Increased Risks of Deep Vein Thrombosis and Pulmonary Embolism in Sjögren Syndrome: A Nationwide Cohort Study

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ABSTRACT. ***Objective.*** Studies of the risks of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with Sjögren syndrome (SS) in Asia are scant. We evaluated the effect of SS on the incidences of DVT and PE in a nationwide, population-based cohort in Taiwan.

Methods. We identified patients in Taiwan diagnosed with SS between 1998 and 2008 in the Catastrophic Illness Patient Database and the National Health Insurance Research Database. Each patient with SS was matched to 4 control patients based on age, sex, and index year, and all patients were followed up from the index date to December 31, 2010. We calculated the hazard ratios (HR) and 95% CI of DVT and PE in the SS and comparison cohorts by using Cox proportional hazards regression models.

Results. We followed 8920 patients with SS and a comparison cohort of 35,680 for about 50,000 and 200,000 person-years, respectively. The mean age of the SS and comparison cohorts was 53.5 and 53.1 years, respectively, and 88.9% of the patients were women. The risks of DVT and PE among the patients with SS were a 1.83-fold and 3.29-fold greater, respectively, than those for the general population after adjusting for age, sex, comorbidities, and frequency of hospitalization. The patients with a secondary SS had a greater risk of PE (adjusted HR: 5.06; 95% CI: 1.22-21.1) than those with a primary SS (adjusted HR: 3.21; 95% CI: 1.96-5.23).

Conclusion. Patients with SS have a significantly greater risk of developing DVT or PE than the general population. (J Rheumatol First Release April 1 2014; doi:10.3899/jrheum.131345)

Key Indexing Terms:
SJÖGREN SYNDROME DEEP VEIN THROMBOSIS PULMONARY EMBOLISM

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Sjögren syndrome (SS) is a systemic autoimmune disease that primarily affects the tear and saliva glands. The hallmark symptoms of SS are generalized dryness, which typically includes dry skin and dry eyes. However, the kidney, blood vessels, lungs, liver, pancreas, peripheral nervous system, and brain may also be affected by SS. Although SS occurs in men and women of all ages, most patients are postmenopausal women[1].

A primary SS (pSS) diagnosis requires symptoms that meet 4 of the 6 American-European Consensus Group (AECG) criteria or 3 of the 4 objective diagnostic criteria. A diagnosis of secondary SS requires the presence of a well-defined major connective tissue disease, 1 subjective SS symptom, and symptoms meeting 2 of the 3 objective AECG diagnostic criteria for SS[2].

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). A potentially fatal complication, VTE is a major health problem worldwide[3]. Multiple acquired and genetic factors are associated with VTE. Traditional risk factors included pregnancy, oral contraceptives, hormone replacement therapy, immobilization, trauma, and specific genetic factors. Studies have demonstrated that atrial fibrillation and cerebrovascular disease (CVA) are risk factors of VTE[4,5,6].

Diabetes, congestive heart failure, leg fractures, and major surgery are also associated with an increased risk of VTE[7,8,9,10,11]. Many cancers have also been shown to correlate with VTE[12,13].

Autoimmune disorders associated with inflammation might also increase the risk of VTE. Epidemiological studies have shown that certain autoimmune diseases are associated with VTE[14,15,16]. Most studies on SS have focused on treatment and improving the quality of life of patients with SS[17,18,19,20]. However, relatively little information is available regarding the relationship between SS and the development of DVT and PE, particularly among Asian patients with SS. We conducted a longitudinal nationwide cohort study in Taiwan to investigate whether SS increases the risks of DVT and PE.

MATERIALS AND METHODS

Data sources. We conducted a retrospective, longitudinal study of a nationwide, population-based cohort in Taiwan, using the National Health Institute Research Database (NHIRD). The NHIRD has been described in our previous studies[16,21]. The NHIRD consists of comprehensive healthcare data that are representative of almost 100% of the 23.7 million residents of Taiwan[22]. The disease diagnoses used in the NHIRD were coded according to the criteria of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). A diagnosis of SS was defined according to AECG diagnostic criteria, and was confirmed through the Registry for Catastrophic Illness Patient Database (RCIPD), which is maintained by the Taiwan National Health Insurance (NHI) system. Our study was approved by the ethics review board at China Medical University (approval no. CMU-REC-101-012).

