Impact of obstructive sleep apnea on outcomes of pulmonary embolism: A systematic review and meta-analysis

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Abstract. The current review aimed to assess the effect of obstructive sleep apnea (OSA) on the severity and outcomes of pulmonary embolism (PE). PubMed, Embase, ScienceDirect, CENTRAL and Google Scholar were searched for studies assessing the impact of OSA on severity and outcomes of PE. A total of 12 studies were included. Meta-analysis revealed that simplified PE severity index of >1 and pulmonary artery obstruction index score was significantly higher in patients with OSA as compared with controls, but there was no difference in right ventricle to left ventricle short-axis diameter. The need for non-invasive ventilation was significantly higher in patients with OSA but there was no difference in the need for mechanical ventilation. Patients with OSA had a significantly higher incidence of recurrence of PE. Meta-analysis also showed a statistically significantly lower risk of in-hospital mortality in patients with OSA as compared with controls, but without any difference in the risk of late mortality. Adjusted data on mortality indicated a significantly lower risk of mortality in PE patients with comorbid OSA. Limited data shows that comorbid OSA increases the severity of PE but has no effect on right ventricular function. OSA may increase the risk of recurrent PE. Paradoxically, the presence of OSA may also reduce the risk of in-hospital mortality. Results must be interpreted with caution owing to high inter-study heterogeneity and lack of matching of baseline characteristics. Current evidence needs to be confirmed by high-quality prospective studies.

Introduction

Pulmonary embolism (PE) is a common thromboembolic condition that is associated with significant morbidity and mortality. Data from the USA suggest that the incidence of the condition has increased from 65/100,000 population in 1999 to 137/100,000 population in 2014 with a similar increase in the incidence of high-risk PE. An alarming finding was the excessive mortality rates of high-risk PE patients which were ~52.2% (1). Indeed, patients with PE present with a wide spectrum of severity and with several predictors of survival. It may manifest as an acute cardiac failure with sudden cardiac arrest and mortality or may be completely asymptomatic with only mild dyspnea (2). It is important to carefully stratify such patients as studies have reported a significant difference in the mortality rates amongst low-risk (3.4%) and high-risk patients (31.8%) (3). Identification of factors and comorbid conditions which influence the severity and outcomes of PE can help in risk stratification and health-resource utilization for such patients (4).

One such comorbid condition of interest is obstructive sleep apnea (OSA). OSA is a sleep-related breathing disorder that presents with repeated upper airway obstructions during sleep causing intermittent hypoxia and sleep fragmentation (5). The hypoxic episodes experienced during nighttime due to OSA leads to several cardiovascular changes including a surge in catecholamine levels, heightened total peripheral resistance, increased heart rate and venous return resulting in increased cardiac output, hypertension, tachyarrhythmias, left ventricular hypertrophy and heart failure (6). Furthermore, research suggests that PE and OSA share a bidirectional relationship with OSA being a risk factor for PE and conversely, patients with PE having an increased risk of moderate-severe OSA (7). Given such associations, it would be worth knowing how OSA influences the severity of PE and if patients with comorbid OSA have worse outcomes. Over the last decade, several studies have evaluated the influence of OSA on patients with PE but with variable results (8-10). Xu *et al* (11) in a systematic review published in 2020 attempted to collate evidence but could include only a limited number of studies and were unable to assess the influence of OSA on patient survival. Therefore, to overcome these limitations, the current review was designed to provide the most current and up-to-date evidence on the effect of OSA on the severity and outcomes of PE.

Materials and methods

The review conforms with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)

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statement (12). The present study protocol was also pre-registered on PROSPERO (CRD42022311475; https://www.crd.york.ac.uk/prospero/).

Database search. Relevant articles were searched by two reviewers separately on the electronic databases of PubMed, CENTRAL, Embase, ScienceDirect and Google Scholar from inception to 1st March 2022. A combination of MeSH and free-text keywords consisting of 'Sleep apnea', 'OSA', 'Sleep breathing', 'PE', 'venous thrombosis', 'thromboembolism' and 'VTE' were used during the search process (Table SI). First all the search results were compiled, duplicates removed and screened by titles and abstracts. Only appropriate studies were selected for complete text analysis, to be conducted by the two reviewers. Disagreements were solved by consensus. The reviewers also went through the reference list of included studies for any missed articles.

