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Increased risk for venous thromboembolism among patients with concurrent depressive, bipolar, and schizophrenic disorders☆

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ABSTRACT

Objective: The study aim was to investigate the risk of venous thromboembolism (VTE) in patients with concurrent depressive, bipolar, and schizophrenic disorders.
Methods: A population-based cohort study was conducted in which information regarding psychiatric illnesses and medical comorbidities in 29,467 patients with concurrent depressive, bipolar, and schizophrenic disorders and regarding 117,868 controls were extracted. We compared the incidence of VTE between the study and control cohorts. Cox proportional hazard regression models were used to analyze the risk of VTE after adjusting for potential confounders, including sex, age, and comorbidities.
Results: Compared with the control cohort, the overall study cohort had a 2.995-fold higher adjusted hazard ratio (aHR) for development of deep vein thrombosis (DVT) and a 2.591-fold higher aHR for development of pulmonary embolism (PE). Moreover, patients with depressive, bipolar, and schizophrenic disorders all exhibited higher aHRs for development of both DVT and PE.
Conclusion: The relative risks of DVT and PE were higher in patients with concurrent depressive, bipolar, and schizophrenic disorders than those of the general population. Further research is needed to develop effective prevention strategies for different patient populations.

1. Introduction

Thromboembolism (VTE) is one of the main causes of morbidity and mortality in non-surgical patients. The annual incidence of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is relatively constant at approximately 1 per 1000 adults [1]. Reported risk factors for VTE vary widely, and increasing age, prolonged immobilization, cancer, surgery, trauma, pregnancy, puerperium, hormone therapy, high metabolic syndrome risk, varicose vein, and major heart failure are the most prominent [2–8].

The risk of VTE is higher in psychiatric patients than in the general population [9,10]. Although previous studies have targeted patients with depressive, bipolar, and schizophrenic disorders individually [11–13], there have been no studies in patients with these concurrent mental illnesses. In addition, there have been some methodological problems within previous studies that may have confounded those results, including small sample sizes [14], under-representations of psychiatric disorders based on the inclusion of involuntarily hospitalized patients alone [14], inclusion of minority groups in which only admitted psychiatric patients were selected [12], and the evaluation of limited clinical variables [12]. Therefore, the risk of DVT or PE development in psychiatric patients remains uncertain, and elucidating this risk may provide crucial information for developing effective prevention strategies.

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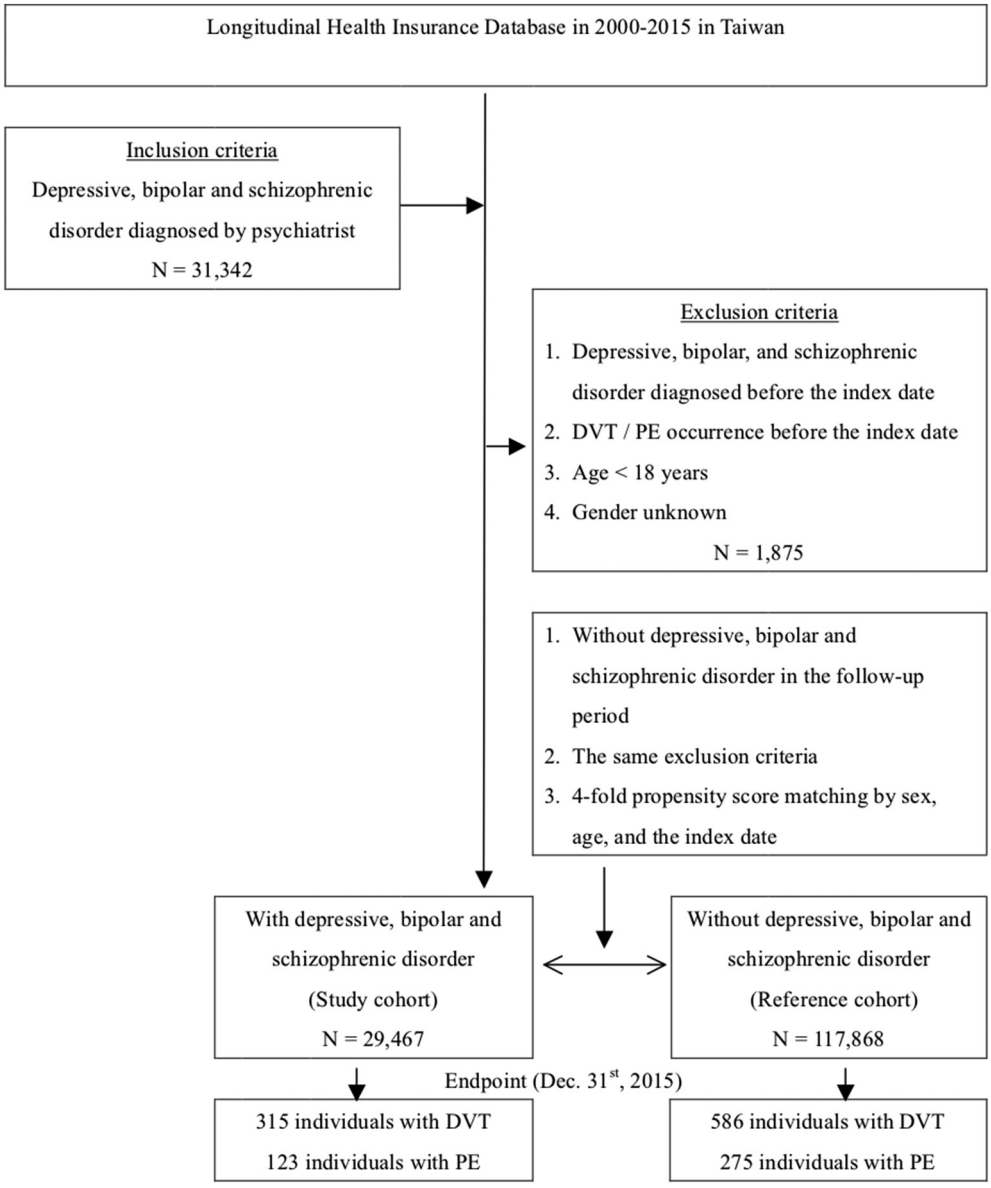

