ORIGINAL ARTICLE

Relationship between obstructive sleep apnea and 30-day mortality among patients with pulmonary embolism

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Background: Pulmonary embolism (PE) is the most life-threatening form of venous thrombosis which causes the majority of mortalities in this category. Obstructive sleep apnea (OSA) has been indicated as one of the risk factors for thromboembolism because of hemostatic alterations. The present study was designed to seek for the relationship between OSA and 30-day mortality of patients with PE. **Materials and Methods:** This prospective cohort study was conducted among 137 consecutive patients referred to hospital with symptoms of PE and preliminary stable hemodynamic. Confirmation of PE was made by multislice computed tomography pulmonary angiography and in the case of contraindication; V/Q lung scan and Doppler sonography were done. A STOP-Bang Questionnaire was used to determine patients with high- and low-risk of OSA. Patients were followed up for 1-month, and their survivals were recorded. **Results:** This study showed that there was no relationship between OSA and 30-day mortality ($P = 0.389$). Chronic kidney disease ($P = 0.004$), hypertension ($P = 0.003$), main thrombus ($P = 0.004$), and segmental thrombus ($P = 0.022$) were associated with 30-day mortality. In the logistic regression analysis, history of chronic kidney disease was diagnosed as a risk factor for 30-day mortality among the PE patients ($P = 0.029$, odds ratio = 4.93). **Conclusion:** Results of this study showed 30-day mortality was not affected by OSA directly. In fact, it was affected by complications of OSA such as hypertension and thrombus. Also, positive history of chronic kidney disease increased the risk of 30-day mortality.

Key words: 30-day mortality, obstructive sleep apnea, pulmonary embolism, STOP-Bang Questionnaire

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INTRODUCTION

Venous thromboembolism (VTE) is the existence of blood clots in venous blood system; it nearly affects more than 300,000 people in the United States annually and leads to at least 100,000 deaths.[1] The most prevalent form of it is deep venous thrombosis (DVT), and the most life-threatening form is a pulmonary embolism (PE) which causes the majority of mortalities in this category. The right ventricular dysfunction is a main cause of death in PE patients. Several risk factors have been determined for PE including genetic and acquired factors.[2,3] PE is the third prevalent cause of an acute cardiovascular disease after acute infarction and cerebrovascular disease. In 2006, nearly 250,000 ones were hospitalized because of PE in the United States of America. In 2005, average 30-day mortality among 140,000 of PE patients was 9%.[2]

Obstructive sleep apnea (OSA) is defined as an incident of repetitive airway obstruction during sleep time which ends in sleep disruption accompanied by oxygen desaturation.[4] It is one of prevalent sleep breathing disorders[5] which causes Cognitive-functional disorders and medical complications because of daytime sleepiness and hypoxia during sleep.[6] OSA is known as one of risk factors for cardiovascular and cerebrovascular diseases such as myocardial infarction, congestive heart failure, hypertension, coronary artery disease, and stroke.[7-12] Also according to recent studies, OSA has been indicated as one of the risk factors for thromboembolism including

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DVT and PE because of hemostatic alterations.[5,13-17] Major symptoms of OSA among the adults are sleepiness, fatigue, concentration problems, snoring, and restlessness during the night. The prevalence of this disorder at the age of 18-45 increases and it changes into plateau between the age of 55 and 65.[6] Its prevalence has been reported to be 2-10% among the adult population in the United States.[18] The main diagnostic tool for OSA is polysomnography but most of time, it is not possible. So using designed questionnaire for this purpose is more common. Among all of them STOP-Bang questionnaire has more methodological validity.[6]

Most of the researches have been studied the prevalence of OSA among PE patients and the relation between OSA and PE,[19-21] however, no study considered 30-day mortality. So the present study was designed to seek for the relationship between OSA and 30-day mortality among patients with PE.

MATERIALS AND METHODS

Study population

This prospective cohort study was conducted between January 21, 2015 and July 23, 2015 in Al-Zahra Educational Medical Center, Isfahan, Iran. The studied population was all referred patients to Al-Zahra hospital with symptoms of PE and preliminary stable hemodynamic within mentioned 6 months and then they were hospitalized.

