

Increased Mortality in Patients with Bullous Pemphigoid: A Nationwide Population-based Cohort Study of 5,738 Patients in Sweden

Zeyad ALBADRI¹, Henrike HÄBEL², Kristofer THORSLUND³, Carina GRÖNHAGEN⁴ and Oliver SEIFERT^{1,5}

¹Division of Cell Biology, Department of Biomedical and Clinical Sciences, The Faculty of Medicine and Health Sciences, Linköping University, Linköping, Sweden, ²Medical Statistics Unit, Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Stockholm, ³Dermatology and Rheumatology Clinic, Region Sörmland County, Nyköping, ⁴Department of Dermatology, Lund University, Skåne University Hospital, Malmö, and ⁵Division of Dermatology and Venereology, Region Jönköping County, Jönköping, Sweden

Bullous pemphigoid (BP) is the most common autoimmune blistering disease and has been linked to increased mortality, although previous studies have generally relied on small populations and no data have been available specifically for the Swedish population. This study aimed to evaluate the 1- and 10-year mortality rates and all-cause mortality in Swedish patients with BP compared with the general population. Using the National Patient Register, we conducted a retrospective cohort study and identified all BP cases in Sweden from 1 January 2005, to 31 December 2016. Age, sex, and county of residence matched controls without BP were drawn from the general population, and mortality data were obtained from the Swedish Cause of Death Register. In total, 5,738 patients with BP and 17,167 controls were included. BP patients had a significantly higher all-cause mortality (HR 2.15, 95% CI 2.06–2.24) than controls, with 1- and 10-year mortality rates of 21.2% and 80.2%, respectively. Cardiovascular diseases accounted for the largest proportion of deaths (25.3%). Notably, improved survival was observed among BP patients treated with methotrexate (MTX), prednisolone, and potent topical corticosteroids (HR 0.76, 95% CI 0.69–0.83). To our knowledge, this is the first nationwide Swedish study on BP mortality and one of the largest to date, confirming a significantly increased mortality risk in BP patients, particularly due to cardiovascular causes, while also suggesting that combined MTX, prednisolone, and potent topical steroid treatment may improve survival outcomes.

Key words: bullous pemphigoid; autoimmune blistering disease; mortality; autoimmune subepidermal bullous disease; public health; epidemiology.

Submitted Jul 4, 2025. Accepted after revision May 7, 2026

Published May 28, 2026. DOI: 10.2340/actadv.v106.44309

Acta Derm Venereol 2026; 106: adv44309.

Corr: Oliver Seifert, MD, Division of Cell Biology, Department of Biomedical and Clinical Sciences, The Faculty of Medicine and Health Sciences, Linköping University, SE-581 83, Linköping, Sweden. E-mail: oliver.seifert@liu.se

Bullous pemphigoid (BP) is the most common acquired autoimmune blistering skin disorder, which mainly affects the elderly causing immune-mediated

SIGNIFICANCE

This nationwide Swedish study shows that patients with bullous pemphigoid, a severe blistering skin disease that mainly affects older adults, have a much higher risk of dying earlier than people without the disease. Heart and blood vessel diseases were the most common causes of death. The study also suggests that some treatment combinations may improve survival. These findings increase understanding of the long-term impact of bullous pemphigoid and may help doctors identify high-risk patients earlier and choose safer, more effective treatments. Ultimately, this research may improve patient care, support healthier ageing, and reduce the burden of serious complications of the disease.

blistering of the skin and mucous membrane (1, 2). BP is associated with an autoantibody response to BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1), 2 components of adhesion complexes promoting dermo-epidermal cohesion (3, 4). Up to 20% of patients with diagnosed BP present with only mild pruritus, excoriations, eczematous, papular, and urticarial lesions, without blistering (5). No proven cause has been found for BP; however, a number of different trigger factors have been described, such as medications, ultraviolet (UV) radiation, and other skin disorders, such as psoriasis and lichen planus. The annual incidence of BP varies between 2.6 and 42.8 cases per million, depending on the population studied (1, 2, 6–9). With an ageing population, the frequency of BP is increasing, with an incidence rate of 71.0 cases per million in Sweden, considered one of the highest rates in Europe (10).

BP has a chronic relapsing course and is associated with high morbidity and mortality, with an estimated 1-year mortality rate of 6% to 41% in Western cohorts (8, 11, 12). Yet, the leading cause of death in patients with BP remains uncertain. Factors associated with a poor prognosis in previous studies were old age, neurological diseases, high dosage of systemic corticosteroids, and autoantibodies against BP180. BP patients often require long-term topical or systemic corticosteroids alone or in combination with other medical therapies (13, 14).

Recent clinical guidelines have refined the therapeutic approach to BP, with increasing emphasis on disease severity, patient age, and comorbidity burden. New European guidance supports the use of potent topical corticosteroids as first-line therapy in many patients, while advocating cautious and individualized use of systemic immunosuppressive agents in older and frail populations, and highlighting emerging evidence for targeted biological therapies as potential future treatment options (15).

Evidence regarding the effect of medical therapy on mortality rates in BP patients is limited. Furthermore, there is a lack of data regarding the prognosis for patients with BP and potential mortality risk factors for patients with BP in Sweden compared with other countries.

The aim of this study was to determine the mortality rate of patients with BP in Sweden and to compare it to the general population. Secondary aims included identifying causes of mortality and evaluating the influence of medical therapy on mortality.

METHODS

Study design

In this nationwide retrospective cohort study, we identified all patients in Sweden (above 18 years of age) diagnosed with BP (International Classification of Diseases (ICD) code, ICD-10: L12.0, L12.0A, L12.0B, L12.0W, L12.8, and L12.9) from the National Patient Register (NPR) during the period 1 January 2005 to 31 December 2016 (Table SI). An age, sex, and county of residence matched cohort of individuals not diagnosed with BP was used to compare mortality rate with the general population. Prevalent diagnoses were those with a record of BP at any point before the end of the observation period. We followed up patients throughout the entire period or until emigration, death, or end of follow-up (31 December 2016), whichever came first.

