (1.5 points), previous DVT (1.5 points), hemoptysis (1 point), and malignancy (1 point). The risks of PE are then assessed according to the scores into low (0–2 points), moderate (3–6 points), and high (>6 points) risks. Each patient was scored separately according to the Wells' criteria, and we considered score of 4 as a cutoff point for conducting CTPA.

Patients under the age of 18, as well as hemodynamic unstable patients and those with contraindications to CTPA such as pregnancy, renal impairment, or sensitivity to contrast material, and with suboptimal images or techniques were excluded from the study.

After clinical stabilization of the acute PE episode, all patients were transported to a sleep center to be evaluated for the existence of sleep abnormalities. The study was approved by the institutional ethics committees, and all patients filled out the consent form.

All patients were subjected to the following:

Age, gender, neck, and waist measurements were recorded along with co-morbid conditions such as diabetes mellitus, chronic pulmonary disease, active cancer, history of venous thromboembolism, acute or chronic heart failure, arterial hypertension, and the type of PE (provoked or unprovoked). Unprovoked PE is defined as PE with no predisposing conditions such as major surgery, immobilization, or active malignancy in the previous 3 months [10].

Pulmonary embolism severity index (PESI): It is a simple and extensively used clinical prognostic score proposed by Aujesky et al. [11] for patients with acute PE. It is composed of 11 indices: age, gender, history of cancer, heart failure, chronic lung disease, temperature < 36 °C, heart rate > 110 beats/min, systolic pressure < 100 mmHg, respiration rate 30 times/min, altered mental status, and arterial oxygen saturation < 90%.

CTPA scanning

Protocol

It was carried out on a Toshiba, Japan, Aquilion 64-channel Multi-detector CT scanner with 16x1.2-mm

