Original Article

Ankylosing spondylitis and risk of venous thromboembolism: A systematic review and meta-analysis

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ABSTRACT

Background: Several immune-mediated inflammatory disorders, such as rheumatoid arthritis, psoriatic arthritis, and systemic lupus erythematosus have been linked to an increased risk of venous thromboembolism (VTE). However, the data on ankylosing spondylitis (AS) are limited. **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 the risk of VTE and possible pulmonary embolism (PE) in patients with AS versus non-AS participants. Pooled risk ratio and 95% confidence intervals were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird. **Results:** Of 423 potentially relevant articles, three studies met our inclusion criteria and thus, were included in the data analysis. The pooled risk ratio of VTE in patients with AS was 1.60 (95% confidence interval: 1.05–2.44). The statistical heterogeneity of this study was high with an I^2 of 93%. **Conclusion:** Our study demonstrated a statistically significant increased VTE risk among patients with AS.

KEY WORDS: Ankylosing spondylitis, epidemiology, meta-analysis, venous thromboembolism

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INTRODUCTION

Venous thromboembolism (VTE) is a common medical problem with a reported annual incidence of 1–2 new cases per 1000 populations in Europe and North America.[1-3] Deep venous thrombosis (DVT) and pulmonary embolism (PE) are its two major subtypes. VTE is associated with a long-term morbidity and mortality with an estimated cumulative incidence of recurrence of 10% at 1 year and 30% at 5 years after the withdrawal of anticoagulation therapy.[4] Several medical comorbidities, such as hospitalization, surgery, cancer, aging, thrombophilic state, and use of certain medications are the well-established risk factors.[5,6]

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Several immune-mediated diseases, such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory myopathy, systemic sclerosis, and psoriasis have been increasingly recognized as predisposing factors for VTE.[7-12] Even though the mechanistic link between these disorders and VTE is not fully understood, several studies have suggested that chronic inflammation might be the major player for the increased VTE tendency.[13,14]

Ankylosing spondylitis (AS), one of the most common subtype of seronegative spondyloarthritis, is a chronic systemic arthritis characterized by enthesitis and axial joint involvement. AS typically affects young males with the peak incidence between 20 and 30 years old and

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male-to-female ratio of 3–1.[15,16] Nonmechanical back pain and progressive stiffness of the spine are the hallmarks of the disease through the involvement of peripheral joints can be seen as well. Extra-articular manifestations, such as uveitis, could be seen in about one-fourth of patients with AS.[17]

In light of the higher inflammatory burden, patients with AS might be at an increased risk of venous thrombosis as seen in other autoimmune disorders. In fact, a recent meta-analysis has demonstrated that patients with AS have a higher risk of arterial thrombosis (i.e., coronary artery disease).[18] Nevertheless, the epidemiological data on VTE risk in this group of the patient is limited. Therefore, to further investigate this possible association, we conducted a systematic review and meta-analysis of population-based studies that compared the VTE risk in patients with AS versus non-AS participants.

METHODS

Search strategy

Two investigators (PU and NS) independently searched published studies indexed in MEDLINE and EMBASE from inception to March 2015 using the search terms described in the supplementary material without any language restriction. References of selected articles were also manually searched [Supplementary Table 1].

Inclusion criteria

The studies were eligible for this meta-analysis if they met these inclusion criteria: (1) Cohort (either prospective or retrospective) or case–control study published as original study to evaluate the association between AS and risk of VTE, (2) odds ratios, relative risk, hazard ratio, and standardized incidence ratio with 95% confidence intervals (CIs) or sufficient raw data to calculate these ratios were provided, and (3) participants without AS and participants without VTE were used as the reference group for cohort study and case–control study, respectively.

Study eligibility was independently evaluated by the two investigators noted above. The quality of each study was also independently appraised, using the 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 the cohort study. The review process was overseen the third investigator (WK) who resolved any different decisions between the first two investigators.

Data extraction

A standardized data collection form were used to extract the following information: Title of the article, first author's last name, year of publication, year of study, country where the study was conducted, criteria used for the diagnosis of AS, definition of VTE, methods used to identify cases and controls, number of cases, number of controls, percentage of male and female, average age of participants, assessed confounders, and adjusted effect estimates with 95% CI. This data extraction was independently conducted by the two investigators. Any data discrepancy was jointly examined by all investigators by referring to the original studies.