Fig. 1. Flowchart of the study sample selection.

We hypothesized that the incidence of DVT or PE would be higher among patients with concurrent depressive, bipolar, and schizophrenic disorders than in the general population. Accordingly, we conducted this population-based study to investigate whether DVT and PE are more prevalent among psychiatric patients in Taiwan.

2. Methods

2.1. Data sources

The National Health Insurance (NHI) program was launched in Taiwan in 1995, and nearly 99% of Taiwanese residents were enrolled [15]. It is comprehensive and its benefit package covers all medically necessary services, including inpatient, outpatient, dental services, traditional Chinese medicine, and nearly 16,000 prescription drugs. Taiwan's NHI is also a compulsory program. For those who cannot pay the premium, the premium is subsidized for households with incomes below the poverty line; people who are unable to pay the premium for various reasons can obtain interest-free loans. Additionally, the NHI refers some people to one of the many charitable organizations for help. With this safety net in place, most single individuals are never denied health care [16]. In this study, we used the Longitudinal Health Insurance Database (LHID) released by the Bureau of the NHI. The LHID contains all longitudinal claims data (from 2000 to 2015) of 2,000,000 individuals who were randomly selected from among the 25.68 million enrollees of the NHI program from January 1, 2005 to January 1, 2006 [17]. The sample was created by the Bureau of NHI by using a systematic sampling method to randomly extract a representative database from the entire Taiwan NHI database. No statistically significant differences in age, sex, and medical costs were identified in the LHID. We adopted a cohort design to investigate the incidences and risks of DVT and PE development in patients with concurrent depressive, bipolar, and schizophrenic disorders from January 1, 2000 to December 31, 2015. Patient consent was not required to access the LHID, and this study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital (No.: 08-XD-014).

2.2. Inclusion criteria for patients with concurrent depressive, bipolar, and schizophrenic disorders and for the control cohort