Inclusion criteria were all patients with PE confirmed by multislice computed tomography (CT) pulmonary angiography and preliminary stable hemodynamic (systolic blood pressure at least 90 mmHg). Exclusion criteria were dissatisfaction of patient for participating in the project, impossibility of 1-month follow-up, negative results of D-dimer, natural results of CT pulmonary angiography or V/Q scan, death before diagnostic tests, and incomplete information. Isfahan University of Medical Sciences approved the study protocol (Research Project Number: 393245).

At first patients had been admitted to Emergency Department of Al-Zahra in mentioned period of time with probable symptoms of PE including orthopnea (≥2 pillow), chest pain, pleuritic pain, cough, hemoptysis, wheeze, palpitation, inflation sign (tenderness, unilateral erythema in lower-extremity with remarkable change in size). In physical examination, patients with tachypnea (respiratory rate ≥ 20/min), tachycardia (100/min), increased P2 in heart examination, rales, and crackles in their lungs, distinct signs of DVT and preliminary stable hemodynamic were considered for more tests.

According to Wells score, patients were categorized into two groups: High-risk (Wells score > 4) and low-risk (Wells score ≤4) patients.[22] Among high-risk patients, the diagnosis was confirmed with multislice CT pulmonary angiography according to the protocols of Al-Zahra hospital. In low-risk patients, at the first D-dimer test was done quantitatively by ELISA or metric immunoassay methods; in the case of negative results, patients were excluded from the study. For patients with positive D-dimer tests, the diagnosis was confirmed by multidetector multislice CT pulmonary angiography and clinical tests and then the subject could be enrolled to the study. The CT scans were reported by two independent radiologists. In the case of contraindication for CT pulmonary angiography (such as severe renal insufficiency and venous contrast sensitivity), the combination method of V/Q lung scan and lower-extremity Doppler sonography were used. Although, pregnancy was not among absolute contraindication for CT pulmonary angiography, alternative methods were used for pregnant women in their third trimester of pregnancy to prevent probable complications. Findings of echocardiography and blood pressure were recorded.

After diagnosis and start of treatment, the patients were transferred to pulmonary division or Intensive Care Unit. Then patients filled the consent form and information was collected by a check list. Follow-up was done by telephone or physical presence. This study did not interfere with a treatment at all. Patients were followed up for 1-month, and their mortality was recorded. End of the study was defined 1-month after the entrance to the study or patients' death.

Measurements

A STOP Questionnaire was filled by all participants and used to determine patients with high- and low-risk of OSA. The STOP-Bang scoring model consists of 8 yes/no questions including 4 main questions about snoring, tiredness during daytime, observed apnea, blood pressure, and an additional score is considered for each of the following clinical data: Body mass index (BMI) >35 kg/m^2, age >50 years, neck circumference >40 cm, and male gender. High-risk of OSA is defined as answering yes to three or more items out of 8 items. The sensitivities of the STOP-Bang questionnaire were 83.6% for apnea-hypopnea index (AHI) >5, 92.9% for AHI >15, and 100% for AHI >30 as AHI cut-off points. The corresponding negative predictive value were 60.8%, 90.2%, and 100%, respectively.[23] Among all screening questionnaire for OSA, STOP and STOP-Bang questionnaire in surgical patients are suggested due to higher methodological quality and easy to use characteristics.[6] Also in this study, the scores were categorized into three groups to increase the accuracy: Low-risk (≤3), intermediate-risk (4-6) and high-risk (>6) patients.

All other required information was extracted from checklist including age, weight, height, and history of patient in ischemic heart disease, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, diabetes

mellitus, hyperlipidemia, cancer, trauma, surgery, VTE, main thrombus, and segmental thrombus. BMI was calculated by weight and height, and patients were categorized into normal (18.5 ≤ BMI ≤ 24.99), overweight (25 ≤ BMI ≤ −29.99), obesity Grade 1 (30 ≤ BMI ≤ 34.99) and obesity Grade 2 (3 ≤ BMI ≤ 39.9), and morbid obesity (BMI ≥ 40).[24]

Statistical methods

Continuous variables are reported as a mean ± standard deviation. In order to compare frequency, Chi-square test or exact Fisher's test was used. For controlling confounders logistic regression was performed; mortality was considered as dependent variable and sex, ischemic heart disease, chronic kidney disease, main thrombus, segmental thrombus, and OSA were included in the model as independent variables. All analysis was done with IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY. The significant level was 0.05.

