Venous thromboembolism in bullous pemphigoid: current evidence from an updated systematic review

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Abstract

Various studies have shown that individuals with bullous pemphigoid (BP) are more likely to develop venous thromboembolism (VTE). However, it is important to acknowledge that these studies primarily focused on individuals in Western nations, which restricts their generalization to a wider demographic. The present systematic review aims to assess the cumulative risk of VTE in individuals with BP compared to healthy individuals. PubMed, Cochrane, and Scopus databases were searched for evidence-based research papers on BP and VTE. Eligibility criteria were based on the PICOS criteria (population, intervention, comparison, outcome, and study design). The Newcastle-Ottawa scale assessed methodological quality. After database searches, 115 studies meeting the inclusion criteria were identified. A manual inquiry yielded an additional 11 articles. After removing duplicates (n=54), 72 publications underwent title and abstract evaluation, resulting in the exclusion of 44 manuscripts. Consequently, the remaining full-text articles were thoroughly reviewed, and ultimately, 9 publications were included. The studies were conducted in Denmark, the USA, the UK, Taiwan, and Italy. The findings enhanced the generalizability of the correlation between VTE and BP. Individuals with systemic autoimmune diseases were found to have a 1.5 to 4 times higher likelihood of developing VTE. The analysis revealed that patients with pemphigus face a twofold higher risk of VTE, especially within the first few years after diagnosis. These results may enhance the recognition of pulmonary embolism in BP patients and motivate the prevention of secondary risk markers associated with VTE. Given the morbidity, the VTE risk in BP patients warrants greater attention in public healthcare.

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Introduction

The well-known autoimmune condition known as bullous pemphigoid (BP) mainly affects the elderly. The prevalence of BP ranges from 5 to 60 new cases per million people annually, with the highest occurrence in individuals over 70 years of age.[1] The condition is distinguished by widespread itchy hives and tight blisters beneath the skin surface.[2] It is defined by the existence of IgG autoantibodies that circulate in the body and target BP180 and BP230, which are proteins found in hemidesmosomes responsible for maintaining the interface between the dermis and epidermis layers of the skin. BP180 antibodies have demonstrated their potential for pathogenesis by initiating an inflammatory pathway that results in tissue destruction and, eventually, the production of blisters beneath the epidermis.[3] The typical clinical presentation is the development of many extensive tension blisters that result in wet erosions and skin scabs upon bursting. Intense pruritus is a prominent characteristic of BP. Mucosal participation is evident in 10% to 20% of instances. Therefore, it significantly impairs quality of life.[4]

Venous thromboembolism (VTE) is the occurrence of blood emboli in the veins, including deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a multifaceted condition with multiple factors involved, and its underlying causes are poorly understood.[5,6] Nevertheless, it is well recognized that risk markers such as genetic, acquired, and environmental components may play a role in a portion of Virchow's triad, traditionally employed to elucidate the pathogenesis of venous thrombosis. The triad and their respective anomalies comprise the stasis of blood flow, hypercoagulability, and vascular endothelial damage.[5] Immune modifications and inflammation of blood vessels are also recognized to have a crucial impact on the formation of blood clots and

the development of VTE.[6] When comparing the general population to those with a BP diagnosis, there was a threefold spike in the frequency of pulmonary embolism.[7] A recent study established that individuals with BP have a 2.69-times higher risk of developing VTE.[4] As a frequent characteristic of systemic autoimmune diseases, long-lasting inflammation is presumably the primary factor responsible for maintaining a dysfunctional endothelial system and encouraging a thrombophilic condition.[4,5] The specific pathways through which this unfolds in any autoimmune disease may differ depending on their underlying molecular etiology. Additionally, oxidative damage can cause disruption to endothelial tissues. Moreover, individuals with active disease who receive Janus kinase (JAK) inhibitors exhibited a greater prevalence of VTE.[4] Professionals should use prudence while utilizing novel medications, such as JAK inhibitors, for the management of autoimmune blistering diseases due to the potential elevation in the likelihood of VTE in these individuals.[8] The accentuated susceptibility to VTE in individuals with BP could impact clinical procedures. Prophylactic anticoagulation may be recommended for individuals with BP, especially if they have additional VTE risk indicators such as malignancy or a recent history of hospitalization.[4,9]

Various studies have shown that individuals with BP have a higher likelihood of developing VTE. However, it is important to acknowledge that these studies primarily focused on individuals in Western nations, which restricts their generalization to a wider demographic.[6] The present systematic review was conducted to determine the cumulative risk of VTE in individuals with BP in comparison with healthy individuals.