Data linkage is permitted for both the BP cohort and the matched non-BP cohort with other national registers such as the NPR, the National Prescribed Drug Register, and the Swedish Cause of Death Register by means of each individual's unique personal identification number (PIN), which is assigned to all individuals residing in Sweden (16). Electronic linkage to these nationwide databases resulted in complete follow-up.

Data sources

Swedish National Patient Health Register. The NPR was first introduced by the National Board of Health and Welfare in 1964 and has had virtually complete coverage of all inpatient care, both public and private, since 1987 in Sweden. The NPR contains information concerning patient characteristics, such as PIN, age, sex and county of residence, hospital identification, and medical data with 1 main and up to 7 secondary diagnoses, coded according

to the International Classification of Diseases version 10 (ICD-10). Inpatient reporting is almost 100% and specialized care outpatient reporting is approximately 87% with both public and private sectors reporting to the NPR (17). In Sweden, all residents have a PIN that ensures accurate linkage of information among all registries including the NPR. The NPR makes it possible to trace information on patients retrospectively, before BP diagnosis, and prospectively, after the diagnosis of BP. Data in the NPR have been shown to be of high quality with a 92% positive predictive value for the diagnosis of BP (18).

Matched non-BP control cohort. From Statistics Sweden (SCB), which collects data on the entire Swedish population, a control cohort of individuals not diagnosed with BP was selected with up to 3 controls per case, matched by age, sex, and county of residence. The control subjects had to be alive with no prior diagnosis of BP and contributing data at the time of the index date. We assigned a date of "pseudo diagnosis" to controls, which was the date of diagnosis of BP of the case to which they were matched. We excluded patients aged under 18 years from both cases and controls, as BP is rare in this age group and may represent different diseases.

Swedish Cause of Death Register. Using the Swedish Cause of Death Registry database, we were able to identify mortality outcomes. This register has been used as a data source for official statistics and for many areas of medical research in Sweden (19). Since 1994, the Swedish National Board of Health and Welfare has been responsible for the register and has published the cause of death statistics. Comorbidities-related deaths coexisting with BP were evaluated according to the ICD-10. Infectious related deaths (A00–B99), neoplasms (C00–C99), and diabetes (E10–E14). Other comorbid diseases studied included dementia (F03), basal ganglia diseases including Parkinson's disease (G20–G26), and degenerative diseases including Alzheimer's (G30–G32). Coexisting cardiovascular diseases (CVD) (I00–I99) were studied including hypertension (I10–I15), ischaemic heart diseases (I20–I25), other heart diseases (I30–I52), and stroke (I60–I69).

Swedish Prescribed Drug Register. The Prescribed Drug Register was established in July 2005 and is maintained by the Swedish National Board of Health and Welfare. It contains data on age, sex, PIN, the prescriber's profession and practice, as well as all prescribed drugs dispensed at pharmacies in Sweden. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. However, the register does not include drugs without prescription, or vaccines. The register offers valuable data on exposure to drugs and is a useful tool to explore drug and disease associations and the risks, benefits, and health economic effects of drug use, thereby offering opportunities for pharmaco-epidemiological research (20).

Treatment groups

Patients were considered exposed to BP-related treatment if they had received dispensed prescriptions for established bullous pemphigoid therapies either after the index diagnosis or within the 90 days preceding the diagnosis, to account for diagnostic delay and treatment initiated for prodromal or initially misclassified disease manifestations. This window was intended to capture treatment initiated for prodromal or misdiagnosed disease rather than unrelated indications. Treatment exposure was therefore not interpreted as therapy initiated independently of BP, but as treatment plausibly attributable to BP prior to formal diagnostic coding.

To compare the effect of treatment on mortality, BP patients were divided into 7 treatment groups. These drugs were used alone or in combination. Combination therapy was defined based on overlapping treatment exposure as recorded in the Prescribed Drug Register. Patients were considered to have received combination therapy when dispensations of 2 or more BP-relevant medications occurred within overlapping time intervals following the index date, indicating concurrent use. Specifically, concomitant therapy with methotrexate, systemic corticosteroids, and potent topical corticosteroids was inferred when prescriptions for these agents were dispensed during overlapping periods, consistent with standard clinical management of BP. Patients who switched or escalated therapy during follow-up were classified according to their final observed treatment regimen to avoid double counting and to reflect cumulative treatment exposure over time.

Observation period. The observation period commenced on 1 January 2005, the date the patient registered within the NPR. The observation period terminated on 31 December 2016, the date of death, or the date of emigration, whichever came first.

Statistical analysis

We compared the baseline characteristics of individuals in the BP cohort and corresponding matched non-BP individuals. Categorical variables are summarized by their total number (percentage) and continuous variables by their mean (standard deviation). Mortality rates in terms of failure probabilities from the Kaplan–Meier failure function at 1 and 10 years following the diagnosis of BP was calculated together with Greenwood pointwise confidence intervals. Kaplan–Meier survival curves were plotted. Cox proportional-hazards regression models were used to examine the all-cause mortality in BP patients vs matched non-BP individuals and to examine the effect of therapy on the all-cause mortality. To control for confounding, the models include all matching variables by adjusting for age, sex, and county of residence. The proportional-hazards assumption was tested using Schoenfeld residuals and so-called log–log plots of the negative logarithm of survival as a function of the

log of the analysis time. Specific causes of death were analysed similarly. These models yielded hazard ratios (HRs) with corresponding 95% confidence intervals (CI). Cumulative incidence functions were estimated (using the *stcompst* STATA command) to further investigate the associations between BP and the specific risk of mortality under competing risks. Only individuals with a positive follow-up time were included in the survival analyses. A 2-sided statistical significance level of α was set at 0.05. The data were analysed using the statistical package STATA® software, version 15.1 (StataCorp LLC, College Station, TX, USA).

RESULTS

Characteristics of the study cohort

A total of 5,738 patients with BP were identified in the NPR between 2005 and 2016, with a mean age of 78.6 years (standard deviation (SD) $\pm$ 12.2) and 52.7% were female. Most diagnoses were made in specialized outpatient care (83.2%). The matched control cohort comprised 17,167 individuals from the general population with comparable age, sex, and county of residence distribution. Follow-up time and additional cohort characteristics are presented in **Table I**.

