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The Incidence of Deep Vein Thrombosis in Asian Patients With Chronic Obstructive Pulmonary Disease

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Abstract: Most studies have focused on the prevalence of deep vein thrombosis (DVT) and pulmonary embolism in patients with chronic obstructive pulmonary disease (COPD) and acute exacerbation in Caucasian populations. DVT is supposedly less likely to occur among Asians than Caucasians, and the primary purpose of this study was to determine the actual incidence of DVT in patients with COPD in Asian populations.

We enrolled patients over the age of 40 with a diagnosis of COPD (ICD-9: 490–492, 496; A-code: A323 and A325) between 1998 and 2008. The index date was the date of first-time COPD diagnosis. We excluded the patients who had been diagnosed with COPD and DVT (ICD-9-CM: 453.8) before index date. The control group was frequency-matched according to age (3-year stratum), sex, and the year of admission, at a 2:1 ratio. Patients were followed from index date to when either a diagnosis of DVT was made, death occurred, December 31, 2009 was reached, or when the patients withdrew from the National Health Insurance program.

The overall incidence rate of DVT was 18.78 per 10,000 person-years in patients with COPD, and the adjusted hazard ratio of DVT in patients with COPD was 1.38 (95% confidence interval 1.06–1.80), which was greater than patients without COPD after adjusting for age, sex, atrial fibrillation, hypertension, diabetes, hyperlipidemia, cerebrovascular accident, congestive heart failure, lower leg fracture or surgery, and cancer.

Asian patients with COPD had a higher incidence of DVT than non-COPD patients.

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Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, DVT = deep vein thrombosis, HR = hazard ratio, IRR = incident rate ratio, KM = Kaplan–Meier, LHID = Longitudinal Health Insurance Database, NHIRD = National Health Insurance Research Database, PE = pulmonary embolism, SD = standard deviation, VTE = venous thromboembolism.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the key cause of mortality and morbidity worldwide. Patients with COPD frequently experience hospitalization due to acute exacerbation.¹ Most of the exacerbations are attributable to infections, and some are related to pulmonary embolism (PE). A systematic review and meta-analysis showed that the prevalence of PE in acute exacerbations of COPD in patients who required hospitalization was 19.9%, and the overall prevalence estimate of deep vein thrombosis (DVT) was 12.4%.² This study included European and American patients presenting with an exacerbation of COPD. Most studies demonstrated the prevalence of DVT in patients with COPD and exacerbation in Caucasian populations,^{3–5} but not in Asian populations. DVT is less likely to occur among Asians than among Caucasians, according to the literature,^{6,7} although the reason for this observation has not been fully understood. Also, there is no long-term follow-up study of the incidence of DVT in Asian COPD patients. The primary purpose of our study was to determine the incidence of DVT in patients with COPD in Asian populations.

METHODS

Data Sources

This population-based retrospective cohort study was carried out using information from the National Health Insurance Research Database (NHIRD) of Taiwan, which contains encrypted computerized outpatient care claims, hospital inpatient care, ambulatory care, dental services, and prescription drugs records. Approximately 99% of the total population in Taiwan was enrolled in the insurance program.

The 2000 Longitudinal Health Insurance Database (LHID) contains all the original claim data of 1,000,000 individuals randomly sampled from the original claim data of the NHIRD. No significant differences were observed in distributions of sex, age, and healthcare costs between patients in the 2000 LHID and in the NHIRD. This study was based in part on data from the NHIRD, which in this study consisted of reidentified secondary data released to the public for research purposes; this study was exempt from full review by the ethical committee (Kaohsiung Medical University Hospital-IRB-EXEMPT-20130008), and informed consent did not need to be obtained from the study participants.

Study Designs

We included cases over the age of 40 years as those having an inpatient hospitalization with a first-time COPD (International Classification of Diseases, Ninth Revision [ICD-9]: 490–492, 496; A-code: A323 and A325) diagnosis between 1998 and 2008 from the 2000 LHID. We assigned index dates as dates of first-time COPD diagnoses.