Participants. We identified 8920 patients with SS (ICD-9-CM code 710.2) in the NHIRD and the RCIPD who were newly diagnosed between January 1, 2000, and December 31, 2008. Patients with a history of DVT (ICD-9-CM 453.8) or noniatrogenic PE (ICD-9-CM 415.1, excluding ICD-9-CM 415.11) and those who lacked complete information in the NHIRD were excluded. The date of the diagnosis of SS was used as the index date. For each patient in our SS cohort, 4 controls without SS (comparison cohort) were randomly selected and frequency matched based on age category (5-year span), sex, and the year of the index date. Controls with a history of DVT or noniatrogenic PE were also excluded from the comparison cohort. A secondary SS was defined as a diagnosis of SS in patients with a previous diagnosis of rheumatoid arthritis (ICD-9-CM code 714), systemic lupus erythematosus (SLE; ICD-9-CM code 710.0), systemic sclerosis (ICD-9-CM code 701.1), or primary biliary cirrhosis (ICD-9-CM code 571.6).

Outcome measurement. The primary outcomes were newly diagnosed PE or DVT from hospitalization records. All of the participants were followed from the index date to the date of a primary outcome, withdrawal from the NHI program, or the end of 2010, whichever came first. Nearly all patients with DVT or PE underwent a comprehensive examination before receiving intensive care. In Taiwan, DVT and PE patients' medical reimbursements and discharge notes are scrutinized in a peer-review process.

Exposure variables. In addition to SS, the demographic characteristics such as sex, age, and the comorbidities were analyzed. The pre-existing comorbidities included atrial fibrillation (ICD-9-CM 427.31), diabetes (ICD-9-CM 250), CVA (ICD-9-CM 430–438), heart failure (ICD-9-CM 428), lower leg fracture or surgery (ICD-9-CM 820–823 and procedure codes 81.51, 81.52, 81.53, and 81.54, respectively), cancer (ICD-9-CM 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).

Statistical analysis. We compared the differences in demographic characteristics, including age, sex, and the comorbidities, of the SS cohort with those of the comparison cohort, using a chi-squared analysis for the categorical variables and t tests for the continuous variables. The followup duration was estimated as the incidence density rate in both cohorts by using a Poisson regression model to estimate the incidence rate ratios (IRR) and 95% CI. A multivariate Cox proportional hazards regression model was used to calculate the hazard ratios (HR) and 95% CI of the risks of DVT and PE in patients with SS, relative to those of the comparison cohort, after adjustments for age, sex, frequency of admission visits and comorbidities of atrial fibrillation, diabetes, CVA, heart failure, lower leg fracture or surgery, cancer, and pregnancy. We also estimated the interaction between comorbidity and SS on the development of PE or DVT by using the Cox model. Further analysis was performed to estimate the risks of DVT and PE among subgroups of SS. Cumulative incidence analyses were conducted using the Kaplan-Meier method, and the differences between the curves were assessed using the log-rank test. Data management and analysis were performed using SAS, version 9.2 (SAS Institute). The cumulative incidence curves were constructed using the R computer software (R Foundation for Statistical Computing). A 2-tailed $p < 0.05$ was considered statistically significant.

RESULTS

The SS cohort included 8920 patients, and the comparison cohort included 35,680 patients without SS (Table 1). Women comprised 88.9% of the SS and control patients. The mean ages of the SS and controls were 53.5 ± 14.4 years and 53.1 ± 14.6 years, respectively, and 59.6% of the patients with SS were 50 years of age or older. Patients with SS had a higher prevalence of atrial fibrillation, heart failure, cancer, and pregnancy than did the controls. The median followup period was 5.09 and 5.13 years for the SS and comparison cohorts, respectively. The overall incidence of DVT was 5.81 and 3.11 per 10^4 person-years for the SS and comparison cohorts, respectively (Table 2). The cumulative DVT incidence curve for the SS cohort revealed a significantly higher incidence of DVT in the patients with SS, compared with those in the comparison cohort (log-rank $p = 0.005$).

After adjusting for age, sex, frequency of admission, and comorbidities, the patients with SS had an increased risk of DVT compared with the comparison cohort (adjusted HR 1.83, 95% CI 1.16–2.89). The sex-specific DVT incidence for patients with SS was highest among women (6.08 per 10^4 person-yrs). Compared to women in the comparison cohort, the women with SS had a greater relative risk of DVT (adjusted HR 2.03, 95% CI 1.26–3.28). The age-specific relative risk of DVT was greatest among patients aged ≤ 65 years (adjusted HR 2.27; 95% CI 1.18–4.37). Among patients with no comorbidity, the incidence of DVT was 2.70 times greater in the SS cohort than in the comparison cohort (2.89 vs 0.82 per 10^4 person-yrs).