Materials and Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards, a framework for selecting, synthesizing, and reporting study results.[10]

The PubMed, Cochrane, and Scopus databases were utilized to conduct a comprehensive search of empirical research on BP and VTE published between January 2009 and October 2023.

After conducting a preliminary review of the available literature, the following combination of Medical Subject Headings (MeSH) terms was used: ("bullous pemphigoid" OR "autoimmune diseases" OR "autoimmune bullous diseases" OR "blistering disorders" OR "venous thromboembolism" OR "pulmonary embolism" OR "deep vein thrombosis" OR "immune-mediated inflammatory diseases" OR "inflammatory skin diseases" OR "impaired fibrinolysis" OR "systemic autoimmune diseases") AND ("ELISA" OR "direct immunofluorescence" OR "recombinant proteins") AND ("subepidermal blisters" OR "thromboprophylaxis" OR "hypercoagulability" OR "dermo-epidermal junction" OR "hemidesmosomes"). A manual search of the citations for each of the listed publications was conducted to identify research that was not identified from the electronic databases. The screening process was concluded based on predetermined criteria.

The authors separately assessed the titles and abstracts of all papers. Publications that did not satisfy the specified eligibility criteria were eliminated from consideration. The chosen full-text papers were subsequently evaluated and analyzed. Furthermore, in the reference lists of the selected studies, relevant published articles were also sought. Disputes were addressed through the process of deliberation among the reviewers. In cases when the two reviewers could not reach an agreement, a third reviewer was brought in to make the decisive judgment. The ultimate conclusion was unequivocally established by all the evaluators involved.

The Newcastle-Ottawa scale was used to assess the methodological quality of the included studies.[11] The three domains evaluated were the inclusiveness of the participants, the comparability of the study groups, and the integrity of the research methods employed to determine the exposure of interest for case-control and the outcome of interest for cohort studies. Responses of superior quality are assigned a star, with a maximum of nine stars possible (the comparability domain can earn up to two stars). A study with a rating of seven or higher is generally considered to be of excellent quality.

A total of 115 studies that met the criteria for inclusion were identified (Figure 1). The manual search resulted in the retrieval of 11 articles. After eliminating duplicate entries (n=54), 72 publications were chosen for assessment after reviewing the title and abstract. As a consequence, 44 papers were excluded. Thus, 34 full-text publications were examined. Following the full-text screening process, 19 papers were excluded due to discrepancies between their conclusions and the established results of the study. Thus, a total of 9 publications[7,12-21] were included in the current systematic review (*Supplementary Table 1*).

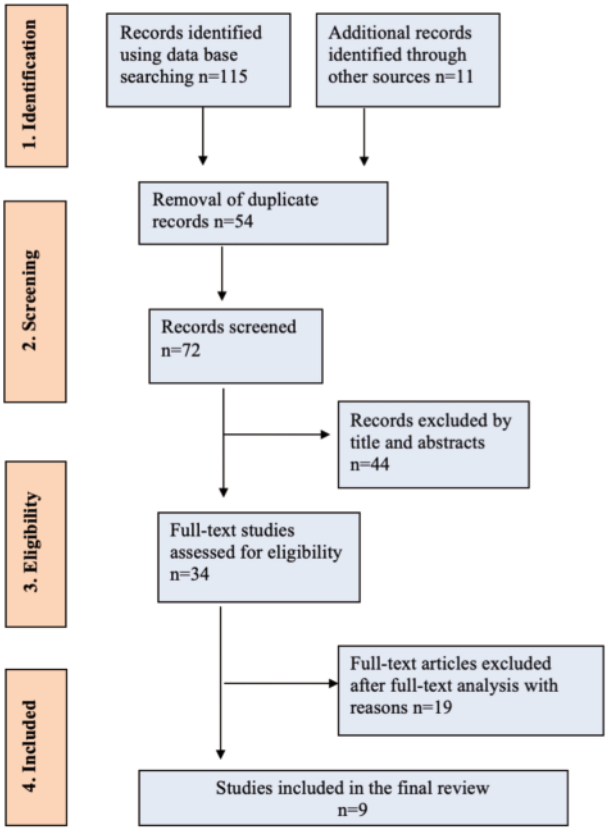

Figure 1. PRISMA flow chart of the included studies (Adapted from Preferred Reporting Items for Systematic Reviews and Meta-analyses 2009 Flow Diagram).

