

Risk of venous thromboembolism in patients with bullous pemphigoid: A systematic review and meta-analysis

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Abstract

Background and Objectives: Increased risk of venous thromboembolism is observed in several autoimmune inflammatory disorders. However, data on bullous pemphigoid, one of the most common autoimmune blistering disorders, is limited. This systematic review and meta-analysis was conducted to summarize all available evidence.

Methods: Two investigators independently searched published studies indexed in MEDLINE and EMBASE from inception to July 2016 using the terms for bullous pemphigoid and venous thromboembolism. The inclusion criteria were as follows: (1) cohort or case-control study evaluated the association between bullous pemphigoid and risk of venous thromboembolism, (2) effect estimates were provided as odds ratios, relative risk, hazard ratio, standardized incidence ratio with 95% confidence intervals, and (3) subjects without bullous pemphigoid were used as comparators for cohort studies, while subjects without venous thromboembolism were used as comparators for case-control studies. Point estimates and 95% confidence intervals were extracted from each study and were pooled together using the random-effect model, generic inverse variance method of DerSimonian and Laird. Cochran's Q test and the I² statistic were used to evaluate the statistical heterogeneity.

Results: Two retrospective cohort studies, one prospective cohort study, and one case-control study met the eligibility criteria and were included in the meta-analysis. The pooled odds ratio was 2.69 (95% confidence interval, 1.79–4.05). Statistical heterogeneity was high with I² of 77%.

Limitation: Limited accuracy of diagnosis of primary studies and high between-study heterogeneity.

Conclusion: This meta-analysis demonstrated that patients with bullous pemphigoid have a significantly increased risk of venous thromboembolism.

Key words: Bullous, meta-analysis as topic, pemphigoid, venous thromboembolism

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Introduction

Deep venous thrombosis and pulmonary embolism, collectively known as venous thromboembolism, are common medical conditions with an estimated incidence of 1–2 incident cases per 1,000 population per year.^{1–3} Despite advances in diagnosis and treatment, patients with venous thromboembolism continue to have significant morbidity and mortality, with a one year all-cause mortality as high as 24 percent.⁴ Traditional risk factors for venous thromboembolism include cancer, hospitalization, surgery, trauma,

aging, inherited hypercoagulability, and use of hormonal therapy including oral contraceptive pills.^{5,6}

Over the past years, chronic inflammation has been increasingly recognized as a non-traditional risk factor of venous thromboembolism. Several epidemiologic studies have revealed an increased risk of both deep venous thrombosis and pulmonary

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embolism among patients with autoimmune disorders, such as systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and systemic vasculitis.^{7–11} The ability of inflammatory cytokines to stimulate the coagulation cascade appears to play a major role in the predisposition towards thrombogenesis among these patients.¹²

Bullous pemphigoid (BP) is defined as an autoimmune blistering disorder, characterized by the presence of autoantibodies binding against two specific structural proteins of the dermal-epidermal junction including bullous pemphigoid antigen 180 (BP180) and bullous pemphigoid antigen 230 (BP230).¹³ Patients with BP usually present with urticarial erythema and tense blisters on the trunk and extremities. Mucosal involvement is observed in 10–20% of cases. The incidence of bullous pemphigoid ranges from 5 to 60 new cases per million per year with the peak incidence observed in the seventh and eighth decade of life.¹⁴

Similar to other autoimmune inflammatory disorders, BP may increase the risk of venous thromboembolism. However, epidemiological data on this association is still limited. This systematic review and meta-analysis was conducted with the attempt to summarize all available studies that compared the venous thromboembolism risk in patients with bullous pemphigoid versus subjects without bullous pemphigoid.

Methods

Search strategy

All investigators independently searched published studies indexed in MEDLINE and EMBASE from inception to July 2016 using the search strategy that comprised of terms for venous thromboembolism and bullous pemphigoid as described in the Supplementary Material 1. No language limitation was applied. Bibliography of included studies and selected review articles were also manually searched for additional studies.

Inclusion criteria

Studies were included in this meta-analysis if they met the following inclusion criteria: (1) cohort (either prospective or retrospective) or case-control study that evaluated the association between BP and risk of venous thromboembolism, (2) effect estimates were provided as odds ratios, relative risk, hazard ratio, standardized incidence ratio with 95% confidence intervals, and (3) subjects without BP were used as comparators for cohort studies, while subjects without venous thromboembolism were used as comparators for case-control studies.

