Systemic sclerosis and risk of venous thromboembolism: A systematic review and meta-analysis

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Abstract

Background. Several chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory myositis, and systemic vasculitides, have been linked to an increased risk of venous thromboembolism (VTE). However, the data on systemic sclerosis (SSc) remains unclear.

Methods. We conducted a systematic review and meta-analysis of observational studies that reported odds ratio, relative risk, hazard ratio, or standardized incidence ratio comparing risk of VTE in patients with SSc versus non-SSc participants. Pooled risk ratio and 95% confidence intervals (CIs) were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird.

Results. Out of 776 potentially relevant articles, five eligible studies were identified and included in the data analysis. The pooled risk ratio of VTE in patients with SSc was 2.51 (95% CI, 1.79–3.54). The statistical heterogeneity of this study was high with an I2 of 90%.

Conclusions. Our study demonstrated a statistically significant increased VTE risk among patients with SSc.

Introduction

Venous thromboembolism (VTE) is one of a major medical problem with a reported annual incidence of 1–2 new cases per 1,000 populations [1,2]. VTE is associated with a significant morbidity and mortality as its reported 30-day mortality rate is as high as 11–30% [1–3]. Deep venous thrombosis (DVT) of veins of lower extremity and pulmonary embolism (PE) are the most common subtypes of VTE. Several medical conditions, such as immobilization, surgery, malignancy, hypercoagulable state, and use of certain medications are well recognized as its risk factors [4,5].

Several autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, inflammatory myositis, psoriasis, and systemic vasculitides have been increasingly recognized as predisposing factors for VTE [6–10]. Though the mechanistic link between these disorders and VTE is not well understood, several in vivo and in vitro studies have suggested that chronic inflammation and vasculopathy might be the pathogenic link between these two conditions [7–9].

Systemic sclerosis (SSc) is another immune-mediated disorder characterized by generalized microangiopathy and diffuse fibrosis of the skin and/or internal organs [11]. Patients with SSc usually present with Raynaud’s phenomena, thickening of the skin, telangiectasia, arthralgia, hand swelling, and esophageal dysfunction. Interstitial lung disease, pulmonary arterial hypertension, cardiac disease, and renal involvement are its late complications that are associated with high mortality [12,13].

In light of chronic inflammation and the prominent vasculopathy, patients with SSc might be at an increased risk of VTE as well. However, the data on VTE risk in this group of patient is still inconclusive as epidemiological studies showed conflicting results [14–18]. Therefore, to further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the VTE risk in patients with SSc versus non-SSc participants.

Method

Search strategy

Two investigators (P.U. and N.S.) independently searched published studies indexed in MEDLINE and EMBASE from inception to December 2014 as well as the American College of Rheumatology Annual Scientific Meeting abstract database from 2007 to 2013 using the search terms described in Supplementary Appendix 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1038456. References of the selected articles were also manually searched.

Inclusion criteria

The studies were eligible for this meta-analysis if they met these inclusion criteria: (1) case–control or cohort studies published as original study or abstract to evaluate the association between SSc and risk of VTE, (2) odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) or standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) or sufficient data to calculate these ratios were provided, and (3) non-SSc participants and non-VTE participants were used as the reference group for cohort study and case–control study, respectively.
Study eligibility was independently evaluated by each investigator mentioned above. Any differences in the determination of study eligibility were resolved by consensus with the third investigator (W.K.). The quality of each study was, again, independently appraised by each investigator using Newcastle–Ottawa quality scale [19]. This scale assessed each study in three domains including (1) the appropriateness of the selection of the participants, (2) the comparability between the study groups, and (3) the ascertainment of the exposure for case–control study and the outcome of interest for cohort study.

Data extraction
A standardized data collection form was used to extract the following information: title of the article, first author’s last name, authors’ institution, year of publication, country where the study was conducted, year of study, study population, criteria used for the diagnosis of SSc, definition and diagnosis of VTE, average duration of follow-up, number of cases, number of controls, gender percentage, average age of participants, and adjusted effect estimates with 95% CI. This data extraction was independently performed by the two investigators. Any discrepancy in data extraction was jointly investigated by all investigators by referring back to the primary studies.

Statistical analysis
All statistical analyses were conducted using Review Manager 5.3 software from the Cochrane Collaboration. Point estimates and their corresponding standard errors were extracted from each study and pooled together using the generic inverse variance method of DerSimonian and Laird [20]. Random-effect model, rather than a fixed-effect model, was used given the high likelihood of between study variance due to the difference in study design, population, and study variance due to the difference in study design, population, and study population, criteria used for the diagnosis of SSc, definition and diagnosis of VTE, average duration of follow-up, number of cases, number of controls, gender percentage, average age of participants, and adjusted effect estimates with 95% CI. This data extraction was independently performed by the two investigators. Any discrepancy in data extraction was jointly investigated by all investigators by referring back to the primary studies.