Because Taiwan's NHI was launched in 1995, patients' medical claims before 1995 were unavailable; information related to diagnosis of any diseases before 1995 was thus unavailable, and the duration of illness could not be determined in some patients. Therefore, we chose to include patients who were newly diagnosed with concurrent depressive, bipolar, and schizophrenic disorders as our study cohort to prevent survival bias. To establish this cohort, we excluded patients who had a diagnosis of depressive, bipolar, or schizophrenic disorder before 2000 or who had diagnoses of DVT and PE before the first diagnosis of concurrent depressive, bipolar, and schizophrenic disorders. Patients with an unspecified sex and those < 18 years of age were also excluded from this study. The enrollment date was considered to be the index date. The study cohort included a total of 29,467 individuals ≥18 years old who were newly diagnosed with concurrent depressive (ICD-9-CM codes 296.2–296.3, 300.4, and 311), bipolar (ICD-9-CM codes 296.0–296.1, 296.4–296.7, 296.0–296.1, 296.4, and 296.5–296.7), and schizophrenic (ICD-9-CM code 295) disorders by board-certified psychiatrists between January 1, 2000 and December 31, 2015 and who did not have a history of depressive, bipolar, or schizophrenic disorder before the index date. To achieve diagnostic validity, all psychiatric diagnoses were required to be specified at least once in inpatient medical records or twice in outpatient medical records.

Our control cohort was selected from the remaining patients during the same period (January 1, 2000 to December 31, 2015). The exclusion criteria applied to the control cohort were similar to those applied to the study cohort; namely, patients who had a diagnosis of depressive, bipolar, or schizophrenic disorder before 2000 and/or during the study period, patients who had an unspecified sex, and/or those who were < 18 years old. We randomly selected a control cohort from the remaining eligible subjects and matched the subjects with the study cohort by age, sex, and index year at a 4:1 ratio. The first time that patients in the control cohort sought non-psychiatric medical consultation during the study period was considered to be the index date. Therefore, those selected for the control group were required to have at least one visit during the study period since we could choose the first one as the index date. The protocol for study patient selection is shown in Fig. 1.

2.3. Main outcome

All study participants were followed from the index date until the development of any new-onset DVT (ICD-9-CM code 453.8) or PE (ICD-9-CM code 415.1, excluding ICD-9-CM 415.11), disenrollment, death, or until the end of the study period.

2.4. Possible confounding variables

Medical comorbidities at enrollment, including atrial fibrillation (AF; ICD-9-CM Code 427.31), hypertension (HTN; ICD-9-CM Codes 401–405), diabetes mellitus (DM; ICD-9-CM Code 250), cerebrovascular disease (CVA; ICD-9-CM Codes 430–438), heart failure (HF; ICD-9-CM Code 428), all types of cancer (ICD-9-CM Codes 140–208), pregnancy (ICD-9-CM Codes 640.x1–676.x1, 640.x 2–676.x2, and 650–659 as well as Procedure Codes 72–74), and lower leg fracture or surgery (ICD-9-CM Codes 820–823 as well as Procedure Codes 81.51, 81.52, 81.53, and 81.54) were identified during the time period between 1995 to the index date in our study. We confirmed that all diagnoses were given by the appropriate board-certified physicians to ensure diagnostic validity. Catastrophic illnesses were also assessed in this study. The LHID categorizes several diseases or injuries as catastrophic illnesses, including schizophrenia, depression, bipolar disorder, malignant neoplasms, systemic lupus erythematosus, and burns that affect > 20% of the total body surface. Records of a patient's catastrophic illness are directly entered into the NHI Card, which enables patients with such illnesses who present their NHI Card when requesting care for the disease to be treated without having to pay a co-payment [18].

2.5. Statistical analysis

All statistical analyses were performed by using SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The chi-squared test was used to evaluate the distributions of categorical variables. Univariable and multivariable Cox proportional hazards regression models were used to compare the risks of DVT and PE in patients with concurrent depressive, bipolar, and schizophrenic disorders with those of the reference 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 of AF, HTN, DM, CVA, HF, cancer, pregnancy, lower leg fracture or surgery, and non-psychiatric catastrophic illnesses were controlled to determine whether these factors caused any significant difference between the two cohorts. Subgroup analyses were performed to individually compare the differences in VTE risk among different mental illnesses. Stratified analysis was used to compare the effects of sex, age, and presence of comorbidities on the development of DVT and PE. Differences in the cumulative risks of DVT and PE between the study and control cohorts were illustrated by Kaplan–Meier plots with the log-rank test. The level of statistical significance was set at a two-tailed P value of < 0.05.

3. Results

3.1. Baseline characteristics of the study population

There were 29,467 subjects in the study cohort and 117,868 subjects in the control cohort. There were no significant differences in sex and age distributions between the study and control groups ($P = 0.999$). Most subjects (79.2%) in the study and control cohorts were < 55 years old, and men comprised 53.4% of the subjects in the study and control cohorts; individuals in the study cohort had significantly more CVA and catastrophic illnesses ($P < 0.001$ and $P = 0.033$, respectively), but lower rates of AF, HTN, DM, and HF (all $P < 0.001$;).

