

Risk of Serious Infections in Patients with Bullous Pemphigoid: A Population-based Cohort Study

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Patients with bullous pemphigoid are susceptible to serious infections, which are the leading cause of death in these patients. The aims of this population-based cohort study were to investigate the incidence and spectrum of serious infections in patients with bullous pemphigoid and to identify associated risk factors. The outcome measure was any infection requiring hospitalization. Hazard ratios with 95% confidence intervals were estimated using subdistribution hazard models. In total, 12,300 patients with bullous pemphigoid and 49,200 matched controls were identified through the National Health Insurance Research Database in Taiwan. Within 2 years of bullous pemphigoid diagnosis, 5,006 (40.7%) patients developed serious infections, with an incidence of 385.5/1,000 person-years. Patients with bullous pemphigoid were twice as likely to develop serious infections as controls (adjusted hazard ratio, 2.01; 95% confidence interval 1.92–2.10). Systemic corticosteroid use was the strongest risk factor, resulting in a 2-fold increase in the risk for serious infections. Other independent risk factors were advanced age, female sex, low income, and certain comorbidities. In conclusion, this study demonstrated an increased risk of serious infections following a diagnosis of bullous pemphigoid. Prophylaxis of serious infections through active intervention with the risk factors may be essential in reducing the morbidity and mortality associated with bullous pemphigoid.

Key words: bullous pemphigoid; cohort studies; infections; pneumonia; sepsis; vesiculobullous skin disease.

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Bullous pemphigoid (BP), the most common autoimmune bullous disease (AIBD), typically manifests as generalized crops of itchy urticarial plaques and tense blisters in elderly patients. The annual incidence of BP has increased over the decades, especially in people aged over 60 years, which imposes a heavy burden on countries with an ageing population (1, 2). The overall

SIGNIFICANCE

Infections were found to be common and severe following diagnosis of bullous pemphigoid. Patients with bullous pemphigoid were 3.3 times as likely to develop serious infections as those without bullous pemphigoid. Bullous pemphigoid per se doubled the risk of serious infections. Systemic corticosteroid use, the first-line therapy for bullous pemphigoid, was the strongest risk factor for serious infection in patients with bullous pemphigoid. Other independent risk factors associated with serious infections were advanced age, female sex, low income, and certain comorbidities. Prophylaxis of serious infections through active intervention with the risk factors might be essential in reducing the morbidity and mortality associated with bullous pemphigoid.

1-year mortality rate is 23.5% (95% confidence interval (95% CI) 20.2–26.8) and the standardized mortality ratio is estimated to be 3.61 (95% CI 2.59–5.03) in patients with BP (3, 4). Risk factors for mortality in patients with BP include advanced age, presence of circulating anti-BP180 autoantibodies, treatment with high-dose corticosteroids, and comorbidities such as dementia and stroke (5, 6).

Infections are common and severe following the onset of BP, accounting for 20–87% of deaths in patients with BP (7–11). Infection-specific standardized mortality ratio significantly increases in these patients, suggesting that infection is a mediator in the association between BP and death (11, 12). Investigating infectious complications is necessary for better preventive strategies, which may lead to a reduction in mortality associated with BP. However, only a few studies have evaluated the incidence and risk factors of serious infections in BP, most of which were single-centre studies limited by small sample sizes and a lack of matched controls (7, 8, 13, 14). Therefore, a nationwide retrospective cohort study was conducted, which aimed to evaluate: (i) the incidence of different categories of serious infections in patients with BP, (ii) the risk of serious infections in patients with BP compared with age- and sex-matched controls, and (iii) the risk factors for serious infections associated with BP by analysing sociodemographic characteristics, comorbidities, and treatment modalities.

MATERIALS AND METHODS

Data source

Data were retrieved from Taiwan's National Health Insurance Research Database (NHIRD), which covers more than 99% of Taiwanese residents (approximately 23 million people) (15). These contain scrambled individual data (including sex, birth date, and insurance premium), inpatient and outpatient department diagnostic data, and data on drug dispensations from pharmacies and medical facilities. To protect the privacy of the participants, each was assigned a unique and anonymous identifier before the data was released to researchers. Participants were followed-up continuously using a unique identifier. The reliability of the NHIRD has been documented in several validation studies, and it has been widely used in epidemiological studies in Taiwan (16–20). This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (VGHIRB 2019-01-007AC); they granted a waiver of informed consent for retrospective studies utilizing data from the NHIRD.