Statistical analysis

All statistical analyses were conducted using Review Manager 5.3 software (London, United Kingdom) from the Cochrane collaboration. Point estimates and their 95% CI were extracted from each study and were 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. Cochran's Q-test, which is complemented with the I^2 statistic, was used to evaluate the statistical heterogeneity. This I^2 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 ≤50% represents low heterogeneity, more than 50% but ≤75% represents moderate heterogeneity, and more than 75% represents high heterogeneity.[21]

RESULTS

Our search strategy yielded 423 potentially relevant articles (73 articles from MEDLINE and 350 articles from EMBASE). After the exclusion of 70 duplicated articles, 353 of them underwent title and abstract review. Two-hundred and seventy articles were excluded since they were case report, letter to editor, review article or interventional study; while 51 articles were excluded since they were not conducted in patients with AS, leaving 32 articles for a full-length article review. Twenty of them were excluded since they did not report our outcome of interest (VTE) while nine articles were excluded since they were descriptive studies without a control group. Therefore, a total of three studies (two retrospective cohort studies and one case–control study) met our inclusion criteria and were included in the data analysis.[22-24] Figure 1 outlines our literature review and selection process. The main characteristics and the quality assessment of the included studies are described in Table 1.

We found a statistically significantly elevated VTE risk among subjects with AS compared with non-AS controls with the risk ratio of 1.60 (95% CI: 1.05–2.44). The risk ratios from individual study varied from 1.16 to 1.93. The statistical heterogeneity was high with an I^2 of 93%. Figure 2 demonstrates the forest plot of this meta-analysis.

Evaluation for publication bias

Since only three primary studies were included in this meta-analysis, an evaluation for publication bias was not performed.

DISCUSSION

Our meta-analysis demonstrated a significant association between AS and VTE with an overall 1.6-folds (95% CI, 1.05–2.44) increased risk compared with non-AS participants.

Why patients with AS are at a higher risk of VTE is a subject for debate but appears to be related to a higher inflammatory burden as seen in other autoimmune disorders.[7-12] Inflammatory cytokines, such as interleukin-6, interleukin-8, and tumor necrosis factor-alpha, have been demonstrated to promote the coagulation cascade, inhibit the anticoagulation pathway and impair the fibrinolytic process, resulting in a thrombophilic state.[25-27] Furthermore, the oxidative stress from chronic inflammation is known to cause a deleterious effect on endothelial cells.[26,28] These thrombophilic state and endothelial dysfunction are two of the three Virchow's triad[5] that could well serve as the fundamental pathophysiology of the increased clotting tendency.

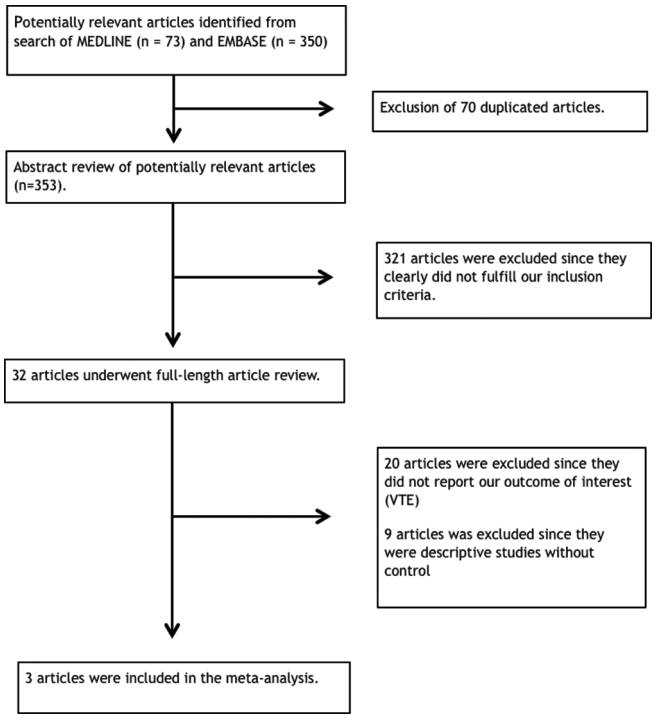

Figure 1: Outline of our search methodology and study selection

Moreover, patients with AS, because of their arthritis and joint immobility, may be less active compared with healthy subjects, rendering them at a higher risk of venous flow stasis, another risk factor for clot formation in the Virchow's triad.

