Epidemiology and Predictors of Short-Term Mortality in Symptomatic Venous Thromboembolism
– A Nationwide Population-Based Study –

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Background: The epidemiology of symptomatic venous thromboembolism (VTE) in Taiwan has not been well investigated. The aim of this study was to report on the epidemiology and short-term prognosis of symptomatic VTE.

Methods and Results: This nationwide population-based cohort study used the Taiwanese National Health Insurance claims databases to identify adults older than 18 years of age with symptomatic VTE diagnosed in 2002. We investigated the clinical features of VTE and determined independent risk factors of 1-month mortality. A total of 2,774 patients were identified with a mean age of 62.8 years and the female-to-male ratio was 1.15:1. The crude incidence of symptomatic VTE was 16.5 per 100,000 persons, which steadily increased with age, ranging from 4 per 100,000 in patients <40 years old to 108 per 100,000 in patients ≥80 years. We observed no seasonal and meteorological variations in the incidence of VTE. The overall 1-month mortality rate was 8.8%, with 7.1% in deep venous thrombosis and 12.9% in pulmonary embolism. Multivariate analysis demonstrated that pulmonary embolism, cancer, neurologic disease with extremity paresis or paralysis, older age, longer hospital stay, and major abdominal and thoracic surgery in the 3 months preceding VTE were independent predictors of 1-month death.

Conclusions: Although the incidence of VTE was lower in Taiwanese populations than in Western ones, short-term mortality rates were high in specific populations. These findings suggest optimal treatment is needed in higher-risk patients. (Circ J 2011; 75: 1998–2004)

Key Words: Deep vein thrombosis; Epidemiology; Prognosis; Pulmonary embolism; Venous thromboembolism
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VTE recurrence in Taiwan is similar to that in Western countries. However, the above-mentioned epidemiologic features of VTE still remain unknown in Taiwan. Therefore, the aim of this study was to analyze the spectrum of VTE disease in the Taiwanese population and epidemiologic characteristics and short-term prognosis of VTE by using a nationwide population-based database. In addition, most other studies were conducted in Western countries where the seasonal changes are remarkable. Taiwan is a subtropical Asian country where the weather in winter is mild. To explore the geographic difference, we also examined the association of meteorological parameters and seasonal variations with VTE throughout the entire country.

Methods

Study Setting and Design

Data for this study were obtained from the Taiwanese National Health Insurance (NHI) medical claims (inpatient and outpatient) databases for 2001 and 2003. A universal NHI program has been implemented in Taiwan since 1995, which has enrolled nearly 99% of the Taiwanese population and is contracted with 97% of hospitals and clinics throughout the nation.19 The claims data include up to 5 diagnoses for each hospital admission and 3 for each ambulatory encounter, recorded by using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. For research use, the data are encrypted to protect patients’ privacy. To avoid diagnostic uncertainty and erroneous document-ation of claims databases, the Bureau of NHI performs auditing reviews on a random sample of 1 per every 100 ambulatory and 20 inpatient claims quarterly, and false reporting of diagnostic information results in a severe penalty from the Bureau.20 21 We identified adult patients older than 18 years-of-age who had a discharge diagnosis of DVT or PE from 1 January through to 31 December 2002. These patients were analyzed for clinical characteristics and followed from the first index hospitalization until death or 1 month after discharge. Using attending physicians and hospital identifiers in the claims, we could obtain the physicians’ specialties and the settings of health-care organizations. We also analyzed VTE-associated hospitalizations by season of admission. Finally, we separated these patients into survival and non-survival groups for determining the risk factors of 30-day mortality.

Definition of VTE

In our study, VTE included DVT and PE. VTE admissions were identified from the inpatient claims database by an ICD9-CM code of 453.0; 453.1; 453.2; 453.4; 453.8; 453.9; and 415.1x. For accurate enrollment of active VTE patients, we carefully selected patients who met the following criteria: (1) the discharge diagnosis was DVT or PE; (2) the patients should have received peripheral venous duplex, chest computed tomography, or angiography examinations during the hospitalization; (3) the patient must have received a course of subcutaneous or intravenous anticoagulation therapy or surgical thrombectomy during hospitalization and continued anticoagulant therapy after discharge; and (4) a length of stay of at least 3 days, unless they died within 2 days.

