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The Risk of Pulmonary Embolism and Deep Venous Thrombosis in Systemic Sclerosis: A General Population-Based Study

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Abstract

Objectives—To determine the risk of venous thromboembolism (VTE) (pulmonary embolism [PE] and deep vein thrombosis [DVT]) in individuals with incident SSc in the general population.

Methods—Using a population database that includes all residents of British Columbia, Canada, we conducted a cohort study of all patients with incident SSc and up to 10 age-, sex-, and entry time-matched individuals from the general population. We compared incidence rates of PE, DVT, and VTE between the two groups according to SSc disease duration. We calculated hazard ratios (HRs), adjusting for confounders.

Results—Among 1,245 individuals with SSc (83% female, mean age 56 years), the incidence rates of PE, DVT, and VTE were 3.47, 3.48, and 6.56 per 1000 person-years respectively, whereas the corresponding rates were 0.78, 0.76, and 1.37 per 1000 person-years among 12,670 non-SSc individuals. Compared with non-SSc individuals, the multivariable HRs among SSc patients were 3.73 (95% CI, 1.98–7.04), 2.96 (95% CI, 1.54–5.69), and 3.47 (95% CI, 2.14–5.64) for PE, DVT and VTE, respectively. The age-, sex-, and entry time-matched HRs for PE, DVT, and VTE were highest during the first year after SSc diagnosis (32.77 [95% CI, 6.60–162.75], 8.50 [95% CI, 3.13–23.04], and 12.03 [95% CI, 5.27–27.45], respectively).

Conclusions—These findings provide population-based evidence that SSc patients are at a substantially increased risk of VTE, especially within the first year after SSc diagnosis. Increased monitoring for this potentially fatal outcome and its modifiable risk factors is warranted in this patient population.

Keywords

Systemic Sclerosis; Pulmonary Embolism; Deep Vein Thrombosis

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An increased risk of venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), has been reported among patients with inflammatory autoimmune diseases. In particular, patients with systemic lupus erythematosus (SLE), dermatomyositis, giant cell arteritis, granulomatosis with polyangiitis (GPA), rheumatoid arthritis (RA), and Behcet's disease are at an increased risk of VTE compared to the general population.^{1–6} Part of the increased risk of PE and DVT in these diseases is thought to be secondary to an underlying inflammatory state, with pro-inflammatory cytokines playing a role in activation of the coagulation cascade and in turn procoagulants, such as thrombin, stimulating the production of a number of inflammatory mediators.^{7–10} In addition, the endothelial dysfunction present in conditions such as RA, SLE, and vasculitis, as well as the presence of other risk factors such as antiphospholipid antibodies, may also contribute to the increased risk of VTE in these patient populations.^{11–13}

Systemic sclerosis (SSc) is an autoimmune disease with no known etiology and with multi-organ system manifestations, clinically characterized by vasculopathy and progressive fibrosis. Patients with SSc experience high morbidity and mortality, with an overall 10 year survival rate anywhere between 66–82% with variation depending on disease manifestations and degree of end organ involvement.^{14–16} While inflammation is less prominent than in many other autoimmune conditions, vascular injury and endothelial dysfunction are important pathophysiologic features of the disease,^{17–20} as manifested clinically by Raynaud's phenomenon, pulmonary hypertension, renal crisis, and gastric antral vascular ectasia (GAVE). As such, patients with SSc may be at an increased risk for VTE.

Several studies of SSc cases identified from hospital admissions^{1,21} or using billing codes from the National Health Institute Research Database in Taiwan²² have reported an increased risk of VTE, except for one.²³ One hospital-based study found the risk of PE during the first year after admission for SSc to be increased seven times, which declined over time to 1.38 times or less by year 5 and later.¹ However, it remains unclear whether this increased risk is generalizable to the unselected general population. Furthermore, as the aforementioned risk decline was observed in only one hospital-based study to date, extrapolation of this potentially important finding to the general population should be carried out with caution. Given that PE is a preventable yet potentially fatal condition in a patient population already at risk for cardiopulmonary problems in the form of interstitial lung disease, pulmonary hypertension, and coronary artery disease,²⁴ a better understanding of this problem is critical to improving outcomes for SSc patients. In order to address these issues, we evaluated the risk of PE, DVT, and VTE according to SSc duration in an unselected general population context.