Eligibility criteria. Inclusion criteria were framed according to Population, Exposure, Comparison, Outcomes and Study Design (PECOS) (12). Included were i) all types of studies carried out on patients with PE (*Population*); ii) the *Exposure* group was patients with a history of OSA; iii) The *comparison* group was patients without any comorbid OSA; iv) *Outcomes* to be reported were (any one): Severity of PE using simplified PE severity index (sPESI) or pulmonary artery obstruction index (PAOI), the occurrence of deep vein thrombosis (DVT), right ventricle to left ventricle short-axis diameter (RV/LV ratio), use of non-invasive ventilation (NIV), mechanical ventilation, mortality, PE recurrence and length of hospital stay (LOS).

Exclusion criteria were: i) Non-comparative studies; ii) studies not reporting relevant outcomes; iii) Editorials, review articles; and iv) studies reporting duplicate data. In case of overlapping data, the study with greater number of patients was included.

Data extraction and quality assessment. The following data were extracted from the studies: Author details, publication year, study type, study location, sample size, demographic details, smokers, comorbidities, such as diabetes mellitus and hypertension and body mass index, diagnostic criteria for PE and OSA and study outcomes.

The Newcastle-Ottawa scale (NOS) was used for assessing risk of bias (13). All studies were judged for selection of study population, comparability and outcomes assessment. These were then given a maximum of four, two, or three points respectively.

Statistical analysis. The meta-analysis was carried out using *Review Manager* [RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration), 2014; https://revman.cochrane.org/#/myReviews]. For quantitative analysis a minimum of two studies reporting similar data for the same outcome was required.

Dichotomous outcomes were pooled in a random effect model and odds ratios (OR) with 95% confidence intervals (CI) were calculated. Continuous outcomes were also combined in a random-effects model to obtain mean difference (MD) and 95% CI. When available, multivariable-adjusted hazard ratios (HR) of mortality were combined using the generic inverse variance function of RevMan. Heterogeneity was assessed using the I^2 statistic. The present study did not assess for publication bias using funnel plots as <10 studies were included in each meta-analysis.

Results

Search and study details. Details of the search results at every stage are presented in Fig. 1. A total of 982 unique articles were retrieved with the search strategy. These were then screened to extract 23 articles relevant to the review topic. After evaluation of full-texts 11 were excluded as they did not satisfy the inclusion criteria. Finally, 12 studies were included in the present review (8-10,14-22).

Study details are shown in Table I. The included studies were published between 2012 and 2021. Of the 12, three studies each were from Germany, Spain and China, two were from the USA and one was a multinational study. The four studies from Germany were from the same institute and with an overlapping database. However, the studies reported different outcomes in each article. For this review, overlapping outcomes were not included from these studies. Except for three cross-sectional studies, all others were cohort in nature. The diagnostic criteria of PE and PSA were not uniform across the included studies; two studies used only the International classification of disease codes for retrieving PE and OSA cases from their database. The sample size of the OSA group ranged from 28-61,050 patients while that of the control group ranged from 26-694,482 patients. All outcomes were not uniformly reported by the included studies. The NOS score ranged from 6 to 8.

Meta-analysis. The severity of PE measured by sPESI and PAOI was reported by only two studies each. Meta-analysis revealed that an sPESI score of >1 was significantly higher in patients with OSA as compared with the control group (OR: 2.81; 95% CI: 1.66, 4.85; I^2=0%; P=0.0001; Fig. 2A). Similarly, PAOI scores were significantly higher in patients with OSA compared with controls (MD: 13.52; 95% CI: 7.20, 19.83; I^2=0%; P<0.0001; Fig. 2B). Incidence of DVT was reported by three studies. Pooled analysis indicated no difference in the incidence of DVT between the two groups (OR: 1.28; 95% CI: 0.58, 2.82; I^2=64%; P=0.54) (Fig. 2C). Data on RV/LV ratio diameter was reported by two studies. Meta-analysis indicated no difference between the two groups (MD: 0.01; 95% CI: -0.04, 0.07; I^2=0%; P=0.63; Fig. 2D).

The need for NIV and mechanical ventilation was reported by two studies each. Pooled analysis indicated that the need for NIV was significantly higher in patients with OSA (OR: 5.93; 95% CI: 5.05, 6.97; I^2=0%; P<0.00001; Fig. 3A) but there was no difference in the need for mechanical ventilation (OR: 1.37; 95% CI: 0.33, 5.72; I^2=95%; P=0.67; Fig. 3B). Data on recurrence of PE and LOS was reported by three studies each. Meta-analysis indicated that the incidence of recurrence of PE was significantly higher in patients with OSA as compared with controls (OR: 2.68; 95% CI: 1.61, 4.97; I^2=0%; P<0.00001; Fig. 3C). However, the present study noted no difference in the LOS between the two groups (MD: 0.40; 95% CI: -1.21, 2.01; I^2=78%; P=0.62; Fig. 3D).