Study eligibility was independently evaluated by the two investigators (P.U. and K.W.). The third investigator (C.T.) served as the deciding vote when disagreement between the first two investigators arose. Newcastle–Ottawa scale was used to evaluate the methodological quality of the included studies.¹⁵ This scale assessed the study in three areas including: (1) the representativeness of the subjects, (2) the comparability between the study groups, and (3) the quality of methods used to ascertain the exposure of interest for case-control studies and the outcome of interest for cohort studies.

Data extraction

The two investigators independently extracted the following data from each study: title of the article, first author's name, year of publication, year when the study was conducted, country of origin, methods used to identify bullous pemphigoid and venous

thromboembolism, number of subjects in each group, demographic data of the subjects (age, sex, and ethnicity), confounders that were assessed and adjusted effect estimates with 95% confidence intervals from multivariate model. A standardized data collection form was used to facilitate this process.

Statistical analysis

Point estimates and 95% confidence intervals were extracted from each study and were pooled together using the random-effect model, generic inverse variance method described by DerSimonian and Laird.¹⁶ We elected not to use fixed-effect model in view of possible high inter-study variance. As the outcome of interest was relatively uncommon, relative risk and hazard ratio of cohort studies was used as an estimate to combine with odds ratio of case-control studies. Cochran's Q test, which is complemented with the I² statistic, was used to evaluate the statistical heterogeneity. This I² statistic quantifies the proportion of the total variation across studies that is due to true heterogeneity rather than chance. A value of I² of 0% to 25% represents insignificant heterogeneity, >25% but <50% represents low heterogeneity, >50% but <75% represents moderate heterogeneity, and >75% represents high heterogeneity.¹⁷ We planned to assess for publication bias by visualizing the funnel plots. All statistical analyses were conducted using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom).

Results

The search strategy yielded 124 potentially relevant articles (9 articles from Medline and 115 articles from EMBASE). After the exclusion of 9 duplicated articles, 115 of them underwent title and abstract review. Ninety-five articles were excluded at this stage as they clearly did not meet inclusion criteria based on the type of article (they were case reports, correspondences, review articles, basic science/animal studies or randomized controlled trials), leaving 20 articles for full-length article review. After full-length review, 16 articles were excluded because they were descriptive studies without comparators or did not report the outcome of interest (venous thromboembolism). Four articles met the inclusion criteria and were included in the meta-analysis.^{18–21} Manual review of the included studies and some selected review articles did not yield additional eligible studies. Figure 1 summarizes the literature review and identification process. The main characteristics and the Newcastle–Ottawa scores of the included studies are summarized in Table 1.

The included articles consisted of two retrospective cohort studies, one prospective cohort study, and one case-control study. All studies were conducted in Europe (England, Italy, and Denmark). All but one study were medical registry-based studies that relied on diagnostic codes for identification and verification of the events of interest.

This meta-analysis found a significantly increased risk of venous thromboembolism among patients with bullous pemphigoid with the pooled odds ratio from the four studies of 2.69 (95% confidence interval, 1.79–4.05). However, the statistical heterogeneity was high with I² of 77%. Figure 2 demonstrates the forest plot of this meta-analysis.

Sensitivity analysis

To confirm the robustness of the pooled results, jack-knife sensitivity analysis, which excluded one study from the meta-analysis at a time

was performed. The pooled odds ratio from this sensitivity analysis changed slightly from the complete analysis, ranged from 2.22 to 3.01 and remained statistically significant. It should be noted that the pooled sensitivity analysis, excluding the only case-control study by Johannesdottir *et al.*,²⁰ was 2.96 (95% confidence interval, 1.83–4.80), which was not significantly different from the complete analysis.

Interestingly, the I^2 of the sensitivity analysis that excluded the study by Cugno *et al.*²¹ was zero, indicating that this study was the major source of the between study variance. Nonetheless, the pooled effect estimate of the sensitivity analysis excluding the study by Cugno *et al.* was not significantly different from the complete analysis with the pooled odds ratio of 2.22 (95% confidence interval, 2.00–2.46).

Evaluation for publication bias

Evaluation for publication bias by visualization of funnel plot was not performed as only four studies were included in this meta-analysis, which would prevent meaningful interpretation of the plot.