PATIENTS AND METHODS

Data Source

Universal health coverage is provided for all residents of British Columbia (BC), Canada (population ~4.5 million). Population Data BC is a population-based database from the provincial health care system that includes all patients with SSc in the province of BC. It captures all provincially funded health care services since 1990, including all outpatient medical visits,²⁵ hospital admissions and discharges,²⁶ interventions,²⁵ investigations,²⁵

demographic data,²⁷ cancer registry data,²⁸ and vital statistics.²⁹ Population Data BC also includes a comprehensive prescription drug database (PharmaNet),³⁰ which provides information about all dispensed medications for BC residents since 1996. This database has been used reliably in a number of other population-based studies.^{31–33}

Study Design and Cohort Definitions

Using Population Data BC, we compared rates of incident PE, DVT, and VTE between an incident SSc cohort and up to 10 age-, sex-, and entry time-matched individuals without SSc randomly selected from the general population. The comparison cohort was chosen from the same Population Data BC database used to select the SSc cohort. We created an incident SSc cohort of cases diagnosed with SSc for the first time between January 1996 and December 2010; age, sex and entry-time matched individuals without a diagnosis of SSc during the same index dates were randomly selected as the comparison cohort. The cohort entry times were the first diagnosis date of SSc for the SSc cohort and the matched date for the comparison group. The study definition for SSc included the following: a) age ≥ 18 years, and either b) one International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code for SSc by a rheumatologist (ICD-9-CM 710.1) or an ICD-9-CM or ICD-10-CM code from a hospitalization (ICD-9-CM 710.1 or ICD-10-CM M34.0); or c) a diagnosis of SSc on at least two visits at least two months apart and within a two-year period by a non-rheumatologist physician. In addition, cases were required to have an absence of an SSc diagnosis between January 1990 and December 1995 in order to ensure incident cases.

In order to ensure that our SSc cohort was made up of individuals with only SSc and not with other autoimmune rheumatic diseases, individuals with at least two visits ≥ two months apart subsequent to the SSc diagnostic visit with a diagnosis of RA, psoriatic arthritis, spondyloarthropathy, or SLE were excluded. SSc cases and controls who had a PE or DVT prior to the index date (date of SSc diagnosis for cases or the matching date for controls) were excluded.

The study duration was from January 1, 1996 to December 31, 2010. SSc patients entered the case cohort after all inclusion and exclusion criteria had been met. Participants were observed until they experienced an outcome, died, disenrolled from the health plan (i.e., left BC; approximately 1% per year), or until the follow-up ended, whichever occurred first.

Ascertainment of PE and DVT

The primary outcomes were the first-ever PE or DVT that occurred during the study period. A patient met the definition for either PE or DVT if he or she had a recorded ICD-9-CM or ICD-10-CM code for PE/DVT and had received a prescription for anticoagulant therapy (heparin, warfarin sodium, or a similar agent). The ICD codes for PE were 415.1, 673.2, or 639.6 (ICD-9-CM) and O88.2 or I26 (ICD-10-CM); the ICD codes for DVT were 453 (ICD-9-CM) and I82.4 or I82.9 (ICD-10-CM). Because VTE is a potentially fatal disease, we also included patients with a fatal outcome. Since a patient may have died before he or she could receive anticoagulation treatment, patients with a recorded diagnosis of PE or DVT were included in the absence of recorded anticoagulant therapy if there was a fatal

outcome within two months of diagnosis. The validity of ICD codes to identify VTE has been well demonstrated, with a positive predictive value of up to 95% when VTE was used in the principal position.³⁴

Assessment of Covariates

Covariates were assessed in the year prior to the index date, and included alcoholism, hypertension, sepsis, varicose veins, inflammatory bowel disease, trauma, fracture, surgery, medication use (glucocorticoids, hormone replacement therapy [HRT], contraceptives, and Cox-2 inhibitors), and healthcare utilization (medical visits and hospitalizations) in the last year prior to cohort entry. The Charlson comorbidity index (CCI) was also calculated in the year prior to the index date.³⁵

Statistical Analysis

We compared baseline characteristic between the SSc and comparison cohorts. We identified incident cases of PE and DVT during the follow-up period and calculated incidence rates (IRs) of PE and DVT, both individually and in combination (i.e., VTE), per 1,000 person-years. We estimated the cumulative incidence of each event accounting for the competing risk of death by using the SAS macro CUMINCID and graphically presented these results.³⁶ We used Cox proportional hazard regression models to assess the risk of PE and DVT associated with SSc after adjusting for covariates. We entered confounders one at a time into the Cox models in a forward selection according to each confounder's impact on the hazard ratio (HR) of the SSc, relative to the HR in the model selected in the previous step. Cut-off for the minimum important relative effect at each step was set to 5%.³⁷ In order to evaluate the impact of duration of SSc (i.e., follow-up time after SSc diagnosis), we estimated the HR yearly for the first five years. We used SAS Version 9.3 (SAS Institute, Inc., Cary, NC, USA) for all analyses. For all HRs, we calculated 95% confidence intervals (CIs). All *p*-values were two sided.