3.2. Incidence and risk of DVT and PE among patients with mental illnesses

During the follow-up period, the overall incidence of DVT was significantly higher (3.214-fold) in the study cohort than in the reference cohort (11.59 *vs.* 4.79 per 10,000 person-years), with an aHR of 3.103 (95% CI: 2.671–3.701, $P < 0.001$) after adjusting the model to control for the effects of age, sex, comorbidities, and catastrophic illnesses other than mental illnesses. In both cohorts, the DVT incidence was higher in women than in men. The sex-specific risks of DVT development in the study cohort, relative to the reference cohort, were significantly higher for both women (aHR: 3.560, 95% CI: 2.776–4.301, $P < 0.001$) and men (aHR: 2.497, 95% CI: 1.812–2.895, $P < 0.001$). The age-specific risks of DVT development in the study cohort, relative to the reference cohort, were significantly higher for patients < 55 years of age (aHR: 4.002, 95% CI: 3.121–5.003, $P < 0.001$), patients 55–69 years of age (aHR: 2.637, 95% CI: 1.975–3.502, $P < 0.001$), and patients ≥70 years of age (aHR: 2.289, 95% CI: 1.410–2.725, $P < 0.001$). Compared with the reference cohort, the study cohort exhibited a higher risk of DVT development in patients without comorbidities (aHR: 4.855, 95% CI: 3.812–6.225, $P < 0.001$; Table 2). Kaplan–Meier analysis showed that the cumulative incidence curves of DVT were significantly higher in the study cohort than in the reference cohort (all log-rank $P < 0.001$; Fig. 2).

Overall, the risk of PE development was 2.626-fold higher in the study cohort than in the reference cohort (95% CI: 2.114–3.398,

Table 1
Baseline characteristics between the study and reference cohorts.

Variables	Study cohort (n = 29, 467)		Reference cohort (n = 117,868)		P
	n	%	n	%	
Gender					0.999
Male	15,724	53.4	62,896	53.4	
Female	13,743	46.6	54,972	46.6	
Age (years)					0.999
≦54	23,341	79.2	93,364	79.2	
55–69	3879	13.2	15,516	13.2	
≧70	2247	7.6	8988	7.6	
Comorbidities					
Atrial fibrillation	86	0.3	581	0.5	< 0.001***
Hypertension	1792	6.1	8668	7.4	< 0.001***
Diabetes mellitus	1513	5.1	8012	6.8	< 0.001***
Cerebral vascular disease	1163	3.9	4078	3.5	< 0.001***
Heart failure	135	0.5	1128	1.0	< 0.001***
Cancer	1314	4.5	4974	4.2	0.069
Pregnancy	1565	5.3	6124	5.2	0.426
Lower leg fracture or surgery	186	0.6	784	0.7	
Catastrophic illness[a]	1768	6.0	6689	5.7	0.033*

P: Chi-square test.
**$P < 0.01$.
* $P < 0.05$.
*** $P < 0.001$.
[a] Non-psychiatric catastrophic illnesses (excluding depression, bipolar disorder, and schizophrenia).

$P < 0.001$) after adjusting the model to control for the effects of age, sex, comorbidities, and catastrophic illnesses other than mental illness. Sex-specific analysis demonstrated that the risk of PE development was significantly higher in the study cohort than in the reference cohort for both women (aHR: 2.994, 95% CI: 2.184–4.306, $P < 0.001$) and men (aHR: 2.179, 95% CI: 1.409–2.915, $P < 0.001$). Age-specific analysis showed that the risk of PE development was significantly higher for patients < 55 years of age (aHR: 3.005, 95% CI: 2.036–4.225, $P < 0.001$), patients 55–69 years of age (aHR: 2.691, 95% CI: 1.504–4.010, $P < 0.001$), and patients ≥70 years of age (aHR: 2.122, 95% CI: 1.389–3.306, $P < 0.001$). Compared with the reference cohort, the study cohort exhibited a higher risk of PE development in patients without comorbidities (aHR: 4.804, 95% CI: 3.380–7.125, $P < 0.001$; Table 2). Kaplan–Meier analysis showed that the cumulative incidence curves of PE were significantly higher in the study cohort than in the reference cohort (all log-rank $P < 0.001$; Fig. 3).

