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Prevalence of obstructive sleep apnea in venous thromboembolism: a systematic review and meta-analysis

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Abstract

Purpose Previous studies revealed that the concomitant prevalence of obstructive sleep apnea (OSA) and venous thromboembolism (VTE) was high, but the results were inconclusive due to various limitations. We aimed to systematically review the literature on the prevalence of OSA in patients with VTE.

Methods Relevant studies were identified on multiple electronic databases through July 2018. The DerSimonian-Laird random effects model was used to calculate the pooled prevalence of OSA, moderate-to-severe OSA, and severe OSA in VTE patients, respectively. Sensitivity analysis was performed based on diagnostic methods of OSA and races.

Results A total of 11 studies comprising 895 patients were available for the meta-analysis, but one study was excluded because of the between-study heterogeneity in the following analysis. The pooled prevalence of OSA, moderate-to-severe OSA, and severe OSA in VTE patients were 70% (95% CI = 65%, 75%), 41% (95% CI = 29%, 54%), and 19% (95% CI = 15%, 23%), respectively. Sensitivity analysis indicated that the prevalence was similar in different diagnostic methods, but the contributions of races to OSA were complex. Although the lower prevalence of all OSA and moderate-to-severe OSA as compared with Western countries, Asian countries have similar or even a little bit higher prevalence of severe OSA.

Conclusions Findings from this meta-analysis supported that the prevalence of OSA in VTE patients was strikingly high. Screening for OSA in patients with VTE is necessary for developing effective treatment strategies.

Keywords Obstructive sleep apnea · Venous thromboembolism · Pulmonary embolism · Prevalence · Meta-analysis

Introduction

Obstructive sleep apnea (OSA) is characterized by episodes of recurrent upper airway obstruction during sleep, leading to intermittent hypoxia and sleep fragmentation. There is growing evidence that untreated OSA is a significant and independent risk factor for venous thromboembolism (VTE), such as deep vein thrombosis (DVT) or pulmonary embolism (PE) [1]. A number of potential pathogenic mechanisms whereby OSA might promote the onset of VTE include vascular endothelial dysfunction, hypercoagulability, platelet abnormalities, hemodynamic alterations, sympathetic nervous system activation, oxidative stress, and systemic inflammation [2–5]. A recent long-term follow-up observational cohort study revealed that OSA was considered to be a risk factor for PE recurrence and recommended resuming anticoagulation to prevent a new thromboembolic event [6]. Therefore, understanding the epidemiology of OSA in VTE patients is of great importance.

So far, several clinical studies concerning the OSA prevalence in VTE patients have been published [2, 7–16]. We, therefore, conducted a systematic review followed by meta-analysis to investigate the prevalence of OSA in VTE patients, diagnosed by polysomnography (PSG), portable diagnostic device (PDD), or questionnaire.

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Methods

Searching strategy

We performed a systematic search for articles published up to July 2018 using PubMed, Embase, ISIWeb of Knowledge, and the Cochrane Library databases without restrictions to

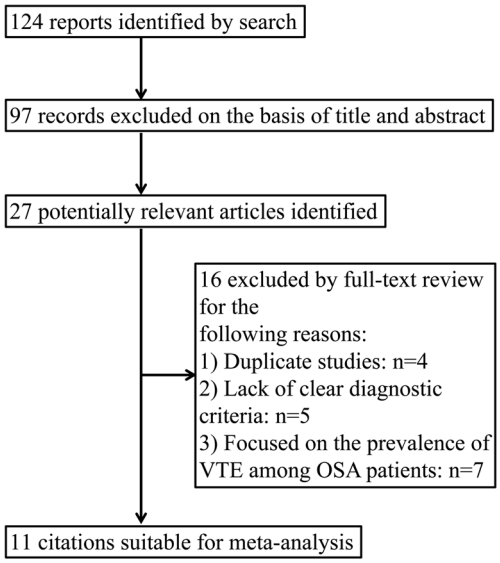

Fig. 1 Meta-analysis flow chart

the language of the publications. The following search terms were included: sleep apnea, sleep-disordered breathing, VTE, DVT, and PE. We also searched for the reference lists of related articles located in the above databases. Our analysis on prevalence was performed in accordance with the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) guidelines.

