Review

Risk of venous thromboembolism in patients with Sjögren's syndrome: a systematic review and meta-analysis

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ABSTRACT

Objective. *Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been linked to an increased risk of venous thromboembolism (VTE). However, the data on Sjögren's syndrome (SS) remain unclear. This study aimed to investigate this association.*

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

Results. *Out of 306 potentially relevant articles, four eligible studies were identified and included in the data analysis. The pooled risk ratio of VTE in patients with SS was 2.05 (95% CI, 1.86–2.27). The statistical heterogeneity of this study was insignificant with an I^2 of 0%.*

Conclusion. *Our study demonstrated a statistically significant increased VTE risk among patients with SS.*

Introduction

Venous thromboembolism (VTE) is one of a major medical problem with a significant morbidity and mortality as its reported 30-day mortality rate is as high as 11–30% (1-3). VTE is a common disorder with a reported annual incidence of 1–2 new cases per 1,000 populations (1-2). Deep venous thrombosis (DVT) of lower extremity and pulmonary embolism (PE) are the most common subtype of VTE. Several medical conditions, such as hospitalisation, surgery, malignancy, immobilisation, thrombophilic state and certain medications are well recognised as its risk factors (4, 5). Several immune-mediated disorders, such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathy, psoriasis and systemic vasculitides have been increasingly recognised as predisposing factors for the development of VTE (6-10). Though the mechanisms underlying this association remain unclear, several *in vivo* and *in vitro* studies have suggested that chronic inflammation and vasculopathy might serve as the pathogenic link between these two conditions (7-9).

Sjögren's syndrome (SS) is another chronic inflammatory disorder characterised by lymphocytic infiltration of exocrine glands, leading to impaired function (11). Dryness of the oral cavity and eyes as a result of the salivary and lacrimal glands involvement is the most common manifestation of this disease though a wide variety of other extraglandular manifestations, such as arthritis, interstitial lung disease, vasculitis and neuropathy, are also seen in about one-fourth of patients (12). SS occurs in a primary form and in a secondary form associated with other rheumatic conditions (13, 14).

As seen in other autoimmune diseases, patients with SS have a higher inflammatory burden compared with the general population and might have a higher risk of VTE. However, epidemiological studies yielded conflicting results and, thus, the VTE risk in these patients remain inconclusive (15-18). 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 SS *versus* non-SS participants.