Data on mortality was reported by six studies. Three reported data on in-hospital mortality while another three
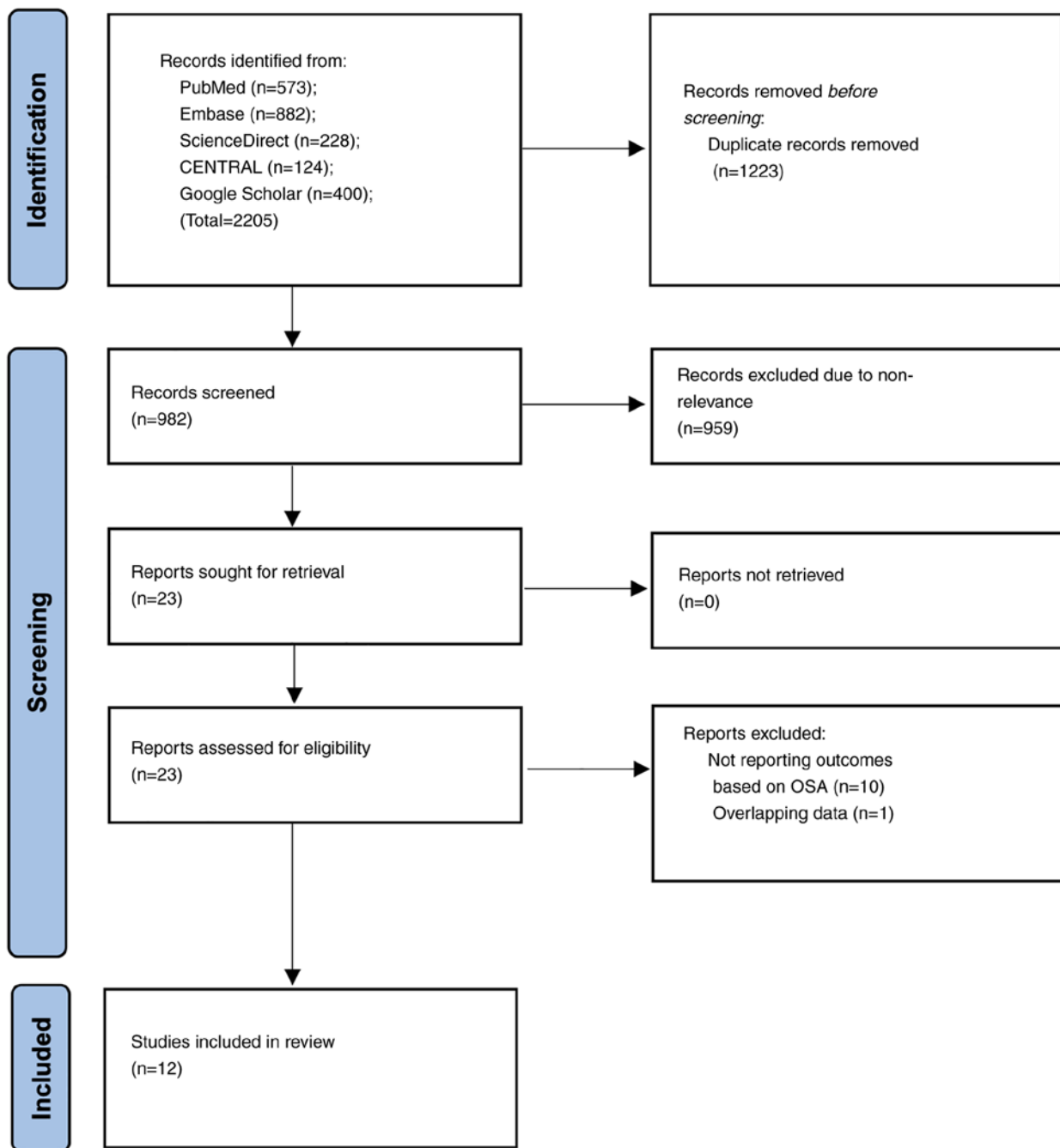
Figure 1. Study flow-chart. OSA, obstructive sleep apnea.

reported on a follow-up of 3-53 months. Meta-analysis revealed statistically significant lower risk of in-hospital mortality in patients with OSA as compared with controls (OR: 0.59; 95% CI: 0.43, 0.81; I^2=92%; P=0.01), but there was no difference in the risk of late mortality (>1 year) (OR: 1.79 95%; CI: 0.54, 5.94; I^2=62%; P=0.34; Fig. 4). Adjusted data on mortality was available from two studies. On pooled analysis, a significantly lower risk of mortality was noted in PE patients with comorbid OSA (HR: 0.56; 95% CI: 0.53, 0.59; I^2=0%; P<0.0001; Fig. 5).