Results

The heightened risk of VTE in individuals with BP was also verified using a meta-analysis of cohort studies.[12] A contemporary study conducted by Chen *et al.* found that the likelihood of VTE surged by a factor of 2.02 within one year of experiencing BP during the first year. When the patient was monitored for two years, the risk was reduced to 1.73 times.[14] Chen *et al.* also observed a comparable result in their extensive population-centered longitudinal analysis. They also noted that the likelihood of pemphigus was highly reported in the first year after diagnosis and gradually declined over time, becoming of unremarkable significance. The multicenter cohort study conducted by Cugno *et al.*[18] demonstrated a fourfold escalation in the probability of developing VTE in individuals with BP in contrast to individuals of similar age and gender in the general community. Specifically, during the acute stage of the illness, the risk of VTE could rise 15-fold. In an extensive study conducted by Schneeweiss *et al.*,[13] a total of 2,654 patients diagnosed with BP and 26,814 participants in the comparison group were considered. The study reported a twofold higher likelihood of clinical VTE occurrences in individuals with BP matched to identical patients without the condition.

A population-based case-control study, reported in Denmark by Johannesdottir *et al.*,[20] aimed to identify individuals with a history of hospitalization for autoimmune disease. The study found that those with autoimmune conditions had a comorbidity-adjusted information ratio (IR) of 1.7 for VTE compared to individuals without autoimmune disorders. Langan *et al.*[7] found that those with BP were three times more at risk of developing PE in contrast to the control group in a British repository. However, DVT was not considered in their study. Various processes have been suggested to elucidate the correlation between BP and blood coagulation. Marzano *et al.*[19] reported that subjects with active BP exhibited decreased fibrinolysis and elevated levels of coagulation biomarkers in either blister fluid or plasma specimens. Ramagopalan *et al.*[21] conducted a study in England to examine the correlation between VTE and various immune-mediated conditions. The study analyzed data from two distinctive databases and found that autoimmune bullous conditions, such as BP, disclosed a VTE ratio of 2.22 to 3.28. Nevertheless, this study examined patients with BP and exclusively enrolled those who were hospitalized for the management of autoimmune disorders. Shaheen *et al.*,[15] established that adult patients admitted to the hospital with atopic dermatitis and pemphigoid have a higher likelihood of developing VTE, which includes DVT and PE. The observed relationships were statistically significant in both genders, spanning across almost all age categories. These relationships remained consistent regardless of whether individuals had a primary or secondary diagnosis of DVT and PE, and regardless of their long-term use of glucocorticoids. However, these associations lacked statistical significance when VTE was the primary diagnosis. These findings concur with earlier research[21] that showed higher risks of VTE among individuals with pemphigus and pemphigoid. The comprehensive report of the outcome variables from the reviewed studies is presented in *Supplementary Table 2*. All of the studies analyzed had a high level of evidence, as assessed using the Newcastle-Ottawa scale (Table 1).

Table 1. Quality assessment tool of the reviewed studies using the Newcastle-Ottawa scale.

	Chen *et al.*, 2023[12]	Schneeweiss *et al.*, 2023[13]	Chen *et al.*, 2022[14]	Shaheen *et al.*, 2021[15]	Cugno *et al.*, 2016[18]	Marzano *et al.*, 2013[19]	Johannesdottir *et al.*, 2012[20]	Ramagopalan *et al.*, 2011[21]	Langan *et al.*, 2009[7]
Representativeness of the exposed cohort	*	*	*	*	*	*	*	*	*
Selection of the nonexposed cohort	*	*	*	*	*	*	*	*	*
Exposure ascertainment	*	*	*	*	*	*	*	*	*
Briefing of outcome of interest was not present during the study commencement	*	*	*	*	*	*	*	*	*
Comparability of cohorts based on the study design or analysis controlled for confounders	**	*	**	**	**	**	**	**	**
Outcome assessment	*	*	*	*	*	*	*	*	*
Was the duration of follow-up adequate for the occurrence of the outcomes	*	*	*	-	*	-	-	*	-
Adequacy of follow-up	*	*	*	-	*	-	-	*	-
Total score	9	8	9	7	9	7	7	9	7