Mortality

A total of 22,875 individuals, including 5,713 patients with BP, were included in the survival analyses. During follow-up, 3,192 BP patients (55.9%) and 6,598 non-BP individuals (38.4%) died. BP was associated with increased all-cause mortality compared with controls (adjusted HR 2.15, 95% CI 2.06–2.24). Median survival was 3.8 years in BP patients vs 7.4 years in controls. 1- and 10-year mortality rates were higher in BP patients (21.2% and 80.2%) than in non-BP individuals (8.0% and 65.7%), respectively (**Tables I and II, Fig. 1**).

Specific cause of death

During 10 years of follow-up, CVD was the leading cause of death among BP patients (25.3%), followed by dementia, stroke, cancer, and infections. BP was associated with higher CVD mortality (HR 2.23, 95%

Table I. Demographics of patients with bullous pemphigoid (BP) cohort and age, sex, and county of residence matched individuals without BP (non-BP cohort)

Item	BP cohort	Non-BP cohort
Subjects, <i>n</i>	5,738	17,167
Male, <i>n</i> (%)	2,712 (47.3)	8,103 (47.2)
Female, <i>n</i> (%)	3,026 (52.7)	9,064 (52.8)
Follow-up time, years, mean $\pm$ SD	3.1 $\pm$ 2.9	4.2 $\pm$ 3.1
Age, years, mean $\pm$ SD	78.6 $\pm$ 12.2	78.7 $\pm$ 12.2
Patient-years of observation	18,022	71,682
Total no. of deaths, <i>n</i> (%)	3,192 (55.9)	6,598 (38.4)
Median survival rate, years	3.8	7.4

SD: standard deviation.

Table II. Hazard ratios (HR) of 1- and 10-year, overall, and specific-cause mortality associated with bullous pemphigoid (BP) adjusted for age, sex, and county of residence cardiovascular diseases (CVD)

Mortality outcome	Death (%)		Adjusted HR (95% CI)	p-value for HRs
	BP	non-BP		
All-cause mortality				
Overall	3,192 (55.9)	6,598 (38.4)	2.15 (2.06–2.24)	<0.001
1 year	1,157 (20.3)	1,301 (7.6)	2.98 (2.75–3.23)	<0.001
10 years	3,175 (55.6)	6,501 (37.9)	2.16 (2.07–2.25)	<0.001
Specific cause of death (ICD-10 codes)				
Infectious diseases (A00–B99)				
Overall	121 (2.1)	170 (1.0)	3.19 (2.52–4.03)	<0.001
1 year	36 (0.6)	37 (0.2)	3.26 (2.06–5.16)	<0.001
10 years	120 (2.1)	166 (1.0)	3.22 (2.54–4.08)	<0.001
Neoplasms (C00–C99)				
Overall	272 (4.8)	1013 (5.9)	1.41 (0.99–1.30)	0.054
1 year	91 (1.6)	222 (1.3)	1.35 (1.06–1.73)	0.014
10 years	269 (4.7)	1,000 (5.8)	1.13 (0.99–1.30)	0.059
Diabetes (E10–E14)				
Overall	107 (1.9)	124 (0.7)	3.58 (2.76–4.64)	<0.001
1 year	44 (0.8)	22 (0.1)	6.59 (3.95–11.00)	<0.001
10 years	107 (1.9)	122 (0.7)	3.63 (2.79–4.71)	<0.001
Dementia, extrapyramidal and movement disorders, and other degenerative diseases of the nervous system (F03, G20–G26, G30–G32)				
Overall		712 (4.1)	2.43 (2.14–2.75)	<0.001
1 year	125 (2.2)	136 (0.8)	3.07 (2.41–3.91)	<0.001
10 years	379 (6.6)	698 (4.1)	2.45 (2.16–2.78)	<0.001
Dementia, unspecified (F03)				
Overall	218 (3.8%)	468 (2.7%)	2.14 (1.82–2.51)	<0.001*
1 year	74 (1.3%)	87 (0.5%)	2.83 (2.07–3.86)	<0.001
10 years	677 (3.0%)	460 (2.7%)	2.15 (1.83–2.53)	<0.001*
Basal ganglia diseases, incl. Parkinson's disease (G20–G26)				
Overall	46 (0.8)	37 (0.2)	5.20 (3.36–8.04)	<0.001
1 year	15 (0.3)	8 (0.0)	6.14 (2.60–14.50)	<0.001
10 years	45 (0.8)	37 (0.2)	5.07 (3.27–7.86)	<0.001
Degenerative diseases, incl. Alzheimer's disease (G30–G32)				
Overall	117 (2.0)	207 (1.2)	2.54 (2.02–3.20)	<0.001
1 year	36 (0.6)	41 (0.2)	2.96 (1.89–4.64)	<0.001
10 years	117 (2.0)	201 (1.2)	2.61 (2.07–3.28)	<0.001
CVD (I00–I99)				
Overall	1,444 (25.3)	2,898 (16.9)	2.23 (2.09–2.38)	<0.001
1 year	527 (9.2)	560 (3.3)	3.17 (2.81–3.57)	<0.001
10 years	1,437 (25.2)	2,854 (16.6)	2.24 (2.10–2.39)	<0.001
Hypertension (I10–I15)				
Overall	105 (1.8)	224 (1.3)	2.22 (1.75–2.80)	<0.001
1 year	43 (0.8)	39 (0.2)	3.71 (2.40–5.72)	<0.001
10 years	104 (1.8)	221 (1.3)	2.22 (1.75–2.81)	<0.001
Ischaemic heart disease (I20–I25)				
Overall	504 (8.8)	1073 (6.3)	2.08 (1.87–2.31)	<0.001
1 year	203 (3.6)	206 (1.2)	3.31 (2.73–4.02)	<0.001
10 years	501 (8.8)	1056 (6.2)	2.09 (1.88–2.33)	<0.001
Other heart diseases (I30–I52)				
Overall	389 (6.8)	798 (4.6)	2.21 (1.95–2.50)	<0.001
1 year	136 (2.4)	152 (0.9)	2.99 (2.37–3.78)	<0.001
10 years	388 (6.8)	783 (4.6)	2.23 (1.97–2.52)	<0.001
Stroke (I60–I69)				
Overall	338 (5.9)	590 (3.4)	2.55 (2.23–2.92)	<0.001
1 year	108 (1.9)	113 (0.7)	3.24 (2.49–4.22)	<0.001
10 years	336 (5.9)	583 (3.4)	2.56 (2.23–2.93)	<0.001

*Proportional-hazards assumption violated.