Discussion

The present study with limited data demonstrated that the presence of OSA resulted in higher severity of PE. However,

OSA was not found to influence the RV/LV ratio of the right heart function, incidence of DVT and LOS. The need for NIV was significantly higher in patients with OSA along with the increased risk of recurrent PE; but by contrast, in-hospital mortality was significantly lower in patients with OSA.

Between the spectrum of mild dyspnoeic symptoms and acute cardiac arrest followed by sudden mortality, PE as a condition can present with a wide range of signs and symptoms with different grades of dyspnea, chest pain, hypoperfusion, respiratory failure and hemodynamic instability (2). The vital signs of patients, presence of right ventricle dysfunction and evidence of myocardial injury are important predictors of early survival (23). Several clinical models based on the medical history and clinical condition of patients have been

Table I. Details of included studies.

Author, year	Location	Study type	Diagnostic criteria for PE	Diagnostic criteria for OSA	Groups	Sample size	Mean age (years)	Male sex (%)	DM (%)	HT (%)	BMI (kg/m²)	NOS score	(Refs)
Zhang, 2012	China	Cross-sectional	Chinese Medical Association guidelines 2001	PSG (AHI >5 events/h)	With OSA	28	NA	NA	NA	NA	NA	6	(14)
					Without OSA	30							
Xie, 2015	China	Cross-sectional	2014 ESC guideline	Portable monitoring (AHI >5 events/h)	With OSA	32	59.9±12.9	62.5	43.7	78.1	30.7±5.4	8	(22)
					Without OSA	65	62.9±12.7	38.5	13.8	55.3	26.1±4.1		
Alonso-Fernandez, 2016	Spain	Cohort	CTPA	Portable monitoring (AHI >10 events/h)	With OSA	71	NR	NR	NR	NR	NR	7	(21)
					Without OSA	59							
Konnerth, 2018	Germany	Cohort	CTPA or V/Q scan	PSG (AHI >15 events/h)	With OSA	89	60±NR	51.7	NR	NR	NR	7	(20)
					Without OSA	164	56±NR	49.4					
Toledo-Pons, 2020	Spain	Cohort	CTPA	Respiratory polygraphy (AHI >15 events/h)	With OSA	55	61±12.5	80	NR	NR	27.9±4.4	6	(18)
					Without OSA	65	54.1±16.2	47.7			28.3±6.1		
Xiao, 2019	China	Cross-sectional	2014 ECS guideline	Portable monitoring (AHI >5 events/h)	With OSA	49	NA	NA	NA	NA	NA	6	(19)
					Without OSA	26							
Berghaus, 2020	Germany	Cohort	CTPA	PSG (AHI >15 events/h)	With OSA	66	71±11	53	NR	NR	NR	7	(9)
					Without OSA	131	55±18	44.3					
Geissenberger, 2020	Germany	Cohort	CTPA	PSG (AHI >15 events/h)	With OSA	45	70.8±11.1	53.7	20	NR	29±NR	7	(8)
					Without OSA	56	53.2±18.1	49.3	3.6		29.4±NR		
Le Mao, 2020	Multicentric	Cohort	CTPA or V/Q scan or signs and symptoms for PE, along with objectively confirmed lower limb deep vein thrombosis	NR	With OSA	241	66.8±12.2	69	NR	NR	NR	7	(16)
					Without OSA	3912	66.2±17	48					
Seckin, 2020	USA	Cohort	CTPA or V/Q scan or signs and symptoms for PE, along	ICD codes	With OSA	3184	66 (54-76)	58.3	34	68.1	34.1 (29-40)[a]	7	(17)
					Without OSA	21854	52 (32-71)	37.5	11.8	34.7	27.4 (24-32)		

Table I. Continued.

Author, year	Location	Study type	Diagnostic criteria for PE	Diagnostic criteria for OSA	Groups	Sample size	Mean age (years)	Male sex (%)	DM (%)	HT (%)	BMI (kg/m²)	NOS score	(Refs)
De-Miguel-Diez, 2021	Spain	Cohort	with objectively confirmed lower limb deep vein thrombosis	ICD codes	With OSA	2561	68.4±12.2	64.4	23.2	NR	NR	7	(15)
					Without OSA	44233	70.8±15.9	45.5	14.3				
Joshi, 2021	USA	Cohort		ICD codes	With OSA	61050	61 (51-71)	58.9	NR	70	NR	7	(10)
					Without OSA	694,482	65 (52-77)	46.3		52.1			

aMedian (Interquartile range). PE, pulmonary embolism; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; BMI, body mass index; CTPA, computed tomography pulmonary angiography; PSG, polysomnography; V/Q scan, ventilation-perfusion scan; ICD, international classification of diseases; NR, not reported; NA, not available; ESC, European Society of Cardiology.