We excluded patients who had been diagnosed with COPD and/or DVT (The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 453.8) before the

TABLE 1. Demographic Characteristics and Comorbidities in Patients With and Without Chronic Obstructive Pulmonary Disease

	Non-COPD (n = 17620)	COPD (n = 8810)	P Value
Age, years (mean ± SD)	72.00 ± 12.21	72.02 ± 12.23	0.9299
Age stratification (%)			
40–49	1096 (6.22)	548 (6.22)	1.0000
50–59	1866 (10.59)	933 (10.59)	
60–69	3382 (19.19)	1691 (19.19)	
≥ 70	11276 (64.00)	5638 (64.00)	
Sex (%)			
Male	11844 (67.22)	5922 (67.22)	1.0000
Female	5776 (32.78)	2888 (32.78)	
Urbanization*			<0.0001
1 (highest)	4843 (27.49)	1704 (19.34)	
2	7345 (41.69)	3836 (43.54)	
3	3036 (17.23)	1784 (20.25)	
4 (lowest)	2396 (13.6)	1486 (16.87)	
Comorbidities			
Atrial fibrillation	528 (3.00)	417 (4.73)	<0.0001
Hypertension	7215 (40.95)	4178 (47.42)	<0.0001
Diabetes	2021 (11.47)	1150 (13.05)	0.0002
Hyperlipidemia	2143 (12.16)	1005 (11.41)	0.0741
Cerebrovascular accident	2471 (14.02)	1853 (21.03)	<0.0001
Congestive heart failure	666 (3.78)	626 (7.11)	<0.0001
Lower leg fracture or surgery	421 (2.39)	228 (2.59)	0.3253
Cancer	1636 (9.28)	583 (6.62)	<0.0001

COPD = chronic obstructive pulmonary disease, SD = standard deviation.

* The level of urbanization was categorized into 4 levels based on the population density of the participants' area of residence, where "1" was most urbanized and "4" was least urbanized.

index date. Furthermore, we also excluded patients who had been diagnosed with PE (ICD-9-CM: 415.1) before the index date in our survey. Control groups were selected from hospitalized patients without COPD, DVT, or PE, and individuals were frequency-matched according to age, sex, and the year of admission at a 2:1 ratio. Patients were followed from the index date to when either a diagnosis of DVT was made, death occurred, December 31, 2009 was reached, or when the patients withdrew from the National Health Insurance program. The baseline history of comorbidities was identified according to the diagnostic code at 1 outpatient diagnosis 1 year, and 1 in inpatient diagnosis before the index date. Comorbidities included atrial fibrillation (ICD-9-CM: 427.31), hypertension (ICD-9-CM: 401–405), diabetes (ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), cerebrovascular accident (ICD-9-CM: 430–438), congenital heart failure (ICD-9-CM: 428), malignancy (ICD-9-CM 140–208), and lower-leg surgery or fracture (ICD-9-CM 820, 821, and 823 or ICD-9 operation code: 81.51–81.54). We also evaluated demographic characteristics in patients with or without COPD, including sex, age group (40–49, 50–59, 60–69, and over 70 years), and urbanization (the level of urbanization was divided into 4 groups based on the population density of the patient's area of residence, where "1" was most urbanized and "4" was the least urbanized).

Statistics

Analyses and calculations were performed using the software SAS ver. 9.3 (SAS Institute, Inc., Cary, NC), and statistical significance was inferred at a 2-sided *P* value of <0.05. The hazard of DVT occurring in COPD and non-COPD patients was examined during the 11-year follow-up period. Continuous and

categorical variables were compared between COPD and non-COPD patients with Student *t* test and chi-square test, as appropriate. Correlations with age, comorbidities, and demographic characteristics were also determined in this study. All data were expressed as the frequency (percentage) and mean ± standard deviation (SD). The incidence of DVT was calculated as the number of the patients with DVT divided by the total person-years, yielding rates per 10,000 person-years in the 2 cohorts. The incident rate ratios (IRRs) of DVT were estimated under Poisson regression.