CI 2.09–2.38), as well as increased mortality from diabetes, infections, stroke, and dementia. An association with cancer mortality was observed only at 1 year after diagnosis. Competing risk analyses demonstrated a consistently higher cumulative incidence of CVD-related death in BP patients compared with non-BP individuals (Table II, Fig. 2).

Systemic treatment

Of the 5,738 BP patients, 5,419 were included in treatment analyses. A total of 25 patients had died on the

index date, and 294 patients received no treatment, and thus were excluded from the treatment groups.

Combination therapy with MTX, prednisolone, and potent topical steroids was associated with significantly reduced mortality compared with prednisolone plus topical steroids (HR 0.76, 95% CI 0.69–0.83). The lowest mortality rate was observed in patients receiving other treatments, primarily MTX- or doxycycline-based regimens (HR 0.53, 95% CI 0.31–0.91). Median survival was shortest in patients treated with prednisolone alone and longest in those receiving MTX, prednisolone, and topical steroids (Fig. 3, Table III).

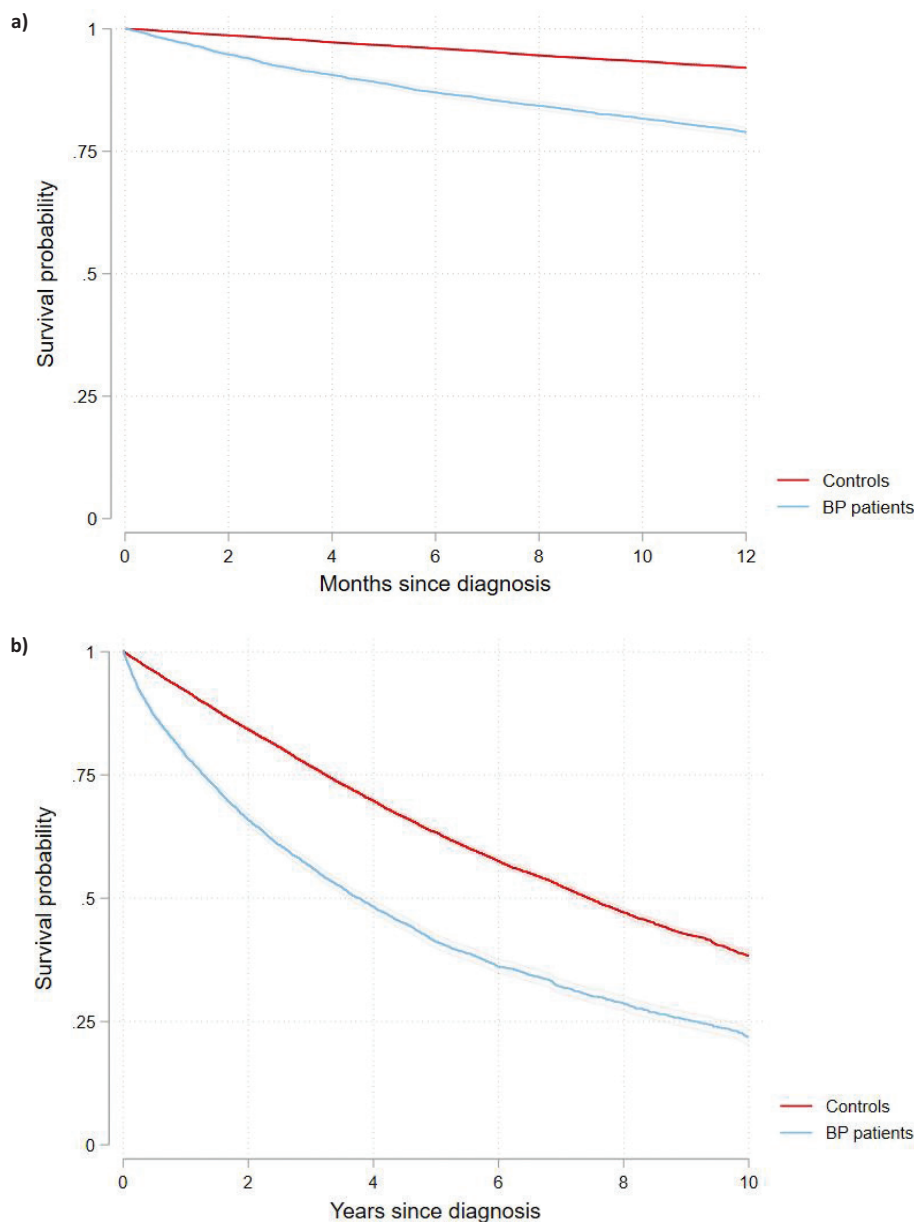


Fig. 1. Kaplan-Meier estimates of overall survival for patients with bullous pemphigoid (BP, blue line) and non-BP individuals (red line) after (A) 1 and (B) 10 years of follow-up.

DISCUSSION

This study represents the first nationwide retrospective matched cohort study of BP patients evaluated for mortality in Sweden and is, to our knowledge, the largest study on BP mortality worldwide. We found that BP patients had higher mortality rates compared with the general population. During the follow-up period we observed 1- and 10-year mortality rates in BP patients of 21.2% and 80.2%, respectively. The 1-year mortality is consistent with previous European studies that have reported mortality rates varying between 19% and 44% (9, 12, 21–26), while a Finnish study of 198 patients with BP revealed a rather lower mortality rate of 16.7% compared with our study (27). Additionally, this study found an increase in the overall-cause mortality in BP patients compared with non-BP individuals after

adjusting for age, sex, and county of residence. The reason for this large discrepancy in prognosis among different countries remains unclear. Nevertheless, these differences are likely multifactorial, which can be largely due to different populations, databases, or methods used.