Comorbid Diseases and Potential Risk Factors of VTE

For each patient, the comorbidities for VTE were retrieved from both the inpatient and outpatient claims databases for 1 year before and during the index VTE hospitalization. Several proven diseases predisposing patients to VTE, other comorbidities and procedures were based on ICD-9-CM codes (Table S1). A history of VTE was defined as a patient having been hospitalized due to VTE before the index VTE event. Hormone therapy included hormone replacement therapy and oral contraceptive use indicating the use of estrogen and/or progesterone. Chronic lung disease included emphysema, chronic bronchitis, bronchiectasis, other obstructive pulmonary disease, and chronic respiratory failure. Serious neurologic diseases encompassed stroke or other central and peripheral nervous diseases with associated extremity paresis or paralysis. The potential risk factors were recorded as present only if documented within 3 months preceding the VTE event. Major trauma included bone fracture or dislocation. Operations were classified as major neurologic, thoracic, abdominal, urogenital, and orthopedic systems. Major neurologic surgery included any procedures involving a cranectomy, operations on spinal cord and spinal canal structures, operations on cranial and peripheral nerves, or operations on sympathetic nerves or ganglia. Major thoracic surgery included excision of the larynx, excision of the lung and bronchus, operations on valves and septa of the heart, operations on heart vessels, operations on peripheral vessels, or heart transplantation. Major abdominal surgery included operations on the esophagus, stomach, liver, spleen, pancreas, small intestine, large intestine, gall bladder, or biliary tract. Major urogenital surgery included operations on the kidney, ureter, urinary bladder, urethra, prostate, seminal vesicles, male genital organs, or female genital organs. Major orthopedic surgery included partial or total hip replacement or knee replacement.

Statistical Analysis

In 2002, the population of Taiwan was approximately 22.5 million (16.9 million adults). The estimate of the Taiwan civilian resident population according to the Taiwan Department of Statistics for the year 2002 was used to calculate the age- and gender-specific incidence of hospitalization for VTE per 100,000 person-years.22 The monthly mean weather temperature, humidity, and pressure in Taiwan were available from the Central Weather Bureau website.23 We used SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC, USA) for the claims data conversion and analysis. Data are expressed as mean (±SD) or percentages. Univariate analysis was conducted using the Student’s t-test for continuous variables and the chi-square test for categorical variables between survivors and non-survivors. Predictors of potential significance (P<0.1) were included in the multivariate analysis (forward stepwise logistic regression). Pearson’s correlation was used to determine the correlation between the average atmospheric pressure, humidity, air temperature values, and VTE number for each month and season. All reported P-values are 2-tailed, and statistical significance was set at P<0.05.

Results

Patient Demographics

We identified 2,774 hospitalized patients ≥18 years of age with a discharge diagnosis of VTE. The mean age at hospitalization was 62.8±16.3 years old and the female-to-male ratio was 1.15 to 1. The spectrum of VTE was 29.2% in PE, 74.1% in DVT of extremities, and 5.5% in co-existing DVT and PE. A history of VTE was found in 14.9% of patients. The common comorbidities were malignant neoplasm (22%),
Figure 1. Incidence of overall venous thromboembolism (VTE) and pulmonary embolism (PE) in different age and gender groups in Taiwan.

Figure 2. Mean monthly weather temperature (Fahrenheit), humidity (%), weather atmosphere pressure (mb), and numbers of patients hospitalized with venous thromboembolism (VTE) in Taiwan by month. There was no correlation between the number of VTE events and meteorological parameters.
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congestive heart failure (18.6%), stroke (13.6%), serious neurologic disease with extremity paresis or paralysis (18.5%), coronary heart disease (31.7%), diabetes mellitus (26.4%), systemic hypertension (51.2%), and renal insufficiency (19.7%). We found that 3.7% of patients had undergone major neurologic surgery, 18.7% major thoracic surgery, 13.9% major abdominal surgery, 8.5% major orthopedic surgery, and 1.6% urogenital surgery in the 3 months preceding VTE. Regarding the hospital settings, 45% of VTE patients received medical care in medical centers, 36.1% in metropolitan hospitals, and 18.9% in community hospitals. Besides, we found that 66.6% of VTE patients belonged to DVT of extremities in medical centers, 68.2% in metropolitan hospitals, and 80.3% in community hospitals (P<0.001 for trend). Furthermore, 30.9% of VTE were PE in medical centers, 29.3% in metropolitan hospitals, and 17.7% in community hospitals (P<0.001 for trend). Just over 64% of patients had been admitted to the department of internal medicine, 34% to the department of surgery, and 1.2% to the department of gynecology & obstetrics.

