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A population-based cohort study on deep vein thrombosis and pulmonary embolism among schizophrenia patients

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ABSTRACT

Objective: Several risk factors of venous thromboembolism (VTE) and pulmonary embolism (PE) were found in patients with schizophrenia. Therefore, we hypothesize that the incidences of VTE and PE are relatively higher among schizophrenia patients in comparison with the general population.
Method: For this population-based cohort study, claims data from 1996 to 2011 were obtained from the National Health Insurance Research Database in Taiwan. We compared the incidence of DVT and PE between schizophrenia and non-schizophrenia cohorts. Cox proportional hazard regression models were used to analyze the risk of DVT and PE, according to sex, age, and comorbidities.
Results: Compared with the non-schizophrenia cohort, the schizophrenia cohort exhibited a 2.02-fold higher adjusted hazard ratio (HR) for developing DVT, and a 1.99-fold higher adjusted HR for developing PE. Furthermore, schizophrenia patients using first-generation or second-generation antipsychotics exhibited a higher adjusted HR for both DVT and PE development.
Conclusion: Compared with the general population, the risk of DVT and PE is relatively higher among schizophrenia patients. Early diagnosis and intervention by physicians could mitigate complications and reduce mortality resulting from VTE.

1. Introduction

In the United States, the annual incidence of venous thromboembolisms (VTEs), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is approximately 1 per 1000 adults, causing discomfort, suffering, and occasionally death (White, 2003). Death occurs within one month of incidence in approximately 6% of patients with DVT and in 10% of those with PE (Cushman et al., 2004). Several studies have identified age, immobilization, obesity, smoking status, allergy, autoimmune disease, heart failure, lower leg fracture, surgery, diabetes, pregnancy, antipsychotics, physical restraint and cancer as acquired risk factors for VTE.

Few studies have investigated DVT and PE in patients with schizophrenia. Schizophrenia is a chronic, severe, and disabling brain disorder. Worldwide, the lifetime prevalence of schizophrenia is approximately 1%. Schizophrenia patients also have more physical problems than general population. In the recent Canada study, they found that schizophrenia patients are at increased risk of death compared to the general population, and the majority of these deaths are occurring in older age from physical disease processes (Kredentser et al., 2014). As we have known, there are several risk factors of DVT and PE in schizophrenia patients. These factors might increase risk of DVT and PE in this population. Patients with schizophrenia may exhibit long-term positive, negative, cognitive, or affective symptoms. Negative symptoms include blunted or flat affect, alogia, avolition, apathy, anticipatory anhedonia, and asociality (Choi and Medalia, 2010; Foussias and Remington, 2010; Blanchard et al., 2011). Avolition was found to be a significant predictor for motor activity levels in patients with schizophrenia (Docx et al., 2013). Immobilization was associated with risk of DVT and PE in previous study (Beam et al., 2009). And, increased risk of VTE among subjects with current antipsychotic use was found (Wu et al., 2013). Besides, high tobacco smoking rate in schizophrenia might increase risk of

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DVT and PE (Severinsen et al., 2009; Cooper et al., 2012; Blondon et al., 2013; Minichino et al., 2013). High metabolic syndrome risk in this population also increases the risk of DVT and PE (Kawasaki et al., 1997; Vazzana et al., 2012; Chang et al., 2013; Klovaite et al., 2014).

We hypothesize that the incidence of VTE is higher among schizophrenia patients in comparison with the general population. Accordingly, this population-based cohort study was conducted to investigate whether DVT and PE are more prevalent among schizophrenia patients in Taiwan.

2. Methods

2.1. Data source

This study used data that were obtained from the National Health Insurance Research Database (NHIRD), which contains claims data from 1996 to 2011 related to inpatient care, ambulatory care, dental care, and prescription drugs. In Taiwan, national health care is obligatory, and few people are excluded from the system. The National Health Insurance (NHI) program, which was implemented on March 1, 1995, provides insurance coverage for approximately 99% of Taiwan's population of approximately 23.74 million people (http://www.nhi.gov.tw/english/index.aspx).

The NHI catastrophic illness files—the Registry of Catastrophic Illnesses Patient Database (RCIPD)—were established to track patients with major or catastrophic illnesses, including cancer, end-stage renal disease, autoimmune diseases, congenital illness, and several mental illness, such as schizophrenia. To validate the diagnosis of patients, the Bureau of NHI routinely reviews the original medical charts of all patients who apply for catastrophic illness registration. This study analyzed depersonalized secondary data; thus, no informed consent was required. This study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012). Diagnostic codes are reported based on the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM).