Most significantly, the 10-year mortality rate in our study is higher than those previously reported in the literature. A study from Israel reported a lower 10-year mortality rate of 69.5% (28), while a study recently conducted in Italy showed a 10-year mortality rate of 51.9% (29). This could be due to the older age structure of the Swedish population compared with other populations. The mean age of patients in our study was 78.6 years, which is approximately 1 year older than those reported in the latter study. A summary of 1- and 10-year

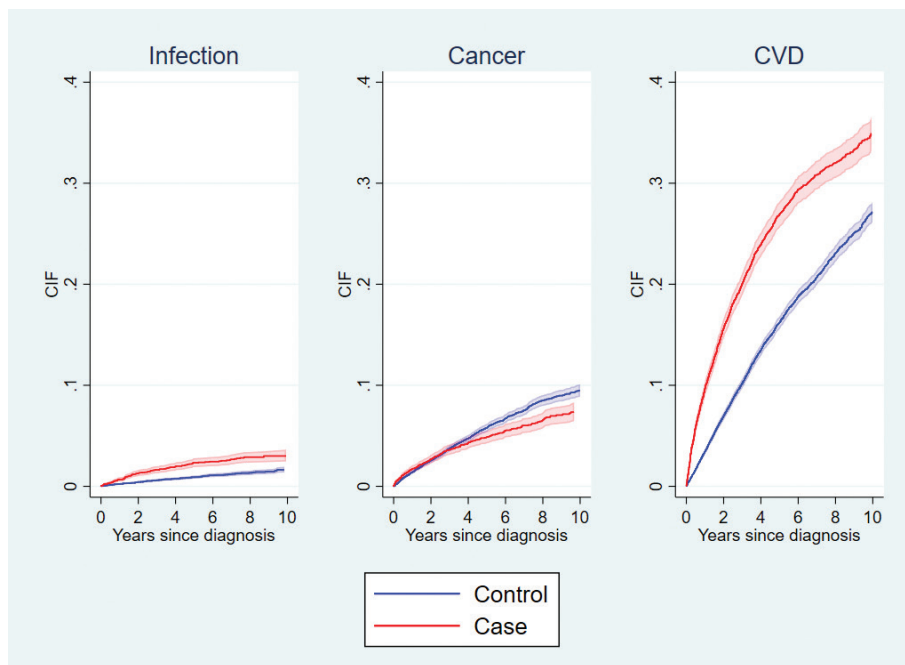


Fig. 2. Competing risk analysis for patients with bullous pemphigoid (BP=red line) and non-BP individuals (blue line), showing main causes of mortality over time (years) since index date, adjusted for age, sex, and county of residence. CVD=cardiovascular diseases, CIF= cumulative incidence function.

mortality rates in BP patients from studies published in the past 10 years is presented in **Table IV**.

Analysis revealed that CVD, mainly ischaemic heart disease, significantly increased mortality in BP patients compared with the matched non-BP individuals. The association between BP and CVD has previously been established in other studies. A recent study had shown a 5-fold increase of CVD mortality among BP patients (30). A study in Singapore reported elevated mortality ratios for BP patients with heart failure but not for infectious disease and cancer (31). However, the pathogenic mechanism is unknown. Medications such as diuretics, which are widely used in heart diseases, have been found to be a risk factor for development of BP (32, 33).

Nevertheless, it is unclear whether the use of diuretics contributed to increased mortality.

Previous studies have suggested a strong association between BP and neurological conditions, such as stroke, Parkinson's disease, multiple sclerosis, and dementia (34). The underlying association between neurological disease and BP is not yet fully established. Studies have suggested cross-immune responses through "epitope spreading" as a possible trigger (35, 36).

However, the results regarding specific cause of death mandate cautious interpretation because determination and registration of death cause are prone to error. Furthermore, sex had no effect on the mortality rates in our study, in contrast to the risk associated with females

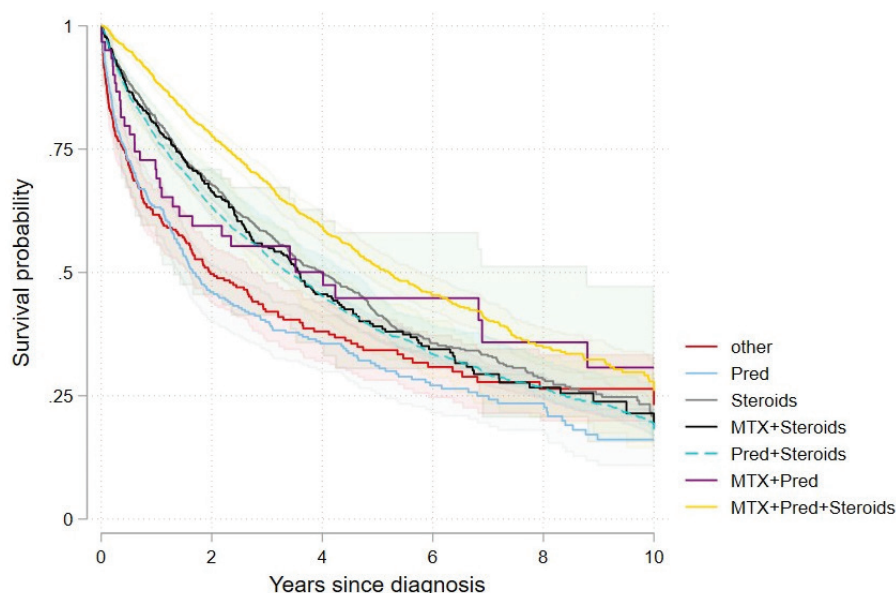


Fig. 3. Kaplan-Meier estimates of 10-year mortality for patients with bullous pemphigoid (BP) according to the treatment used for BP. Other: treatment with other medications listed in Table SI. MTX: methotrexate. Pred: oral prednisolone. Steroids: topical steroids.