The incidence densities and the adjusted HR of PE in the SS and comparison cohorts are shown in Table 2. The overall incidence of PE was 6.43 and 1.97 per 10^4 person-years in the SS and comparison cohorts, respectively. The cumulative incidence of PE was significantly higher for the

Table 1. Demographic characteristics and comorbidity in patient with and without Sjögren syndrome.

Variable	Sjögren Syndrome, n (%)		p
	No, N = 35,680	Yes, N = 8920	
Sex, n (%)			
Female	31,600 (88.6)	7900 (88.9)	0.99
Male	4080 (11.4)	1020 (11.4)	
Age, yrs, mean (SD)	53.1 (14.6)	53.5 (14.4)	0.03[#]
Stratify age, yrs			
≤ 49	14,420 (40.4)	3605 (40.4)	0.99
50–65	13,140 (36.8)	3285 (36.8)	
65+	8120 (22.8)	2030 (22.8)	
Comorbidity			
Atrial fibrillation	546 (1.53)	169 (1.89)	0.01
Diabetes	3375 (9.46)	619 (6.94)	< 0.0001
CVA	2330 (6.53)	575 (6.45)	0.77
Heart failure	1017 (2.85)	302 (3.39)	0.008
Lower leg fracture or surgery	1130 (3.17)	265 (2.97)	0.34
Cancer	1330 (3.73)	418 (4.69)	< 0.0001
Pregnancy	3386 (9.49)	879 (9.85)	0.30

Chi-square test. [#]2-sample t test. CVA: cerebrovascular disease.

Table 2. Comparison of incidence and hazard ratio of DVT and PE stratified by sex, age, and comorbidity between patients with and without Sjögren syndrome.

Variables	Sjögren Syndrome						IRR (95% CI)	Adjusted HR[†] (95% CI)
	No			Yes				
	Event	PY	Rate[#]	Event	PY	Rate[#]		
DVT	60	192,743	3.11	28	48,210	5.81	1.87 (1.80, 2.01)***	1.83 (1.16, 2.89)**
Sex								
Female	50	170,929	2.93	26	42,748	6.08	2.08 (1.92, 2.25)***	2.03 (1.26, 3.28)**
Male	10	21,815	4.58	2	5462	3.66	0.80 (0.60, 1.06)	0.65 (0.14, 3.11)
Stratify age								
≤ 65	24	152,519	1.57	15	38,209	3.93	2.49 (2.29, 2.72)***	2.27 (1.18, 4.37)*
65+	36	40,224	8.95	13	10,001	13	1.45 (1.24, 1.70)***	1.36 (0.72, 2.60)
Comorbidity[‡]								
No	12	146,323	0.82	10	34,645	2.89	3.52 (3.22, 3.84)***	2.70 (1.10, 6.61)*
Yes	48	46,420	10.3	18	13,565	13.3	1.28 (1.11, 1.48)***	1.40 (0.81, 2.42)
PE	38	192,812	1.97	31	48,231	6.43	3.26 (3.04, 3.50)***	3.29 (2.03, 5.31)***
Sex								
Female	33	170,983	1.93	24	42,774	5.61	2.91 (2.70, 3.13)***	3.04 (1.78, 5.18)***
Male	5	21,829	2.29	7	5457	12.8	5.59 (4.64, 6.74)***	5.76 (1.74, 19.2)**
Stratify age								
≤ 65	13	152,541	0.85	14	38,216	3.66	4.30 (3.97, 4.66)***	4.22 (1.95, 9.13)***
65+	25	40,270	6.21	17	10,015	17	2.74 (2.39, 3.12)***	2.66 (1.43, 4.97)**
Comorbidity[‡]								
No	5	146,360	0.34	9	34,648	2.6	7.60 (6.96, 8.30)***	4.51 (1.36, 14.9)***
Yes	33	46,452	7.1	22	13,583	16.2	2.28 (2.01, 2.59)***	2.45 (1.42, 4.21)**

