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Venous thromboembolism in bullous pemphigoid: current evidence and update on 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. 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 examined. Following full-text screening, 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, VTE risk in BP patients warrants greater attention in public healthcare.

Introduction

The well-known autoimmune condition known as bullous pemphigoid (BP) mainly affects the elderly. The prevalence of BP varies between 5 and 60 new cases per million people annually, exhibiting the highest occurrence in individuals above 70 years of age.[1] The condition is distinguished by widespread itchy hives and tight blisters beneath the skin surface.[2] This condition 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 three-fold spike in the frequency of pulmonary embolism.[7] A recent study established that individuals with BP have a 2.69-times elevated 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 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 recent history of hospitalization.[4,9]

Various studies have shown that individuals with BP had 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 employed to perform a comprehensive search on empirical research on the BP and VTE published between January 2009 and October 2023. After conducting an initial review of the available literature, the following Medical Subject Headings (MeSH) phrase combination was used: (“bullous pemphigoid” or “autoimmune diseases” or “autoimmune bullous disease” or "blistering disorder” 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 disease”) and ("ELISA" or "direct immunofluorescence" or “recombinant proteins”) and ("subepithelial 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 chosen studies, relevant published articles were also looked for. 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 (NOS) was employed to determine the methodological quality of the studies that were included.[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[7,12-15,18-21] were included in the current systematic review (Table 1).

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 upon diagnosis and gradually declined with time until turning into unremarkable significance. The multicenter cohort study conducted by Cugno *et al.*[18] demonstrated a four-fold 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 up to 15 folds. 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 IR ratio 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 some patients with BP, and exclusively enrolled patients 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 held true regardless of the extent to which the individuals had the primary or secondary diagnoses of DVT and PE and regardless of their long-term usage 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 Table 2.

All of the studies analyzed had a high level of evidence, as assessed using the Newcastle-Ottawa scale (Table 3).

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 offering detailed pragmatic information about the risk of VTE among those 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 OR of 1.64 (95% 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.[16,18,21,24] Yet another retrospective cohort analysis indicated that BP is a significant risk component for VTE, with an HR of 2.02 and a 95% CI of 1.01 to 4.06.[25] 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. He found individuals with bullous pemphigoid (BP) have a significantly higher risk of developing venous thromboembolism (VTE). This was demonstrated in a study that found a hazard ratio (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. In addition, various other medical conditions such as cardiovascular, renal, hepatic, and chronic obstructive pulmonary diseases have been identified as risk indicators for VTE.[14]

A number of autoimmune skin diseases have a higher likelihood of developing blood clotting, with BP presenting a significant risk.[5] Bullous pemphigoid (BP) has been linked to a higher risk of venous thromboembolism (VTE); however, the precise timeline remains uncertain.[26] Podolec-Rubiś *et al.*[27] 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 mostly characterized by the presence of IgG1 immunoglobulin that circulates in the body and targets certain 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.[27]

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.[20,23] This study found no link between autoimmune skin diseases and venous thromboembolism (VTE) (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 risk increases.[20] Another study

reached similar findings, as among 94 patients who died from skin diseases such as pemphigoid, 15% experienced venous thromboembolism (VTE), and 8.5% of those with VTE subsequently developed pulmonary embolism (PE).[23]

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] Additionally, there is a greater frequency of VTE in individuals with active disease contrasted to those with inactive disease.[31,32]

While the precise process remains incompletely comprehended, other investigations have offered molecular indications that strengthen 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) contrasted 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 prospective 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 have the ability to 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 bullous pemphigoid (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] 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. Specifically, neither of the studies analyzed in this review accounted for the impact of glucocorticoid administration on the estimated effects despite the fact that it is a recognized risk component for VTE.[50] The diagnoses of BP and VTE were mostly determined using 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 is still uncertain and warrants additional research.

Conclusions

This systematic review provides compelling evidence of a significantly increased risk of venous thromboembolism (VTE) in patients with bullous pemphigoid (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's 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 appropriate prophylactic measures, such as anticoagulation in high-risk individuals, should be considered.