Age-Specific VTE Incidence

The crude incidence of VTE was 16.5 per 100,000 persons and the incidence of PE was 4.8 per 100,000 persons in Taiwanese adults. The incidence of VTE steadily increased with age, ranging from 4 per 100,000 in patients <40 years to 108 per 100,000 in patients ≥80 years (P<0.001) (Figure 1). The incidence of PE also steadily increased with age, ranging from 1.2 per 100,000 in patients <40 years to 34.5 per 100,000 in patients ≥80 years (P<0.001) (Figure 1). We found similar trends in men and women.

Seasonal Variation

Distribution of VTE among the months is illustrated in Figure 2. The average weather temperature (Fahrenheit), humidity (%), and atmosphere pressure (mb) over the months in Taiwan is also shown in Figure 2. The highest numbers of cases were seen in December (274), August (269), and January (250), and this distribution was not statistically significant (r=0.42, P=0.18). With regard to atmospheric pressure, the lowest level was in August (996 mb) and the highest in December (1,009 mb) (Figure 2). In 2002, VTE occurred 25.2% of the time in winter, 24.4% in spring, 25.7% in summer, and 24.7% in autumn, representing insignificant seasonal differences of r=0.05, P=0.886. In terms of months, there was no correlation between cases and atmospheric pressure (r=0.16, P=0.61), temperature (r=−0.17, P=0.61), or humidity (r=−0.12, P=0.72).

Table 1. Clinical Characteristics of 2,774 Adult Patients With VTE in 2002

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survival (n=2,530)</th>
<th>Non-survival (n=244)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>62.7±16.2</td>
<td>64.8±15.6</td>
<td>0.044</td>
</tr>
<tr>
<td>Female, %</td>
<td>53.7</td>
<td>51.6</td>
<td>0.546</td>
</tr>
<tr>
<td>History of VTE, %</td>
<td>15.1</td>
<td>12.3</td>
<td>0.240</td>
</tr>
<tr>
<td>Pulmonary embolism, %</td>
<td>27.9</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep vein thrombosis, %</td>
<td>75.5</td>
<td>59.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignant neoplasm, %</td>
<td>20.8</td>
<td>35.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>18.4</td>
<td>20.9</td>
<td>0.344</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>31.7</td>
<td>32.4</td>
<td>0.829</td>
</tr>
<tr>
<td>Stroke*, %</td>
<td>13.5</td>
<td>14.8</td>
<td>0.625</td>
</tr>
<tr>
<td>Serious neurologic disease*</td>
<td>17.8</td>
<td>25.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>26</td>
<td>29.6</td>
<td>0.196</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51.2</td>
<td>50.4</td>
<td>0.841</td>
</tr>
<tr>
<td>Chronic lung disease, %</td>
<td>28.7</td>
<td>34.8</td>
<td>0.047</td>
</tr>
<tr>
<td>Renal insufficiency, %</td>
<td>19.6</td>
<td>21.3</td>
<td>0.555</td>
</tr>
<tr>
<td>Varicose vein disease, %</td>
<td>4.1</td>
<td>2.9</td>
<td>0.397</td>
</tr>
<tr>
<td>Primary hypercoagulable states†</td>
<td>0.2</td>
<td>1.2</td>
<td>0.027</td>
</tr>
<tr>
<td>Recent major spine trauma, %</td>
<td>2.1</td>
<td>2.0</td>
<td>1</td>
</tr>
<tr>
<td>Recent extremity trauma, %</td>
<td>5.5</td>
<td>7.8</td>
<td>0.147</td>
</tr>
<tr>
<td>Recent major surgery§</td>
<td>3.4</td>
<td>6.1</td>
<td>0.035</td>
</tr>
<tr>
<td>Neurologic surgery, %</td>
<td>18.1</td>
<td>25.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Thoracic surgery, %</td>
<td>13.4</td>
<td>21.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal surgery, %</td>
<td>1.3</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>Urogenital surgery, %</td>
<td>8.3</td>
<td>10.7</td>
<td>0.229</td>
</tr>
</tbody>
</table>

