Psoriasis and risk of venous thromboembolism: a systematic review and meta-analysis

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Summary

Background: Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, have been shown to increase venous thromboembolism (VTE) risk but the data on psoriasis is 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 VTE risk in patients with psoriasis vs. non-psoriasis participants. Pooled risk ratio and 95% confidence intervals were calculated using a random effect, generic inverse variance method.

Result: Four studies were identified and included in our data analysis. The pooled risk ratio of VTE in patients with psoriasis was 1.46 (95% CI, 1.29–1.66). The statistical heterogeneity of this meta-analysis was high with an I² of 86%.

Conclusion: Our study demonstrated a statistically significant increased VTE risk among patients with psoriasis.

Introduction

Deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), are common medical problems with a reported annual incidence of 1–2 new cases per 1000 populations.¹ ² Recognition of their risk factors and appropriate preventive interventions are vital as their reported mortality is as high as 11–30% in the first 30 days.¹ ³–⁵ Several medical conditions, such as immobilization, surgery/trauma, cancer and thrombophilia are well recognized as risk factors for VTE.

Chronic inflammation, though is not generally regarded as a traditional risk factor for VTE, might increase the risk of developing VTE as inflammatory cytokines have been demonstrated to modulate the coagulation cascade by up-regulating procoagulants and down-regulating antiocoagulant and fibrinolytic systems.⁴ Moreover, several chronic inflammatory diseases, including systemic lupus erythematosus, rheumatoid arthritis and systemic vasculitis, have
been shown to increase VTE risk in large epidemiologic studies.\textsuperscript{5,6}

While there are an extensive amount of studies confirming the increased cardiovascular morbidity and mortality in patients with psoriasis, one of the most common chronic cutaneous inflammatory disorder affecting \textsuperscript{\textasciitilde}2\% of population,\textsuperscript{7,8} the data on VTE risk is still limited. Several recent studies demonstrated an increased VTE risk among these patients though the results were fairly heterogeneous among the studies. Thus, to obtain a more accurate and precise estimated effect, we conducted a systematic review and meta-analysis of observational studies that compared the VTE risk in patients with psoriasis vs. non-psoriasis participants.

**Method**

**Search strategy**

Two investigators (P.U. and A.S.) independently searched published studies indexed in MEDLINE, EMBASE, Cochrane database and Google Scholar from inception to December 2013 using the terms ‘pulmonary embolism,’ ‘deep venous thrombosis’ and ‘venous thromboembolism’ combined with the term ‘psoriasis’ and ‘psoriatic arthritis’. A manual search of references of selected retrieved articles was also performed. Abstract and unpublished studies were not included. Detailed search strategy is available as online supplementary data.

**Inclusion criteria**

The inclusion criteria were as follows: (i) observational studies (case-control, cross-sectional or cohort studies) published as original studies to evaluate the association between psoriasis and risk of VTE, DVT or PE; (ii) odds ratios (OR’s), relative risk (RR’s) or hazard ratio (HR’s) or standardized incidence ratio (SIR’s) with 95\% confidence intervals (CI’s) were provided; and (iii) random non-psoriasis participants were used as the reference group.

Study eligibility was independently determined by each investigator noted above. Differing decisions were resolved by consensus with the senior investigator. The quality of each study was independently evaluated by each investigator using Newcastle–Ottawa quality assessment scale.\textsuperscript{9}

**Data extraction**

A standardized data collection form was used to extract the following information: last name of the first author, title of the article, year of publication, country where the study was conducted, year of publication, study size, study population, method used for the verification of psoriasis and VTE, mean duration of follow up and adjusted effect