A Cox proportional-hazards model was used to assess the risk of DVT with COPD cases and non-COPD controls during follow-up. The multivariable model was adjusted for age group, sex, urbanization, and comorbidities. The difference in the cumulative incident rate of DVT between the case and the control groups was calculated with the Kaplan–Meier (KM) estimates. KM estimates were used to generate time-to-event curves for each outcome and tested with the log-rank test. All participants with no predefined DVT or who died before the end of the study period (ie, December 31, 2009) were censored.

RESULTS

The study population comprised of 8810 patients with COPD, with hospitalization records from 1998 to 2008. The mean age and corresponding SD of the study population was 72.02 (±12.23) years. Approximately 67% were men, and only 33% were women. By far, the proportion of patients aged 60 and above comprised 83% of the studied COPD population.

In this population, patients with COPD had higher prevalence of comorbidities, including atrial fibrillation, hypertension,

diabetes, hyperlipidemia, cerebrovascular accident, and congestive heart failure. Table 1 presents the distributions of demographic characteristics and comorbidities in patients with and without COPD. Table 2 shows the incidence rate of DVT (per 10,000 person-years), IRR, and adjusted hazard ration (HR) between the patients with COPD and patients without COPD. The overall incidence rate of DVT was 18.78 per 10,000 person-years in patients with COPD and 13.36 per 10,000 person-years in non-COPD patients. The case number of DVT in patients with COPD and comorbidities was small, except for patients with hypertension. Generally speaking, the IRR (1.42, 95% confidence interval [CI] 1.09–1.84) and adjusted HR (1.38, 95% CI 1.06–1.80) of DVT increased in patients with COPD without comorbidities, including atrial fibrillation, diabetes, hyperlipidemia, cerebrovascular accident, congestive heart failure, lower leg fracture or surgery, and cancer.

There was no significant impact of age on DVT onset in COPD patients. The adjusted HR of DVT in male patients with COPD compared with male patients without COPD with adjusted HR was 1.43 (95% CI 1.00–2.06).

In Table 3, the incidence of DVT was stratified by age, sex, and comorbidities among patients with and without COPD. The age-specific IRR of DVT was not significant in either cohort. However, the adjusted HR of age-specific COPD cohort to the non-COPD cohort in male patients was the highest for those between 40 and 49 years of age, with an adjusted HR of 6.53 (95% CI 1.37–31.11).

Figure 1 illustrates the cumulative incidence of DVT, comparing the COPD cohort and the non-COPD cohort. The incidence of DVT (log-rank $P=0.0125$) was significantly higher for patients with COPD than for those without COPD.

DISCUSSION

To our knowledge, this is the first nationwide population-based cohort study to evaluate the association between COPD and DVT in an Asian population. We used data from the NHIRD, which cover more than 99% of the citizens of Taiwan, to determine the incidence of DVT in Asian patients with COPD. We found that the risk of DVT was 38% higher in

TABLE 2. Incidence of Deep Vein Thrombosis in Patients With And Without Chronic Obstructive Pulmonary Disease