Study selection

Studies were considered eligible for analysis if they met all of the following criteria: (1) a prospective or cross-sectional design was used; (2) study population was patients who were securely diagnosed with VTE (either DVT or PE); (3) the criterion of OSA diagnosed by PSG, PDD, or questionnaire was defined as AHI ≥ 5 events/h or the high risk of having OSA; (4) Mild, moderate, and severe degrees of OSA were defined as 5 ≤ AHI < 15, 15 ≤ AHI < 30, and AHI ≥ 30, respectively. Exclusion criteria were as follows: (1) patients younger than 18; (2) OSA was diagnosed by other methods, or no clear result was presented. When the same data set was presented in multiple reports, we selected only the one with the largest study and the most detailed information. In one special article, the results were presented in the form of a histogram [12]. In order to increase the sample size, the estimated values according to the histogram were also analyzed.

Data extraction and quality assessment

Two investigators independently extracted information about geographical location, year of publication, diagnostic method of OSA, sample size, mean age, BMI, gender, and numbers of each AHI level included from each eligible study, with differences resolved by discussion. We evaluated the quality of each included study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17].

Data synthesis and statistical analysis

Standard meta-analytic methods were applied [18]. We calculated the odds ratio (OR) and 95% confidence intervals (CI) to assess the prevalence of OSA in VTE patients for each individual study. The prevalence of all OSA, OSA diagnosed by PSG/PDD (AHI ≥ 5) or questionnaire, moderate-to-severe OSA (AHI ≥ 15), and severe OSA (AHI ≥ 30), was calculated separately for each study.

Stata SE (version 11, Stata Corporation, College Station, TX, USA) software was utilized for statistical analysis. The standard error of the OSA prevalence was estimated based on binomial distribution formula. The heterogeneity of the studies was evaluated using the Cochran's Q (reported as X^2 and p values) and I^2 statistic. Significant heterogeneity was defined by $I^2 > 50\%$. The random effects model was recommended when significant heterogeneity between studies exists, as it added an extra term to the variance, gave wider CIs around the point estimate, and could be more conservative than a fixed effects model [19, 20]. Thus, all pooled outcome measures were determined using the random effects model. Meta-regression models were employed to identify the source of heterogeneity. Moreover, we also performed a sensitivity analysis to identify the studies that were more influenced by the above-mentioned heterogeneity. In our sensitivity analysis, the prevalence of OSA in different geographical locations (Western countries and Asian countries) was also calculated to provide estimates for different races. The funnel plot and Egger's test were used to analyze publication bias.

Results

Literature search

A total of 124 citations resulted from electronic databases, of which 27 articles met the inclusion criteria and were selected for detailed assessment. Nine studies were excluded because of duplicate data or the lack of clear diagnostic criteria. Of the remaining 18 papers, 7 studies which focused on the prevalence of VTE among OSA patients were further excluded. Finally, a total of 11 studies [2, 7–16] were included in our meta-analysis. A flow diagram of the selection process was presented in Fig. 1.

Characteristics of the included studies and quality assessment

Table 1 presents the characteristics of the selected reports. Among these reports, 5 were from Europe, 5 from Asia, and