developed for risk stratification of PE, of which, the sPESI has been one of the most validated tools. In a meta-analysis, Zhou et al (24) showed that the sPESI has good discrimination power to predict early survival and adverse events in patients with PE. The sPESI encompasses six clinical variables and patients showing none of them (0 points) are classified as low-risk while those with any of the six variables (1-6 points) are classified as high risk (25). Similarly, PAOI is another common tool used for risk stratification of PE based on computed tomography pulmonary angiography (CTPA) findings (26). The present meta-analysis noted that sPESI >1 and mean PAOI scores were significantly higher in patients with OSA as compared with controls indicating high-risk PE in such patients.

Results should be interpreted with caution as such data was not universally reported and each meta-analysis could include just two studies. The increased severity of PE in OSA can be due to several reasons. Notably, a difference in age and comorbidities between OSA and control groups was noted in some studies (20). It is known that elderly patients have a more complicated course of venous thromboembolism (20). Furthermore, the majority of OSA patients have several comorbidities such as hypertension, dyslipidemia, obesity, depression, obstructive lung disease, diabetes and other cardiovascular diseases which can significantly affect the clinical course of PE (27,28). However, Konnerth et al (20) in their study noted that OSA was independently associated with a worse clinical course of PE irrespective of other confounding variables. The authors hypothesized that reduced oxygen saturation in patients with OSA could worsen the myocardial injury and lead to high-risk PE. Additionally, apneic events and desaturation episodes in OSA patients lead to a prothrombotic state with increased levels of blood coagulability markers. This in turn could result in higher pulmonary thrombus load and increased right ventricular strain leading to high-risk PE (29). Research has also noted that D-dimer levels in PE patients with comorbid OSA are higher as compared with controls. Elevated levels of D-dimer suggest a hypercoagulable state and are associated with high rates of PE recurrence (30). Thus, it was not surprising to note a higher risk of recurrent PE in patients with OSA in our meta-analysis.