Characteristics	Non-COPD (n = 15,478)			COPD (n = 7739)			IRR (95% CI)	Adjusted HR (95% CI)
	Event	PY	Incidence Rate	Event	PY	Incidence Rate		
DVT	137	103298.10	13.26	94	50051.07	18.78	1.42 (1.09–1.84)	1.38 (1.06–1.80)
Age stratification								
40–49	6	7608.232	7.89	5	3622.91	13.80	1.74 (0.53–5.73)	2.34 (0.66–8.25)
50–59	13	11699.40	11.11	13	5732.46	22.68	2.04 (0.95–4.40)	1.85 (0.84–4.09)
60–69	35	21596.88	16.21	20	10831.50	18.46	1.14 (0.66–1.97)	1.07 (0.62–1.87)
≥ 70	83	62393.59	13.30	56	29864.19	18.75	1.41 (1.00–1.98)	1.36 (0.97–1.92)
Sex								
Male	71	67841.72	10.47	52	32840.55	15.83	1.51 (1.06–2.16)	1.43 (1.00–2.06)
Female	66	35456.38	18.61	42	17210.52	24.40	1.31 (0.89–1.93)	1.30 (0.88–1.93)
Comorbidities								
Atrial fibrillation								
Yes	5	3459.89	14.45	6	2511.46	23.89	1.65 (0.50–5.42)	2.01 (0.59–6.86)
No	132	99838.21	13.22	88	47539.60	18.51	1.40 (1.07–1.83)	1.35 (1.03–1.78)
Hypertension								
Yes	67	39733.12	16.86	52	22152.79	23.47	1.39 (0.97–2.00)	1.34 (0.93–1.94)
No	70	63564.99	11.01	42	27898.28	15.05	1.37 (0.93–2.00)	1.41 (0.96–2.08)
Diabetes								
Yes	18	12706.08	14.17	15	6836.81	21.94	1.55 (0.78–3.07)	1.42 (0.70–2.86)
No	119	90592.02	13.14	79	43214.25	18.28	1.39 (1.05–1.85)	1.37 (1.03–1.83)
Hyperlipidemia								
Yes	31	11373.55	27.26	16	5469.97	29.25	1.07 (0.59–1.96)	1.03 (0.55–1.91)
No	106	91924.55	11.53	78	44581.09	17.50	1.52 (1.13–2.03)	1.49 (1.11–2.01)
Cerebrovascular accident								
Yes	22	14263.61	15.42	16	9543.35	16.77	1.09 (0.57–2.07)	1.07 (0.56–2.06)
No	115	89034.49	12.92	78	40507.72	19.26	1.49 (1.12–1.99)	1.44 (1.08–1.93)
Congestive heart failure								
Yes	7	3492.81	20.04	9	2738.97	32.86	1.64 (0.61–4.40)	1.42 (0.52–3.88)
No	130	99805.29	13.03	85	47312.09	17.97	1.38 (1.05–1.81)	1.38 (1.04–1.82)
Lower leg fracture or surgery								
Yes	8	2322.36	34.45	2	1116.55	17.91	0.52 (0.11–2.45)	0.52 (0.10–2.62)
No	129	100975.74	12.78	92	48934.52	18.80	1.47 (1.13–1.92)	1.43 (1.09–1.89)
Cancer								
Yes	19	9353	20.31	8	3245.92	24.65	1.21 (0.53–2.77)	1.11 (0.48–2.56)
No	118	93945.10	12.56	86	46805.15	18.37	1.46 (1.11–1.93)	1.41 (1.06–1.86)

CI = confidence interval, HR = hazard ration, IRR = incidence rate ratio, PY = per 10,000 person-years.

TABLE 3. Incidence of Deep Vein Thrombosis Stratified by Sex, Age, and Comorbidity, With the Hazards Ratio for Patients With Chronic Obstructive Pulmonary Disease Compared With Those Without Chronic Obstructive Pulmonary Disease

Characteristics	Non-COPD (n = 17620)			COPD (n = 8810)			IRR (95% CI)	Adjusted HR (95% CI)
	Event	PY	Incidence Rate	Event	PY	Incidence Rate		
Male								
40–49	3	4869.19	6.16	5	2265.58	22.07	3.58 (0.86–4.99)	6.53 (1.37–31.11)
50–59	7	7195.75	9.73	7	3525.88	19.85	2.04 (0.72–5.82)	1.96 (0.67–5.68)
60–69	14	14294.87	9.79	8	7168.61	11.16	1.15 (0.48–2.74)	1.08 (0.45–2.61)
≥70	47	41481.91	11.33	32	19880.48	16.10	1.42 (0.91–2.23)	1.32 (0.84–2.08)
Female								
40–49	3	2739.04	10.95	0	1357.34	0.00	–	–
50–59	6	4503.65	13.32	6	2206.58	27.19	2.04 (0.66–6.33)	1.48 (0.44–5.03)
60–69	21	7302.01	28.76	12	3662.90	32.76	1.14 (0.56–2.32)	1.11 (0.54–2.29)
≥70	36	20911.68	17.22	24	9983.71	24.04	1.40 (0.83–2.34)	1.40 (0.83–2.38)
Comorbidities								
40–49	6	7608.23	7.89	5	3622.91	13.80	1.75 (0.53–5.73)	2.14 (0.64–7.15)
50–59	13	11699.40	11.11	13	5732.46	22.68	2.04 (0.95–4.40)	1.91 (0.88–4.16)
60–69	35	21596.88	16.21	20	10831.50	18.46	1.14 (0.66–1.97)	1.11 (0.64–1.92)
≥70	83	62393.59	13.30	56	29864.19	18.75	1.41 (1.00–1.98)	1.34 (0.95–1.89)