Table 1 Summary of included study characteristics

Author	Year	Country	No. of patient (% men)	Age	BMI	Diagnostic method of OSA	No. of patient with OSA or AHI ≥ 5 (M/F)	No. of patient with AHI ≥ 15 (M/F)	No. of patient with AHI ≥ 30 (M/F)
Mañas [7]	2017	Spain	62 (55%)	68 ± 14	29 ± 5	PSG or PDD	41 (NA)	24 (NA)	12 (NA)
Berghaus [8]	2016	Germany	206 (48%)	60 ± 1	30 ± 1	PSG or PDD	136 (NA)	51 (25/27)	28 (NA)
Jiang [2]	2014	China	97 (46%)	60 ± 13 OSA 63 ± 13 non-OSA	31 ± 5 OSA 26 ± 4 non-OSA	PSG or PDD	32 (20/12)	18 (NA)	NA
Alonso-F [11]	2013	Spain	107 (62%)	57 ± 15	28 ± 5	PSG or PDD	80 (NA)	64 (NA)	27 (NA)
Kosovali [10]	2013	Turkey	28 (50%)	55 ± 17	31 ± 7	PSG or PDD	20 (10/10)	12 (NA)	6 (NA)
Arzt [13]	2012	Germany	82 (51%)	57 ± 17	28 ± 5	PSG or PDD	62 (36/26)	33 (17/16)	18 (9/9)
Kezban [12]	2012	Turkey	30 (53%)	61 ± 3	31 ± 2 risk factor+ 29 ± 1 risk factor−	PSG or PDD	17 (10/7)	8 (NA)	5 (NA)
Arnulf [15]	2002	France	68 (NA)	NA	16% > 30	PSG or PDD	56 (NA)	43 (NA)	NA
Hasegawa [16]	2000	Japan	7 (14%)	71 ± 9	27 ± 3	PSG or PDD	2 (1/1)	2 (1/1)	2 (1/1)
Ghiasi [9]	2015	Iran	137 (58%)	49 ± 18 low risk 63 ± 10 high risk	24 ± 2 low risk 34 ± 4 high risk	STOP-Bang questionnaire	95 (54/41)	NA	NA
Epstein [14]	2010	America	71 (61%)	60 ± 16	29 ± 7	Berlin questionnaire	46 (NA)	NA	NA

PDD portable diagnostic device, *PSG* polysomnography

1 from America. The number of participants varied from 7 to 206. OSA was diagnosed by PSG/PDD in 9 studies and by questionnaire in the other 2 studies. Nine studies included diagnostic results for both AHI ≥ 5 and AHI ≥ 15 ($n = 687$), while 7 studies had AHI ≥ 30 ($n = 522$). Quality assessment using STROBE statement showed that scores of included studies ranged from 15 to 20 points, with a mean score of 19.3 ± 1.7 points.

Prevalence of OSA in VTE

The pooled prevalence of all OSA, OSA diagnosed by PSG/PDD (AHI ≥ 5), OSA diagnosed by questionnaire, moderate-to-severe OSA (AHI ≥ 15), and severe OSA (AHI ≥ 30) in VTE, was calculated, respectively.

As shown in Fig. 2 a, estimates of prevalence ranged from 29 to 82% for all OSA. Heterogeneity was present ($\chi^2 = 75.68$, $p < 0.001$; $I^2 = 86.8\%$). The pooled prevalence was 65% (95% CI = 56%, 73%) by random effects analysis. After excluding one study from China, [2], between-study heterogeneity was decreased dramatically ($\chi^2 = 20.61$, $p = 0.014$; $I^2 = 56.3\%$). Statistically significant differences between China and others were confirmed by meta-regression models ($p = 0.001$). When excluding one study from China, the pooled prevalence increased to 70% (95% CI = 65%, 75%). In the studies that OSA was diagnosed by PSG/PDD, pooled prevalence was similar to the studies which OSA was diagnosed by questionnaire (70% vs 68%) (Fig. 2b). Pooled prevalence in Western studies was 72% (95% CI = 66%, 77%), which was higher than that in Asian studies (62%, 95% CI = 50%, 75%).

For moderate-to-severe OSA (AHI ≥ 15), estimates of prevalence ranged from 25 to 63% among 8 studies (Fig. 3). Heterogeneity was present ($\chi^2 = 61.8$, $p < 0.001$; $I^2 = 88.7\%$). The pooled prevalence was 41% (95% CI = 29%, 54%) by random effects analysis. Pooled prevalence in Western studies was 45% (95% CI = 29%, 61%), which was still much higher than in Asian studies (33%, 95% CI = 22%, 44%).