RESULTS

A total of 137 consecutive patients were eligible to enter to the study. Among them, 30.7% of patients were low-risk of OSA and 69.3% of them were high-risk of OSA. Mean of Age was 48.64 ± 18.38 and 63.26 ± 10.31 in low- and a high-risk group, respectively. Average of BMI was 23.78 ± 2.35 in the low-risk group and 33.57 ± 3.90 in a high-risk group. Mortality was 16.7% in low-risk and 27.4% in a high-risk group. Characteristics of patients at admission were reported in Table 1.

Result of Chi-square test or Fisher's exact test showed that there was association between OSA and BMI ($P < 0.001$), ischemic heart disease ($P < 0.001$), hypertension ($P < 0.001$), diabetes mellitus ($P < 0.001$), hyperlipidemia ($P < 0.001$), cancer ($P = 0.046$), surgery ($P = 0.011$), and segmental thrombus ($P = 0.026$). However, no association was seen between OSA and sex ($P = 0.77$), Chronic obstructive pulmonary disease ($P = 0.6$), chronic kidney disease ($P = 0.503$), Trauma ($P = 1$), VTE ($P = 0.776$), and main thrombus ($P = 0.178$) [Table 1].

Considering three categories for OSA, association had been seen between OSA and BMI ($\chi^2 = 195.81$, $P < 0.001$), ischemic heart disease ($\chi^2 = 24.97$, $P < 0.001$), hypertension ($\chi^2 = 77.24$, $P < 0.001$), diabetes mellitus ($\chi^2 = 29.58$, $P < 0.001$), hyperlipidemia ($\chi^2 = 64.78$, $P < 0.001$), cancer ($P = 0.004$), trauma ($P = 0.031$), and surgery ($\chi^2 = 9.73$, $P = 0.008$). However, there was no association between OSA and sex ($\chi^2 = 0.18$, $P = 0.912$), chronic obstructive pulmonary disease ($\chi^2 = 4.8$, $P = 0.091$), chronic kidney disease ($P = 0.117$), VTE ($\chi^2 = 1.98$, $P = 0.372$), main thrombus ($\chi^2 = 1.99$, $P = 0.369$), and segmental thrombus ($\chi^2 = 5.08$, $P = 0.079$).

Table 1: Characteristics of patients at admission in low- and high-risk group of OSA

Variables	Low-risk of OSA ($n = 42$) (%)	High-risk of OSA ($n = 95$) (%)	χ^2	P
Sex				
Female	17 (40.5)	41 (43.2)	0.086	0.77
Male	25 (59.5)	54 (56.8)		
BMI				
18.5-24.99	26 (61.9)	0 (0)	97.173	<0.001
25-29.99	15 (35.7)	15 (15.8)		
30-34.99	1 (2.4)	29 (30.5)		
≥35	0 (0)	51 (53.7)		
Ischemic heart disease				
Yes	3 (7.1)	36 (37.9)	13.53	<0.001
No	39 (92.9)	59 (62.1)		
Chronic obstructive pulmonary disease				
Yes	6 (14.3)	17 (17.9)	0.27	0.6
No	36 (85.7)	78 (82.1)		
Hypertension				
Yes	3 (7.1)	79 (83.2)	70.03	<0.001
No	39 (92.9)	16 (16.8)		
Chronic kidney disease				
Yes	2 (4.8)	9 (9.5)	–	0.503*
No	40 (95.2)	86 (90.5)		
Diabetes mellitus				
Yes	6 (14.3)	45 (47.4)	13.64	<0.001
No	36 (85.7)	50 (58.1)		
Hyperlipidemia				
Yes	1 (2.4)	35 (36.8)	17.85	<0.001
No	41 (97.6)	60 (63.2)		
Cancer				
Yes	7 (16.7)	5 (5.3)	–	0.046*
No	35 (83.3)	90 (94.7)		
Trauma				
Yes	2 (4.8)	6 (6.3)	–	1*
No	40 (95.2)	89 (93.7)		
Surgery				
Yes	11 (26.2)	9 (9.5)	6.53	0.011
No	31 (73.8)	86 (90.5)		
Venous thromboembolism				
Yes	4 (9.5)	12 (12.6)	–	0.776*
No	38 (90.5)	83 (87.4)		
Main thrombus				
Yes	13 (31)	41 (43.2)	1.817	0.178
No	29 (69)	54 (56.8)		
Segmental thrombus				
Yes	36 (85.7)	64 (67.4)	4.97	0.026
No	6 (14.3)	31 (32.6)		