We performed two sensitivity analyses. First, we estimated the cumulative incidence of each event accounting for the competing risk of death.³⁸ We also determined the potential impact that a hypothetical unmeasured confounder might have had on our estimates of the association between SSc and the risk of PE and DVT.³⁹ We simulated unmeasured confounders with their prevalences ranging from 10% to 20% in the SSc and control cohorts, and odds ratios (ORs) ranging from 1.3 to 3.0 for the associations between the unmeasured confounder and PE/DVT.

No personal identifying information was made available as part of this study; procedures used were in compliance with BC's Freedom of Information and Privacy Protection Act. Ethics approval was obtained from the University of British Columbia.

RESULTS

Our primary analysis included 1,245 incident SSc cases (mean age 56.5 years, 82.8% female) and 12,670 age-, sex-, and entry time-matched individuals in the comparison cohort for both PE and DVT. The total follow-up time for the SSc and the comparison cohort was 4,570 person-years and 57,556 person-years, respectively. The baseline characteristics of the

SSc and comparison cohorts are summarized in Table 1. Compared with the non-SSc group, the SSc group tended to have higher health care utilization, higher CCI scores, higher frequencies of varicose veins, trauma, and fractures, and more prescriptions for glucocorticoids, HRT, and Cox-2 inhibitors.

SSc was associated with an increased incidence of PE and DVT (Table 2 and Figure 1). IRs were 3.47 and 3.48 events per 1,000 person-years for PE and DVT in the SSc group, respectively, whereas the corresponding IRs in the comparison cohort were 0.78 and 0.76 events per 1,000 person-years (Table 2).

The age-, sex-, and entry time-matched HRs among SSc patients compared to the comparison cohort were 5.11 (95% CI, 2.85–9.19) for PE, 5.13 (95% CI, 2.86–9.22) for DVT, and 5.25 (95% CI, 3.41–8.07) for VTE. After adjusting for confounding covariates, the corresponding HRs were 3.73 (95% CI, 1.98–7.04), 2.96 (95% CI, 1.54–5.69), and 3.47 (95% CI, 2.14–5.64) (Table 2).

Overall, when we evaluated the impact of follow-up time after SSc diagnosis, the HRs for PE, DVT and VTE were greatest in the first year after diagnosis, with age-, sex- and entry time-matched HRs of 32.77 (95% CI, 6.60–162.75), 8.50 (95% CI, 3.13, 23.04) and 12.03 (95% CI, 5.27–27.45), respectively (Table 3). The risk of PE, DVT, and VTE was attenuated in the following years, but remained statistically significant for over five years following the initial diagnosis.

Our sensitivity analysis for the potential impact of unmeasured confounders suggested that our results were robust over the range of simulated parameters. HRs remained significant even at the extreme values of 20% prevalence and an OR of 3.0 for the association between the hypothetical confounder and VTE (Table 4).

DISCUSSION

Our goal was to evaluate the risk of PE and DVT among SSc patients and its time trends according to disease duration in a general population context. In this large general population-based study, we found that SSc was associated with an increased risk of PE, DVT, and VTE particularly in the first year following the diagnosis of SSc. This increased risk was attenuated over time but remained significantly elevated for all outcomes even after five years. Overall, we observed a three-fold increased risk of PE, DVT, and VTE in SSc patients compared to those without SSc, independent of relevant risk factors such as age, sex, history of hospitalization, and overall comorbidity index. Our findings provide general population-based evidence that SSc, regardless of prior hospitalization, is associated with a substantially increased risk of PE and DVT, and they lend insight into the relative risks over the duration of SSc.

The overall increased risk of PE and VTE found in our study is consistent with two hospital-based studies^{1,21} and one study that identified SSc cases from billing codes and the Taiwanese Registry for Catastrophic Illness Patient Database.²² Specifically, a nationwide Swedish study that followed hospitalized SSc patients found a 60% increased risk of PE overall¹ in the multivariable analysis. A Danish study reported a nearly four-fold increased

coagulability through a number of mechanisms, including the upregulation of procoagulant factors, the downregulation of anticoagulants such as Protein C and S, and the suppression of fibrinolysis⁷. In addition, inflammation has been proposed to be a potential contributor to the increased risk of VTE seen in other inflammatory conditions such as RA.^{5,47} Finally, it is possible that patients with a new diagnosis of SSc, particularly those with diffuse cutaneous SSc who tend to be sicker, could have more frequent encounters with the healthcare system in their first year after diagnosis, which could theoretically account for the highest risk of VTE in the first year.