Discussion

The present systematic review provided a comprehensive summary of all existing studies from various populations to foster

the generalizability of our findings on the correlation between VTE and BP. The findings were in agreement with prior research that reported a likelihood of VTE that is roughly 1.5 to 4 times higher in individuals with systemic autoimmune diseases.[21,22] The results of our review expanded the generalizability of prior research by providing detailed, pragmatic information about the risk of VTE among individuals with BP. An earlier meta-analysis conducted in 2018 examined the correlation between BP and VTE and found a strong positive relation.[4]

A cross-sectional study found a positive relationship between BP and VTE, with an odds ratio (OR) of 1.64 (95% confidence interval [CI]: 1.47-1.83). Additionally, plasma viscosity and VTE had a positive relationship, with an OR of 1.96 (95% CI: 1.68-2.28).[15] The temporal link, however, remained elusive for the authors. Furthermore, numerous cohort studies have examined the likelihood of VTE in individuals with BP.[16,18,21,23] Yet another retrospective cohort analysis indicated that BP is a significant risk component for VTE, with a hazard ratio (HR) of 2.02 and a 95% CI of 1.01-4.06.[24] In contrast to that study, Chen *et al.*[12] evaluated the risk of VTE in pemphigus and used meta-analysis to organize all the information that was published. They found that individuals with BP have a significantly higher risk of developing VTE. This was demonstrated in a study that found an HR of 1.85 (95% CI: 1.52-2.24; P<0.001) for incident VTE in patients with BP. Asians had a lower occurrence of VTE, and the use of thromboprophylaxis in Asia was not fully utilized. In addition to genetic variations, individuals who are older, have cancer, experience or undergo surgeries are frequently found to have an elevated risk of VTE. Moreover, various other medical conditions, such as cardiovascular, renal, hepatic, and chronic obstructive pulmonary diseases, have been identified as risk indicators for VTE.[14]

Several autoimmune skin diseases are associated with an increased risk of blood clotting, with BP presenting a particularly significant risk.[5] BP has been linked to a higher risk of VTE; however, the precise timeline remains uncertain.[25] Podolec-Rubiś *et al.*[26] documented another instance of pemphigoid gestationis in a woman who was pregnant for the first time. The management of this condition was complicated by the suspicion of a PE. The condition is primarily characterized by the presence of IgG1 immunoglobulin, which circulates in the body and targets specific proteins, such as BP180 (BPAG2) type XVII collagen or BP230. IgG adherence to the basement membrane results in the development of subepidermal bullae and vesicles. Pemphigoid gestationis is genetically associated with HLA-DR3 in 80% of individuals and HLA-DR4 in 53% of subjects. Additionally, 43-50% of individuals exhibit both *MHC II* genes. The histological examination reveals the presence of a blister beneath the epidermis, swelling in the dermis, and infiltration of eosinophils, lymphocytes, and histiocytes around the blood vessels.[26]

Although the majority of the conducted studies established a positive relationship between BP and VTE, two studies have indicated that BP may be an insignificant risk variable for VTE.[20,27] This study found no link between autoimmune skin diseases and VTE (incidence rate ratio [IRR] 1.0; 95% CI: 0.9-1.2). However, individuals with connective tissue diseases had a higher risk of VTE, especially within the first year after diagnosis. Among these diseases, juvenile rheumatoid arthritis and systemic lupus erythematosus showed the highest increases in risk.[20] Another study reached similar findings, as among 94 patients who died from skin diseases such as pemphigoid, 15% experienced VTE, and 8.5% of those with VTE subsequently developed PE.[27]

Chronic inflammation is the characteristic shared by systemic autoimmune illnesses. It is presumably the primary factor in maintaining endothelial dysfunctions and causing a state of increased blood clotting in these situations. Furthermore, oxidative damage can cause disruption to endothelial cells.[28,29] Additional evidence supporting the involvement of inflammation in VTE is the greater occurrence of these events during or shortly after the diagnosis of autoimmune conditions.[22,30] Furthermore, there is a greater frequency of VTE in individuals with active disease compared to those with inactive disease.[31,32]