Inclusion criteria

All individuals diagnosed with BP between 1 January 2007 and 31 December 2018 were identified. The diagnosis of BP in the NHIRD was based on the Ninth Edition of the International Classification of Diseases, Clinical Modification (ICD-9-CM) code 694.5 and ICD-10-CM codes L12.0, before and after 1 January 2016, respectively. To enhance diagnostic validity, only patients with at least 3 outpatient diagnoses or 1 inpatient diagnosis of BP from a board-certified dermatologist within any given 1-year period were enrolled into the BP cohort. The positive predictive value of BP diagnosis using this algorithm in the NHIRD is 98.0% (95% CI 96.3–99.7%) (18). Each patient with BP was randomly matched with 4 reference individuals (those without a diagnosis of BP during the study period) on age and sex, identified through the NHIRD. To reduce detection bias, more than 5 outpatient visits within 1 year prior to enrollment were required for matched individuals without BP.

Study outcome

The study outcome was serious infections, defined as any infection requiring hospitalization. The diagnosis of serious infections was identified through the major hospital discharge ICD-9-CM and/or ICD-10-CM codes (Table S1). Serious infections were categorized based on the specific organ system affected; infections leading to intensive care unit (ICU) admission were also identified.

Follow-up

Patients with BP were followed-up from the date of first BP diagnosis (index date). Reference individuals were followed-up from the date of BP diagnosis for the matched patients with BP. Since only 28.4% (3497/12300) of patients with BP remained in the cohort 2 years after the index date, the follow-up period was restricted to 2 years. Follow-up ended at the time of diagnosis of serious infections, death, 2 years after the index date, or on 31 December 2018, whichever occurred first. In the analysis of serious infections in specific organ systems, follow-up continued when serious infections occurred in other organ systems.

Covariates

Directed acyclic graphs were performed to identify confounders and mediators in each analysis, to prevent collider bias. The income-related monthly premium at cohort entry was representative of socioeconomic status. Chronic comorbidities that might

have contributed to serious infections were identified, including diabetes mellitus (DM), heart failure, cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), chronic liver disease (CLD), chronic kidney disease (CKD), nephrotic syndrome, connective tissue disease (CTD), psoriasis, dementia, Parkinson's disease, depression, and malignancies. Comorbidities were defined as at least 3 outpatient diagnoses or 1 inpatient diagnosis based on their corresponding ICD-9-CM and/or ICD-10-CM codes during the follow-up period (Table SII). Systemic immunosuppressant use for BP was assessed during the follow-up period. These immunosuppressants included corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, cyclophosphamide, and chlorambucil. The dose of systemic corticosteroids was calculated using the defined daily dose (DDD) assigned by the World Health Organization Collaborating Centre for Drug Statistics Methodology. The DDD of systemic corticosteroids is prednisolone 10 mg/day, or equivalent doses of other corticosteroid compounds.

Statistical analysis

Sociodemographic characteristics and comorbidities are expressed as mean with standard deviation or median with interquartile range (IQR) for continuous variables and count with percentage for categorical variables. The independent *t*-test and Wilcoxon rank-sum test were used to compare continuous variables between cohorts, while Pearson's χ^2 test was used for categorical variables. Cumulative incidences of serious infections were compared between cohorts using the Kaplan–Meier method and the modified log-rank test proposed by Gray (21). Incidence rates (IRs) of serious infections were calculated by dividing the number of study outcomes by total person-time at risk, presented as case number per 1,000 person-years. IR ratios (IRRs) with 95% CIs were computed as the ratio of IR between the cohorts.

Subdistribution hazard models were used to estimate hazard ratios (HRs) with 95% CIs of the association between BP and each category of serious infection, adjusting for the competing risk of death (crude model) (22). Covariates adjusted in the multivariable models were age, sex, monthly premium, annual number of outpatient visits, annual number of hospitalizations, and chronic comorbidities. A sensitivity analysis was performed by excluding study outcomes within the first 4 weeks of the index date to avoid the possible scenario that the serious infection preceded BP onset.

We also applied subdistribution hazard models to determine risk factors for serious infections in patients with BP. The risk factors analysed included age, sex, monthly premium, chronic comorbidities, and systemic immunosuppressant use within 12 weeks before the study endpoint. Two separate multivariable models were built for the 2 potential risk factors regarding systemic immunosuppressant use (i.e. systemic immunosuppressant regimens and systemic corticosteroid doses) due to presence of collinearity when they were included in the same regression model.