Data are presented as number (percentage within OSA group); *Fisher's exact test; OSA = Obstructive sleep apnea; BMI = Body mass index

To assess the relationship between mortality and other variables, results of Chi-square test or Fisher's exact test showed that mortality with hypertension ($P = 0.003$), chronic kidney disease ($P = 0.004$), main thrombus

(P = 0.004), and segmental thrombus (P = 0.022) were associated significantly. However, there was not significant association between mortality and OSA (P = 0.177), sex (P = 0.103), BMI (P = 0.123), ischemic heart disease (P = 0.249), chronic obstructive pulmonary disease (P = 0.189), diabetes mellitus (P = 0.478), hyperlipidemia (P = 0.131), cancer (P = 0.293), trauma (P = 0.679), surgery (P = 1), and VTE (P = 1) [Table 2].

Considering three categories for OSA, results showed that mortality was not related to OSA (χ^2 = 2.79, P = 0.248).

To evaluate the relationship between mortality and OSA in the presence of other risk factors, logistic regression was performed. Results showed that the only significant variable was chronic kidney disease (P = 0.029, odds ratio [OR] = 4.93, 95% confidence interval [CI] for OR = [1.17, 20.71]). However, OSA was not significant (P = 0.389, OR = 1.582, 95% CI for OR = [0.56, 4.49]) [Table 3].

DISCUSSION

The result of this study showed that there was no relationship between OSA and 30-day mortality. However, history of chronic kidney disease was diagnosed as a risk factor for 30-day mortality among PE patients; in patients with history of chronic kidney disease, the odds of mortality was 4.93 times higher than patients without history of chronic kidney disease. In addition to chronic kidney disease, results of the univariate analysis revealed that hypertension, main thrombus, and segmental thrombus were associated with 30-day mortality. The association between mortality and main thrombus was stronger than segmental thrombus.

To the best knowledge of authors, there are rare researches which have studied the relationship between mortality of PE patients and their OSA status. Most of the studies have confirmed the relationship between OSA and PE. Arzt *et al*.[5] investigated the prevalence of sleep-disorder breathing (SDB) among DVT and/or acute PE patients in a nested case-control study. Eighty-two patients with DVT and/or PE were matched by patients without DVT and/or PE according to their sex, age, and BMI. Respiratory disturbance index was measured by polygraphy to diagnose the mild, moderate, and severe degree of SDB. The prevalence of SDB was significantly greater in case group (40%) in comparison with control group (26%) (P = 0.046). Also, multivariate binary regression analysis between thromboembolic events and risk factors showed that SDB was significantly related to DVT and/or PE (OR = 2.28, P = 0.046). However, sex-specific subanalysis revealed that this association was only significant in females (OR = 4.14, P = 0.042) and not in males (OR = 1.55, P = 0.391).