While the precise process remains incompletely understood, other investigations have provided molecular evidence that supports our findings. Coagulation pathways have been reported to be activated in subjects with BP.[33] Individuals with BP had significantly elevated levels of serum indicators for thrombin production (plasma prothrombin fragments F1+2) and fibrin breakdown (D-dimer) compared to the control group.[34,35] Moreover, it was observed that individuals with BP exhibited elevated levels of various proinflammatory cytokines. This indicates that BP can be classified as an autoimmune disorder characterized by widespread inflammation.[36-38] Type 2 inflammation is considered to initiate the production of autoantibodies in BP.[39] Individuals with BP had higher concentrations of interleukin (IL-4, IL-5, and IL-13) in their serum, blister fluid, and skin biopsy tissues.[40] These mediators may also contribute to the development of VTE.[41] The soluble E-selectin and vascular endothelial growth factor in BP were also correlated with the concentrations of circulating autoantibodies, indicating the connection between activated endothelium inflammation and immunological responses.[42] Eosinophils present in BP are also thought to play a role in activating blood clotting at the skin level.[43] Additionally, antiphospholipid antibodies have been identified in individuals diagnosed with BP.[44,45] Antiphospholipid antibodies are a diverse set of antibodies that can cause a state of increased blood clotting and are associated with the occurrence of blood clots.[45] Prophylactic anticoagulation may be necessary for individuals with BP, especially if they have additional VTE risk indicators, including cancer or recent hospitalization.[16] Nevertheless, additional prospective trials are necessary to ascertain the impact of VTE prophylaxis in the sample population.[4] Glucocorticoids are used as the initial treatment option because they quickly produce therapeutic benefits and alleviate the acute episode. However, prolonged use may result in significant negative consequences that surpass the advantages. Therefore, it is necessary to implement additional supplementary treatments to reduce the potential damage and improve the quality of life.[46]

The capacity to produce monoclonal antibodies that may selectively target certain disease mediators has greatly transformed the treatment of numerous autoimmune illnesses. Rituximab and other anti-CD20 antibodies can eliminate B cells that produce autoantibodies. The combination of rituximab and short-term systemic corticosteroids is currently regarded as the primary therapeutic approach.[47] Rituximab therapy has shown promising results in treating BP. Studies have reported significant reductions in autoantibodies (anti-BP180 and anti-BP230), disease activity, and the need for steroid medications following rituximab treatment.[48] For instance, a retrospective study found that 75% of BP patients achieved remission after an average of 169 days of rituximab treatment, indicating its potential efficacy. Furthermore, this study suggests that rituximab can be a relatively safe treatment option for BP patients.[17]

Additional research is warranted to specifically evaluate the effect of rituximab on the risk of VTE in patients with BP.[49] The elevated likelihood of VTE may be attributed to unadjusted confounding factors in the primary investigations rather than BP itself. In particular, neither of the studies analyzed in this review accounted for the impact of glucocorticoid administration on the estimated effects, even though it is a recognized risk component

for VTE.[50] The diagnoses of BP and VTE were mainly determined using International Classification of Diseases (ICD) codes. Despite the stated strong positive predictive values, misclassification bias was inherent in the validation of the codes.[51] Additionally, it is imperative to exercise prudence when interpreting the systematic review and meta-analysis findings. Nevertheless, the need to manage this risk in clinical procedures remains uncertain and warrants further research.

Conclusions

This systematic review provides compelling evidence of a significantly increased risk of VTE in patients with BP, with a roughly twofold higher incidence compared to the general population. While observational studies can only demonstrate an association, the consistent findings across multiple studies strongly suggest a clinically relevant link. However, it is crucial to acknowledge the limitations of these studies, particularly the potential for unmeasured confounding factors, such as the impact of glucocorticoid use. Further research, including well-designed prospective studies, is necessary to confirm this association and investigate the underlying mechanisms. Despite these limitations, the findings of this review have important clinical implications. Healthcare providers should be vigilant for VTE in patients with BP, especially within the first few years after diagnosis. Risk stratification and the implementation of appropriate prophylactic measures, such as anticoagulation in high-risk individuals, should be considered.

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Online Supplementary Material:

Supplementary Table 1. General characteristics of the reviewed studies.
Supplementary Table 2. Outcome measures of the reviewed studies.