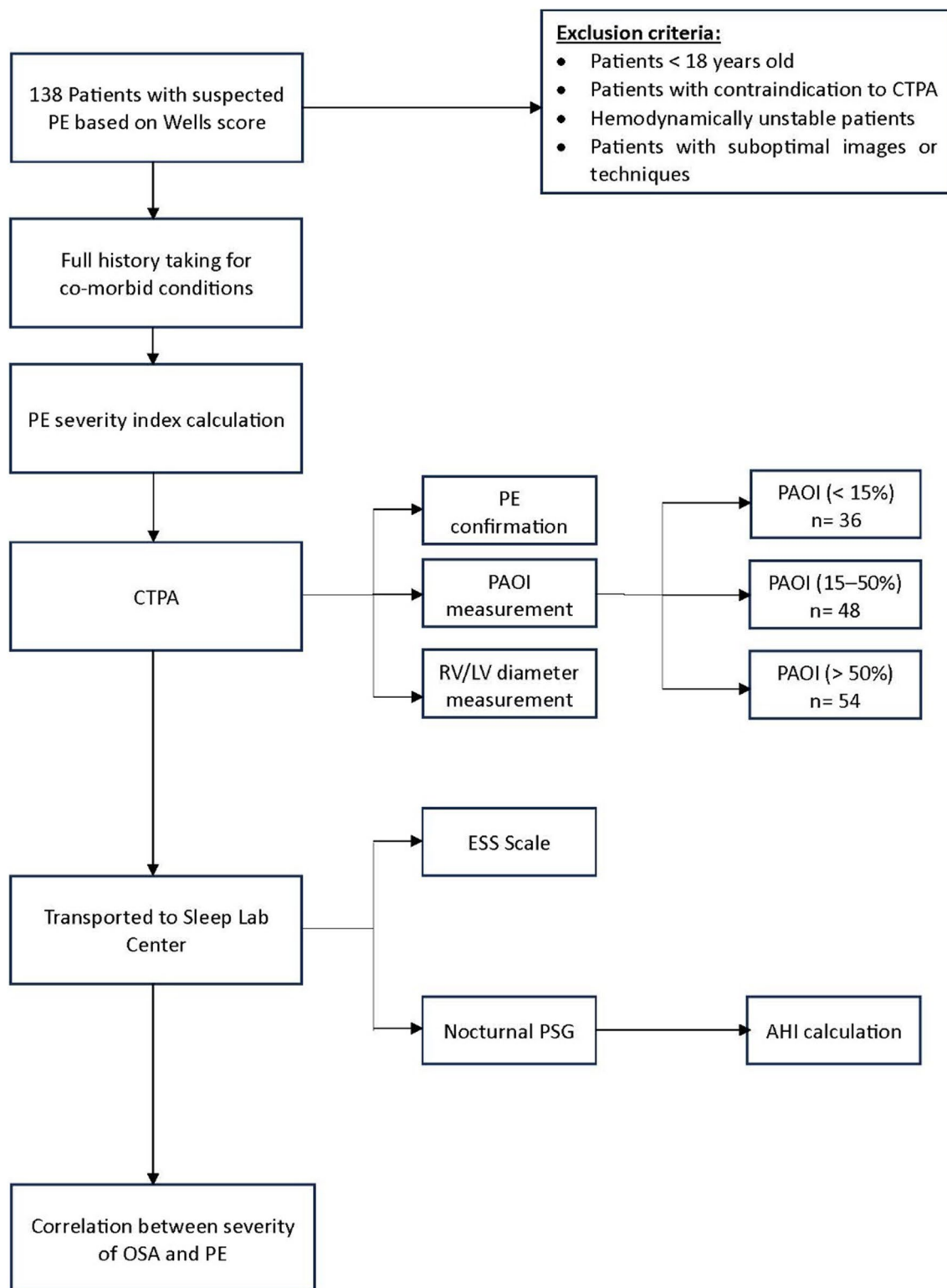


Fig. 1 Flowchart of enrollment of study subjects

collimation, tube current 150–280 mA, and 120–140 kV. The axial images were all reconstructed into 0.625-mm slices. Scanning was done craniocaudally from the apices of the lungs down to the diaphragm during full inspiration, while the patient was supine with his arms over his head, and a 70–90-ml dose of the non-ionic contrast agent Ultravist 370-mg iodine concentration (Iopromide 0.769 g) was automatically injected into the antecubital vein according to the body weight of the patient at a rate of 4 ml/sec.

Image analysis and interpretation

All images were transferred to a Vitrea Vital Image (VPM-C-Revision C) with manufacturer software that allows generation of multiplanar reconstructed images; then, image analysis and interpretation was done by two radiologists of 10–15 years' experience in CT chest imaging.

PE was defined as the presence of non-enhancing endoluminal clots within the pulmonary arteries. Central emboli were defined as emboli within the major arteries, lobar arteries, or both, whereas peripheral emboli are described as emboli outside the main arteries.

Then, the pulmonary artery obstructive index (PAOI) and the ratio of the RV/LV diameter were calculated.

- **PAOI:** Each lung is composed of 10 segmental arteries, with three in the upper lobes, two in the middle lobe and in the lingula, and five in the lower lobes, according to Qanadli et al. [6]. One point was given for an embolus in a segmental artery, and the number of segmental arteries emerging distally was given for central or paracentral emboli. According to the degree of vascular obstruction, each value was given a score (0=no thrombus, 1=partial occlusion, and 2=total occlusion), with the isolated sub-segmen-

tal embolus receiving a value of 1 because it was regarded as a partially occluded segmental artery.

Three groups of patients (<15% vs. 15–50% vs. >50%) were created based on the degree of vascular obstruction [6], with the percentage of obstruction = $\frac{\sum (n.d)}{40} \times 100$, where n = the number of segmental branches arising distally (minimum, 1 and maximum, 20) and d = degree of obstruction (minimum, 0 and maximum, 2) (Fig. 2).

- **Ratio of RV/LV diameter:** It was evaluated using a conventional axial view from the maximal ventricular endocardium to the interventricular septum to assess the right ventricular dysfunction. The right ventricular dysfunction was characterized as a ratio greater than 0.9 (Fig. 3) [12].