It is known that desaturation episodes in OSA cause changes in intrathoracic pressure and pulmonary hypertension which can affect right heart performance. Furthermore, increased severity of OSA is known to worsen right ventricular dysfunction (31). CTPA-based assessment of right ventricular dilation measured by RV/LV ratio is a proxy for right ventricular dysfunction and can accurately predict early outcomes in PE patients (32). However, the present meta-analysis noted no difference in RV/LV ratio in PE patients based on the presence or absence of OSA. One reason for such lack of difference could be due to the hypothesis that heightened pulmonary arterial pressure is mild in OSA and severe right ventricular dysfunction is noted only with other comorbid conditions such as chronic heart failure (33). Second, right ventricular strain is not seen in all patients with a high thrombus burden. The RV/LV ratio may be unchanged even with increasing thrombus load up to a critical point, after which right ventricular strain may be evident (34). Also, long-term OSA patients may develop right ventricular compensatory mechanisms which
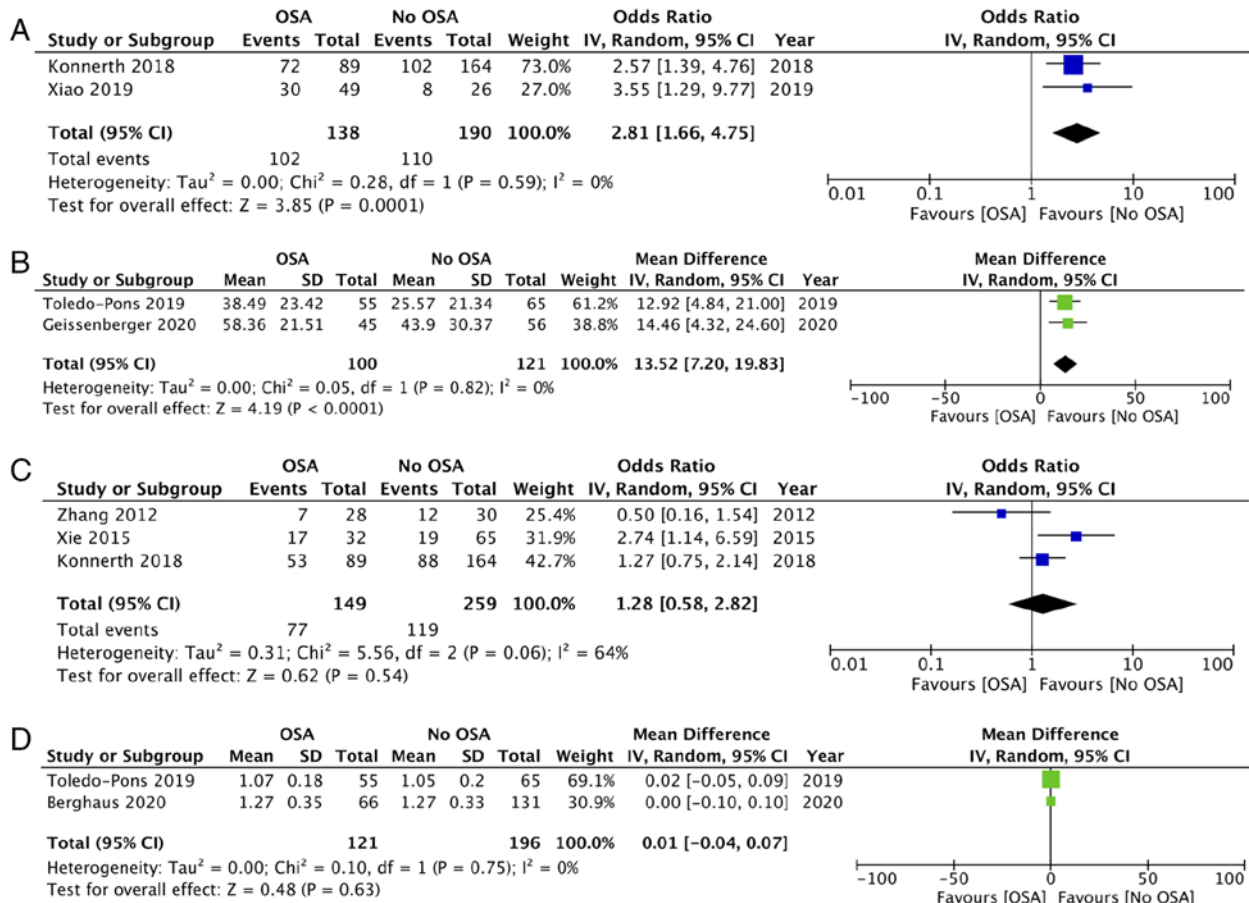
Figure 2. Meta-analysis of severity of PE and DVT. (A) sPESI >1 between OSA and controls and (B) PAOI between OSA and controls. (C) Meta-analysis of incidence of DVT in patients with PE with or without OSA. (D) Meta-analysis of RV/LV ratio diameter in patients with PE with or without OSA. PE, pulmonary embolism; sPESI, simplified PE severity index; OSA, obstructive sleep apnea; PAOI, pulmonary artery obstruction index; RV/LV, right ventricle to left ventricle short-axis diameter.
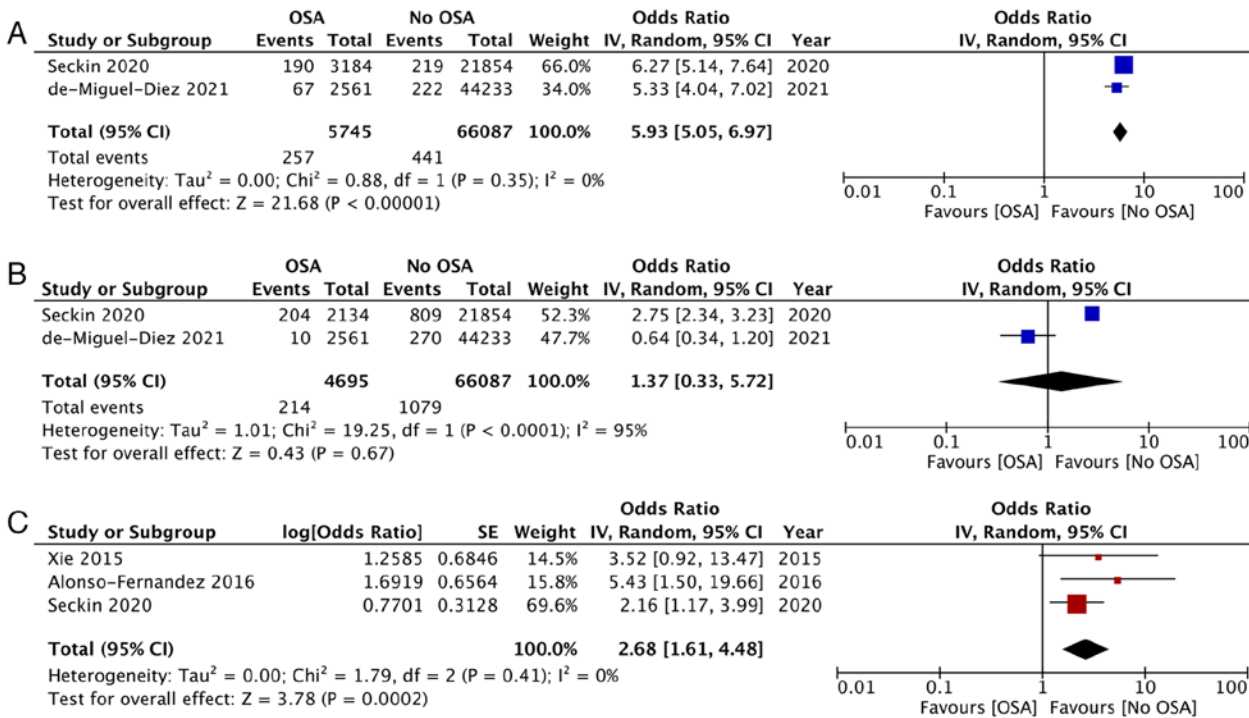