For severe OSA (AHI ≥ 30), estimates of prevalence ranged from 17 to 29% among 7 studies (Fig. 4). Low heterogeneity was observed between studies ($\chi^2 = 7.8$, $p = 0.253$; $I^2 = 23.1\%$). The pooled prevalence was 19% (95% CI = 15%, 23%) by random effects analysis. Pooled prevalence in Western studies was 19% (95% CI = 13%, 25%), which was similar to or even a little bit lower than that in Asian studies (20%, 95% CI = 10%, 29%).

Publication bias

After testing by Egger's method using a threshold of p value < 0.05, there was no evidence of publication bias for AHI ≥ 15

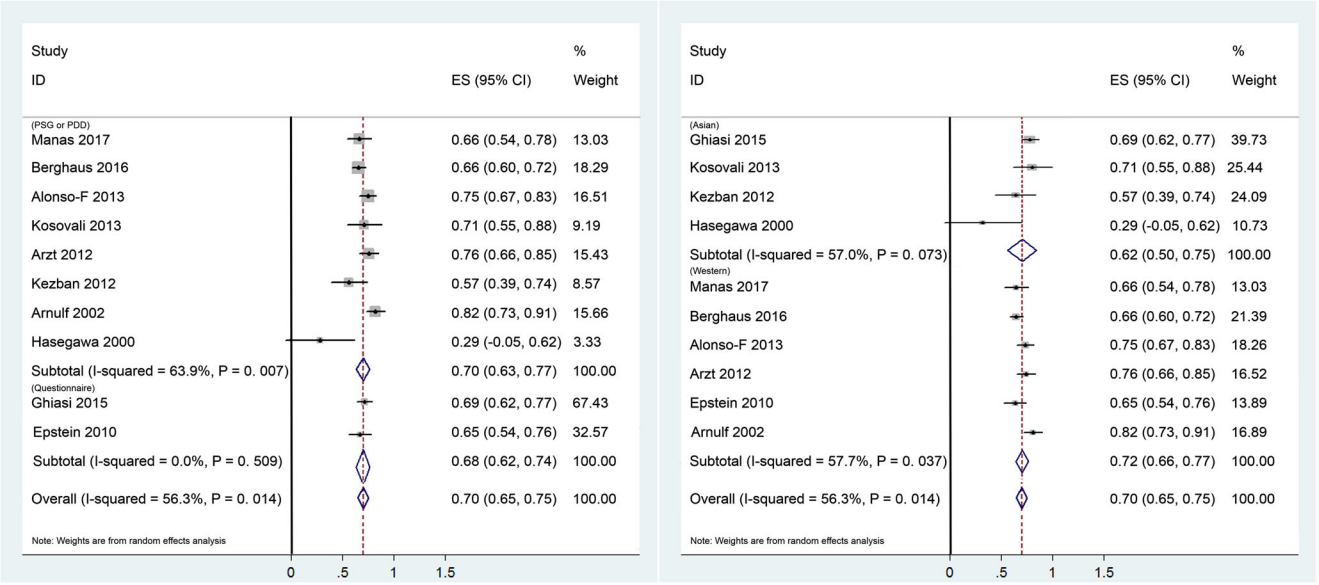

Fig. 2 Prevalence of OSA in VTE. Note: The pooled prevalence of OSA was 70%. Subgroup analysis showed that the pooled prevalence of OSA diagnosed by PSG/PDD, diagnosed by questionnaire, in Asian studies, and in Western studies was 70%, 68%, 62%, and 72%, respectively

($p = 0.358$) and AHI ≥ 30 ($p = 0.161$). However, there was some evidence of publication bias for total OSA ($p = 0.001$).

Discussion

This is the first study to perform a meta-analysis on the prevalence of OSA among patients with VTE. In the present study, a much higher prevalence of OSA was found in VTE patients (70%) than in general population (2–4%) [21], and 41% of subjects suffered from moderate-severe OSA. In addition, OSA was diagnosed to be severe in 19% of the total study population.