CI = confidence interval, HR = hazard ration, IRR = incidence rate ratio, PY = per 10,000 person-years.

the COPD cohort than in the non-COPD cohort, followed for 11 years, with an adjusted HR of 1.38 after adjusting for age, sex, and comorbidities.

The COPD patients exhibited a higher risk of DVT than the those without comorbidities. Generally, Asian patients with COPD, regardless of comorbidities, had a higher incidence of developing DVT during the follow-up period.

DVT in Asian Populations

The incidence of DVT has traditionally been considered low in Asia. A retrospective study that enrolled all DVT patients

in a single hospital in India between 1996 and 2005 showed that the incidence of venous thromboembolism (VTE) was 17.46 per 10,000 admissions, with the most common reason being malignancy (31%). The second leading cause of DVT was post-operative status (30%).⁸ In our study, the incidence of DVT in the non-COPD cohort was 13.3 per 10,000 person-years and 18.8 per 10,000 person-years in the COPD cohort. Our results were similar with the Indian study, and it also showed the incidence of DVT was higher in the COPD cohort than in the general population. Another epidemiologic study in Korea⁹ calculated crude annual incidences of DVT by using the number of individuals with DVT for the numerator and the total Korean

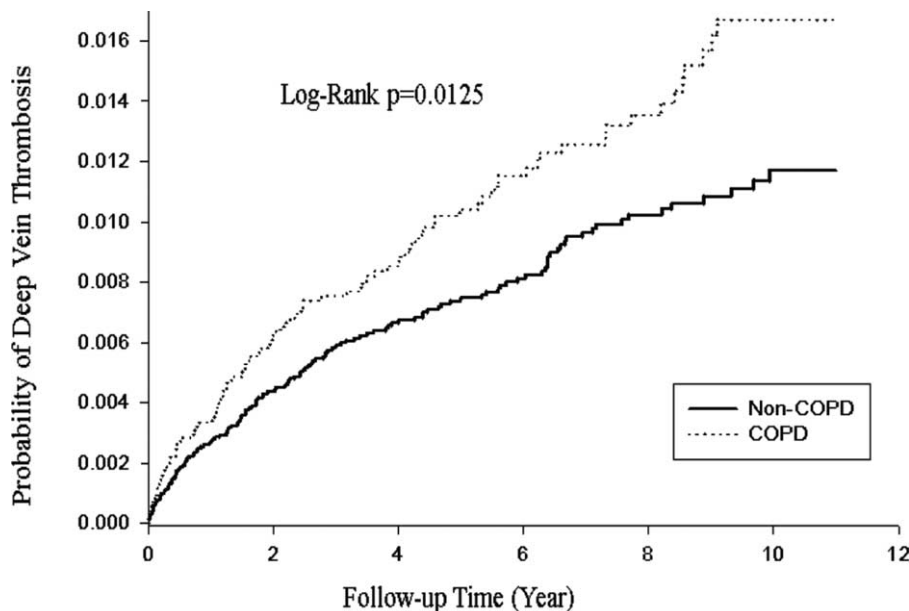


FIGURE 1. Cumulative incidence of deep vein thrombosis in patients with chronic obstructive pulmonary disease and patients without chronic obstructive pulmonary disease.

population for the denominator to show an incidence of 5.31 (per 100,000 individuals), which is much lower than the incidence of DVT in America (104–117 per 100,000 individuals).^{10–12} The study was conducted in Korea by using a total population sample. Our study also used a nationwide database, but focused on hospitalized COPD patients and showed a higher incidence than their study. In addition to the general population, the incidence of DVT in patients receiving operation was also low in Asians. A prospective observational study conducted in Taiwan,¹³ to evaluate the incidence of DVT in patients receiving total knee arthroplasty without thromboprophylaxis, showed that the overall incidence of DVT was 8.6% (62/724), which is much lower than the incidence of DVT (40%–60%) of patients after total hip or total knee arthroplasty without thromboprophylaxis in the western countries.¹⁴