[#]Incidence rate per 10,000 person-years. [†]Adjusted HR: multivariable analysis including age, sex, frequency of admission visits and comorbidities of atrial fibrillation, diabetes, CVA, heart failure, lower leg fracture or surgery, cancer, and pregnancy. [‡]Any of the comorbidities including atrial fibrillation, diabetes, CVA, heart failure, lower leg fracture or surgery, cancer, and pregnancy. *p < 0.05. **p < 0.01. ***p < 0.001. IRR: incidence rate ratio; DVT: deep vein thrombosis; PE: pulmonary embolism; PY: person-years; HR: hazard ratio; CVA: cerebrovascular disease.

patients with SS (log-rank p < 0.001) than that for patients without SS (Figure 1). Patients with SS had a 3.29-fold greater risk of PE (95% CI 2.03–5.31) than the controls did, after adjusting for age, sex, and the comorbidities. The sex-specific adjusted HR of PE was 5.76-fold higher for men in the SS cohort than for men in the comparison cohort (95% CI 1.74–19.2). The incidence of PE increased with increasing age in both cohorts. The effect of SS on the development of DVT or PE was greater in patients aged ≤ 65 years (adjusted HR 4.22, 95% CI 1.95–9.13) than in

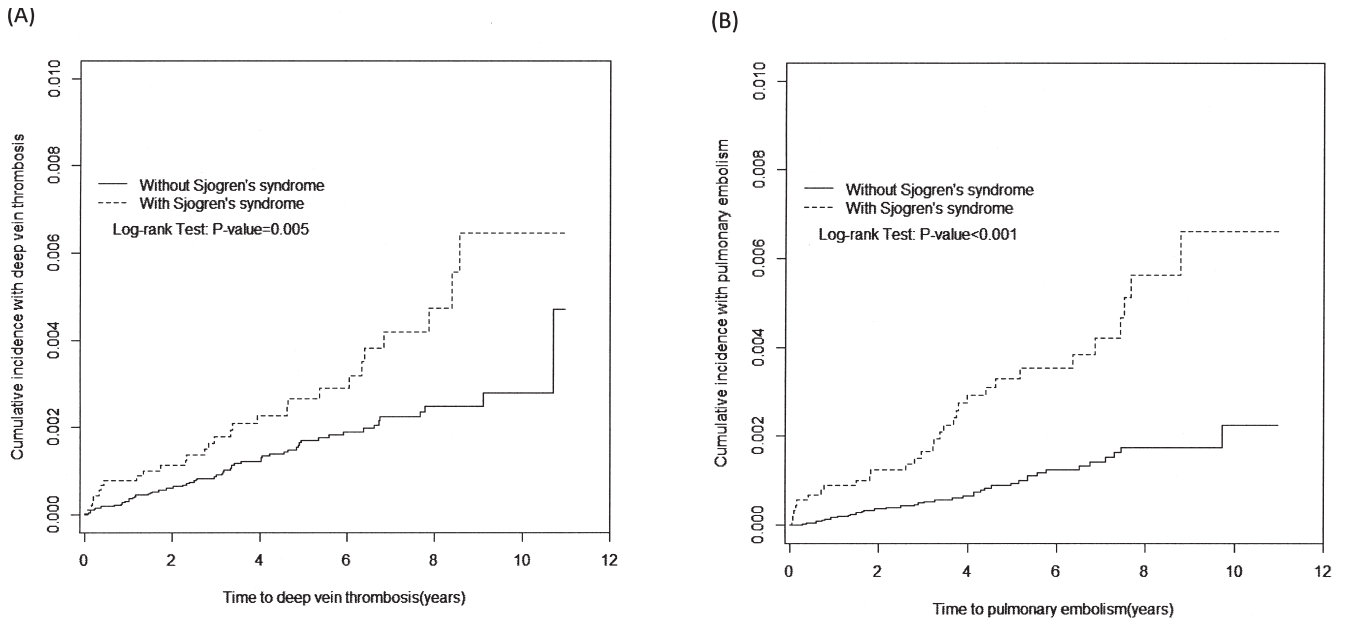

Figure 1. Cumulative incidence of (A) deep vein thrombosis and (B) pulmonary embolism in patients with and without Sjögren syndrome.

patients aged ≥ 65 years (adjusted HR 2.66, 95% CI 1.43–4.97). The patients with SS without comorbidities had a greater risk of PE than the controls without comorbidities (adjusted HR: 4.51, 95% CI: 1.36–14.9).