The mechanisms underlying the increased prevalence of OSA in VTE patients are very complex. As reviewed by Rosendaal [22], there are three major causes of VTE: vascular endothelial impairment, stasis of blood flow, and increased coagulability. However, several lines of evidence now attest that OSA may affect all three pathways: the collapse of upper airways during sleep results in oxidative stress, systemic inflammation, and hemodynamic alterations [3–5, 23]. All these pathophysiological derangements could finally lead to

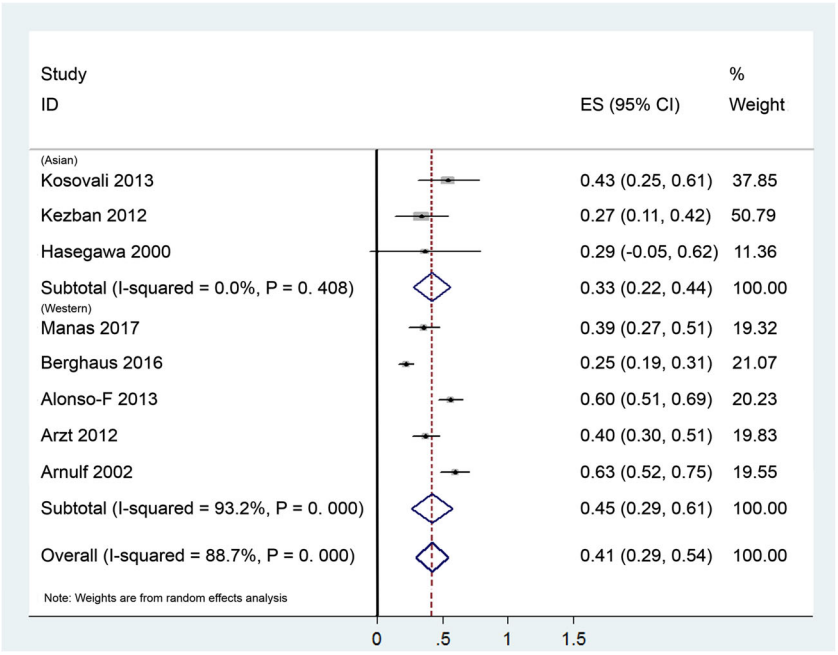

Fig. 3 Prevalence of moderate-to-severe OSA (AHI ≥ 15) in VTE. Note: The pooled prevalence of moderate-to-severe OSA was 41%. Subgroup analysis showed that the pooled prevalence of OSA in Asian studies and Western studies was 33% and 45%, respectively