Figure 3. Meta-analysis of ventilation and LOS. (A) need for NIV or (B) need for mechanical ventilation in patients with PE with or without OSA. (C) Meta-analysis of LOS in patients with PE with or without OSA. LOS, length of hospital stay; NIV, non-invasive ventilation; PE, pulmonary embolism; OSA, obstructive sleep apnea.
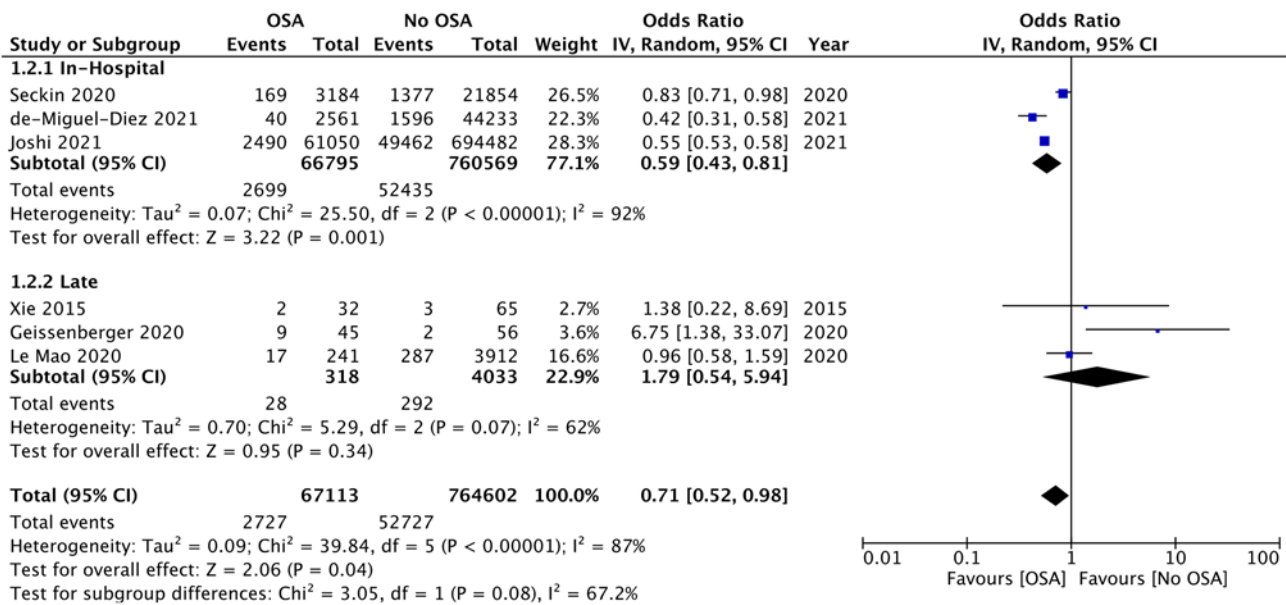
Figure 4. Meta-analysis of mortality in patients with PE with or without OSA. PE, pulmonary embolism; OSA, obstructive sleep apnea.
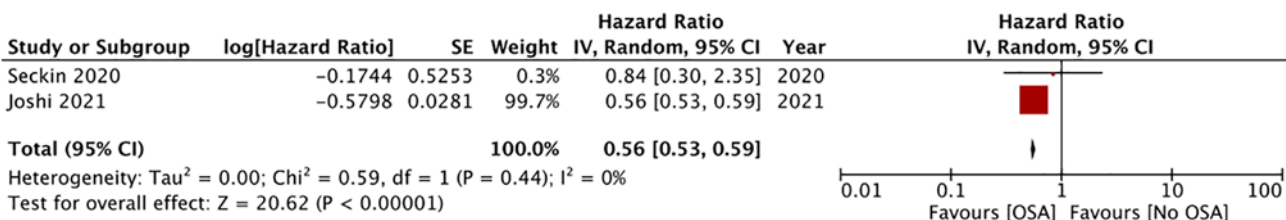