Table III. 10-year mortality rates and age, sex, and county of residence adjusted hazard ratios (HR) for patients with bullous pemphigoid (BP) according to the treatment used for BP

Treatment	Patients, <i>n</i> (%)	Deaths, <i>n</i>	Person-years (x1,000)	Mortality rate (per 1,000 person-years)	HRs (95% CI)	P-value
Prednisolone + topical steroids	2287 (40.1)	1399	7.34	191 (181–201)	1.000 (Reference)	—
Prednisolone	299 (5.2)	205	0.77	267 (233–306)	1.63 (1.41–1.89)	< 0.001
Topical steroids	1060 (18.6)	559	3.20	175 (161–190)	0.93 (0.84–1.02)	0.136
MTX+ topical steroids	440 (7.7)	229	1.22	188 (165–213)	0.9 (0.78–1.03)	0.137
MTX+ prednisolone	61 (1.1)	32	0.18	174 (123–246)	1.12 (0.79–1.59)	0.526
MTX+ prednisolone + topical steroids	1225 (21.5)	564	4.38	129 (119–140)	0.76 (0.69–0.83)	< 0.001
Other treatments	47 (0.9)	13	0.19	68 (39–116)	0.53 (0.31–0.91)	0.023

MTX: methotrexate; other treatments see Table SI.

observed in a previous smaller study including only 237 patients with a short follow-up time of 6 months (12).

MTX, prednisolone, and topical steroids either alone or in combination show varying levels of association with the 10-year mortality compared with the reference treatment group. Notably, a significant finding in our study was that combination therapy with MTX, prednisolone and potent topical steroids was associated with better survival prognosis. This was significant even after adjusting for age, sex, and county of residence. Kridin et al. (37) showed that systemic steroid therapy in BP is associated with increased mortality and major adverse cardiovascular events compared with topical steroids.

We further observed that BP patients who received combination therapy with MTX, prednisolone, and potent topical corticosteroids had a longer median survival time of 5.2 years. The combination of MTX and topical corticosteroids may be more effective in controlling the symptoms of the disease, but it may also carry a higher risk of side effects and complications compared with a single medication. It is important to note that the mortality rate reported in BP patients treated with combination therapy may not necessarily be due to the use of these medications, but rather due to other factors such as underlying severity of the disease or the presence of comorbidities.

Overall, these results suggest that treatment with MTX in combination with topical or systemic corticosteroids may be associated with a reduced mortality rate in BP patients. Additionally, the other treatment group consisted mainly of MTX, and doxycycline showed the lowest mortality rate (HR: 0.53, $p=0.023$), suggesting a reduced risk of death compared with prednisolone with topical steroids. This survival benefit is likely due to

lower cumulative steroid exposure, reducing infection risk, cardiovascular complications, and metabolic side effects. The emergence of targeted therapies in BP further supports the concept that minimizing systemic steroid exposure may be critical in improving long-term outcomes in BP patients (38). Doxycycline's anti-inflammatory properties and MTX's immunosuppressive but less toxic profile may contribute to better long-term outcomes (39). Furthermore, a recent study found lower mortality associated with MTX monotherapy in patients with moderate to severe BP (40).

However, it is important to consider the small size of some of the groups, and the possibility of confounding factors that may have influenced the results, which may limit the generalizability of the findings. Moreover, it is important to recognize that treatment decisions are often influenced by a variety of factors beyond clinical guidelines. Differences in mortality between treatment groups may be shaped by treatment switching, disease severity, and underlying comorbidities. Selection bias is also a concern, as patients receiving certain therapies may have different characteristics compared with others due to clinician preferences, hospital protocols, or individual health conditions.

There are several strengths of this study. It is the largest population-based cohort study, allowing robust estimation of mortality, and includes a comprehensive patient cohort that is representative of the whole Swedish general population. All data are obtained from a well-validated NPR. The long-term follow-up for mortality is supporting our results. Using incident BP cases minimizes the selection bias that may underestimate the risk of mortality if prevalent BP cases were included in the analysis. As all new cases of BP, irrespective of

Table IV. 1- and 10 year mortality rates shown for cohorts including patients with bullous pemphigoid (BP) from recently published studies

Authors	Patients, <i>n</i>	Mean age, years	1-year mortality	10-year mortality	Study type	Control group	Year published	Country
Cai et al. (31)	359	75.7	26.7	ns	Retrospective	Yes	2013	Singapore
Forsti et al. (27)	198	77.5	16.7	ns	Retrospective	Yes	2016	Finland
Kibsgaard et al. (34)	3,281	76.5	27	ns	Retrospective	Yes	2017	Denmark
Kridin et al. (28)	287	77.6	26.9	69.5	Retrospective	Yes	2019	Israel
Persson et al. (8)	2,639	81*	20.4	ns	Retrospective	Yes	2020	UK
Shen et al. (30)	252	78*	29	ns	Retrospective	Yes	2021	Taiwan
Bardazzi et al. (29)	572	78*	3.2	51.9	Retrospective	No	2022	Italy
Current study	5,738	78.6	21.2	80.2	Retrospective	Yes	2023	Sweden

*Median age; ns: not studied.

their severity, were included, it is unlikely that there is a selection bias for patients in poor general condition.