The *Epworth Sleepiness Scale (ESS)* was used to assess sleepiness in all study participants [13].

Nocturnal polysomnography (PSG): All patients underwent it, and the outcomes were examined and restored following the accepted standards [14]. By dividing the total number of apneas and hypopneas by the number of hours of recorded nightly sleep, the apnea–hypopnea index (AHI), which measures the combined number of apneas and hypopneas that occur per hour of sleep, was determined.

Statistical analysis

SPSS for Windows, version 15.0, SPSS Inc., Chicago, Illinois, USA, was used to conduct the statistical analysis. After reviewing incidence of PE in critical care units in this studied population, a sample size of 800 patients with an approved PE diagnosis was calculated with a power of

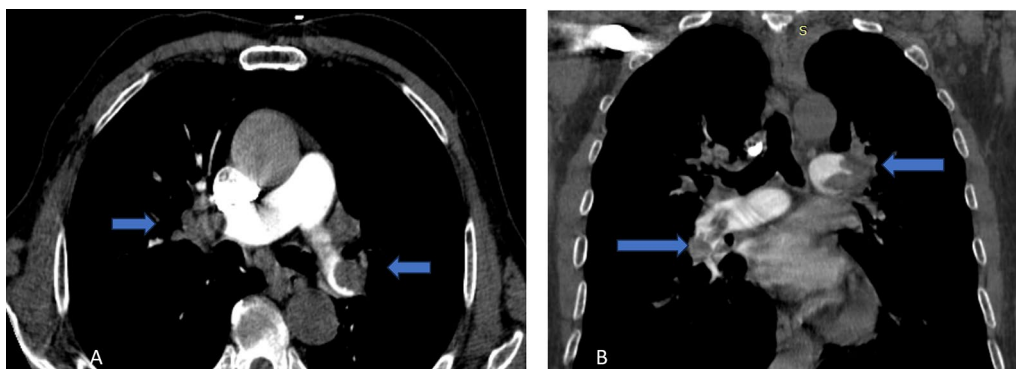


Fig. 2 **A** and **B** Axial and coronal post-contrast MSCT show partial occlusion in both the right and left main pulmonary arteries (arrows), this means that the number of segmental branches arising distally is 10 for each lung, and the obstruction degree is 1, so the pulmonary obstructive index will be $(20 \times 1/40 \times 100) = 50\%$

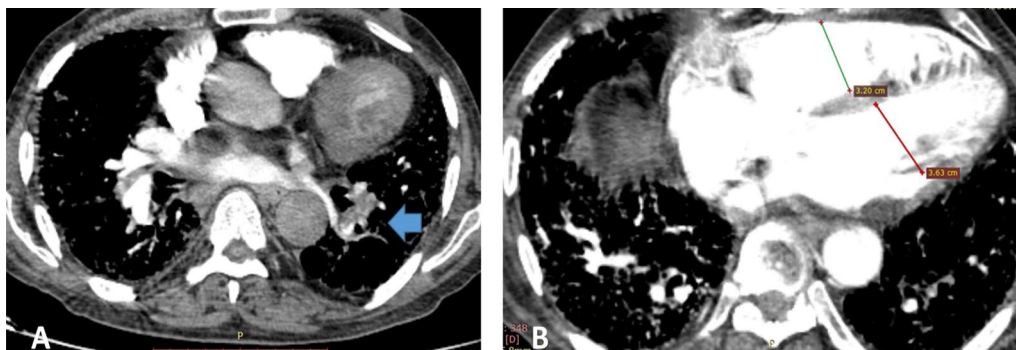


Fig. 3 **A** Axial post-contrast MSCT shows a partially occluded left lower lobar artery (arrow), so the obstructive index was scored as 12.5%. **B** The ratio of RV/LV diameter for the same patient was 0.9 cm

80% and a type I error of 5% to detect the CTPA indices indicating the severity of PE with higher AHI.