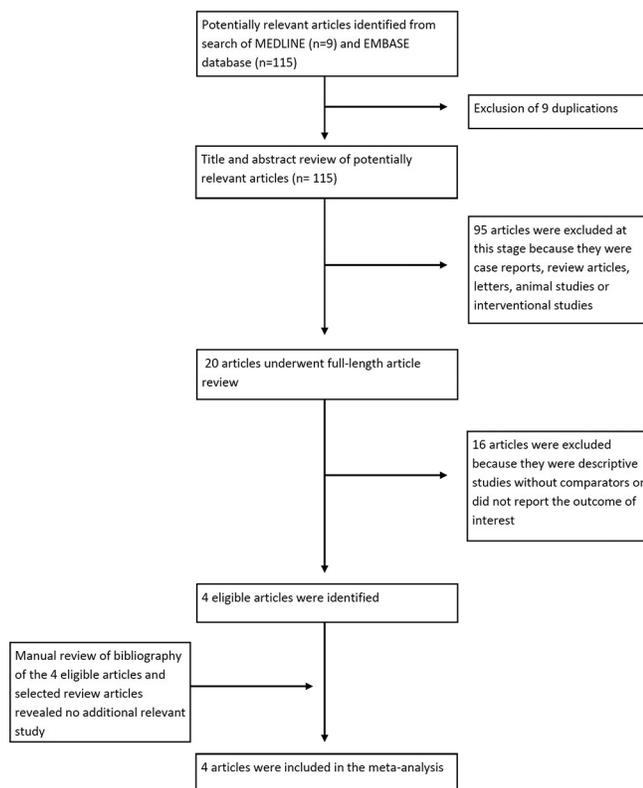


Figure 1: Literature review and study selection process

Discussion

The current study is the first systematic review and meta-analysis that summarizes all available studies on the association between venous thromboembolism and bullous pemphigoid. We found a 2.69-fold increased risk of venous thromboembolism among patients with bullous pemphigoid. The results are in line with previous studies that observed approximately 1.5 to 4-fold increased risk of venous thromboembolism among patients with systemic autoimmune disorders.^{19,22}

Chronic inflammation is the common feature of systemic autoimmune disorders and therefore most likely the key element in perpetuating endothelial dysfunction and promoting a thrombophilic state among these conditions. Specific mechanisms by which this occurs in each autoimmune disease may vary based on their predominant molecular pathogenesis. However, common underlying mechanisms of inflammation-induced thrombosis include upregulation of coagulation factors, downregulation of anticoagulants, and decreased fibrinolysis by inflammatory cytokines as well as injury to endothelial cells by oxidative stress.^{12,23} Further support that inflammation plays a key role in the development of venous thromboembolism is the higher proportion of events occurring at the time of diagnosis or soon after diagnosis of autoimmune diseases,^{22,24,25} as well as the higher incidence of venous thromboembolism with active disease compared with inactive disease.^{26,27}

The increased risk of venous thromboembolism among patients with bullous pemphigoid may have implications on clinical practice. Physicians should have a higher index of suspicion for deep venous thrombosis/pulmonary embolism in patients with bullous pemphigoid who present with leg swelling, leg pain, or respiratory symptoms. Prophylactic anticoagulation may be indicated in patients with bullous pemphigoid, particularly those with other traditional venous thromboembolism risk factors such as malignancy or when they were hospitalized. However, further prospective studies are required to determine the role of venous thromboembolism prevention among these patients.

Limitations

Even though the literature review process was rigorous and the quality of the included studies was high as reflected in the high Newcastle-Ottawa scores, we acknowledge that there are some limitations. Firstly, most of the included studies were medical registry-based studies, with the exception of the study by Cugno *et al.*²¹, which are inherently at risk of inaccurate and incomplete coding for both bullous pemphigoid and venous thromboembolism. Secondly, statistical heterogeneity was high in this study. Interestingly, the I^2 dropped dramatically to 0% with the sensitivity