All data processing and statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute, Cary, NC, USA). A 2-tailed *p*-value < 0.05 was considered statistically significant. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

RESULTS

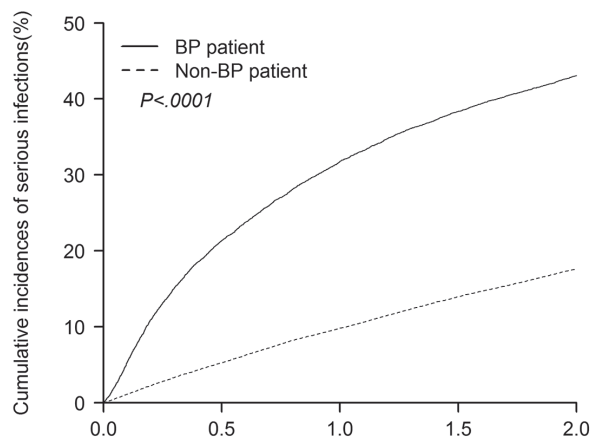
Baseline characteristics

A total of 12,300 patients with BP and 49,200 controls were identified (Table I). Age (median 81 years) and sex (men 51.6%) were well matched between cohorts. Most comorbidities were significantly more common in patients

Table I. Descriptive characteristics of the bullous pemphigoid (BP) and reference (patients without BP) cohorts

	BP cohort (n = 12,300)	Non-BP cohort (n = 49,200)	p-value
Age, years, mean (SD) ^a	78.2 (12.9)	78.2 (12.9)	0.92
Median (IQR)	81.4 (74.0–86.5)	81.3 (73.7–86.8)	0.93
Sex, n (%)			
Female	5,956 (48.4)	23,824 (48.4)	> 0.99
Male	6,344 (51.6)	25,376 (51.6)	> 0.99
Monthly premium, US dollars, mean (SD) ^a	672.1 (820.7)	754.0 (809.5)	< 0.001
Median (IQR)	730.0 (41.6–800.0)	800.0 (41.6–800.0)	< 0.001
Annual number of hospitalizations, mean (SD) ^b	2.4 (3.6)	0.5 (1.4)	< 0.001
Median (IQR)	0.9 (0.0–3.2)	0.0 (0.0–0.4)	< 0.001
Annual number of outpatient visits, mean (SD) ^b	43.4 (34.9)	25.2 (20.4)	< 0.001
Median (IQR)	37.8 (24.5–54.6)	20.6 (12.3–32.7)	< 0.001
Comorbidities, n (%)			
Diabetes mellitus	6,213 (50.5)	18,170 (36.9)	< 0.001
Heart failure	3,518 (28.6)	9,896 (20.1)	< 0.001
CVD	5,424 (44.1)	8,439 (17.2)	< 0.001
COPD	3,552 (28.9)	8,052 (16.4)	< 0.001
CLD or cirrhosis	2,026 (16.5)	8,073 (16.4)	0.88
CKD or renal failure	2,526 (20.5)	8,867 (18.0)	< 0.001
Nephrotic syndrome	180 (1.5)	477 (1.0)	< 0.001
CTD or systemic vasculitis	296 (2.4)	1,450 (3.0)	< 0.001
Psoriasis	351 (2.9)	549 (1.1)	< 0.001
Dementia	5,535 (45.0)	10,354 (21.0)	< 0.001
Parkinson's disease	1,895 (15.4)	2,871 (5.8)	< 0.001
Depression	623 (5.1)	1,998 (4.1)	< 0.001
Malignancy	1,158 (9.4)	6,545 (13.3)	< 0.001
Systemic immunosuppressants for BP ^c , n (%)			
Corticosteroids + other immunosuppressants	1,382 (11.2)	N/A	
Corticosteroids alone	10,128 (82.3)	N/A	
Immunosuppressants other than corticosteroids	15 (0.1)	N/A	
No systemic immunosuppressants	775 (6.3)	N/A	
Follow-up duration, years, mean (SD) ^d	1.1 (0.8)	1.5 (0.7)	< 0.001
Median (IQR)	0.9 (0.3–2.0)	2.0 (0.9–2.0)	< 0.001
Serious infection, n (%)	5,006 (40.7)	7,418 (15.1)	< 0.001
Mortality after index date, n (%)	2,612 (21.2)	2,984 (6.1)	< 0.001

^aAt cohort entry. ^bDuring the follow-up period. ^cSystemic immunosuppressant use for bullous pemphigoid during the follow-up period; these immunosuppressants included corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, cyclophosphamide, and chlorambucil. ^dFollow-up for 2 years at most, ended at the time of serious infection or death or study end, whichever occurred first. BP: bullous pemphigoid; CKD: chronic kidney disease; CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; CTD: connective tissue disease; CVD: cerebrovascular disease; N/A: not applicable; IQR: interquartile range; SD: standard deviation.