The mean, standard deviation, and/or number (%) were used to express the data. The Kolmogorov–Smirnov test was used to analyze the distribution of the variables. We also used Mann–Whitney U and Student’s tests when necessary for evaluating the differences between the two groups of parametric and non-parametric variables. The Chi-square test was used to ascertain how the categorical variables related to one another, and the logistic regression analysis was done to assess the correlation between the AHI and PAOI as well as the ratio of RV/LV diameter. By the way, the variables were distributed, and Pearson correlation analysis was utilized. Statistical significance was defined as a *p* value of 0.05.

Results

One hundred and thirty-eight patients with acute PE verified by CTPA were included in this study, thirty-six, forty-eight, and fifty-four of whom had a PAOI of <15%, 15–50%, and >50%, respectively. Age, sex, neck, and waist circumference were not significantly different across groups. However, a statistically significant correlation was found between patients with greater PAOI and increased BMI ($p < 0.001$), more often provoked PE ($p = 0.001$), an increased rate of thrombolysis ($p < 0.001$), a longer length of hospital stay ($p < 0.001$), an increase in the recurrence of VTE, and a higher ratio of RV/LV diameter ($p < 0.001$) (Table 1).

Snoring was observed in 55.6% of patients with a greater PAOI, and excessive daytime drowsiness was prevalent in 38.9% of these patients. Additionally, the Epworth Sleepiness Scale increased significantly. According to PSG records, an increase in the PAOI resulted in a statistically significant increase in the AHI, obstructive apnea, and hypopnea indices. Patients with a higher

PAOI also had a significantly higher desaturation index and time on oxygen (Table 2).

The mean percentages of PAOI and AHI have a significant correlation ($r = 0.957$, $p < 0.001$), with the mean percentage of PAOI being 32.521.9% (range 5–70%) (Fig. 4). Additionally, a significant correlation ($r = 0.825$, $p < 0.001$) between the RV/LV diameter ratio and AHI was found (Fig. 5 and Table 3). We also deduced using the logistic regression analysis that the ratio of RV/LV diameter > 1 and the obstruction index of the pulmonary artery > 40% were significant predictors of severe sleep apnea among acute PE patients. However, neck and waist circumference were not thought to be predictors (Table 4).

Discussion

PE and OSA continue to be substantial global health concerns. Additionally, there are many risk factors and pathogenic mechanisms that both share, and recent studies now consider OSA a separate risk factor for PE. Due to the high prevalence of OSA and the high morbidity and mortality rates associated with PE, this is regarded as a major concern [7, 15].

The main conclusions of the current study are that patients with higher PAOI had significantly higher OSA severity as determined by PSG and also a significantly higher desaturation index and time spent with oxygen, and the obstruction index of the pulmonary artery > 40% and the ratio of RV/LV diameter > 1 were significant predictors of severe sleep apnea among acute PE patients. This is consistent with Toledo et al.’s findings [16], which showed that 45.8% of patients with acute PE had AHI > 15 events/h, and the majority of those with moderate-to-severe OSA (AHI > 15) had obstruction index in the third and fourth quartiles as opposed to those in the group with AHI < 15 events/h, as they evaluated whether OSA is connected to PE severity scores and looked at OSA prevalence among 120 acute PE patients. Similarly, a