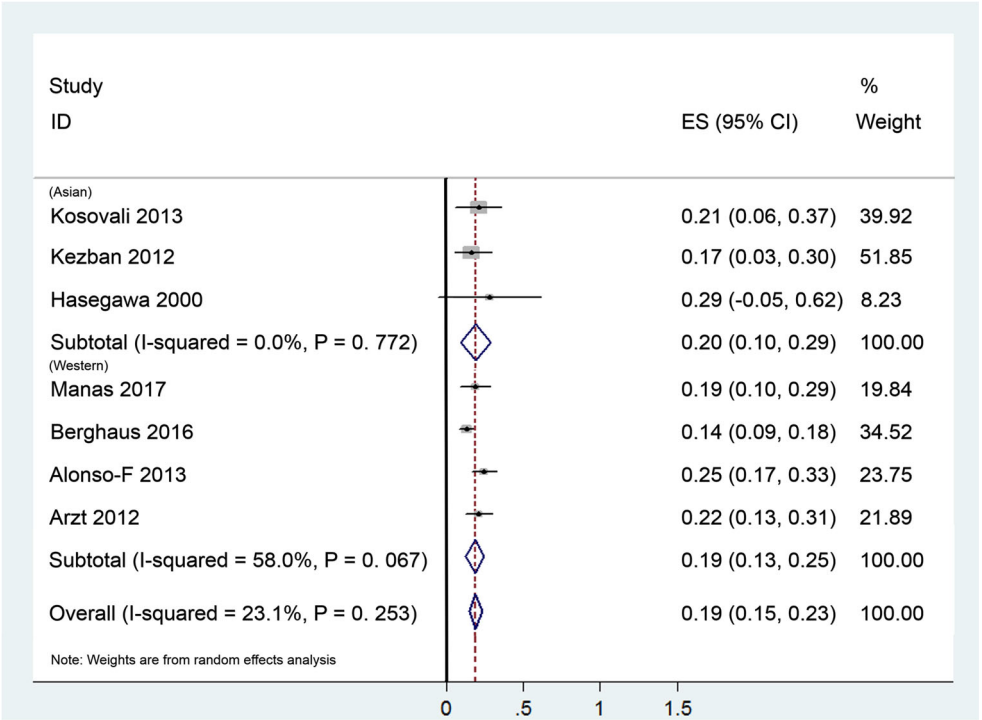

Fig. 4 Prevalence of severe OSA (AHI ≥ 30) in VTE. Note: The pooled prevalence of moderate-to-severe OSA was 19%. Subgroup analysis showed that the pooled prevalence of OSA in Asian studies and Western studies was 20% and 19%, respectively

endothelial dysfunction, the slow-down of intravenous flow, increased coagulability, platelet activity abnormalities, and decreased fibrinolytic capacity [1, 24, 25]. In addition, the hypercoagulable state seems to increase with the severity of OSA [26], and was reversed by continuous positive airway pressure (CPAP) in some trials [27–29]. Thus, further studies need to be conducted in order to evaluate whether CPAP treatment is able to reduce the recurrence of VTE.

There was true heterogeneity among the individual studies, especially the pooled prevalence of all OSA. When excluding each study one by one, we found that the between-study heterogeneity in both the pooled prevalence and subgroup analysis was dramatically decreased after excluding one study from China [2], which later proved again to be the source of heterogeneity by meta-regression models. Gender, age, obesity, ethnicity, and craniofacial anatomy were all well-known risk factors for the development of OSA. However, as shown in Table 1, there does not appear to be a significant difference in the characteristics (% men, age, and BMI) between Jiang et al. [2] and other studies, indicating that the heterogeneity may be related to the racial variations, environment, living and diet habits, culture, or other factors. In the following subgroup analysis, we found that, despite the lower prevalence of all OSA and moderate-to-severe OSA as compared with Western countries, Asian countries have similar or even a little bit higher prevalence of severe OSA. This quite interesting finding might due to the decreased cranial base dimensions which would render that Asians were more prone to severe OSA [30, 31].

Limitations

Limitations of the present meta-analysis should be mentioned. As with any meta-analysis, heterogeneity was a threat to the accuracy. We dealt with heterogeneity among the studies in several ways: (1) we excluded one study from China [2], (2) we used the DerSimonian-Laird random effects method to do the analysis, and (3) we calculated the prevalence of OSA by diagnostic methods, severity, and regions, respectively. However, variability still existed. Clearly, men were at higher risk for OSA than women. Unfortunately, we failed to reduce heterogeneity by calculating the prevalence of OSA by sex since most of the inclusion studies did not differentiate between men and women. Lastly, the total number of studies related to OSA and VTE was limited, and the sample size was relatively small. These may impact the publication bias of our study. Larger studies, especially prospective multicenter studies, are necessary to answer the question of prevalence more definitively.

Conclusion

In summary, this meta-analysis demonstrated a high prevalence of OSA, moderate-to-severe OSA, and severe OSA in patients suffering from VTE. Thus, there is an urgent need to evaluate for OSA in patients with VTE to diagnose and treat these patients properly. Further large prospective cohort

studies are needed to determine whether or not treatment for OSA after VTE will improve outcomes for VTE. Such studies promise to clarify the association of OSA and VTE and may lead to effective treatment strategies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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