DVT and Sex

The incidence rate of DVT and PE was not significantly different in patients of both sexes between the COPD and the non-COPD cohort, and this result was also observed in the effect of spinal cord injury and sleep apnea on the development of DVT.^{15,16} However, these results may be different in some autoimmune diseases, such as system lupus erythematosus,¹⁷ rheumatoid arthritis,¹⁸ and systemic sclerosis,¹⁹ because of these disease predilections for female patients. Although previous data showed no consistent differences in the incidence of DVT among men and women,²⁰ from our study, the incidence rate of DVT in Asian patients with COPD was a little higher in men.

DVT and Age

Studies showed incidence rate of DVT increased with age in patients with rheumatoid arthritis,¹⁸ but not in patients with systemic lupus erythematosus.¹⁷ A retrospective study using the Korean Health Insurance Review and Assessment Service database found that the incidence of DVT in the Korean population steadily increased with age.²¹ Previous studies also demonstrated that the incidence of first-time DVT rises exponentially with age, and the incidence of DVT increases dramatically in persons over 60 years old.²⁰ Although COPD itself is a risk factor for DVT,²² our study found that there was no age predilection of DVT in Asian patients with COPD during the long-term follow-up period.

DVT and COPD

Most acute exacerbations of COPD are attributable to infections. Many studies also focus on the relationship between PE and acute exacerbations of COPD.^{23,24} Overall, there were few studies about the DVT and COPD,^{5,25,26} and most of them were focused on the Caucasian populations. A previous study showed that DVT patients with COPD were older, with median age of 72.5 years, more likely to be male, and have a greater medical utilization than other DVT patients.⁵ A study enrolled 100 patients with COPD in India and found that the prevalence of DVT in patients with acute exacerbation of COPD was 9%.²⁷ However, the limitations of these observational studies were the small sample sizes, lack of controls, no long-term follow-ups, and no focus on epidemiology of DVT incidence. Our study is a nationwide Asian database and included 7739 patients with COPD followed for 11 years. Our study is representative of DVT incidence in COPD patients. The data were derived from a variety of practice settings (inpatient and outpatient) and

hospital levels (local hospital, regional hospital, and medical center). On the basis of the analysis of these data, we found the overall incidence of DVT in patients with COPD was 38% higher than the control group. On the contrary, a previous study that also examined Asian COPD patients found the incidence of DVT to be similar amount the different age groups. In general, we determined that the overall incidence rate of DVT was higher in patients with COPD, with 18.78 events per 10,000 person-years.

LIMITATIONS

The results of this study highlight a gap in the epidemiology proposed to assess the incidence of DVT in Asian patients with COPD. In our study, patients with COPD and comorbidities were in general less likely to possess DVT and led to a small case number of DVT in COPD patients with atrial fibrillation, congestive heart failure, lower leg fracture or surgery, and cancer. Further studies should be conducted to evaluate the risk of developing DVT in patients with COPD associated with a variety of comorbidities; nevertheless, this study draws attention to the incidence of DVT in different races.

There are some additional limitations in the study. As the data were obtained from the NHI system, we were unable to evaluate the influence of some risk factors of DVT, including sedentary status and smoking. The database does not contain detailed information about pulmonary function and body mass index. These components may be important confounding factors for the development of DVT. The diagnosis of DVT was made from clinical findings, and it is possible that DVT may be underdiagnosed. Further prospective studies with routine screening duplex ultrasounds are required to evaluate the percentage of occult DVT.

CONCLUSIONS

Asian patients with COPD have a higher incidence of DVT than non-COPD patients, but the incidence rate of DVT is smaller in the Asian population than in the Caucasian populations. The incidence of DVT had no age predilection in Asian patients with COPD.

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