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

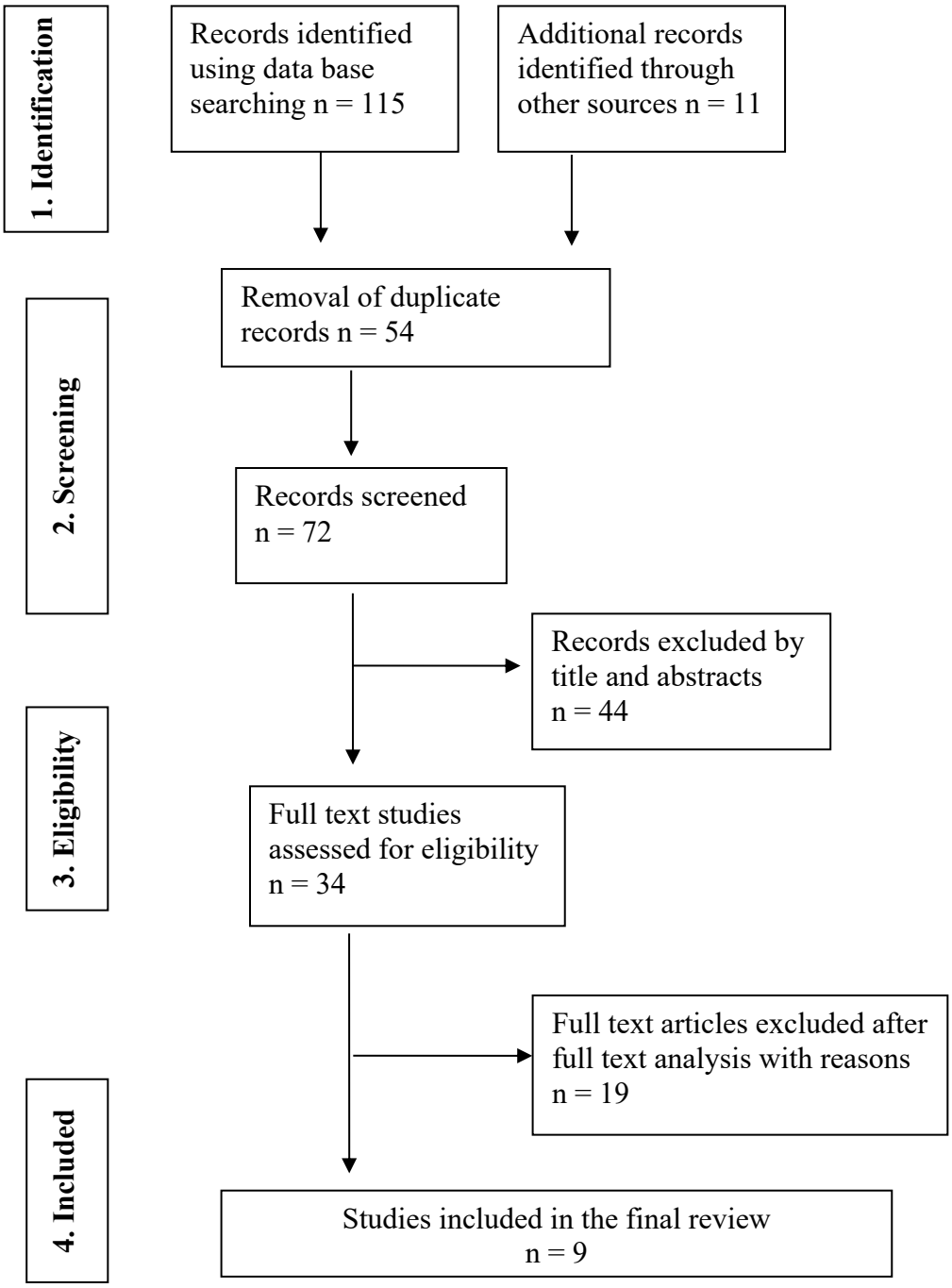

Table 1. General characteristics of the reviewed studies.