Number at risk	Follow-up (years)				
	0	0.5	1.0	1.5	2.0
BP	12300	8071	5891	4477	3497
Non-BP	49200	41638	35410	29509	27551

Fig. 1. Kaplan–Meier curves. Cumulative incidence of serious infections in bullous pemphigoid (BP) and reference cohorts (patients without BP). The difference between the cohorts was calculated using the modified log-rank test.

with BP than in controls. The median follow-up duration was 0.9 (IQR 0.3–2.0) and 2.0 (IQR 0.9–2.0) years for patients with BP and controls ($p < 0.001$), respectively.

Incidence of serious infections

The cumulative incidence is shown in **Fig. 1**. The cumulative incidence of serious infections in patients with BP was significantly higher than that in controls ($p < 0.001$). A total of 5,006 (40.7%) patients with BP and 7,418 (15.1%) controls had serious infections during the follow-up period ($p < 0.001$) (**Table II**). The IR (per 1,000 person-years) of any serious infection was 385.5 (95% CI 375.0–396.4) for patients with BP and 102.7 (95% CI 100.3–105.0) for controls (IRR, 3.76; 95% CI 3.62–3.89). Serious infections occurred within the first year of the index date in 3,795 (75.8%) patients with BP and 4,516 (60.9%) controls. Common serious infections in patients with BP were lower respiratory tract infections (LRTIs), sepsis/septicaemia, urinary tract infections (UTIs), and skin and soft tissue infections (SSTIs),

Table II. Incidence rate of serious infections in the bullous pemphigoid (BP) and reference cohorts (patients without BP)

Serious infections	BP cohort (n = 12,300)			Non-BP cohort (n = 49,200)			
	Events, n	PYs	IR ^a (95% CI)	Events, n	PYs	IR ^a (95% CI)	IRR (95% CI)
Any	5,006	12,984.7	385.5 (375.0–396.4)	7,418	72,251.9	102.7 (100.3–105.0)	3.76 (3.62–3.89)
Skin and soft tissue infections	898	15,855.5	56.6 (53.1–60.5)	910	76,721.5	11.9 (11.1–12.7)	4.77 (4.35–5.24)
Musculoskeletal infections	119	16,495.8	7.2 (6.0–8.6)	141	77,322.6	1.8 (1.5–2.2)	3.96 (3.09–5.05)
Upper respiratory tract infections	64	16,541.5	3.9 (3.0–4.9)	126	77,313.0	1.6 (1.4–1.9)	2.37 (1.76–3.21)
Lower respiratory tract infections	2,316	15,139.3	153.0 (146.9–159.3)	3,655	75,108.4	48.7 (47.1–50.3)	3.14 (2.98–3.31)
Heart infections	46	16,564.5	2.8 (2.1–3.7)	113	77,349.3	1.5 (1.2–1.8)	1.90 (1.35–2.69)
Sepsis/septicaemia	2,256	15,433.7	146.2 (140.3–152.3)	2,409	76,288.8	31.6 (30.3–32.9)	4.63 (4.37–4.90)
Central nervous system infections	27	16,577.8	1.6 (1.1–2.4)	49	77,397.5	0.6 (0.5–0.8)	2.57 (1.61–4.12)
Gastrointestinal infections	306	16,371.5	18.7 (16.7–20.9)	660	76,956.1	8.6 (7.9–9.3)	2.18 (1.90–2.49)
Urinary tract infections	1,725	15,222.9	113.3 (108.1–118.8)	2,609	75,520.7	34.5 (33.2–35.9)	3.28 (3.09–3.49)
Infections leading to ICU admission	979	16,053.4	61.0 (57.3–64.9)	1,386	76,717.0	18.1 (17.1–19.0)	3.38 (3.11–3.66)

^aIncidence rate (IR) per 1000 person-years.