2.2. Participant selection

The study subjects were identified from the following two subsets of the NHIRD: First, cases were confirmed from the RCIPD. The schizophrenia cohort comprised patients aged 20 years who were newly diagnosed with schizophrenia (ICD-9-CM Code 295 except 295.8) between 2000 and 2011. The index date was set as the date at which the schizophrenia patients were registered for catastrophic illness; second, the control patient data were obtained from the LHID2000, which is a database containing longitudinally linked claims data (from 1996 to 2011) of one million people randomly sampled from the NHIRD. The National Health Research Institutes reported that the difference in age, sex, and health care costs between the LHID2000 and all enrollees is nonsignificant. A nonschizophrenia comparison cohort was randomly selected from the LHID2000, comprising patients without schizophrenia and frequency matched with the schizophrenia cohort at a 4:1 ratio based on age (in 5-year increments), sex, and year of diagnosis. For both cohorts, patients with a history of DVT (ICD-9-CM 453.8) or PE (ICD-9-CM 415.1, excluding ICD-9-CM 415.11) before the index date, as well as those with incomplete age or sex information were excluded.

2.3. Variables

We considered atrial fibrillation (ICD-9 Code 427.31), hypertension (ICD-9 Codes 401–405), diabetes (ICD-9 Code 250), cerebral vascular disease (CVA; ICD-9 Codes 430–438), heart failure (ICD-9 Code 428), all types of cancer (ICD-9 Codes 140–208), pregnancy (ICD-9 Codes 640.×1–676.×1, 640.×2–676.×2, and 650–659, as well as Procedure Codes 72–74), and lower leg fracture or surgery (ICD-9 Codes 820–823, as well as Procedure Codes 81.51, 81.52, 81.53, and 81.54) as preexisting comorbidities that were potential confounders in the association with DVT and PE. Information on benzodiazepine (BZD) treatment at the baseline was obtained. We hypothesized that first-generation antipsychotics, and second-generation antipsychotics have different effects on DVT and PE in schizophrenia patients.

2.4. Main outcome

The study participants were followed from the index date until DVT or PE diagnosis, withdrawal from the insurance program, censoring because of death, or the end date of the database (December 31, 2011).

2.5. Statistical analysis

All analyses were performed using SAS for Windows (version 9.3; SAS Institute, Inc., Cary, NC, USA). A two-tailed *P* value of 0.05 was considered statistically significant. Pearson's chi-square test was used for categorical variables, such as age group (20–34, 35–49, and ≥50 years), sex, comorbidities, and BZD treatment between the schizophrenia and nonschizophrenia cohorts. Continuous variables were analyzed using a two-sample t test. The cumulative incidence of DVT or PE among the schizophrenia and nonschizophrenia cohorts was assessed using the Kaplan–Meier method, and the differences were assessed with a log-rank test. The overall, gender-, age-, and comorbidity-specific incidence rates (per 10 000 person-years) were calculated for each cohort. Univariable and multivariable Cox proportional hazard regression analyses were used to assess the risk of DVT and PE development associated with schizophrenia, compared with that of the nonschizophrenia cohort. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated in the Cox models. For the multivariable model, the effects of sex, age, and comorbidities were controlled to determine whether these factors cause any significant difference between the two cohorts (Table 1).

Table 1
Comparison of demographics and comorbidity between schizophrenia patients and controls.

	Control subjects (N = 60,264) n(%)	Schizophrenia (N = 60,264) n(%)	*P*-value
Age, years			0.99
20–34	26,777(44.4)	26,777(44.4)	
35–49	21,635(35.9)	21,635(35.9)	
>50	11,852(19.7)	11,852(19.7)	
Mean (SD)†	38.7(13.8)	38.8(13.3)	0.08
Gender			0.99
Female	28,609(47.5)	28,609(47.5)	
Male	31,655(52.5)	31,655(52.5)	
Comorbidity			
Atrial fibrillation	130(0.22)	107(0.18)	0.13
Hypertension	7406(12.3)	7219(12.0)	0.10
Hyperlipidemia	5615(9.32)	4498(7.46)	<0.001
Diabetes	2064(3.42)	2737(4.54)	<0.001
CVA	602(1.00)	991(1.64)	<0.001
Heart failure	402(0.67)	532(0.88)	<0.001
All cancer	673(1.12)	440(0.73)	<0.001
Pregnancy	5874(9.75)	3463(5.75)	<0.001
Lower leg fracture or	711(1.18)	1276(2.12)	<0.001
Surgery			
BZD	31,327(52.0)	55,826(92.6)	<0.001

Chi-square test examined categorical data.
CVA denotes cerebral vascular disease.
BZD denotes Benzodiazepines.
† t-Test examined continuous.