Further subgroup analysis was performed to assess whether depressive, bipolar, and schizophrenic disorders individually influenced the DVT and PE outcomes. Compared with the risk in the reference cohort, the risk of DVT was relatively higher in patients with depressive (aHR: 3.800, 95% CI: 2.813–4.565, $P < 0.001$), bipolar (aHR: 3.049, 95% CI: 2.456–3.489, $P < 0.001$), and schizophrenic disorder (aHR: 2.848, 95% CI: 2.425–3.486, $P < 0.001$). Similarly, the results showed that the risks of PE in patients with depressive (aHR: 3.464, 95% CI: 2.284–4.635, $P < 0.001$), bipolar (aHR: 2.728, 95% CI: 1.784–3.125, $P < 0.001$), and schizophrenic disorder (aHR: 2.245, 95% CI: 1.704–3.186, $P < 0.001$) were also significantly higher than those in the reference cohort (Supplementary Tables S1–3).

4. Discussion

Our study showed that patients with concurrent depressive, bipolar, and schizophrenic disorders had a 3.103-fold (2.626-fold) higher aHR for DVT (PE) development than that of the control cohort. Considering each psychiatric group separately, patients with depressive, bipolar, and schizophrenic disorders (separately) all had an approximately 3-fold higher risk of developing DVT (PE) than that of the control cohort. To the best of our knowledge, this is the first study to investigate the risks of DVT and PE in patients with different mental illnesses as a whole and to analyze them individually. Although with varying effect estimates and uncertainties, this study should help to better target subpopulations that may benefit most from VTE prevention trials.

These results are consistent with the findings of several previous reports. Two studies demonstrated an association between depression and VTE risk [19,20], although the researchers were unable to adjust for several important risk factors for VTE. A study by Strudsholm et al. showed that patients with bipolar disorder had a significantly higher occurrence of PE [12], although the diagnoses were made based on different classification systems (transition from ICD-8 to ICD-10). A nationwide population-based cohort study by Hsu et al. indicated a potentially higher risk of DVT and PE among schizophrenia patients [11].

In contrast with many other studies that found higher rates of DM, HTN, and heart disease in patients with depressive, bipolar, and schizophrenic disorders [21,22], our study showed higher rates of AF, HTN, DM, and HF in the control population than those of people with mood and psychotic disorders. The reason for this discrepancy remains unclear. Possible explanations include the heterogeneity of our study group, and potential bias in ascertaining that people with severe mental illnesses may reduce their access to medical care, which could lead to delayed diagnosis of physical illnesses [23,24].

In the present study, the study cohort exhibited a higher risk of DVT and PE relative to that in the reference cohort, which could be related to several potential mediators (diseases that may have been caused by mood or psychotic disorders) or confounders (factors that could affect the risk of developing mental illnesses and VTE but cannot be caused by mental illnesses) [25]. First, higher rates of smoking among patients with depressive [26], bipolar [27], and schizophrenic disorders [28] could increase the risk. Some have suggested that such patients use cigarettes as a means of self-medication of psychiatric symptoms [29,30]. Second, increasing evidence suggests that patients with severe mental disorders are at an increased risk for obesity [31–34], both from the illness itself and from its treatment. With regard to the mental illness itself, obesity may produce not only poor outcomes of mental illness treatment but also generalized medical conditions, such as metabolic syndrome (MetS) [4,35,36], a constellation of risk factors for CVA disease that include central obesity, glucose intolerance, HTN, and dyslipidemia [37]. With regard to the mental illness treatment, growing evidence indicates that some antipsychotic, mood stabilizing, and antidepressant agents cause obesity in the severely mentally ill [31–33,38]. Parkin et al. found that use of antidepressants or antipsychotics carry 4.9-fold and 13.3-fold higher risks of VTE, respectively [39]. Thus far, in addition to obesity and metabolic syndrome, there is no clear explanation for the increased risk of VTE among patients treated with psychotropic drugs, and several theories have been proposed, including enhanced anticardiolipin antibodies [40,41], exacerbation of venous stasis during sedation [42], increased adrenaline secretion in the acute psychotic phase [43], and hyperhomocysteinemia [44,45]. Third, other illness-related factors, including unhealthy lifestyle habits and binge eating, have been associated with obesity or MetS in both schizophrenia and bipolar disorder [31,46–48]. Unhealthy lifestyle habits, such as hypoactivity and immobilization are established risk factors of DVT and PE [2,49,50]. Neuropsychological symptoms, such as negative symptoms of schizophrenia [51] or catatonia [52], could lead to a reduction in the activities of daily living and further increase the risk of developing VTE. Finally, the use of physical restraint among psychiatric patients may predispose them to the development of DVT and PE [53–56]. Based on the above evidence, these illness-related (*e.g.*, smoking, obesity, MetS, and neuropsychological symptoms) or treatment-related factors (*e.g.*, psychotropic agents and physical restraint) would be more like mediators than confounders.