Table 3 shows that, among the patients with SS and comorbidity, the risks of DVT (adjusted HR 3.66; 95% CI 2.61–8.33) and PE (adjusted HR 11.4; 95% CI 5.12–25.2) were significantly greater than those of the controls without a comorbidity. We observed that 8482 (95%) of the patients in the SS cohort were pSS, and 438 (5%) of the patients in the SS cohort were secondary SS. After adjusting for the covariates, the IRR and adjusted HR of DVT among the patients with a primary SS were significantly greater than those of the controls (adjusted HR 1.77; 95% CI 1.11-2.82). The risk of PE among patients with a pSS diagnosis was 3.21 times greater (95% CI 1.96-5.23) than that for the comparison cohort, whereas patients with a secondary SS diagnosis had a 5.06 times greater risk of PE than did the comparison cohort (95% CI 1.22-21.1).

DISCUSSION

Our study showed that the average annual incidence rate of SS in Taiwan was 4.3 per 100,000 persons in the population. Most of the patients with SS in our study were women with an age of onset > 50 years. These data are consistent with the findings of previous studies[1,23]. We determined that

Table 3. Cox proportional hazard regression analysis for the risk of Sjögren syndrome-associated DVT and PE with interaction of comorbidity.

Variables	Interaction		N	Events, n	Adjusted HR† (95% CI)	p&
DVT	Sjögren syndrome	Comorbidity‡				0.05
	No	No	33,340	44	1 (Reference)	
	No	Yes	2340	16	1.52 (0.80, 2.89)	
	Yes	No	8377	21	1.68 (0.99, 2.83)	
	Yes	Yes	543	7	3.66 (2.61, 8.33)**	
PE						0.05
	Sjögren syndrome	Comorbidity‡				
	No	No	33,340	24	1 (Reference)	
	No	Yes	2340	14	4.12 (2.06, 8.24)***	
	Yes	No	8377	22	3.59 (2.01, 6.41)***	
	Yes	Yes	543	8	11.4 (5.12, 25.2)***	

†Adjusted for age, sex, and frequency of admission visits. **p < 0.01. ***p < 0.001. &p value for interaction. ‡Any of the comorbidities including atrial fibrillation, diabetes, CVA, heart failure, lower leg fracture or surgery, cancer, and pregnancy. DVT: deep vein thrombosis; PE: pulmonary embolism; HR: hazard ratio; CVA: cerebrovascular disease.

Table 4. Incidence and adjusted hazard ratio (HR) of DVT and PE among subgroups of Sjögren syndrome (SS).

	Event	PY	Rate[#]	IRR[†] (95% CI)	Adjusted HR[&] (95% CI)
DVT					
Without SS	60	192,743	3.11	1 (Reference)	1 (Reference)
Primary SS	26	45,746	5.68	1.83 (1.69, 1.97)***	1.77 (1.11, 2.82)*
Secondary SS	2	2454	8.15	2.62 (2.06, 3.32)***	3.31 (0.81, 13.6)
PE					
Without SS	38	192,812	1.97	1 (Reference)	1 (Reference)
Primary SS	29	45,778	6.33	3.21 (2.99, 3.45)***	3.21 (1.96, 5.23)***
Secondary SS	2	2453	8.15	4.14 (3.35, 5.12)***	5.06 (1.22, 21.1)*

[#]Incidence rate per 10,000 person-years. [†]Multivariable analysis including age, sex, frequency of admission visits, and comorbidities of atrial fibrillation, diabetes, CVA, heart failure, lower leg fracture or surgery, cancer, and pregnancy. *p < 0.05. ***p < 0.001. IRR: incidence rate ratio; DVT: deep vein thrombosis; PE: pulmonary embolism; PY: person-years.

patients in our SS cohort had 1.83-fold and 3.29-fold greater risks of developing DVT or PE, respectively, compared with people in the general population.

Ramagopalan, *et al*[14] studied the patients with various immune-mediated diseases who were admitted to hospitals in England and showed that patients with SS had a 2.02-fold greater risk of VTE. However, Ramagopalan, *et al*[14] estimated the risk of VTE without adjusting for comorbidities. Zoller, *et al*[24] performed a large-scale study of the relationship between PE and autoimmune diseases in Sweden, and determined that patients with a history of SS had a 2.19-fold greater risk of PE. However, Zoller, *et al*[24] did not examine the difference in the risk of PE between patients with a pSS and those with a secondary SS.

Our nationwide population-based cohort study in Taiwan revealed increased risks of DVT and PE among Asian patients with SS, compared with those in the general population, after adjusting for the potential covariates. Genetic and environmental factors might have contributed to the inconsistencies between our findings and those of other studies[25,26].