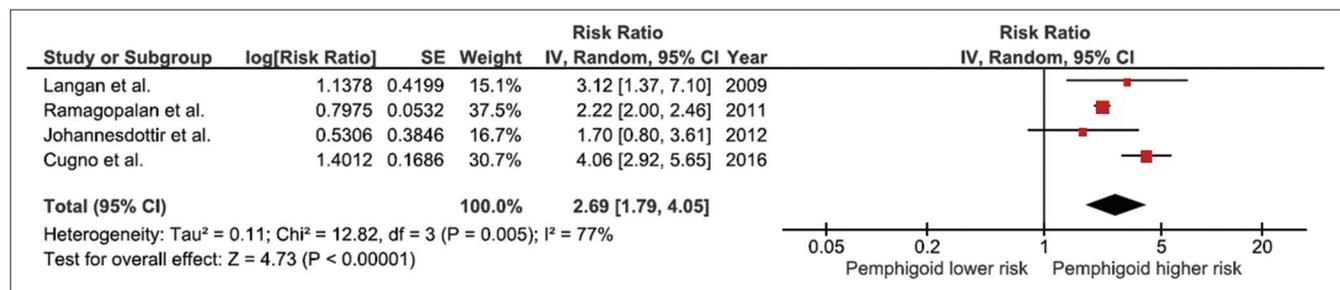


Figure 2: Forest plot of all included studies

Table 1: Main characteristics of the included studies

Characteristics	Langan <i>et al.</i> ¹⁸	Ramagopalan <i>et al.</i> ¹⁹	Johannesdottir <i>et al.</i> ²⁰	Cugno <i>et al.</i> ²¹
Country	England	England	Denmark	Italy
Study design	Retrospective cohort	Retrospective cohort	Case-control	Prospective cohort
Year	2009	2011	2012	2016
Cases	All patients with diagnosis of BP between 1996 and 2006 who were identified from the health improvement network database, which covered 328 general practices across England	All patients with diagnosis of BP between 1999 and 2008 who were identified from the English National Hospital Episode Statistics	All patients with diagnosis of VTE between 1980 and 2010 who were identified from the Danish National Patient Registry	Consecutive patients with BP seen at 11 study centers from January 2006-2011
Comparators/controls	Sex and age matched comparators without BP were randomly selected from the same database	All hospitalized patients without a diagnosis of any autoimmune diseases identified from the same database	Sex and age matched controls without VTE were randomly selected from Danish Civil Registration System	Expected VTE rates in general population (age and sex adjusted) were used to calculate SIRs
Diagnosis of BP	Diagnostic code from the database	Diagnostic code from the database	Diagnostic codes from the database	Clinical+histopathological+immunopathologic criteria
Definition of VTE	PE	DVT and/or PE	DVT and/or PE	DVT and/or PE
Diagnosis of VTE	Diagnostic code from the database	Diagnostic code from the database	Diagnostic code from the database	Medical interview, medical record review and appropriate diagnostic work-up
Follow up	NA	Until death, first record of VTE or March 31, 2008	NA	Subjects were followed monthly for 3 months then on clinical ground. Average follow up was 4.2 years
Number of cases	868	11,480	14,721	432
Number of comparators/controls	3469	3,707,315	147,210	NA
Mean age for cases and comparators/controls (years)	80.0/79.0	NA	67.0/67.0	76.0/NA
Percentage of female for cases and comparators/controls	62.0/62.0	57.0/41.0	52.9/52.9	59.3/NA
Confounder adjusted for	Age, sex, and Charlson index	Age, sex, and region of residence	Age, sex, and co-morbidity	Age, sex, and co-morbidity
Quality assessment (Newcastle–Ottawa scale)	Selection: 3 stars Comparability: 2 stars Outcome: 3 stars	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 3 stars Comparability: 2 stars Outcome: 3 stars	Selection: 3 stars Comparability: 1 star Outcome: 3 stars

BP: Bullous pemphigoid, VTE: Venous thromboembolism, PE: Pulmonary embolism, DVT: Deep venous thrombosis, NA: Not available, SIR: Standardized incidence ratio

analysis that excluded the study by Cugno *et al.*²¹ We suspect that the difference in study methodology was responsible for this high heterogeneity, as Cugno *et al.*'s study was the only one that was not medical registry based, and confirmed the diagnosis of BP and venous thromboembolism by office visits and medical record reviews. However, the pooled odds ratio of the sensitivity analysis, excluding the study by Cugno *et al.*, was not significantly different from the complete analysis. Similarly, exclusion of the only case-control study²⁰ did not significantly alter the pooled result. Thirdly, this is a meta-analysis of observational studies that can only demonstrate an association but cannot determine causality. It is possible that confounders that were not adjusted in the primary studies, rather than bullous pemphigoid itself, are responsible for the increased tendency of venous thromboembolism. In particular, none of the included studies adjusted their effect estimates for glucocorticoid

exposure, a known risk factor for venous thromboembolism.²⁸ Lastly, surveillance bias may also play a role. It is possible that patients with BP may have more investigations performed on them, including imaging studies because they have more visits to medical providers because of their chronic illness. Therefore, interpretation of the findings of this meta-analysis needs to be performed with caution.

Conclusion

In conclusion, this meta-analysis demonstrated a statistically significant increased venous thromboembolism risk among patients with bullous pemphigoid. How this risk should be addressed in clinical practice remains unclear and requires further investigation.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Material

Supplementary Material 1: Search strategy

EMBASE

1. bullous pemphigoid.mp. or exp bullous pemphigoid
2. exp pemphigoid/or pemphigoid.mp.
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

Medline

1. exp Thromboembolism
2. Thromboembolism.mp.
3. exp Venous Thrombosis
4. venous thrombosis.mp.
5. exp Pulmonary Embolism
6. pulmonary embolism.mp.
7. or/1-6
8. bullous pemphigoid.mp. or exp Pemphigoid, Bullous
9. pemphigoid.mp.
10. or/8-9
11. 7 and 10