Several limitations must be considered when interpreting our findings. First, this was an observational study; thus, potential residual

Table 2
Incidence and risk of DVT and PE, stratified by sex, age groups and comorbidities for the study cohort compared to the reference cohort.

DVT / PE	Variables	Reference cohort (n = 117,868)			Study cohort (n = 29, 467)			Compared to reference cohort					
		Events	PYs	Rate	Events	PYs	Rate	Crude HR	95% CI	*P*	Adjusted HR	95% CI	*P*
DVT	Overall	586	1,223,646.10	4.79	315	271,773.96	11.59	3.214	2.757–3.746	< 0.001***	3.103	2.671–3.701	< 0.001***
	Gender												
	Male	303	655,070.35	4.63	142	144,382.78	9.83	2.773	2.223–3.460	< 0.001***	2.497	1.812–2.895	< 0.001***
	Female	283	568,575.75	4.98	173	127,391.18	13.58	3.689	2.980–4.566	< 0.001***	3.560	2.776–4.301	< 0.001***
	Age (years)												
	≦54	204	631,994.38	3.23	181	163,587.02	11.06	4.133	3.309–5.161	< 0.001***	4.002	3.121–5.003	< 0.001***
	55–69	166	335,259.33	4.95	70	66,318.73	10.56	2.747	2.013–3.749	< 0.001***	2.637	1.975–3.502	< 0.001***
	≧70	216	256,392.38	8.42	64	41,868.21	15.29	2.728	2.001–3.714	< 0.001***	2.289	1.410–2.725	< 0.001***
	Comorbidities												
	No	292	786,700.15	3.71	100	79,016.68	12.66	4.896	3.805–6.301	< 0.001***	4.855	3.812–6.225	< 0.001***
	Yes	294	436,945.95	6.73	215	192,757.28	11.15	2.076	1.706–2.527	< 0.001***	2.179	1.897–2.804	< 0.001***
PE	Overall	275	1,225,468.47	2.24	123	272,428.34	4.51	2.662	2.106–3.364	< 0.001***	2.626	2.114–3.398	< 0.001***
	Gender												
	Male	143	656,045.56	2.18	59	144,681.33	4.08	2.379	1.710–3.311	< 0.001***	2.179	1.409–2.915	< 0.001***
	Female	132	569,422.91	2.32	64	127,747.00	5.01	2.997	2.149–4.179	< 0.001***	2.994	2.184–4.306	< 0.001***
	Age (years)												
	≦54	95	632,274.22	1.50	65	163,848.98	3.97	3.188	2.259–4.500	< 0.001***	3.005	2.036–4.225	< 0.001***
	55–69	67	335,729.37	2.00	30	66,553.99	4.51	3.072	1.896–4.980	< 0.001***	2.691	1.504–4.010	0.001**
	≧70	113	257,464.88	4.39	28	42,025.36	6.66	2.154	1.376–3.372	0.001**	2.122	1.389–3.306	0.001**
	Comorbidities												
	No	144	787,695.52	1.83	42	79,225.10	5.30	4.847	3.295–7.131	< 0.001***	4.804	3.380–7.125	< 0.001***
	Yes	131	437,772.95	2.99	81	193,203.24	4.19	1.538	1.144–2.067	0.004**	1.612	1.358–2.394	0.001**

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; PYs, person-years.
Rate: per 10,000 PYs.
Adjusted HR: adjusted for gender, age, and comorbidities of atrial fibrillation, hypertension, diabetes mellitus, cerebral vascular disease, heart failure, cancer, pregnancy, lower leg fracture or surgery, and non-psychiatric catastrophic illnesses (excluding depression, bipolar disorder, and schizophrenia)
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