The strengths and limitations of our study deserve discussion. We used a large database spanning the entire province of BC, making our findings generalizable to the population at large. Because our data captures both primary care physician and specialist records, both mild and severe cases of SSc are likely to be included in our analysis, further contributing to the generalizability of our results. In addition, disease ascertainment was restricted to patients with incident SSc to better capture the entire span of the natural history of the disease as it relates to the development of PE and DVT and to reduce the risk of bias associated with prevalent exposure (i.e., survivor cohorts).

The potential limitations of our study are inherent to all observational studies that use administrative data. Specifically, there exists the potential for inaccurate diagnosis by using only ICD coding data. However, ICD coding for SSc in Canadian administrative databases has been found to have a specificity of nearly 95%.⁴⁸ Because 80% of our cases met the definition from rheumatologist or hospitalization diagnoses, our identified cases were more likely to be germane SSc cases rather than false positives. However, non-differential misclassification would bias our results towards the null, resulting in conservative estimates. In addition, although outcomes including PE, DVT, and VTE were assessed using administrative data, our definition of VTE has been shown to have a high confirmation rate (94%) in similar databases.¹⁷ Even though we adjusted for a number of risk factors that may have influenced our outcomes in our multivariable analysis, we were unable to account for all potentially relevant confounders. To that effect, our administrative data did not have information about lifestyle parameters such as smoking status, activity level, or BMI, although the lack of relevant association of these variables with SSc makes confounding by these variables unlikely.²⁴ Nevertheless, in our sensitivity analysis for plausible ranges of these unmeasured confounders, our estimates were robustly significant. We were unable to measure the prevalence of the antiphospholipid antibody syndrome (APS) within our SSc cohort because of the absence of laboratory data, but given the lack of any known significant association between SSc and APS,^{49,50} the presence of APS is unlikely to provide an explanation for the increased risk of VTE observed in our SSc cohort. Similarly, we did not have information regarding the subtype of SSc (i.e. diffuse versus limited) or the auto-antibody profile. We were therefore unable to draw conclusions about the potential differences in risk for VTE between groups of SSc patients. Nonetheless, our finding of a three-fold increased risk of VTE among all SSc patients is important in and of itself and calls for future studies looking at the risk of VTE in subsets of SSc patients.

In conclusion, this general population-based study demonstrates that SSc is associated with an increased risk of PE, DVT, and VTE, especially during the first year following the

diagnosis of SSc. These findings support increased monitoring and vigilance for VTE risk factors among patients with SSc, regardless of recent hospitalization, to help avoid this potentially devastating outcome.

Acknowledgments

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SIGNIFICANCE AND INNOVATIONS

- First study assessing the risk of venous thromboembolism (VTE) in an incident cohort of patients with systemic sclerosis in a general population context.
- Patients with systemic sclerosis have an increased risk of deep vein thrombosis and pulmonary embolism.
- The highest risk of deep vein thrombosis and pulmonary embolism is within the first year after the disease diagnosis, suggesting that inflammation may play a role in the pathogenesis of VTE.
- Our findings support increased monitoring and vigilance for VTE risk factors among patients with systemic sclerosis, regardless of recent hospitalization, to help avoid this potentially devastating outcome.

Figure 1. Cumulative incidence of pulmonary embolism (upper panel), deep vein thrombosis (middle panel) and venous thromboembolism (lower panel) in the 1245 patients with incident systemic sclerosis (SSc) as compared with the 12,670 age-, sex- entry-time-matched, non-SSc subjects.

Table 1

Characteristics of SSc and Comparison Cohorts at Baseline

Variable	SSc N=1,245	Non-SSc N=12,670	p-value
Age (mean yrs)	56.5 ± 15.0	56.5 ± 14.9	0.965
Female	1031 (82.8)	10473 (82.7)	0.937
Hospitalized	413 (33.2)	2020 (15.9)	<0.001
No. MSP visits (mean)	20.8 ± 17.7	9.0 ± 11.0	<0.001
Charlson's comorbidity index (mean)	1.19 ± 1.51	0.34 ± 1.07	<0.001
Alcoholism	8 (0.6)	102 (0.8)	0.736
Hypertension	307 (24.7)	2824 (22.3)	0.059
Sepsis	3 (0.2)	24 (0.2)	0.730
Varicose veins	24 (1.9)	103 (0.8)	<0.001
Inflammatory bowel disease	9 (0.7)	55 (0.4)	0.181
Trauma	6 (0.5)	23 (0.2)	0.040
Fractures	30 (2.4)	177 (1.4)	0.009
Surgery	12 (1)	77 (0.6)	0.135
Glucocorticoids	323 (25.9)	497 (3.9)	<0.001
Hormone replacement therapy	138 (11.1)	964 (7.6)	<0.001
Contraceptives	45 (3.6)	472 (3.7)	0.937
Cox2 inhibitors	113 (9.1)	389 (3.1)	<0.001

Values are N (percentages) unless otherwise noted.