Limitations

However, there are some limitations to this study. The data were collected retrospectively and thus rely mainly on the accuracy of information in the medical records, which is a potential source of information bias. While it is possible that unmeasured confounding factors may contribute to the observed increased mortality risk, efforts were made to address confounding by matching cases with controls based on age, sex, and county of residence. The data in this current study, sourced from the NPR, lack clinical and immunological patient characteristics, and administrative data may be susceptible to coding errors. Although recent validation of the NPR demonstrated a high positive PPV for BP diagnosis (18), it remains a possibility that individuals with a single BP diagnosis in the NPR may not be genuine cases, potentially resulting in an overestimation of BP occurrences (41). Better results could be obtained if comparing mortality rates with that of subjects matched for comorbidities, treatment, and other risk factors rather than comparing with the general population. Whether the findings in this study could be generalized to other populations with different ethnic and environmental backgrounds warrants further research. Another important limitation is that patients' treatment dose and duration was unknown, and treatment variations were inevitable in clinical practice, which might influence mortality. Previous studies revealed that BP patients given high-dose corticosteroids were associated with higher mortality and increased side effects (25, 37). 294 patients diagnosed with BP did not receive treatment, which may be due to various factors, including medical contraindications, potential adverse effects, lost follow-up of patients before initiating treatment, or that they withdrew voluntarily for other reasons. Given the number of untreated patients, the results comparing different treatment groups should be interpreted with caution, as this may introduce selection bias and affect the generalizability of the findings. Patients with a 90-day pre-diagnosis treatment exposure were included to account for potential initial misdiagnoses, such as nummular eczema. Some patients may have received treatment before ultimately being diagnosed with BP. Excluding these cases could lead to an overestimation of the treatment effect by omitting those who had already been on therapy. However, this approach may also introduce bias by including patients who received treatment for other conditions before their BP diagnosis.

Conclusion

This study provides novel data on the mortality rates of Swedish patients with BP, revealing a substantial increase

in mortality rate compared with the general population and confirming the poor prognosis of BP patients. CVD was the most common cause of death in BP patients with a 3-fold increase compared with the general population. While our findings suggest a possible survival benefit with certain treatments, these results should be interpreted with caution, considering the potential impact of unmeasured confounders. Despite these limitations, we believe our study provides valuable preliminary insights that highlight the need for further research to better understand optimal treatment strategies for BP and their effects on patient survival.

ACKNOWLEDGEMENTS

Funding: This work was in part funded by grants from the Futurum – Academy for health and care in Jonköping, Sweden. FUTURUM-981224 and FUTURUM-990062.

Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

The authors have no conflicts of interest to declare.

REFERENCES

1. Zillikens D, Wever S, Roth A, Weidenthaler-Barth B, Hashimoto T, Bröcker EB. Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; 131: 957–958. <https://doi.org/10.1001/archderm.1995.01690200097021>
2. Bernard P, Vaillant L, Labeille B, Bedane C, Arbeille B, Denoeux JP, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; 131: 48–52. <https://doi.org/10.1001/archderm.1995.01690130050009>
3. Hertl M. Humoral and cellular autoimmunity in autoimmune bullous skin disorders. *Int Arch Allergy Immunol* 2000; 122: 91–100. <https://doi.org/10.1159/000024364>
4. Stanley JR. Cell adhesion molecules as targets of autoantibodies in pemphigus and pemphigoid, bullous diseases due to defective epidermal cell adhesion. *Adv Immunol* 1993; 53: 291–325. [https://doi.org/10.1016/S0065-2776\(08\)60503-9](https://doi.org/10.1016/S0065-2776(08)60503-9)
5. Di Zenzo G, Marazza G, Borradori L. Bullous pemphigoid: physiopathology, clinical features and management. *Adv Dermatol* 2007; 23: 257–288. <https://doi.org/10.1016/j.yadr.2007.07.013>
6. Brick KE, Weaver CH, Lohse CM, et al. Incidence of bullous pemphigoid and mortality of patients with bullous pemphigoid in Olmsted County, Minnesota, 1960 through 2009. *J Am Acad Dermatol* 2014; 71: 92–99. <https://doi.org/10.1016/j.jaad.2014.02.030>
7. Försti AK, Jokelainen J, Timonen M, Tasanen K. Increasing incidence of bullous pemphigoid in Northern Finland: a retrospective database study in Oulu University Hospital. *Br J Dermatol* 2014; 171: 1223–1226. <https://doi.org/10.1111/bjd.13189>
8. Persson MSM, Harman KE, Vinogradova Y, et al. Incidence, prevalence and mortality of bullous pemphigoid in England 1998–2017: a population-based cohort study. *Br J Dermatol* 2021; 184: 68–77. <https://doi.org/10.1111/bjd.19022>
9. Joly P, Baricault S, Sparsa A, et al. Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol* 2012; 132: 1998–2004. <https://doi.org/10.1038/jid.2012.35>
10. Thorslund K, Seifert O, Nilzén K, Grönhagen C. Incidence of bullous pemphigoid in Sweden 2005–2012: a nationwide population-based cohort study of 3761 patients. *Arch Der-*