Author-Year	Country	Design	Cases	Controls	Sample size of cases and controls	Mean age of cases / controls	M/F % of in cases and controls	Diagnosis of BP	Definition of VTE	Diagnosis of VTE	Confounder adjusted for	Follow up duration
Chen et al., 2023[1,2]	Taiwan	Nation-wide Cohort study	Adults with PV or BP from Taiwan's NHIRD between 2001 and 2017	Unexposed cohort from the same database	Cases: 12162 Controls: 12162	Cases: 74.4 Controls: 75.5	Cases: 52.57/47.43 Controls: 52.11/47.89	Diagnostic code from the database	DVT and PE	Diagnostic code from the database	Age and sex-matched	Till 2018
Schneeweiss et al., 2023[13]	USA	Nation-wide Cohort study	BP patient identified from nationwide US health care between 2004 and 2020	Healthy patients without BP from the same database	Cases: 2654 Controls: 26814	Cases: 73 Controls: 55	Cases: 44.3/55.7 Controls: 43.4/56.6	Diagnostic code from the database	DVT and PE	Diagnostic code from the database	Propensity-score matching	2 years
Chen et al., 2022[14]	Taiwan	Nation-wide population-based	Adults diagnosed with BP from the	Adults without BP from	Cases: 12692 of BP	Cases: 80.3 Controls: 80.2	Cases: 54.1/45.9 Controls: 54.1/45.9	Diagnostic code from the database	DVT and PE	Diagnostic code from the database	Age, gender, and comorbidities	2 years

		Cohort study	NHIRD-MOHW in Taiwan between 2007 and 2018	the same data base								
Shaheen et al., 2021[15]	USA	Hospital-based case control study	Cases from NIS database between 2002 and 2012	Subjects with inflammatory skin diseases such as atopic dermatitis, psoriasis, pemphigus, pemphigoid and/or hidradenitis supurativa	459 BP cases 1,003,322 subjects without BP	Above 18 years	With BP: 3.6/3.3 Without BP: 1.6/1.2	Diagnostic code from the database	DVT and PE	Diagnostic code from the database	age, gender, insurance, income, ethnicity, hospitalization matched	NR
Cugno et al., 2016[18]	Italy	Cohort	Consecutive BP patients from 11	Age and gender-matched VTE rates	Cases: 432 Controls: NR	76/NR	Cases: 40.7/59.3 Controls: NR	Clinical, histopathological, and	PE and / or DVT	Medical interview, medical	Age, sex, and comorbidities	4.2 years

			centers between 2006 and 2011	in the general population				immunopathological criteria		record review and appropriate diagnostic work-up		
Marzano et al., 2013[19]	Italy	Case control	Consecutive patients with previously untreated active BP from tertiary care hospital from 2010 to 2011	age- and sex-matched apparently healthy subjects	Cases: 20 Controls: 20	76/75	Cases: 50/50 Controls: 50/50	Clinical and immunopathological Criteria	Greater levels of PAI-1 activity and t-PA antigen	Plasma levels of PAI-1 antigen	Age- and sex-matched	NR
Johannesdottir et al., 2012[20]	Denmark	Population-based case control	VTE diagnosed between 1980 and 2010, identified from the DNPR	Matched controls from DCRS	Cases: 14721 Controls: 147210	67/67	Cases: 47.1/52.9 Controls: 47.1/52.9	Diagnostic code from the database	PE and / or DVT	Diagnostic code from the database	Age, sex, and comorbidities	NR
Ramagopalan	UK	Population-based cohort	Patients with BP diagnosed between 1999	Matched controls from the	ORLS 1: 313716	NR	ORLS1: 53/47	Diagnostic code from	PE and / or DVT	Diagnostic code from the database	Age, sex, and resident area	Until death, first record of

et al., 2011[21]			and 2008 from the ORLS 1, ORLS 2, and NHES	same data set	ORLS2: 187,609 NHES: 3,707,315		ORLS2: 54/46 NHES: 59/41	the database				VTE or for a period of 10 years
Langan et al., 2009[7]	UK	Population-based cohort	BP patients diagnosed between 1996 and 2006, from the HIN database, including 328 general practices	Matched controls from the HIN database	Cases: 868 Controls: 3469	80/79 (median)	Cases: 38/62 Controls: 38/62	Diagnostic code from the database	PE	Diagnostic code from the database	Age, sex, and Charlson index	NR

BP, bullous pemphigoid; VTE, venous thromboembolism; NHIRD, National Health Insurance Research Database; NHIRD-MOHW, National Health Insurance Research Database, Ministry of Health and Welfare; DCRS, Danish Civil Registration System; ORLS, Oxford Record Linkage Study; NIS, Nationwide Inpatient Sample; CHS, Clalit Healthcare Services; NHES, National Hospital Episode Statistics; DVT, Deep vein thrombosis; PAI-1, plasminogen activator inhibitor type 1; t-PA, tissue plasminogen activator; DNPR, Danish National Patient Registry; HIN, health improvement network; NR, not reported.