Even though our search methodology was vigorous and the primary studies included in this analysis were of high quality, we acknowledged that there were some limitations. Therefore, our results should be interpreted with caution. First, all of the included studies were medical registry-based study which was at risk of coding inaccuracy and incompleteness for both AS and VTE. In fact, the study by Zöller *et al*.[24] was the only study that confirmed the accuracy of diagnosis of VTE by chart review, while the other two studies relied exclusively on the database's diagnostic codes. Second, statistical heterogeneity was high in this meta-analysis. We suspect that the difference in population, study design, and definition of VTE (the studies by Ramagopalan *et al*.[22] and Johannesdottir *et al*.[23] included both DVT and PE while the study by Zöller included only patients with PE) were responsible for

Table 1: Main characteristics of included studies

	Ramagopalan *et al*.[22]	Johannesdottir *et al*.[23]	Zöller *et al*.[24]
Country of origin	England	Denmark	Sweden
Study design	Retrospective cohort	Case-control	Retrospective cohort
Year of publication	2011	2012	2012
Cases	All patients who were diagnosed with AS between 1999 and 2008. Cases were identified by the English National Hospital Episode Statistics	All northern Denmark residences who were diagnosed with DVT and/or PE between 1999 and 2009. Cases were identified from Danish national registry database	All patients who were diagnosed with AS between 1964 and 2008. Cases were identified by the Swedish national hospital admission database
Controls	Hospitalized patient randomly selected from the same database	Sex- and age-matched subjects randomly selected from the same database	General Swedish population was used as reference to calculate age, sex, period, and socioeconomic status-specific standardized incidence ratio
Diagnosis of AS	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
Follow-up	Until death, first record of DVT and/or PE or March 31, 2008	NA	Until death, the first record of PE, emigration or December 31, 2008
Mean age of cases, Y	NA	67.0	NA
Woman, %	29.0	52.9	27.3
Number of cases	22,001	14,721	9498
Number of control	22,001	147,210	NA
Confounder assessed	Age, sex, and region of residence	Hospitalization, comorbidity, and medications used	Age, sex, hospitalization, and comorbidity
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

AS: Ankylosing spondylitis, NA: Not available, DVT: Deep vein thrombosis, PE: Pulmonary embolism

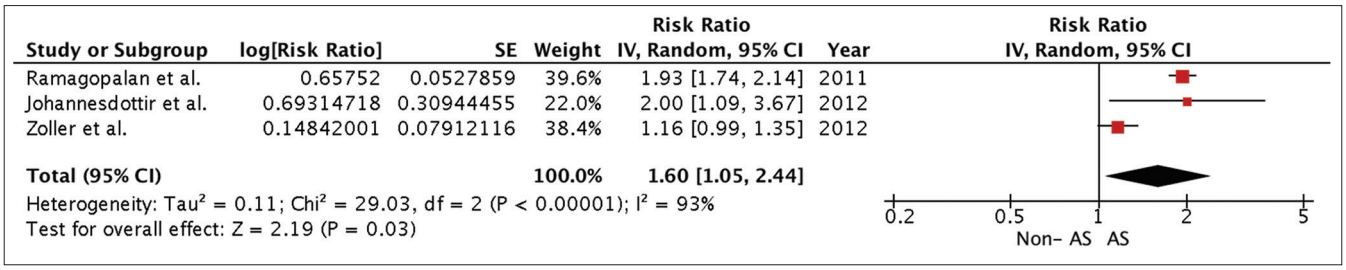

Figure 2: Funnel plot of all included studies

this. Third, this is a meta-analysis of observational studies that can only illustrate an association but cannot establish causalty. Several potential confounders, such as smoking and medications, rather than the disease itself, might be accountable for the increased VTE risk. Furthermore, detection bias might also play a role as patients with AS may have more medical examinations and laboratory investigations just because of their chronic illness.[29]

CONCLUSION

Our meta-analysis demonstrated a statistically significant increased VTE risk among patients with AS. In light of high morbidity and mortality associated with VTE, our study suggests that it would be prudent for physicians to carefully monitor patients with AS for VTE, especially those with other conventional risk factors.

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Conflicts of interest
There are no conflicts of interest.

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