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Regular Article

Association between obstructive sleep apnea and deep vein thrombosis / pulmonary embolism: A population-based retrospective cohort study

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is a major contributor to cardiovascular disease, and may cause severe morbidity and mortality. Recent studies have indicated that OSA patients exhibited elevated platelet activity, fibrinogen levels, and platelet aggregation.
Objectives: We investigated the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients diagnosed with OSA compared with age- and sex-matched unaffected people.
Patients/Methods: This longitudinal, nationwide, population-based cohort study was conducted using data from Taiwan National Health Insurance Research Database (NHIRD) recorded between January 2000 and December 2011. The study consisted of 3511 patients with OSA and 35110 matched comparison individuals. A Cox proportional hazard regression was used to compute the risk of DVT and PE in patients with OSA compared with those without OSA.
Results: The DVT and PE risks were 3.50- and 3.97-fold higher (95% CI = 1.83–6.69 and 1.85–8.51) respectively, in the OSA cohort than in the reference cohort after we adjusted for age, sex, and comorbidities.
Conclusion: This nationwide population-based cohort study indicates that patients with OSA exhibit a higher risk of subsequent DVT and PE.

Introduction

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing characterized by repetitive episodes of partial or complete upper airway closure with apnea, hypopnea, and intermittent hypoxia. This disorder affects 24% of men and 9% of women in the middle-aged population in the United States [1]. Because of the potentially large economic burden of OSA, OSA comorbidities are focus of numerous researchers. OSA is a major contributor to cardiovascular disease, and may cause severe morbidity and mortality [2,3]. In addition, increasing evidence has indicated that OSA patients exhibit a high risk of other comorbidities, such as depressive disorders, type 2 diabetes mellitus, and motor-vehicle accidents [4–6].

Recent evidence has indicated that OSA patients exhibited elevated platelet activity, fibrinogen levels, plasminogen activator inhibitor-1 levels, erythrocyte adhesiveness, and aggregation [7–9]. All of these conditions may cause OSA patients to develop a hypercoagulopathy status and predispose them to venous thromboembolism (VTE), which consist of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Many previous studies exploring the link between OSA and VTE have been observational or case-controlled [10–14]. However, according to our research, data regarding the longitudinal frequency of PE and DVT development in OSA patients are scant, creating difficulty in generalizing the study results. Thus, we conducted this nationwide population-based study by using data derived from the Taiwan National

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Health Insurance Research Database (NHIRD) to investigate whether OSA increases the subsequent risk of subsequent DVT and PE.

Methods and Materials

Data Source

This retrospective cohort study used data from the Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD established by the Bureau of National Health Insurance (NHI), The NHIRD covered over 99% of the population of Taiwan (http://www.nhi.gov.tw/). One million insurants were randomly selected from the 2000 registry in the LHID. These data represent all medical claims and insurant information documented from 1996 to 2011. To protect personal information, the identities of insurants were encrypted. This study was approved by the Institutional Review Board of China Medical University Hospital. Diseases were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Participants

We included 6788 patients with OSA (ICD-9-CM 780.51, 780.53, and 780.57) between 2000 and 2011 in the study, and the date of OSA diagnosis was defined as the index date. Patients with a history of other sleep disorders (ICD-9-CM 307.4 and 780.50, 780.52, 780.54 − 780.56 and 780.58 − 780.59), DVT (ICD-9-CM 453.8), or PE (ICD-9-CM 415.1) were excluded. Comparisons were selected from the population of people with no a history of OSA, DVT, or PE documented in the LHID, The comparison individuals were randomly assigned an index date and were frequency-matched with the OSA patients according to age (5-y stratum) and sex in a 10:1 ratio. All of the participants were followed from the index date to the date of the outcome or the end of 2011.

Baseline Comorbidity

The baseline history of comorbidity for each participants was identified, including hypertension (ICD-9-CM 401-405), atrial fibrillation (AF, ICD-9-CM 427.31), hyperlipidemia (ICD-9-CM 272), diabetes (ICD-9-CM 250), cerebral vascular disease (CVD, ICD-9-CM 430-438), heart failure (ICD-9-CM 428), malignancy (ICD-9-CM 140-208), and lower-leg fracture or surgery (ICD-9-CM 820, 821, and 823 or ICD-9 operation code: 81.51 − 81.54). Malignancy was defined based on the data from the Registry for Catastrophic Illness Patient Database. In Taiwan, patients with malignancies can applied for catastrophic illness certificates, and these malignancies are verified according to histological test results or radiology reports.

Statistical Analysis

All statistical analyses were conducted using SAS Version 9.3 (SAS Institute, Cary, NC), and significance was determined using 2-tailed tests in which the significance level was set at $P < .05$. The chi-square and *t*-tests were used to determine the distributions of categorical and continuous variables. The incidence of PE and DVT (per 10000 person-y) in the 2 cohorts was calculated. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the OSA cohort compared with the comparison cohort were determined using Cox proportional hazard regression. The multivariable model was controlled for age, sex, and comorbidity, and significant differences are shown in Table 1 and the crude Cox proportional HR regression. The risks of DVT and PE were estimated. Based on the number of developed PEs and DVTs, the follow-up duration was stratified into the first 2 years and subsequent 10 years to assess the risks of DVT and PE. Kaplan-Meier analysis was used to plot the cumulative incidence, and a log-rank test was used to determine the differences between the 2 cohorts. The chi-square test, Fisher's exact test, and *t* test were used to identify the characteristics of study subjects with and without VTE.

Results

Baseline Characteristics

We examined 3511 patients with OSA and 35 110 sex- and age-matched comparison individuals in this study. The mean age was 42.4 years (standard deviation = 16.9), and the OSA cohort predominately consisted of men (74.5% vs 25.5%). The OSA patients exhibited a higher prevalence of comorbidity than did the comparison individuals, and the 3 most common comorbidities were hypertension (29.7% vs 16.4%), hyperlipidemia (23.5% vs 11.9%), and diabetes (9.88% vs 6.72%) (Table 1).

Table 1
Demographics between study subjects with and without OSA.

	OSA (N = 3511)		Comparison (N = 35110)		p-value
	n	%	n	%	
Age, years,					0.99
<25	498	14.2	4980	14.2	
25-44	1478	42.1	14780	42.1	
45-64	1204	34.3	12040	34.3	
≥65	331	9.43	3310	9.43	
Mean (SD)†	42.4	(16.9)	42.3	(17.0)	0.66
Sex					0.99
Women	896	25.5	8960	25.5	
Men	2615	74.5	26150	74.5	
Comorbidity					
CVD	108	3.08	611	1.74	<0.0001
AF	34	0.97	132	0.38	<0.0001
Heart failure	108	3.08	380	1.08	<0.0001
Malignancy	84	2.39	476	1.36	<0.0001
Hypertension	1042	29.7	5773	16.4	<0.0001
Hyperlipidemia	824	23.5	4192	11.9	<0.0001
Diabetes	347	9.88	2360	6.72	<0.0001
Lower leg fracture or surgery	72	2.05	530	1.51	0.01

Chi-square test and †t-test.
SD, standard deviation.