Although the patients with SS in our study had a higher prevalence of comorbidities associated with DVT and PE than the comparison cohort did, SS remained an independent risk factor for developing DVT and PE after adjusting for the covariates. The inflammatory response triggered by SS may drive arterial, venous, and microvascular thrombosis[27,28]. Cytokine induction of tissue factor expression, endothelial dysfunction, the inhibition of the protein C system, and the inhibition of fibrinolysis are central features of inflammation-induced hypercoagulability, and thus may contribute to the development of DVT or PE[28,29].

Most of our patients with SS were women, and both men and women with SS had a greater risk of PE, which is consistent with the findings of previous studies[24]. The effect of SS on the development of DVT or PE was greater in patients aged ≤ 65 years than in patients aged ≥ 65 years. As people age, they become less active, and their cardiopulmonary systems deteriorate. Thus, age-related changes in blood hemostasis and coagulation in the deep veins of people ≥ 65 years of age might exert greater effects on the development of DVT than those related to SS[3,30,31].

The incidence of both DVT and PE increased in patients with any comorbidity in both our SS and comparison cohorts. The multiplicative risks of DVT and PE were significantly greater in patients with SS and any comorbidity. These results are significant using Cox proportional hazards regression analysis for the increased risks of DVT and PE in SS with joint effect of any comorbidity (Table 3).

The patients in our study who had pSS had 1.77-fold and 3.21-fold greater risks of DVT and PE, respectively, compared with those for the comparison cohort (Table 4). In addition, patients with secondary SS had a greater risk of PE (adjusted HR 5.06; 95% CI 1.22-21.1) than patients with pSS (adjusted HR 3.21; 95% CI 1.96-5.23). Cervera, *et al*[32] indicated that antiphospholipid antibodies are present in a lower proportion of patients with pSS than that of patients with secondary SS. Antiphospholipid antibodies are associated with arterial and venous thrombosis[33]. Thromboembolic events are common in SLE, but not in pSS[34].

Our study is the first, to our knowledge, to investigate the risks of DVT and PE in a cohort of Asian patients with SS. The strengths of our findings lie in the nationwide population-based design of a longitudinal study and a followup period of about 50,000 person-years for our SS cohort. In addition, the diagnoses of all the patients with SS identified in the NHIRD were confirmed through their inclusion in the RCIPD, which establishes a high level of reliability for our results. To avoid selection bias, we estimated the risks of DVT and PE only in patients newly diagnosed with SS who had no previous history of DVT and PE. Because each NHI beneficiary is assigned a unique personal identification number, every patient could be traced through the records of the NHIRD for the entire followup period. Thus, our findings can be generalized to the entire population of Taiwan.

However, several limitations to the interpretation our findings should be considered. Hospitalized patients with

SS were enrolled in our study, which might have resulted in an overestimate of the risks of DVT and PE in our SS cohort. Ramagopalan, *et al*[14] suggested that people admitted to hospitals for autoimmune disorders may have an increased risk of subsequent VTE. However, our comparison cohort also comprised inpatients and we estimated the risk of SS on the development of DVT and PE, adjusting for comorbidities and frequency of hospitalization[35]. The SS cases based on AECG classification criteria[2], essentially a clinical diagnosis, may not be properly confirmed. The NHIRD does not provide family history of VTE and detailed lifestyle information such as smoking habits, body mass index, and physical activity, which are all potential confounding factors for our study. The lack of prescription drug data, such as that for hormone replacement therapy, contraceptive drugs, glucocorticosteroid treatments, and biological therapies, may also have influenced the risk of DVT or PE among the patients in our SS cohort[20,36]. The lack of information regarding genetic factors [i.e., specific genetic deficiencies, such as Factor V Leiden (G 1691A), Factor II G20210A], and deficiencies of the natural anticoagulants (i.e., antithrombin, protein C, and protein S) in our study cohorts may become another limitation.

Our nationwide population-based cohort study of 8920 patients with SS showed that patients with SS have a 1.83-fold greater risk of DVT and a 3.29-fold greater risk of PE, compared with the risks of DVT and PE among people in the general population. In addition, the multiplicative risks of DVT and PE were also significantly greater among patients with SS and a comorbidity. Therefore, providing adequate care for comorbidities is critical to the prevention of DVT and PE in patients with SS. Thus, a multidisciplinary team should guide the assessment, treatment, and holistic care of patients with SS. Future studies of the biological mechanisms of SS are warranted to determine its contribution to the development of DVT and PE.

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