Methods

Search strategy

Two investigators (P.U. and N.S.) independently searched published studies

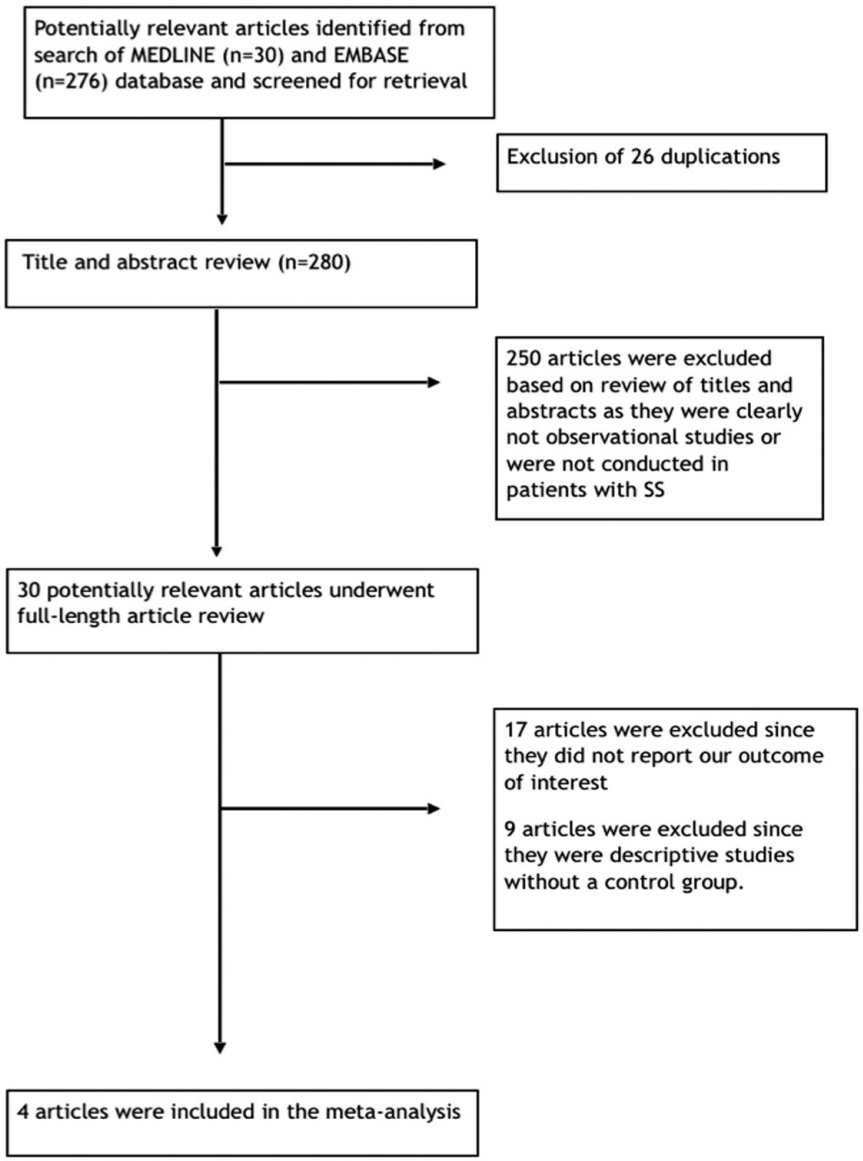

Fig. 1. Search methodology and literature review process.

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 data. References of 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 SS and risk of VTE (2) odds ratios (ORs), relative risk (RRs) or hazard ratio (HRs) or standardised incidence ratio (SIRs) with 95% confidence intervals (CIs) or sufficient data to calculate these ratios were provided, and (3) non-SS 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 noted above. Any differing decisions 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 areas including (1) 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 standardised data collection form was used to extract the following information: title of the article, first author's last name, authors' institution, year of publication, year of study, study population, criteria used for the diagnosis of SS, definition and diagnosis of VTE, average duration of follow-up, number of cases, number of controls, percentage of male and female, 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 standard errors were extracted from each study and was pooled together using the generic inverse variance method of DerSimonian and Laird (20). In light of the high likelihood of between study variance due to the difference in study design, population and the definition of VTE, random-effect model, rather than a fixed-effect model, was used. Statistical heterogeneity was assessed using the Cochran's Q test which is complemented with the I^2 statistic. This statistic quantifies the proportion of the total variation across studies that is due to true heterogeneity rather than chance. A value of I^2 of 0% to 25% represents insignificant heterogeneity, more than 25% but less than or equal to 50% low heterogeneity, more than 50% but less than or equal to 75% moderate heterogeneity, and more than 76% high heterogeneity (21).

Result

Our search strategy yielded 306 potentially relevant articles (30 articles from Medline and 276 articles from EMBASE). After exclusion of 26 duplicated articles, 280 of them underwent title and abstract review. Two hundred and fifty articles were excluded as they

Table I. Characteristics of included studies.

	Ramagopalan *et al*. (15)	Johannesdottir *et al*. (16)	Zoller *et al*. (17)	Chung *et al*. (18)
Country of origin Study design Year of publication	England Retrospective cohort 2011	Denmark Case–control 2012	Sweden Retrospective cohort 2012	Taiwan Retrospective cohort 2014
Cases	All patients who were diagnosed with SS between 1999 and 2008. Cases were identified by using the English National Hospital Episode Statistics. The diagnosis was made by any licensed practitioners in England.	All northern Denmark residences who were diagnosed with DVT and/or PE between 1999 and 2009. Cases were identified from Danish national registry database. The diagnosis was made by any licensed practitioners in Denmark.	All patients who were diagnosed with SS between 1964 and 2008. Cases were identified by using the Swedish national hospital admission database. The diagnosis was made by any licensed practitioners in Sweden.	All patients who were diagnosed with SS between 2000 and 2008. Cases were identified by using Taiwan national health institute research database which covered nearly 100% of the Taiwanese population. The diagnosis was made by any licensed practitioners in Taiwan.
Controls	Hospitalised patient randomly selected from the same database.	Sex and age-matched subjects randomly selected from the same 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).	Sex and age-matched subjects randomly selected from the same database.
Diagnosis of Sjogren syndrome	Diagnostic code from the database.	Diagnostic code from the database.	Diagnostic code from the database.	Diagnostic code from the database.
Diagnosis of VTE	Diagnostic code from the database.	Diagnostic code from the database.	Diagnostic code, confirmed by peer review.	Diagnostic code from the database.
Follow-up	Until death, first record of VTE or 31 March 2008.	N.A.	Until death, first record of PE, emigration or 31 December 2008.	Until first record Of VTE, emigration from the system or 31 December 2010.
Mean age, Y	N.A.	67.0	N.A.	53.5
Woman, %	89.0	52.9	89.9	88.9
Number of cases	12,680	14,721	3,410	8,920
Number of control	12,680	147,210	N.A.	35,680
Confounder assessed	Age, sex and region of residence.	Hospitalisation, classic risk factors (cancer, pregnancy, surgery, trauma), co-morbidities (infection, cardiac disease, COPD, DM, liver disease, obesity, osteoporosis, renal failure) and medications used (HRT, NSAIDs, steroid, vitamin K antagonist, antipsychotics)	Age, sex, hospitalisation and co-morbidity (COPD, obesity, liver disease, coronary heart disease, stroke, HTN, sepsis, varicose vein, PVD, CHF).	Age, sex, hospitalisation and co-morbidity (AF, DM, stroke, CHF, fracture, surgery, pregnancy).
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 3 stars Comparability: 1 star Exposure: 1 star	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars

VTE: indicates venous thromboembolism; PE: pulmonary embolism; DVT: deep venous thrombosis; N.A.: not available; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HRT: hormone replacement therapy; NSAIDs: non-steroidal anti-inflammatory drugs; HTN: hypertension; PVD: peripheral vascular disease; CHF: congestive heart failure; AF: atrial fibrillation.

were clearly not observational studies or were not conducted in patients with SS, leaving 30 articles for a full-length article review. Seventeen of them were excluded since they did not report our outcome of interest (*i.e*. VTE) while nine 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 did not yield any more eligible studies. Therefore, a total of four studies (three retrospective cohort studies and one case-control study) met our inclusion criteria and were included in the data analysis (15-18). Figure 1 outlines our literature search and review process. The main characteristics and the quality assessment (Newcastle-Ottawa scores) of the included studies are illustrated in Table I.

The pooled risk ratio of VTE of subjects with SS *versus* controls was 2.05 (95% CI, 1.86–2.27). The risk ratios from individual study were fairly consistent, ranging from 1.60 to 2.44. The statistical heterogeneity was insignificant with an I^2 of 0%. Figure 2 demonstrates the forest plot of this meta-analysis.

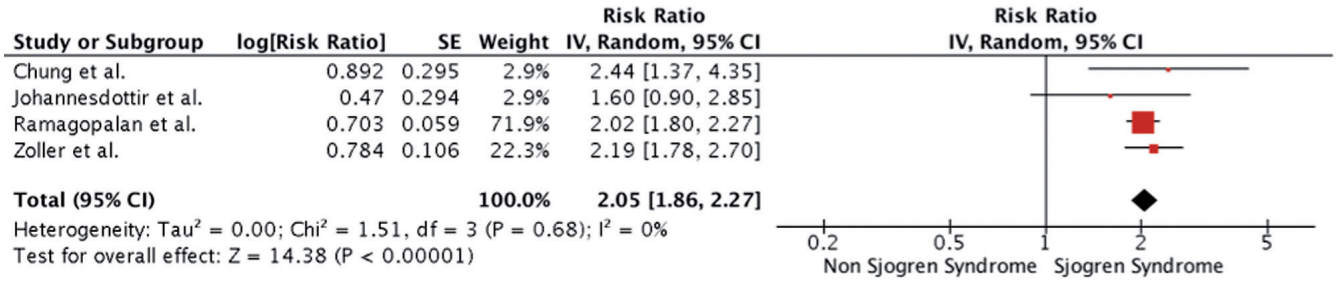

Fig. 2. Forest plot of all included studies.

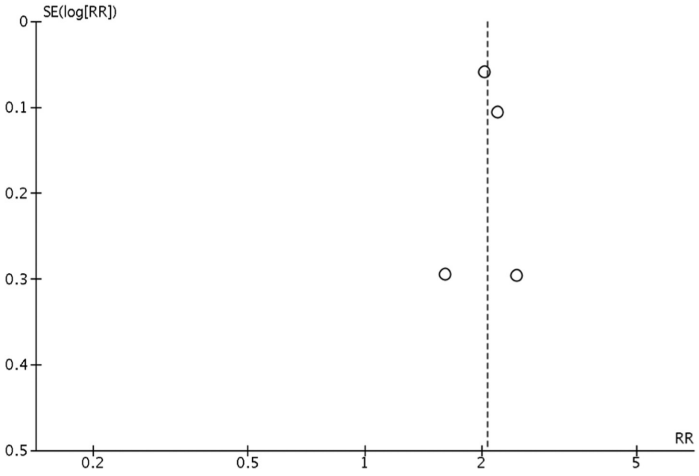

Fig. 3. Funnel plot of all included studies.

To confirm the robustness of our results, we performed jackknife sensitivity analysis by excluding one study at a time (22). The results of this sensitivity analysis suggested that our results were vigorous as the pooled risk ratios remained significantly elevated, ranging from 2.02 to 2.14, with the corresponding 95% CI bounds remained more than one.