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**Figure 1.** Outline of our search methodology.
Table 1: Main characteristics of cohort studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Year</th>
<th>Cases</th>
<th>Diagnosis of psoriasis</th>
<th>Controls</th>
<th>Follow up</th>
<th>Mean age, Y</th>
<th>Woman, %</th>
<th>Number of cases</th>
<th>Number of control</th>
<th>Average range of follow up, Y</th>
<th>Confounder assessed</th>
<th>Quality assessment (Newcastle–Ottawa scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>Retrospective cohort</td>
<td>2011</td>
<td>All patients who were diagnosed with psoriasis between 1999 and 2008. Cases were identified by using the English National Hospital Episode Statistics.</td>
<td>Diagnostic code from the registry.</td>
<td>Hospitalized patient randomly selected from the same database.</td>
<td>Until death, first record of VTE or 31 March 2008.</td>
<td>N/A</td>
<td>48.0</td>
<td>85     358</td>
<td>85     358</td>
<td>N/A</td>
<td>Age, sex, region of residence.</td>
<td>Selection: 3 stars</td>
</tr>
<tr>
<td>Denmark</td>
<td>Retrospective cohort</td>
<td>2011</td>
<td>All patients who were diagnosed with psoriasis between 1997 and 2006. Cases were identified by using the Danish national registry.</td>
<td>Diagnostic code from the registry + prescription for topical vitamin-D derivatives.</td>
<td>The rest of the subjects in the registry.</td>
<td>Until first record of VTE or 31 December 2006.</td>
<td>47.7</td>
<td>50.0</td>
<td>35     138</td>
<td>4       126 075</td>
<td>5.0</td>
<td>None</td>
<td>Selection: 4 stars</td>
</tr>
<tr>
<td>USA</td>
<td>Retrospective cohort</td>
<td>2012</td>
<td>All patients who were diagnosed with psoriasis between 1991 and 2004. Cases were identified by using The Iowa Women’s Health Study which includes 38 608 women age 65–84.6 years in the state of Iowa. This cohort is linked to Medicare database.</td>
<td>Diagnostic code from the Medicare database.</td>
<td>The rest of the subjects in the cohort.</td>
<td>Until death, first record of VTE or December 2004.</td>
<td>68.1</td>
<td>100.0</td>
<td>859</td>
<td>37     749</td>
<td>N/A</td>
<td>Education, smoking, BMI, DM, HRT use.</td>
<td>Selection: 4 stars</td>
</tr>
<tr>
<td>Sweden</td>
<td>Retrospective cohort</td>
<td>2012</td>
<td>All patients who were diagnosed with psoriasis between 1964 and 2008. Cases were identified by using the Swedish national registry.</td>
<td>Diagnostic code from the registry.</td>
<td>The rest of the subjects in the registry.</td>
<td>Until death, first record of PE, emigration or 31 December 2008.</td>
<td>N/A</td>
<td>47.2</td>
<td>25     869</td>
<td>N/A</td>
<td>N/A</td>
<td>Sex, age, hospitalization, COPD, obesity, alcohol use, CAD, stroke, hypertension, varicose vein, sepsis, CHF, PVD.</td>
<td>Selection: 4 stars</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; N/A, not available; PE, pulmonary embolism; BMI, body mass index; DM, diabetes mellitus; HRT, hormone replacement therapy; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; PVD, peripheral vascular disease.
estimates with 95% CI. The two investigators independently performed this data extraction.

**Statistical analysis**

Review Manager 5.2 software from the Cochrane Collaboration was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance with the different study designs and populations, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran’s Q test. This statistic is complemented with the $I^2$ statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of $I^2$ of 0–25% represents insignificant heterogeneity, 25–50% low heterogeneity, 50–75% moderate heterogeneity and 75–100% high heterogeneity.

**Result**

Our search strategy yielded 114 potentially relevant articles. One hundred and four articles were excluded as they were not observational studies or were not conducted in patients with psoriasis. Ten articles underwent full-length article review. Five of them were excluded since they did not report our outcome of interest (VTE) while one study was excluded because of potential patient duplication with another study. Four studies (all are retrospective cohort studies) with 147,224 patients with psoriasis met our inclusion criteria and were included in the data analysis. Figure 1 outlines our search methodology and selection process. The detailed characteristics and quality assessment of the included studies are described in Table 1.

The pooled risk ratio of VTE of subjects with psoriasis vs. control subjects was 1.46 (95% CI, 1.29–1.66). The statistical heterogeneity was high with an $I^2$ of 86%. Figure 2 demonstrates the forest plot of this study.

Since only four studies were included in this meta-analysis, the evaluation for publication bias was not performed.

**Discussion**

Our meta-analysis demonstrated a significant association between psoriasis and VTE with an overall 1.46-folds (95% CI 1.29–1.66) increased risk compared with non-psoriasis participants. The risk ratios were fairly consistent across the studies, ranging from 1.35 to 1.66.

Heterogeneity between studies was present in this meta-analysis. We suspect that the difference in populations was the main source of this heterogeneity.

Why patients with psoriasis have a higher risk of VTE compared with non-psoriasis subjects are unclear. The occurrence of VTE is associated with three determinative factors, known as Virchow triad, including hypercoagulability, endothelial injury and venous stasis. Chronic inflammation related to autoimmune disorders has been demonstrated to promote the coagulation cascade, impair the anticoagulation pathway and inhibit the fibrinolytic process. Endothelial dysfunction in patient with psoriasis has also been extensively documented. Moreover, methotrexate, one of the most commonly used medication in psoriasis, is associated with hyperhomocysteinemia, which is a well-established risk factor for thrombophilia.

Even though the four included studies were of relatively high quality, there are some limitations and, thus, the result should be interpreted with caution. First, all of the included studies were conducted using medical registry-based database thus the possibility of coding inaccuracy. Second, statistical heterogeneity is high in this meta-analysis. Third, this is a meta-analysis of observational studies which, at best, can demonstrate an association but cannot establish cause and effect. Therefore, we cannot be certain that psoriasis itself vs. other potential confounders cause the increased VTE risk.
Furthermore, the higher detection rate of VTE in patients with psoriasis might be partly due to the fact that they have chronic illness and, thus, are exposed more to medical community.

In conclusion, our meta-analysis demonstrated a statistically significant increased VTE risk among patients with psoriasis. As VTE confers a high morbidity and mortality, our study suggests that physicians should carefully monitor patients with psoriasis for VTE, especially those with other traditional risk factors.

Disclosure

None.

Supplementary material

Supplementary material is available at QIMED online.

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

Conflict of interest: None declared.

References