Table 2. Outcome measures of the reviewed studies.

Author-Year	Outcome measures
Chen et al., 2023[12]	In contrast to the control group, individuals with BP or PV had a greater threat of developing VTE (HR of 1.87; p<0.001). The IR of VTE was 6.47 and 2.20 per 1000 person-years in the BP and PV groups, respectively. The risk of developing VTE substantially heightened in individuals with BP (HR of 1.85; p<0.001) and PV (HR of 1.99; p=0.04).
Schneeweiss et al., 2023[13]	The IR of VTE in individuals with evidence of treatment, was 8.5 cases per 1000 person-years in individuals with CISD, relative to 1.8 cases in individuals without CISD. This indicates a 5-fold higher chance of VTE in individuals with CISD, as determined by an unadjusted hazard ratio of 4.85; 95% CI = 3.60-6.55). Following a 1:1 propensity score matching procedure, 60 VTE risk and severity markers were accounted for BP and were significantly linked with a twofold elevated risk of VTE (adjusted HR = 2.24) contrasted to individuals in the non-CISD category.
Chen et al., 2022[14]	The BP group (0.17%) had a substantially elevated IR of VTE (2.02 times) than the non-BP group (0.08%) (p=0.015) in the first year following diagnosis. BP was a primary risk factor for VTE (HR=2.02) which showed a decline in the strength of association during the follow-up period to 2 years (HR=1.73; p<0.05). Other risk factors include cancer, chronic hepatic diseases, and females.
Shaheen et al., 2021[15]	The multivariable logistic regression models comprising of age, gender, income, insurance, ethnicity, and hospitalization for atopic dermatitis (adjusted OR=1.22), pemphigus (1.96), and pemphigoid (1.64) were associated with VTE.
Cugno et al., 2016[18]	The IR of VTE per 1000 patient-years was 17.2 overall, 56.7 during the acute stage (22 VTE), and 6.3 during remission (9 VTE). The standardized IRR was 4.06, which was greater during the acute stage than during

	remission (1.48). The adjusted HR of VTE was 2.74 for ABSIS > 48 against ABSIS < 28, and 2.56 among those with more than two concurrent risk variables.
Marzano et al., 2013[19]	The BP patients with active conditions (25.06±8·88 ng/mL and 15.65±5.75 ng/mL) had markedly greater PAI-1 antigen and active PAI-1 than the controls (10.04 ± 7.80 ng/mL and 7.25 ± 5.49 ng/mL) (p=0.0001). The plasma d-dimer and F1+2 levels were significantly greater in the individuals with active BP (2350±3676 ng/mL and 551±484 ng/mL) as compared to the controls (188±107 ng/mL and 106±42 ng/mL). The plasma t-PA levels were also considerably more in the patient group (34.70±33.22 ng/mL) compared to controls (6.60±6.78 ng/mL) (p=0.0001).
Johannesdottir et al., 2012[20]	There was no correlation seen between VTE and autoimmune skin disease (IRR=1). Connective tissue disease showed an elevated risk of VTE over 90 days (IRR=2.3) and 91–365 days (IRR=2) following diagnosis, though not beyond the time frame (IRR=1.1). The two connective tissue ailments with the highest risk were systemic lupus erythematosus (IRR=2.8) and juvenile rheumatoid arthritis (IRR=3).
Ramagopalan et al., 2011[21]	Increased risk of VTE was found in selective autoimmune diseases. Rate ratios were higher for systemic lupus erythematosus the rate ratios were 3.61 in the ORLS1 population, 4.60 in ORLS2, and 3.71 in the England dataset.
Langan et al., 2009[7]	The adjusted rate ratio of pneumonia and PE was 2.94 and 3.12 respectively as contrasted with controls. A statistically insignificant surge was observed for myocardial infarction and sepsis with an adjusted rate ratio of 1.24, and 2.02 respectively.

BP, bullous pemphigoid; VTE, venous thromboembolism; PE, pulmonary embolism; CISD, chronic inflammatory skin diseases; HR, Hazard ratio; IR, incidence rate; ABSIS, autoimmune bullous skin disorder intensity score; PAI-1, plasminogen activator inhibitor type 1; IRR, incidence rate ratio; ORLS, Oxford Record Linkage Study

Table 3. Quality assessment tool of the reviewed studies using the Newcastle-Ottawa scale.

Author-Year	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