Result
Our search strategy yielded 776 potentially relevant articles (129 articles from MEDLINE and 647 articles from EMBASE). After exclusion of 106 duplicated articles, 670 of them underwent title and abstract review. Six hundred and thirty articles were excluded as they were clearly not observational studies or were not conducted in patients with SSc, leaving 40 articles for a full-length article review. Twenty of them were excluded since they did not report our outcome of interest (VTE), while sixteen of them were excluded since they were descriptive studies without a control group. Additional search of the American College of Rheumatology Annual Scientific Meeting abstract database yielded one more eligible study.

Therefore, a total of five studies (four retrospective cohort studies and one case–control study) were eligible according to our inclusion criteria and were included in the data analysis [14–18]. Figure 1 outlines our search methodology and literature review process. The main characteristics and the Newcastle–Ottawa scores of the included studies are illustrated in Table 1.

The pooled risk ratio of VTE of subjects with SSc versus controls was 2.51 (95% CI, 1.79–3.54). The risk ratios from individual study varied considerably from 1.50 to 8.41. The statistical heterogeneity was high with an I² of 90%. Figure 2 demonstrates the forest plot of all included studies.

To further explore the high heterogeneity, we conducted sensitivity analyses. First, we excluded the study by Johannesdottir et al. [15] as it was the only study with case–control design. However, exclusion of this study did not significantly change the statistical heterogeneity (RR: 2.75; 95% CI: 1.89–4.01; I² 93%). Second, we excluded the study by Zoller et al. [16] as it was the only study that included only patients with PE (in contrast to DVT and/or PE in other studies). This sensitivity analysis, again, did not significantly alter the value of I² (RR: 3.12; 95% CI: 1.65–5.90; I² 89%). Third, we excluded both the study by Zoller et al. [16] and Ramagopolan et al. [14] as these two studies recruited their cohorts from hospital admission record and, thus, were potentially at risk of selection bias. Exclusion of these two studies slightly reduced I² to 85% (RR: 3.77; 95% CI: 1.58–8.99).

We then performed a subgroup analysis on the subtype of VTE. Three studies provided data on subgroup of PE [16–18], while two studies provided data on subgroup of DVT [17–18]. We found that the pooled risk ratio of PE of subjects with SSc versus controls was 3.25 (95% CI: 1.35–7.83; I² of 89%), while the pooled risk ratio of DVT of subjects with SSc versus controls was 6.25 (95% CI: 2.94–13.27; I² of 39%). Figures 3 and 4 demonstrate the forest plots for PE and DVT, respectively.

Evaluation for publication bias
Funnel plot was used to evaluate for publication. The forest plot was relatively symmetric and all studies resided within the funnel. Thus, concern for publication bias was low in this meta-analysis. Figure 5 illustrates the funnel plot of this study.
| Country of origin | Study design   | Year of publication | Cases                                                                 | Controls                                                                 | Diagnosis of systemic sclerosis | Diagnosis of VTE | Follow-up | Mean age, Y | Woman, % | Number of cases | Number of controls | Confounder assessed | Quality assessment (Newcastle–Ottawa scale) |
|------------------|----------------|---------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------|------------------|-----------|-------------|-----------|----------------|------------------|-------------------|-----------------------|---------------------|----------------|----------------|----------------|
| England          | Retrospective cohort | 2011               | All patients who were diagnosed with SSc between 1999 and 2008. Cases were identified using the English National Hospital Episode Statistics. | Hospitalized patient randomly selected from the same database.            | Diagnostic code from the database. | Diagnostic code from the database. | Until death, first record of VTE or March 31, 2008, | N.A.        | 82.0         | 11,643             | 11,643            | Age, sex, and region of residence. | Selection: 3 stars | Comparability: 1 star | Outcome: 3 stars |
| Denmark          | Case-control    | 2012               | All northern Denmark residences who were diagnosed with DVT and/or PE between 1999 and 2009. Cases were identified from Danish National Registry database. | Sex- and age-matched subjects randomly selected from the same database.   | Diagnostic code from the database. | Diagnostic code, confirmed by peer review. | N.A.       | 52.9        | 14,721               | 147,210           | Hospitalization, co-morbidity, and medications used. | Selection: 3 stars | Comparability: 1 star | Exposure: 1 star |
| Sweden           | Retrospective cohort | 2012               | All patients who were diagnosed with SSc between 1964 and 2008. Cases were identified by using the Swedish National Hospital admission database. | The rest of the subjects in the same database who did not have any autoimmune diseases (i.e., the rest of the population of Sweden). | Diagnostic code from the database. | Diagnostic code, confirmed by prescription of anticoagulant. | Until death, first record of PE, emigration or December 31, 2008. | N.A. | 48.8 | 9,323 | N.A. | Age, sex, hospitalization, and co-morbidity. | Selection: 4 stars | Comparability: 2 stars | Outcome: 3 stars |
| Canada           | Retrospective cohort | 2013               | All patients who were diagnosed with SSC between 1990 and 2010. Cases were identified using regional health database which covered the entire population of the province of British Columbia. | Sex- and age-matched subjects randomly selected from the same database. | Diagnostic code from the database. | Diagnostic code from the database. | Until first record of VTE, emigration from the system or December 31, 2010. | 57.0 | 83.0 | 1,284 | 12,080 | Age, sex, and co-morbidity. | Selection: 4 stars | Comparability: 2 stars | Outcome: 2 stars |
| Taiwan           | Retrospective cohort | 2014               | All patients who were diagnosed with SSC between 1998 and 2010. Cases were identified using Taiwan National Health Insurance Research Database which covered nearly 100% of the Taiwanese population. | Sex- and age-matched subjects randomly selected from the same database. | Diagnostic code from the database. | Diagnostic code from the database. | Until first record of VTE, emigration from the system or December 31, 2010. | 50.3 | 74.9 | 1,895 | 7,580 | Age, sex, and co-morbidity. | Selection: 4 stars | Comparability: 2 stars | Outcome: 3 stars |
coagulation cascade, inhibit the anticoagulation pathway, and impair the fibrinolytic process, resulting in a thrombophilic state [25–28]. Vasculopathy and endothelial dysfunction, as previously mentioned, are the hallmark of the pathogenesis of SSc [11]. This endothelial dysfunction can be further jeopardized by chronic inflammation as the deleterious effect of inflammatory cytokines and oxidative stress on endothelial cells has also been extensively documented [29,30]. Moreover, patients with SSc may be less active compared with healthy subjects because of the non-cutaneous manifestations of their disease, such as arthritis, interstitial lung disease, and pulmonary arterial hypertension [11,12], rendering them at more risk of venous flow stasis and DVT.