Data are presented as percentages or mean values ± SD.
P value compared with survival and non-survival groups using a Student’s t-test or χ² test.
VTE, venous thromboembolism.
*Stroke includes ischemic and hemorrhagic stroke.
†Serious neurologic disease means stroke or other central and peripheral nervous disease with associated extremity paresis or paralysis.
§Recent major surgery means surgery within 3 months preceding the index VTE event.
Table 2. Multivariate Model for Independent Risk Factors Associated With 30-Day Mortality in Patients With VTE

<table>
<thead>
<tr>
<th>HR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of initial hospitalization</td>
<td>1.01 (1.00–1.01)</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (1.01–1.02)</td>
</tr>
<tr>
<td>Recent major thoracic surgery</td>
<td>1.38 (1.08–1.75)</td>
</tr>
<tr>
<td>Serious neurologic disease*</td>
<td>1.44 (1.08–1.91)</td>
</tr>
<tr>
<td>Recent major abdominal surgery</td>
<td>1.47 (1.13–1.91)</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.28 (1.81–2.87)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.40 (1.94–2.98)</td>
</tr>
</tbody>
</table>

*Serious neurologic disease means stroke or other central and peripheral nervous disease with associated extremity paresis or paralysis.

**Treatment and Short-Term Prognosis**
We found that 54.7% (n=1,517) of VTE patients had received unfractionated heparin during hospitalization and the others (n=1,257) received low molecular heparin including enoxaparin (n=733), fraxiparine (n=353), or dalteparin (n=171). After these patients were discharged, they received different courses of oral anticoagulant therapy. The overall mean (SD) duration of oral warfarin therapy after the index hospitalization was 146 (66) days. For patients with a history of VTE, the mean duration of oral warfarin therapy was 165 (72) days. For patients with malignant neoplasm, the mean duration of oral warfarin therapy was 161 (78) days. For patients with idiopathic VTE, the mean duration of oral warfarin therapy was 178 (60) days. The proportion of inferior vena cava (IVC) filter implantation after the VTE event was 2.2% (n=60).

In the present study, we did not observe the different effect of the IVC filter and the type of heparin in terms of short-term prognosis. The overall 1-month mortality was 8.8%. For patients with DVT, the 1-month mortality rate was 7.1%. For patients with PE, the 1-month mortality rate was 12.9%. Among non-survivors, 103 patients (42.2%) died of PE, 57 (23.4%) of cancer, 27 (11.1%) of pneumonia and asthma, 26 (10.7%) of cardiovascular diseases, 25 (10.2%) of sepsis, and 5 (2.0%) of uremia. Therefore, the mortality rate related to VTE after the initial VTE event was 3.7%. In univariate analysis, the significant variables associated with 30-day death were PE presentation, older age, presence of morbidities including malignant neoplasm, primary hypercoagulable disease, serious neurologic diseases with associated extremity paresis or paralysis, chronic lung disease, and recent operations including major neurologic, thoracic, and abdominal surgery (Table 1). For the female population, there were no observable significant differences in hormone therapy (12.2% vs. 7.9%, P=0.19) and pregnancy (3.3% vs. 1.4%, P=0.46) between survival and non-survival groups. When these factors were analyzed using multivariate logistic regression (Table 2), PE, malignant neoplasm, serious neurologic disorder with extremity paresis or paralysis, and major abdominal surgery in the 3 months preceding VTE were independent predictors of 30-day mortality.

**Discussion**
This population-based study estimated the crude incidence of symptomatic VTE in Taiwan to be 16.5 per 100,000 in the general population and the incidence of PE to be 4.8 per 100,000 persons. In Taiwan, VTE occurs most frequently in elderly women and equally distributes through the year, without seasonal clustering phenomenon. Physicians in Taiwan used a longer duration of warfarin in the high-risk population than in the low-risk population after the initial VTE event. We found that PE, malignant neoplasm, serious neurologic diseases with extremity paresis or paralysis, older age, longer hospital stay, and undergoing major abdominal and thoracic surgery in the 3 months preceding VTE were independent predictors of 30-day mortality.