Table 1 Patient baseline characteristics by PAOI

	PAOI < 15% (n = 36)	PAOI 15–50% (n = 48)	PAOI > 50% (n = 54)	P1	P2	P3
Age (years)	50.4 ± 8.4	49.5 ± 9.3	50.6 ± 7.8	0.543	0.234	0.321
Female/male [n (%)]	15(41.7%)/21(58.3%)	27(56.2%)/21(43.8%)	24(44.4%)/30(55.6%)	0.345	0.326	0.321
BMI (kg/m ²)	27.22 ± 3.2	26.41 ± 4.1	29.11 ± 4.1	0.543	0.001	0.001
Neck circumference (cm)	39.4 ± 4.2	40.5 ± 3.7	40.8 ± 5.6	0.543	0.234	0.321
Waist circumference (cm)	104.4 ± 4.6	103.6 ± 5.2	104.3 ± 5.2	0.436	0.121	0.325
Smoking: n(%)	18(50%)	15(31.2%)	30(55.6%)	0.243	0.342	0.432
Hypertension: n(%)	24(66.7%)	15(31.2%)	27(50%)	0.001	0.001	0.000
Diabetes mellitus: n(%)	12(33.3)	18(37.5%)	18(33.3%)	0.342	0.032	0.043
Heart failure ^a n(%)	9(25%)	15(31.2%)	12(22.2%)	0.002	0.432	0.342
Chronic pulmonary disease ^b n(%)	15(41.7%)	18(37.5%)	18(33.3%)	0.001	0.012	0.321
Provoked PE: n (%)	0(0)	9(18.7%)	12(22.2%)	0.001	0.002	0.001
Recurrent VTE: n (%)	3(8.3%)	0(0)	9(16.7%)	0.000	0.001	0.002
<i>Treatment</i>						
Thrombolytic, n (%)	0(0)	6(12.5)	33(61.1%)	0.001	0.002	0.000
Hospitalization duration (days)	5.2 ± 1.1	7.2 ± 1.1	10.3 ± 2.5	0.001	0.000	0.000
PESI (points)	96.2 ± 2.1	97.4 ± 1.4	104.4 ± 2.1	0.213	0.001	0.001
RV/LV diameter ratio	0.9 ± 0.1	1.1 ± 0.19	1.3 ± 0.15	0.014	0.001	0.000

PAOI/pulmonary arterial obstruction index, BMI body mass index, VTE venous thromboembolism, PESI pulmonary embolism severity index, RV right ventricular, and LV=left ventricular

^a Heart failure = systolic or diastolic heart failure left or right-sided heart failure or a known left ventricular ejection fraction of < 40%

^b Chronic pulmonary disease = chronic obstructive pulmonary disease, asthma, lung fibrosis, or bronchiectasis

Table 2 Baseline polysomnographic parameters

	PAOI < 15% (n = 36)	PAOI 15–50% (n = 48)	PAOI > 50% (n = 54)	P1	P2	P3
ESS scale	9.2 ± 1.2	9.3 ± 2.4	11.3 ± 3.1	0.342	0.001	0.001
Snoring, n%	12(33.3%)	15(31.2%)	30(55.6%)	0.432	0.002	0.000
Excess daytime sleepiness, n%	9(25%)	12(25%)	21(38.9%)	0.761	0.001	0.001
AHI	10.9 ± 2.5	15.2 ± 3.8	25.6 ± 2.3	0.002	0.000	0.000
Obstructive index: (n/h)	5.6 ± 3.04	6.37 ± 4.5	8.6 ± 8.2	0.629	0.341	0.241
Hypopnea index: (n/h)	4.45 ± 1.8	5.04 ± 1.3	7.09 ± 1.9	0.324	0.001	0.001
Desaturation index: (n/h)	5.39 ± 3.4	9.2 ± 3.40	15.1 ± 3.8	0.006	0.000	0.000
Minimum SaO ₂ %	69.5 ± 5.08	66.6 ± 4.8	65.2 ± 5.06	0.139	0.415	0.031
T 90%, min	4.37 ± 3.3	8.7 ± 4.6	13.1 ± 6.2	0.011	0.027	0.000

Values expressed as mean ± SD. * = significant difference. ESS = Epworth Sleepiness Scale

AHI = apnea hypopnea index n/h sleep; Min. SaO₂% = minimum arterial oxygen saturation, and SaO₂ < 90% min = time in bed with oxygen saturation < 90% in minutes

cross-sectional study Konnerth et al. [17] that included 253 patients (89 with AHI ≥ 15 events/h) showed that moderate-severe OSA was significantly more frequent among intermediate and high-risk PE patients, compared with the low-risk PE group.