Evaluation for publication bias

Funnel plot was used to evaluate for publication. The forest was relatively symmetric and all studies resided within the funnel. Thus, concern for publication bias was low in this meta-analysis. Figure 3 illustrates the funnel plot.

Discussion

Our meta-analysis demonstrated a significant association between SS and VTE with an approximately 2-fold increased risk compared with non-SS participants. The results are in line with a recent meta-analysis that found a higher-than–expected cumulative incidence of VTE in patients with SS (2.18% with 95% CI of 0.79%–3.57%) (23).

Why patients with SS are at higher risk of VTE are not well-understood but probably related to chronic inflammation. The propensity of VTE is associated with three provocative factors, including hyper-coagulability, endothelial dysfunction and venous flow stasis, collectively known as Virchow triad. Chronic inflammation related to autoimmune diseases has been demonstrated to stimulate the coagulation cascade, inhibit the anticoagulation pathway and impair the fibrinolytic process, resulting in a thrombophilic state (24-28). Premature endothelial dysfunction is also seen in patients with SS (29) which is probably a consequence of chronic inflammation as the detrimental effect of inflammatory cytokines and oxidative stress on endothelial cells has also been extensively documented (30, 31). The increased inflammatory burden observed in patients with SS, particularly those who present with systemic form of the disease, might serve as the cornerstone of the increased VTE risk (11, 13). Moreover, patients with SS may be less active compared with general population because of the extra-glandular manifestations of their disease, such as arthritis, interstitial lung disease and neuropathy (13), rendering them at more risk of venous flow stasis and VTE.

Another possible explanation for this increased VTE risk is related to the presence of antiphospholipid antibodies, which are associated with both arterial and venous thrombosis. A recent study had demonstrated that antiphospholipid antibodies were found in up to one-third of patients with primary SS (32).

We do not have any data that assess the influence of treatment of SS on the VTE risk. However, as inflammation is believed to be the cornerstone of this increased risk, we postulate that immunomodulation therapy that could control the disease activity might help lessening the risk.

Supplementary data

Search strategy

Database: Medline

1. Sjögren.mp.
2. exp Sjögren's syndrome/
3. or/1-2
4. exp Thromboembolism/
5. Thromboembolism.mp.
6. exp Venous Thrombosis/
7. venous thrombosis.mp.
8. exp Pulmonary Embolism/
9. pulmonary embolism.mp.
10. or/6-11
11. 3 and 10

Database: EMBASE

1. Sjögren.mp. or
2. exp Sjögren's syndrome/
3. or/1-2
4. pulmonary embolism.mp. or exp lung embolism/
5. deep vein thrombosis.mp. or exp deep vein thrombosis/
6. venous thromboembolism.mp. or exp venous thromboembolism/
7. exp thromboembolism/ or thromboembolism.mp.
8. or/4-7
9. 3 and 8

Even though the included primary studies were of high quality, there were some limitations in this meta-analysis and, thus, our results should be interpreted with caution. First, all of the studies included in this analysis were medical registry-based study which were at potential risk of coding inaccuracy for both SS and VTE. This issue is particularly of concern for this study as several other inflammatory conditions such as IgG-4 related disease could potentially be misdiagnosed as SS. Second, two primary studies included only hospitalised patients, leading to a potential selection bias of more severe cases (15, 17). Nevertheless, it should be noted that the study by Zoller *et al*. (17) found an increased risk even ten years after the admission. Third, the definition of VTE was not completely consistent as the study by Zoller *et al*. (17) included only PE in the outcome measurement while other studies included both DVT and PE. Nonetheless, the sensitivity analysis excluding this study did not significantly alter the result (RR, 2.02; 95% CI, 1.80-2.25). Fourth, this is a meta-analysis of observational studies that, at the best, can only demonstrate an association but cannot establish causality. Therefore, we cannot be certain that SS itself *versus* other potential confounders were responsible for the increased VTE risk. The problem with potential confounders is particularly of concern for this study as SS often occurs in association with other rheumatologic disorders such systemic lupus erythematosus and rheumatoid arthritis which are well-linked to the increased VTE risk (6-10). Furthermore, the increased VTE incidence might merely be a result of detection bias as patients with SS might be exposed more to medical examinations and laboratory testing just because of their chronic illness (33).

In conclusion, our meta-analysis demonstrated a statistically significant increased VTE risk among patients with SS, even though we cannot establish the causality of this association as our study has several limitations. As DVT and PE are associated with high morbidity and mortality, our study suggests that it would be prudent for physicians to carefully monitor patients with SS for VTE, especially those with systemic form of disease.

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