Most clinical studies have reported the incidence of clinically diagnosed DVT to be approximately twice that of PE. Although the overall VTE incidence was lower in Taiwan than in Western countries, a similar ratio of DVT to PE incidence was observed also in this study. VTE was noted to affect the elderly population in previous studies. Also, the incidence of VTE raised exponentially with age, from a negligible rate among children <15 years of age to values in the range of 450–600 per 100,000 person-years over the age of 80 years, and the incidence increased profoundly after age 60 years. Similarly, the incidence of VTE steadily increased with age in Taiwan, ranging from 4 per 100,000 in patients <40 years to 108 per 100,000 in patients ≥80 years. Several Japanese studies also demonstrated a similar incidence of PE (2.8–6.2 per 100,000 persons) and DVT (11.6 per 100,000).

According to previous literature obtained from Western countries in temperate zones, seasonal variation of VTE incidence is controversial. Taiwan is a subtropical country without profound variations in weather temperatures, humidity, and pressure, and neither seasonal variations nor meteorological parameters were observed to influence VTE occurrence in this study. One recent MASTER registry trial showed a significant rhythmic annual pattern, with a main September–October peak for several subgroups (men, age 41–80 years, previous VTE, immobilization), and a trend for most of the others. Oztuna et al reported that there were no VTE correlations with months and pressure, temperature, or humidity; however, there was a statistically significant positive correlation between VTE incidence and atmospheric pressure and humidity.

According to our previous VTE study, histories of VTE or malignant neoplasm, major extremity trauma, serious neurologic diseases, or having major surgery were associated with higher risks of VTE recurrence. In this study, we observed that physicians used a longer duration of warfarin in the high-risk population (such as cancer, history of VTE and idiopathic VTE) than in the low-risk population. Based on the ACCP Evidence-based Clinical Guidelines (8th edition), a different duration of anticoagulant therapy after VTE is indicated for patients with unprovoked and provoked VTE. In our study, 1-month mortality rates in patients with DVT and PE were 7.1% and 12.9%, respectively. Malignant neoplasm, PE, serious neurological diseases with extremity paresis or paralysis, older age, longer hospital stay, and undergoing major abdominal and thoracic surgery in the 3 months preceding VTE were independent predictors of 1-month mortality. Cushman et al noted a 1-month case-fatality rate of 9.4% after first-time DVT and 15.1% after first-time PE. The cohort of Silverstein et al had 1-month case fatality rates of 5.5% for patients with DVT and 8.0% for those with PE not diagnosed at autopsy. The risk of early death among patients with symptomatic PE is 18-fold higher compared to patients with DVT alone. PE is an independent predictor of reduced survival for up to 3 months after onset. Independent predictors of reduced early survival after VTE include increasing age, longer hospital stay, having a history of VTE, and recent major surgery.
age, male gender, lower body mass index, confinement to a hospital or nursing home at VTE onset, congestive heart failure, chronic lung disease, serious neurological disease, and malignancy. 29-31 We did not observe the beneficial effect of an IVC filter on short-term prognosis and it might be related to a low proportion of IVC filter implantations among these patients. 

This study has several advantages. It is one of the largest epidemiologic studies to investigate the clinical features of VTE in Asian populations. The cohorts included virtually all Taiwanese adult patients with VTE and allowed us to observe the disease patterns and features from different hospital settings and physician specialists. Therefore, our findings provide the explicit feature on VTE epidemiology derived from the clinical scenario in Taiwan. However, the main limitations of this study include misclassification bias because coding of diagnoses is undertaken for administrative purposes. To overcome this possibility, we limited the inclusion cases to VTE admissions. Prior validation studies have shown that the codes used to define VTE in this study have a positive predictive value of approximately 90%. 6,23 Another weakness is that DVT and PE likely remained asymptomatic in a number of patients and therefore went undetected. Thus, the true incidence of VTE in Taiwanese patients might be higher than the estimate because deaths from PE associated with other medical diseases might be under-reported. Nonetheless, this nationwide study provided the crude incidence of VTE in the real world. Additionally, some confounders of interest such as body mass index, smoking status, and drinking status were not available in this database.

In conclusion, the incidence of VTE was relatively low in general Taiwanese populations, and the influence of changes in meteorological parameters and seasonal variations in VTE were not noted in Taiwan. However, patients with identified risk factors were exposed to higher mortality, similar to that of Western populations, and should be provided with optimal therapy or interventions.

Acknowledgments

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Disclosure

Conflicts of interest: none to be declared.

References


**Supplemental Files**

**Supplemental File 1**

Table S1. World Health Organization International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] Used for Present Study Analysis

Please find supplemental file(s);