Advanced published studies that have been conducted on PAOI and RV/LV diameter ratio concluded that they can be used as reproducible and objective tools to stratify

the severity of pulmonary embolism [7, 18]. Also, recent studies that support the link between OSA and PE have found a high prevalence of sleep-disordered breathing in patients who have DVT or PE [18, 19], which was in agreement with the results of our research.

Additionally, this study found that snoring and excessive daytime sleepiness (EDS) were more common clinical manifestations in patients with higher PAOI by

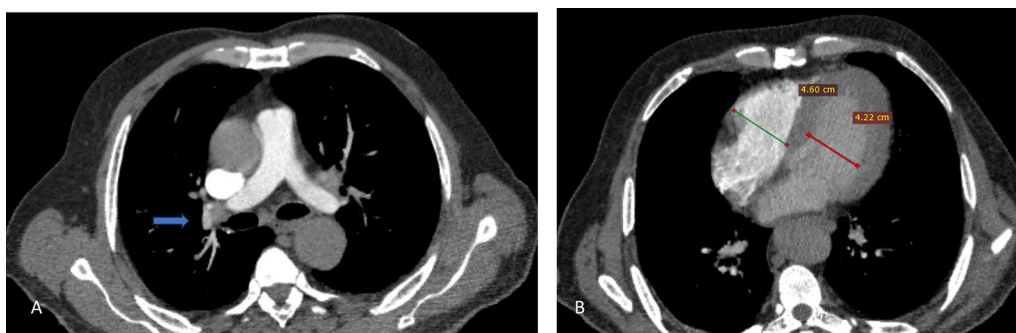


Fig. 4 **A** Axial post-contrast MSCT shows a partially occluded right main pulmonary artery, so the obstructive index was scored as 25%. **B** The ratio of RV/LV diameter for the same patient was 1.06 cm