Nevertheless, there were some limitations in this meta-analysis and, thus, the results should be interpreted with caution. First, all of the included studies were medical registry-based studies which were at potential risk of coding inaccuracy for both SSc and VTE. In fact, only two studies [16,17] utilized other information to verify the diagnosis of VTE, while the rest relied solely on the database’s diagnostic codes. Second, statistical heterogeneity was high in this meta-analysis. The difference between subgroups of VTE (DVT and PE) might be partly responsible for this as the heterogeneity was lower for each subgroup analysis. Third, this is a meta-analysis of observational studies that, at the best, can only illustrate an association but cannot establish causality. Therefore, we cannot be certain that SSc itself versus other potential confounders, such as a higher prevalence of lower extremity venous stasis in these patients, were accountable for the increased VTE risk. Furthermore, detection bias might also play a role as patients with SSc might be exposed more to medical examinations and tests just because of their chronic illness [31].

In conclusion, our meta-analysis demonstrated a statistically significant increased VTE risk among patients with SSc. In light of these findings, further research is needed to elucidate the mechanistic underpinnings and identify potential therapeutic targets.

### Discussion

Our meta-analysis demonstrated a significant association between SSc and VTE with an overall increased risk of 2.51-folds (95% CI, 1.79–3.54) compared with non-SSc participants. Our results were in line with previous descriptive cohorts that observed a higher number of cases of VTE [22–24].

Why patients with SSc are at higher risk of VTE remain unclear, but it is probably related to chronic inflammation and vasculopathy, as seen in other chronic immune-mediated disorders [6–10]. The propensity of VTE is associated with three essential factors, including hyper-coagulability, endothelial dysfunction, and flow stasis, collectively known as “Virchow triad.” SSc appears to interfere with all of these three factors as chronic inflammation related to autoimmune disorders has been demonstrated to promote the coagulation cascade, inhibit the anticoagulation pathway, and impair the fibrinolytic process, resulting in a thrombophilic state [25–28]. Vasculopathy and endothelial dysfunction, as previously mentioned, are the hallmark of the pathogenesis of SSc [11]. This endothelial dysfunction can be further jeopardized by chronic inflammation as the deleterious effect of inflammatory cytokines and oxidative stress on endothelial cells has also been extensively documented [29,30]. Moreover, patients with SSc may be less active compared with healthy subjects because of the non-cutaneous manifestations of their disease, such as arthritis, interstitial lung disease, and pulmonary arterial hypertension [11,12], rendering them at more risk of venous flow stasis and DVT.

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In conclusion, our meta-analysis demonstrated a statistically significant increased VTE risk among patients with SSc. In light of these findings, further research is needed to elucidate the mechanistic underpinnings and identify potential therapeutic targets.
of high morbidity and mortality associated with DVT and particularly PE, our study suggests that physicians should carefully monitor patients with SSc for VTE, especially those with other conventional risk factors.

**Authors’ contributions**

All authors had access to the data and a role in writing the manuscript.

**Conflict of interest**

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