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Increased Risk of Venous Thromboembolism in Patients with Dermatomyositis/Polymyositis: A Nationwide Cohort Study

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SUMMARY

Objectives: The number of previous studies on the risk of venous thromboembolism (VTE) in patients with dermatomyositis/polymyositis (DM/PM) is limited. Therefore, we conducted a nationwide retrospective cohort study to investigate the effects of DM/PM on the risk of VTE.
Methods: We identified patients with newly diagnosed DM/PM in Taiwan between 2000 and 2010 using the National Health Insurance Research Database (NHIRD) and the Catastrophic Illness Patient Database. Each DM/PM patient was frequency-matched to 4 control patients according to age, sex, and index year. All of the patients were observed from the index date until the occurrence of a VTE event, censor, or until December 31, 2010. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) of VTE in the DM/PM and comparison cohorts using the Cox proportional hazards regression model.
Results: We followed up with the 2031 DM/PM patients (67.8% women, mean age of 46.1 y) and 8124 control patients for 9987 and 48 081 person-years, respectively. The DM/PM patients exhibited an 11.1-fold increased risk of VTE compared with that of the non-DM/PM comparison cohort after adjusting for age, sex, and comorbidities (95% CI = 5.21–23.6). The older patients with DM/PM exhibited a multiplicative increased risk of VTE development compared with that of the control patients (adjusted HR = 26.8, 95% CI = 8.55–84.2), and the DM/PM patients with any comorbidity showed an additive risk of developing VTE (adjusted HR = 33.3, 95% CI = 11.2–99.4).
Conclusion: The risk of VTE is significantly higher in DM/PM patients than in non-DM/PM patients.

What is known about this topic?

1. Together, deep vein thrombosis (DVT) and pulmonary thromboembolism (PE) constitute venous thromboembolism (VTE), which has a 30-day case fatality rate of 11%–30%.
2. The number of previous studies on the risk of VTE in patients with dermatomyositis/polymyositis (DM/PM) is limited.

What does this paper add?

1. The DM/PM patients exhibited an 11.3-fold increased risk of VTE compared with that of the comparison cohort.
2. The older patients with DM/PM exhibited a multiplicative increased risk of VTE development compared with that of the control patients.
3. DM/PM patients with any comorbidity exhibited a multiplicative increased risk of VTE development compared with that of the control patients.

Introduction

Together, deep vein thrombosis (DVT) and pulmonary thromboembolism (PE) constitute venous thromboembolism (VTE), which has a 30-day case fatality rate of 11%–30% [1–3]. Previous studies have identified multiple acquired risk factors for VTE, including age, previous VTE episodes, atrial fibrillation, and cerebrovascular disease (CVA) [4–7]. Diabetes, congestive heart failure, leg fractures, and major surgery are also associated with an increased risk of VTE [8–12]. Studies have also indicated the association between certain cancers and VTE [13,14]. In addition, pregnancy, prolonged bed rest, and oral contraceptives use may also contribute to an increased risk for VTE.

Dermatomyositis (DM) is a connective tissue disease related to polymyositis (PM), and is characterized by chronic idiopathic inflammation

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of the skin and muscles. Both DM and PM are systemic disorders and affect the muscles, skin, joints, esophagus, lungs, and heart. Previous studies on pulmonary involvement in patients with DM/PM have focused on interstitial lung disease [15,16]. However, DM/PM is not traditionally considered a risk factor for DVT and PE. Studies have demonstrated that chronic inflammation is associated with prothrombotic factors and endothelial dysfunction during atherothrombosis development [17,18]. Recent studies have identified associations between autoimmune diseases and the risk of VTE [19–21]. The number of epidemiological research on the relationship between DM/PM and VTE is limited [19]. Therefore, we conducted a nationwide retrospective cohort study to investigate the effects of DM/PM on the risk of VTE development in Taiwan.

Methods

Data Source

Data were accessed from the National Health Insurance Research Database (NHIRD) of the National Health Institute (NHI). Information on the identity of an insurant is encrypted in the NHIRD to ensure patient privacy. A committee of the Bureau of National Health Insurance is responsible for randomly selecting and checking the accuracy of claims. The NHI program was initiated in 1995 and covers > 99% of the 23.74 million people living in Taiwan [22]. The insurant identification codes were used to link 3 data files: inpatient claims, the Registry for Catastrophic Illness Patient Database (RCIPD), and demographic information. The International Classifications of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to define diseases documented in the claims data. All of the data were deidentified and analyzed anonymously. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101-012).

Diagnostic Criteria of DM/PM

The classification criteria of DM/PM is based on [1] a typical skin rash of DM, including a heliotrope rash, Gottron sign, and Gottron papules; [2] symmetrical proximal muscle weakness; [3] elevation of serum skeletal muscle enzyme; [4] a characteristic electromyographic pattern; [5] a muscle biopsy consistent with myositis [23].