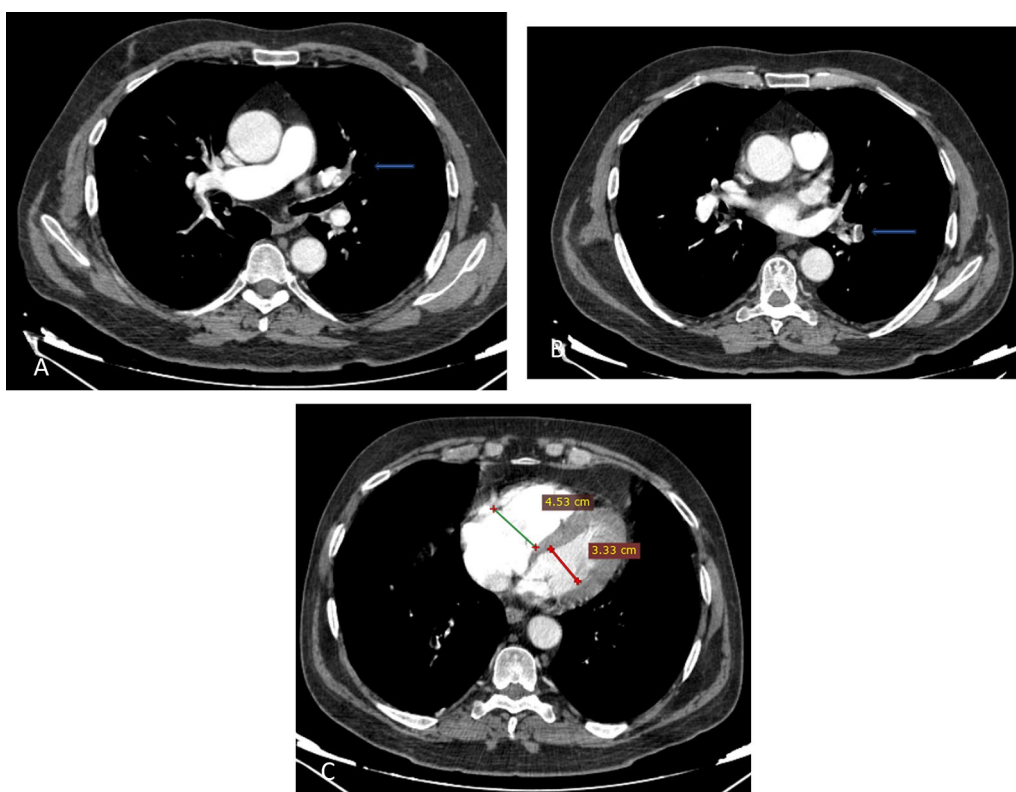


Fig. 5 Axial post-contrast MSCT. **A** A partially occluded left upper lobe segmental branch. **B** A partially occlusive clot involving the left lower lobe segmental branch, so the obstructive index was scored as 5%. **C** The ratio of RV/LV diameter for the same patient was 1.3 cm

Table 3 Association of PAOI, RV/LV diameter ratio, and PESI with AHI

	<i>r</i>	P value
PAOI [#]	0.957	0.000
RV/LV diameter ratio	0.825	0.000
PESI	0.821	0.324

[#] Calculated as the mean of percentage, *PAOI* pulmonary arterial obstruction index, *RV* right ventricular, *LV* left ventricular, *PESI* pulmonary embolism severity index, and *AHI* apnea hypopnea index *n/h* sleep

Table 4 Logistic regression analysis of CT parameters and AHI

	<i>p</i> value	OR	95% CI	
			Lower	Upper
PAOI > 40%	0.000	1.34	0.91	1.59
RV/LV > 1	0.000	2.791	1.472	4.252
Neck circumference (≥ 40 cm)	0.831	3.19	2.66	5.14
Waist circumference (≥ 102 cm)	0.223	2.45	1.65	5.16

OR odds ratio and CI confidence interval

55.6% and 38.6%, respectively. These findings are consistent with those of Epstein et al. [20], who found that PE patients with OSA risk were more likely to complain of snoring. However, Kosoval et al. [21] assessed the clinical symptoms of OSA in patients with acute PE and discovered that witnessed apnea and snoring were more prevalent in the control group.

The main limitation of our study is that hemodynamic unstable patients with massive PE were excluded, as if this group was included, the correlation between OSA and PE could be more obvious, and probably, the results could have been different. Also, because of a limited number of comparable studies, the results were interpreted with caution, and an updated meta-analysis should be conducted with inclusion of recent researches in the future.

Conclusions

We deduced from this study that the patients with higher pulmonary arterial obstruction had severe OSA, and both the obstruction index of the pulmonary artery >40% and the ratio of RV/LV diameter >1 were considered significant predictors for the severity of OSA among the acute PE patients.

Abbreviations

OSA	Obstructive sleep apnea
PE	Pulmonary embolism
CTPA	Computed tomography pulmonary angiography
CTPOI	Computed tomography pulmonary artery obstructive index
PAOI	Pulmonary artery obstructive index
DVT	Deep venous thrombosis
PESI	Pulmonary embolism severity index
ESS	Epworth Sleepiness Scale
PSG	Polysomnography
RV/LV	Right ventricular to left ventricular
AHI	Apnea-hypopnea index

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Author contributions

All authors wrote and provided feedback on the initial draft of the paper, and all authors reviewed and approved the final version. All writers participated in the conception and design of the study. They also prepared the materials, collected the data, and conducted the analysis.

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Availability of data and materials

The corresponding author will provide the datasets used or analyzed during the current work upon reasonable request.

Declarations

Ethics approval and consent to participate

According to the guidelines of the Helsinki Declaration, this study was conducted. The Assiut University Ethics Committee approved the request. Each patient who took part in the study signed an informed consent form.

Consent for publication

Each patient who took part in the study signed the informed permission form for publication.

Competing interests

The authors declare no competing interests.

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