Figure 5. Meta-analysis of adjusted mortality rates in patients with PE with or without OSA. PE, pulmonary embolism; OSA, obstructive sleep apnea.

may counterbalance right ventricular dysfunction (18). The present meta-analysis demonstrated increased use of NIV in OSA patients but no difference in the use of invasive ventilation. The higher use of NIV in OSA patients could be due to the inability of the retrospective studies to differentiate between NIV used for respiratory failure compared with nighttime airway support for OSA (17).

An intriguing and paradoxical finding of the present study was lower in-hospital mortality in PE patients with comorbid OSA. Such findings are inconsistent with the fact that OSA and PE patients are known to have a higher incidence of comorbidities as compared with those with only PE (27,28). Furthermore, the present meta-analysis also revealed that OSA patients had higher severity of PE which should, in turn, lead to worse outcomes in these patients. However, all three studies in the meta-analysis of in-hospital mortality reported improved survival in patients with OSA as compared with controls. The consistent results and the large sample size of all the three studies in the analysis further add support to the results. There are several hypotheses put forward to support these results. First, it has been suggested that right ventricle dysfunction due to PE may be more tolerated in patients with OSA as they are adapted to recurring right heart pressure overloads provoked by poor pulmonary perfusion due to repeated oxygen desaturation during sleep. Thus, the right ventricles in OSA patients may be more resistant to injury

and hemodynamic collapse due to acute PE which may, in turn, reduce the risk of early mortality (9,15). Second, Joshi et al (10) suggested that OSA patients have higher hemoglobin levels due to repeated hypoxemias which may have a protective role in PE by preventing worsening of hypoxia. Third, OSA patients have higher rates of obesity (27). An obesity paradox has been noted wherein patients with higher body mass index have improved outcomes in acute diseases possibly due to improved medical care or due to higher metabolic reserves (35,36). It is plausible that such associations could have led to improved survival in OSA patients (15). However, it should also be noted that the data for in-hospital mortality was mostly from registry-based studies which are prone to errors in record-keeping and data entry. Furthermore, several other confounding factors could influence survival in PE patients and multivariable-adjusted data represents improved evidence rather than crude mortality rates. However, such data was reported by just two studies and the results were skewed by the outcomes of Joshi et al (10) (weight 99.7%). Further robust studies considering all major confounding variables are needed to assess the impact of OSA on mortality rates in PE patients.

There are several limitations to the present review. First, despite including several new studies (9,10,15-17) as compared with a previous review (11), the total number of studies in the present review was not very high. A significant

limitation was the difference in the reporting of outcomes by the studies which significantly restricted the number of studies in each meta-analysis. Second, some of the analyses such as in-hospital mortality and use of mechanical ventilation had very high heterogeneity. This was expected as the studies pooled were registry-based including a very heterogeneous group of PE patients of different severity, clinical status and treated with varied treatment protocols. The low number of studies in the meta-analyses prevented the present review from exploring the source of heterogeneity by subgroup analysis or a meta-regression. Also, in the meta-analysis of mortality, the study of Joshi *et al* (10) with its large sample size could have skewed the results. Third, there were variations in the included studies in relation to the diagnostic criteria of PE and OSA. Not all studies used CTPA or polysomnography to diagnose PE and OSA respectively. Fourth, the present review was unable to segregate outcomes based on the severity of OSA due to the limited availability of data. Last, the majority of the studies did not conduct baseline matching of study groups and did not report adjusted outcome data. Thus, the influence of confounding variables on the outcomes of the studies and the present review cannot be ignored.

Data from a limited number of retrospective studies indicate that comorbid OSA increases the severity of PE but has no effect on right ventricular function. OSA may increase the risk of recurrent PE. Paradoxically, the presence of OSA may reduce the risk of in-hospital mortality. Results must be interpreted with caution owing to high inter-study heterogeneity and lack of matching of baseline characteristics. Current evidence needs to be confirmed by high-quality prospective studies.

Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

WZ conceived and designed the study. WZ and YD collected the data and performed the literature search. WZ was involved in the writing of the manuscript. All authors read and approved the final manuscript. Data sharing is not applicable to this article.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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