Participants

We identified 2063 patients with newly diagnosed DM/PM (ICD-9-CM codes 710.3 and 710.4) from 2000 to 2010. These patients were confirmed in the RCIPD as the DM/PM cohort. The date on which a DM/PM patient registered for a catastrophic illness was defined as the index date. The patients with DM/PM were diagnosed with VTE (ICD-9 codes 453.8 and 415.1, except iatrogenic PE, ICD-9-CM 415.11) prior to the index date (n = 18), or those with missing information regarding age or sex (n = 14), were excluded from our study. A non-DM/PM comparison cohort randomly selected from all of the NHI beneficiaries was frequency matched with the DM/PM cohort at a 4:1 ratio based on age (in 5-y spans), sex, and year of DM/PM diagnosis. The same exclusion criteria were also applied to non-DM/PM controls.

Outcome Measurement

The person-years of the follow up for each participant were estimated from the index date until they were hospitalized for VTE, withdrew from the NHI, lost to follow up, or until December 31, 2010.

Exposure Measurement

In addition to DM/PM, demographic characteristics such as age, sex, and comorbidities were evaluated. Patient histories of atrial fibrillation (ICD-9-CM code 427.31), hypertension (ICD-9-CM codes 401-405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), CVA (ICD-9-CM codes 430-438), heart failure (ICD-9-CM code 428), lower leg fracture or surgery (ICD-9-CM codes 820, 821; 823; 81.51, 81.52, 81.53, 81.54), cancers (ICD-9-CM codes 140–208) and pregnancy (ICD-9-CM procedure 72-74 or ICD-9-CM code 640.x1-676.x1, 640.x2-676.x2, 650-659) were identified according to hospital admissions prior to the endpoint to control for any potential confounding effects of VTE risk factors.

Statistical Analysis

All analyses were performed using SAS, version 9.2, computer software (SAS Institute Inc, Cary, NC, USA), with $P < 0.05$ being considered significant for a 2-tailed test. The demographic characteristics and comorbidities of the DM/PM and non-DM/PM comparison cohorts were presented using the total number (percentage) for the categorical variables and the median (with IQR) for the continuous variables. The differences were examined using the Chi-square test for the categorical variables and the Mann-Whitney U test for the continuous variables. The sex-, age- and comorbidity-specific incidence rates and 95% confidence interval (CI) of VTE per 10 000 person-years of follow up were calculated for each cohort. A Poisson regression model was applied to measure the incidence rate ratio (IRR) and 95% CIs of VTE for the DM/PM cohort compared with that of the non-DM/PM cohort. Hazard ratios (HRs) and 95% CIs were estimated using multivariable Cox proportional hazard models, using the non-DM/PM cohort as the reference, to evaluate the association between DM/PM and the risk of VTE development. The multivariable models were simultaneously adjusted for demographic characteristics and comorbidities. The joint effects of sex, age, comorbidities, and DM/PM were also assessed using Cox proportional hazard models. The cumulative incidence of VTE was calculated using the Kaplan-Meier method. Statistical significance was evaluated by using the log-rank test.

Results

Table 1 shows the demographic characteristics and comorbidities of the 2 cohorts. Women outnumbered men (67.8% vs 32.2%) for both cohorts. The median age of the non-DM/PM cohort was 47.1 years and that of the DM/PM cohort was 48.0 years, with 55.2% of the patients aged ≤49 years. The DM/PM cohort was more likely to have atrial fibrillation, hypertension, diabetes, hyperlipidemia, CVA, heart failure, lower

Table 1
Demographic characteristics and comorbidity in patient with and without PM&DM.

Variable	DM/PM	
	No	Yes
	N = 8124	N = 2031
Gender	n(%)	n(%)
Female	5508(67.8)	1377(67.8)
Male	2616(32.2)	654(32.2)
Age, median(IQR)	47.1(35.1-57.9)	48.0(35.2-58.1)
Stratify age		
≤34	2004(24.7)	501(24.7)
35-49	2476(30.5)	619(30.5)
50-64	2412(29.7)	603(29.7)
65+	1232(15.2)	308(15.2)
Comorbidity		
Atrial fibrillation	100(1.23)	33(1.62)
Hypertension	1001(12.3)	424(20.9)
Diabetes	572(7.04)	231(11.4)
Hyperlipidemia	262(3.23)	180(8.86)
CVA	421(5.18)	108(5.32)
Heart failure	177(2.18)	114(5.61)
Lower leg fracture or surgery	213(2.62)	50(2.46)
Cancer	243(2.99)	213(10.5)
Pregnancy	742(9.13)	159(7.83)