- matol Res 2017; 309: 721–727. <https://doi.org/10.1007/s00403-017-1778-4>
11. Colbert RL, Allen DM, Eastwood D, Fairley JA. Mortality rate of bullous pemphigoid in a US medical center. *J Invest Dermatol* 2004; 122: 1091–1095. <https://doi.org/10.1111/j.0022-202X.2004.22504.x>
 12. Roujeau JC, Lok C, Bastuji-Garin S, Mhalla S, Enginger V, Bernard P. High risk of death in elderly patients with extensive bullous pemphigoid. *Arch Dermatol* 1998; 134: 465–469. <https://doi.org/10.1001/archderm.134.4.465>
 13. Fine JD. Management of acquired bullous skin diseases. *N Engl J Med* 1995; 333: 1475–1484. <https://doi.org/10.1056/NEJM199511303332207>
 14. Korman NJ. Bullous pemphigoid: the latest in diagnosis, prognosis, and therapy. *Arch Dermatol* 1998; 134: 1137–1141.
 15. Borradori L, Van Beek N, Feliciani C, et al. Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol* 2022; 36: 1689–1704. <https://doi.org/10.1111/jdv.18220>
 16. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; 24: 659–667. <https://doi.org/10.1007/s10654-009-9350-y>
 17. Ludvigsson JF, Andersson E, Ekblom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; 11: 450. <https://doi.org/10.1186/1471-2458-11-450>
 18. Grönhagen C, Nilzén K, Seifert O, Thorslund K. Bullous pemphigoid: validation of the national patient register in two counties in Sweden, 2001 to 2012. *Acta Derm Venereol* 2017; 97: 32–35. <https://doi.org/10.2340/00015555-2456>
 19. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol* 2017; 32: 765–773. <https://doi.org/10.1007/s10654-017-0316-1>
 20. Wettermark B, Hammar N, Forel CM, et al. The new Swedish Prescribed Drug Register opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007; 16: 726–735. <https://doi.org/10.1002/pds.1294>
 21. Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris incidence and mortality in the UK: population based cohort study. *BMJ* 2008; 337: a180. <https://doi.org/10.1136/bmj.a180>
 22. Bernard P, Enginger V, Venot J, Bedane C, Bonnetblanc JM. Pronostic vital de la pemphigoïde. Analyse d'une cohorte de 78 malades. *Ann Dermatol Venereol* 1995; 122: 751–757.
 23. Garcia-Doval I, Conde Taboada A, Cruces Prado MJ. Sepsis associated with dermatologic hospitalization is not the cause of high mortality of bullous pemphigoid in Europe. *J Invest Dermatol* 2005; 124: 666–667. <https://doi.org/10.1111/j.0022-202X.2005.23628.x>
 24. Joly P, Benichou J, Lok C, et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol* 2005; 141: 691–698. <https://doi.org/10.1001/archderm.141.6.691>
 25. Rzyan B, Partscht K, Jung M, et al. Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol* 2002; 138: 903–908. <https://doi.org/10.1001/archderm.138.7.903>
 26. Doffoel-Hantz V, Sparsa A, Marin B, Durox H, Bonnetblanc JM, Bédane C. Profil évolutif des patients atteints de pemphigoïde bulleuse au cours de la première année de traitement. *Ann Dermatol Venereol* 2009; 136: 407–411. <https://doi.org/10.1016/j.annder.2009.01.009>
 27. Försti AK, Jokelainen J, Timonen M, Tasanen K. Risk of death in bullous pemphigoid: a retrospective database study in Finland. *Acta Derm Venereol* 2016; 96: 758–761. <https://doi.org/10.1038/srep37125>
 28. Kridin K, Shihade W, Bergman R. Mortality in patients with bullous pemphigoid: a retrospective cohort study, systematic review and meta-analysis. *Acta Derm Venereol* 2019; 99: 72–77. <https://doi.org/10.2340/00015555-2930>
 29. Bardazzi F, Filippi F, Chessa MA, et al. Mortality and prognostic factors in patients with bullous pemphigoid: a retrospective multicenter Italian study. *J Eur Acad Dermatol Venereol* 2022; 36: 2473–2481. <https://doi.org/10.1111/jdv.18441>
 30. Shen WC, Chiang HY, Chen PS, Lin YT, Kuo CC, Wu PY. Risk of all-cause mortality, cardiovascular disease mortality, and cancer mortality in patients with bullous pemphigoid. *JAMA Dermatol* 2022; 158: 167–175. <https://doi.org/10.1001/jamadermatol.2021.5125>
 31. Cai SC, Allen JC, Lim YL, Chua SH, Tan SH, Tang MB. Mortality of bullous pemphigoid in Singapore: risk factors and causes of death in 359 patients seen at the National Skin Centre. *Br J Dermatol* 2014; 170: 1319–1326. <https://doi.org/10.1111/bjd.12806>
 32. Bastuji-Garin S, Joly P, Picard-Dahan C, et al. Drugs associated with bullous pemphigoid: a case-control study. *Arch Dermatol* 1996; 132: 272–276. <https://doi.org/10.1001/archderm.1996.03890270044006>
 33. Bastuji-Garin S, Joly P, Lemordant P, et al. Risk factors for bullous pemphigoid in the elderly: a prospective case-control study. *J Invest Dermatol* 2011; 131: 637–643. <https://doi.org/10.1038/jid.2010.301>
 34. Kibsgaard L, Rasmussen M, Lamberg A, Deleuran M, Olesen AB, Vestergaard C. Increased frequency of multiple sclerosis among patients with bullous pemphigoid: a population-based cohort study on comorbidities anchored around the diagnosis of bullous pemphigoid. *Br J Dermatol* 2017; 176: 1486–1491. <https://doi.org/10.1111/bjd.15405>
 35. Brown A, Bernier G, Mathieu M, Rossant J, Kothary R. The mouse dystonia musculorum gene is a neural isoform of bullous pemphigoid antigen 1. *Nat Genet* 1995; 10: 301–306. <https://doi.org/10.1038/ng0795-301>
 36. Li L, Chen J, Wang B, Yao Y, Zuo Y. Sera from patients with bullous pemphigoid (BP) associated with neurological diseases recognized BP antigen 1 in the skin and brain. *Br J Dermatol* 2009; 160: 1343–1345. <https://doi.org/10.1111/j.1365-2133.2009.09122.x>
 37. Kridin K, Bieber K, Vorobyev A, Moderegger EL, Hernandez G, Schmidt E, et al. Risk of death, major adverse cardiac events and relapse in patients with bullous pemphigoid treated with systemic or topical corticosteroids. *Br J Dermatol* 2024; 191: 539–547. <https://doi.org/10.1093/bjd/ljae219>
 38. Karakioulaki M, Eyerich K, Patsatsi A. Advancements in bullous pemphigoid treatment: a comprehensive pipeline update. *Am J Clin Dermatol* 2024; 25: 195–212. <https://doi.org/10.1007/s40257-023-00832-1>
 39. Williams HC, Wojnarowska F, Kirtschig G, et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. *Lancet* 2017; 389: 1630–1638. [https://doi.org/10.1016/S0140-6736\(17\)30560-3](https://doi.org/10.1016/S0140-6736(17)30560-3)
 40. Wojtczak M, Nollbrzak A, Woźniacka A, Żebrowska A. Can methotrexate be employed as monotherapy for bullous pemphigoid? analysis of efficiency and tolerance of methotrexate treatment in patients with bullous pemphigoid. *J Clin Med* 2023; 12: 1638. <https://doi.org/10.3390/jcm12041638>
 41. Leisti P, Pankakoski A, Jokelainen J, Varpuloma O, Huilaja L, Panelius J, et al. Accurate diagnosis of bullous pemphigoid requires multiple health care visits. *Front Immunol* 2023; 14: 1281302. <https://doi.org/10.3389/fimmu.2023.1281302>