Table 2

Hazard Ratios of Incident PE and DVT According to SSc Status

	SSc N= 1,245	Non-SSc N=1,2670
PE		
Cases, N	16	44
Incidence Rate/1000 Person-Years	3.47	0.78
Age-, Sex-, Entry Time-Matched Cox HR (95% CI)	5.11 (2.85, 9.19)	1.0
*Fully-Adjusted Cox HR (95% CI)	3.73 (1.98, 7.04)	1.0
DVT		
Cases, N	16	44
Incidence Rate/1000 Person-Years	3.48	0.76
Age-, Sex-, Entry Time-Matched Cox HR (95% CI)	5.13 (2.86, 9.22)	1.0
*Fully-Adjusted Cox HR (95% CI)	2.96 (1.54, 5.69)	1.0
VTE		
Cases, N	30	79
Incidence Rate/1000 Person-Years	6.56	1.37
Age-, Sex-, Entry Time-Matched Cox HR (95% CI)	5.25 (3.41, 8.07)	1.0
*Fully-Adjusted Cox HR (95% CI)	3.47 (2.14, 5.64)	1.0

* Fully-adjusted models include the following selected covariates for each outcome (see methods): **PE** Charlson's comorbidity Index and glucocorticoids; **DVT** No. of outpatient visits and glucocorticoids; **PE or DVT** No. outpatient visits and glucocorticoids. See statistical section for details about the covariate selections.

Table 3

Age and sex adjusted Hazard Ratios (HRs) for PE, DVT or both (VTE) in SSc according to follow-up period

Time after diagnosis	PE HR (95% CI)	DVT HR (95% CI)	VTE HR (95% CI)
<1 year	32.77 (6.60, 162.75)	8.50 (3.13, 23.04)	12.03 (5.27, 27.45)
<2 years	10.26 (4.14, 25.41)	10.22 (4.69, 22.29)	10.16 (5.55, 18.60)
<3 years	7.44 (3.35, 16.54)	8.52 (4.15, 17.50)	8.14 (4.70, 14.09)
<4 years	6.52 (3.12, 13.64)	6.00 (3.07, 11.74)	6.25 (3.76, 10.38)
<5 years	5.03 (2.56, 9.89)	5.06 (2.64, 9.71)	5.17 (3.20, 8.36)
Total follow-up	5.11 (2.85, 9.19)	5.13 (2.86, 9.22)	5.25 (3.41, 8.07)

Table 4

Sensitivity analyses on the risk of VTE in patients with systemic sclerosis

Outcome	Primary Analysis HR (95% CI)	Sensitivity Analysis 1 HR (95% CI)	Sensitivity Analysis 2 HR (95% CI)			
			Prevalence=10 % ^a OR ^b =1.3	Prevalence=10 % ^a OR ^b =3.0	Prevalence=20 % ^a OR ^b =1.3	Prevalence=20 % ^a OR ^b =3.0
PE	3.73 (1.98, 7.04)	2.92 (1.45, 5.89)	3.67 (1.94, 6.92)	3.22 (1.68, 6.16)	3.33 (1.75, 6.32)	2.90 (1.53, 5.52)
DVT	2.96 (1.54, 5.69)	2.40 (1.15, 5.01)	2.96 (1.54, 5.70)	2.85 (1.46, 5.56)	2.94 (1.52, 5.66)	2.26 (1.14, 4.46)
VTE	3.47 (2.14, 5.64)	2.90 (1.71, 4.91)	3.45 (2.13, 5.59)	3.11 (1.89, 5.12)	3.28 (2.02, 5.34)	2.75 (1.67, 4.52)

DVT, Deep vein thrombosis; HR, Hazard ratio; OR, Odds ratio; PE, Pulmonary embolism; VTE, Venous thromboembolism

^ahypothetical prevalence of the unmeasured confounder in the SSC cases

^bhypothetical level of association between the unmeasured confounder and the outcome

Sensitivity analyses 1; accounting for the competing risk of death

Sensitivity analyses 2; accounting for unmeasured confounders