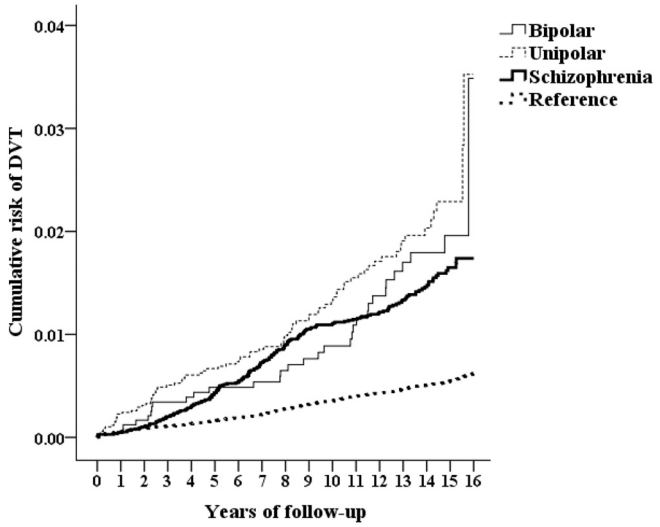

Fig. 2. Cumulative risks of DVT in patients with unipolar, bipolar, and schizophrenic disorders and the reference cohort.
Log-rank tests:
Overall, $P < .001^{***}$
Unipolar *vs.* Reference, $P < .001^{***}$
Bipolar *vs.* Reference, $P < .001^{***}$
Schizophrenic *vs.* Reference, $P < .001^{***}$.

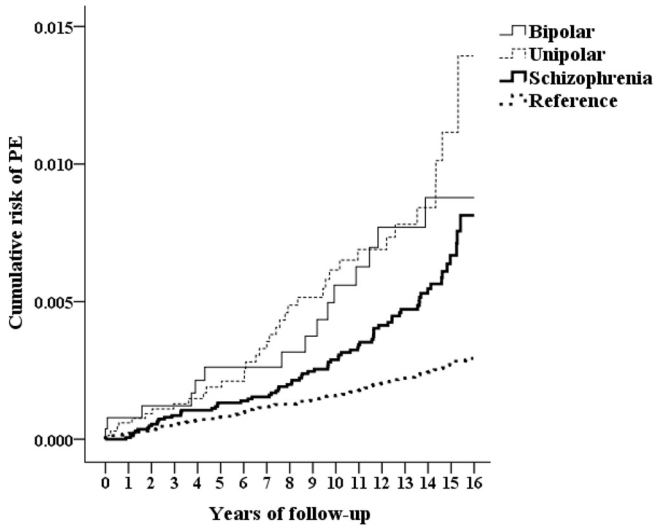

Fig. 3. Cumulative risks of PE in patients with unipolar, bipolar, and schizophrenic disorders and the reference cohort.
Log-rank tests:
Overall, $P < .001^{***}$
Unipolar *vs.* Reference, $P < .001^{***}$
Bipolar *vs.* Reference, $P < .001^{***}$
Schizophrenic *vs.* Reference, $P < .001^{***}$.

factors, including hormone replacement therapy [57] and use of oral contraceptive pills [58], which were known risk factors of VTE, may have contributed to the results, but these factors were not measured in our study. Second, a lack of data availability [*e.g.*, mental illness severity, family history of VTE, remote history of VTE (prior to 1995), trauma, smoking status, obesity, body mass index, lack of exercise, hypercoagulable state, lower leg paralysis, immobilization, and physical restraint] in the LHID, which may be more prevalent in psychiatric patients, may have influenced the results of our study. Third, potential ascertainment bias should be considered because people with mood or psychotic disorders would like to have more frequent contact with health services [59–61], so VTE would be more likely to be recognized or diagnosed. On the other hand, the incidence of DVT and PE may have been underestimated, as some patients may have exhibited silent DVT or PE; moreover, related imaging studies, such as Doppler ultrasound scanning, are not routinely performed for asymptomatic psychiatric patients. Therefore, the possibility of ascertainment bias cannot entirely be rejected.

In conclusion, the incidence of VTE was considerably higher in psychiatric patients with concurrent depressive, bipolar, and schizophrenic disorders than in the reference cohort. Given the paucity of the data regarding this clinically relevant issue, further studies are needed to investigate the actual clinical outcomes of VTE and determine effective prevention strategies in various patient populations.

Contributors

Dr. Lin wrote the first draft of the manuscript. All authors contributed to and have approved the design, study protocol, and final manuscript.

Declaration of competing interest

All authors have no financial or other conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2019.10.003.

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