Table 2: Mortality status of patients

Variables	Alive (%)	Dead (%)	χ^2	P
OSA				
Low-risk (*n*=42)	35 (83.3)	7 (16.7)	1.82	0.177
High-risk (*n*=95)	69 (72.6)	26 (27.4)		
Sex				
Female (*n*=58)	40 (69)	18 (31)	2.655	0.103
Male (*n*=79)	64 (81)	15 (19)		
BMI				
18.5-24.99 (*n*=26)	21 (80.8)	5 (19.2)	5.785	0.123
25-29.99 (*n*=30)	27 (90)	3 (10)		
30-34.99 (*n*=30)	20 (66.7)	10 (33.3)		
≥35 (*n*=51)	36 (70.6)	15 (29.4)		
Ischemic heart disease				
Yes (*n*=39)	27 (69.2)	12 (30.8)	1.33	0.249
No (*n*=98)	77 (78.6)	21 (21.4)		
Chronic obstructive pulmonary disease				
Yes (*n*=23)	15 (65.2)	8 (34.8)	1.73	0.189
No (*n*=114)	89 (78.1)	25 (21.9)		
Hypertension				
Yes (*n*=82)	55 (67.1)	27 (32.9)	8.728	0.003
No (*n*=55)	49 (89.1)	6 (10.9)		
Chronic kidney disease				
Yes (*n*=11)	4 (36.4)	7 (63.6)	–	0.004*
No (*n*=126)	100 (79.4)	26 (20.6)		
Diabetes mellitus				
Yes (*n*=51)	37 (72.5)	14 (27.5)	0.5	0.478
No (*n*=86)	67 (77.9)	19 (22.1)		
Hyperlipidemia				
Yes (*n*=36)	24 (66.7)	12 (33.3)	2.28	0.131
No (*n*=101)	80 (79.2)	21 (20.8)		
Cancer				
Yes (*n*=12)	11 (91.7)	1 (8.3)	–	0.293*
No (*n*=125)	93 (74.4)	32 (25.6)		
Trauma				
Yes (*n*=8)	7 (87.5)	1 (12.5)	–	0.679*
No (*n*=129)	97 (75.2)	32 (24.8)		
Surgery				
Yes (*n*=20)	15 (75)	5 (25)	–	1*
No (*n*=117)	89 (76.1)	28 (23.9)		
Venous thromboembolism				
Yes (*n*=16)	12 (75)	4 (255)	–	1*
No (*n*=121)	92 (76)	29 (24)		
Main thrombus				
Yes (*n*=54)	34 (63)	20 (37)	8.17	0.004
No (*n*=83)	70 (84.3)	13 (15.7)		
Segmental thrombus				
Yes (*n*=100)	81 (81)	19 (19)	5.24	0.022
No (*n*=37)	23 (62.2)	14 (37.8)		

Data are presented as number (percentage within variables); *Fisher's exact test; OSA = Obstructive sleep apnea; BMI = Body mass index

In another study by Bosanquet *et al*.[14] the relationship between OSA and VTE was studied. In this retrospective study, 840 patients were found with VTE and their

Table 3: Logistic regression analysis between mortality and potential risk factors

Variables	OR	95% CI	*P*
Sex	0.49	0.21-1.16	0.104
Ischemic heart disease	1.12	0.42-2.98	0.823
Chronic kidney disease	4.93	1.17-20.71	0.029
Main thrombus	2.57	0.73-9.01	0.141
Segmental thrombus	1.12	0.30-4.20	0.862
OSA	1.58	0.56-4.49	0.389

CI = Confidence interval; OR = Odds ratio; OSA = Obstructive sleep apnea

demographic information and comorbidities were collected. OSA was defined as AHI equal or more than 5. Prevalence of OSA was 15.5 (13-17.9%) which was higher than the general population. Prevalence of obesity, diabetes, coronary artery disease, and congestive heart failure were significantly higher among patients with OSA.

A prospective cross-sectional study was done to evaluate the prevalence of snoring and risk of OSA among patients with PE by Epstein *et al*.[15] The presence of PE was confirmed by CT angiogram among 270 patients. Snoring and risk of OSA were determined by Berlin Questionnaire. Twenty-six percent of patients had PE. Prevalence of snoring and OSA was significantly higher in patients with PE (75% and 65% respectively) in comparison with patients without PE (50% and 36% respectively). Also, multivariate logistic regression was performed to evaluate the association of snoring and risk of OSA with PE. Results showed that PE was related to the risk of OSA (OR = 2.78, $P = 0.001$) which suggested OSA as a probable risk factor for PE.

As mentioned, in most of the studies, the association between prevalence of OSA and PE and prevalence of OSA were studied. However, in our study, the relation between 1-month mortality and OSA as a risk factor among PE patients was evaluated. So our achievements are not in contrast with their results.

Our study has some limitations. This study is not multi-central, so our sample may be inaccurate representative of the population. Also, the effect of OSA treatment on 1-month mortality among patients with high-risk of OSA was not evaluated. So, more studies are suggested to explore the effect of noninvasive ventilation on the decrease of mortality among PE patients with high-risk of OSA.

CONCLUSION

Results of this study showed 30-day mortality was not affected by OSA directly. In fact, it was affected by complications of OSA such as hypertension and thrombus. Also, positive history of chronic kidney disease increased the risk of 30-day mortality.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

AA and FG contributed in the conception and design of the work, conducting the study, data acquisition, analysis and interpretation of data, drafting, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. BA contributed in the conception and design of the work, interpretation of data and agreed for all aspects of the work.

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