CI: confidence interval; ICU: intensive care unit; IRR: incidence rate ratio; PYs: person-years.

similar to the pattern in the reference cohort. The IRs of serious infections in specific organ systems were all higher in patients with BP, with the highest IRR of 4.77 (95% CI 4.35–5.24) for SSTIs.

Association between bullous pemphigoid and risk of serious infections

The subdistribution hazard models showed significant associations between BP and the risk of any serious infection before (crude HR 3.27; 95% CI 3.15–3.38) and after (adjusted HR [aHR] 2.01; 95% CI 1.92–2.10) adjusting for potential confounders (Table III). A significant association was observed between BP and the risk of SSTIs (aHR 2.63; 95% CI 2.37–2.92), sepsis/septicaemia (aHR 2.49; 95% CI 2.32–2.67), musculoskeletal infections (aHR 1.86; 95% CI 1.40–2.47), LRTIs (aHR 1.75; 95% CI 1.65–1.87), UTIs (aHR 1.69; 95% CI 1.57–1.82), and gastrointestinal infections (aHR 1.25; 95% CI 1.06–1.47); no association was observed for upper respiratory tract, heart, and central nervous system infections. A significant association was also observed between BP and serious infections leading to ICU admission (aHR 2.06; 95% CI 1.86–2.29). Table SIII and SIV show the results of sensitivity analysis. The association between BP and any serious infection (aHR 2.06; 95% CI 1.97–2.15) on sensitivity analysis was similar to that observed on primary analysis.

Risk factors for serious infections

In the analysis of risk factors for any serious infection in patients with BP, a modest association was observed for age, female sex, lower monthly premium, and comorbidities including DM, heart failure, CVD, COPD, CKD, dementia, and Parkinson's disease (Table IV). Sex, nephrotic syndrome, CLD, CTD, psoriasis, depression, and malignancy were not independently associated with the risk of serious infections. The strongest association was observed with systemic immunosuppressant use within

12 weeks before the study endpoint. Compared with those who did not receive systemic immunosuppressants, patients who received systemic corticosteroids alone (aHR 1.96; 95% CI 1.83–2.10) or in combination with other immunosuppressants (aHR 1.80; 95% CI 1.60–2.03) had higher risks of developing serious infections; those who received systemic immunosuppressants other than corticosteroids did not have an increased risk of serious infections. The increased risk of serious infections among systemic corticosteroid users was dose-dependent with an aHR of 1.53 (95% CI 1.41–1.66) for DDD <0.5 up to 2.33 (95% CI 2.16–2.52) for DDD ≥ 1.

DISCUSSION

This study showed that patients with BP were 2.0 times as likely to develop serious infections as those without BP after adjusting for sociodemographic factors and comorbidities. Systemic corticosteroid use, the first-line therapy for BP, was the strongest risk factor for serious infection in patients with BP, doubling their risk of serious infections compared with those who did not receive systemic immunosuppressant therapy.

These findings are consistent with previous retrospective studies in which patients with BP were commonly affected by serious infections (7, 8, 13, 14, 23). Single-centre longitudinal studies showed that infections requiring hospitalization or leading to death occurred in 44.4–55.7% of patients with BP; 77.7% of these infections appeared in the first year following BP diagnosis (7, 13). Identical to the current findings, the most common infections were pneumonia, UTIs, bacteraemia, and SSTIs (7,8). However, these studies did not enroll a control group for comparison; hence, the additional risk of serious infections contributed by BP could not be ascertained. A cross-sectional study using representative inpatient samples from the USA revealed significant association between BP and serious infections (adjusted odds ratio (aOR), 2.38; 95% CI 2.28–2.49) (23). Types

of infections found to be significantly associated with BP in this previous study including SSTIs, musculoskeletal infections, pneumonia, UTIs, gastrointestinal infections, and septicaemia were similar to those observed in the current study. However, this previous study only enrolled inpatients for analysis and the directionality of the association could not be determined due to the cross-sectional design. Although infections are common and severe following the diagnosis of BP, routine antimicrobial prophylaxis is not recommended by updated guidelines (24, 25). Instead, clinicians should aim for early recognition of signs of infection and timely management with appropriate antimicrobials.

Table III. Risk of serious infection in patients with bullous pemphigoid vs those without bullous pemphigoid

Serious infections	CHR (95% CI)	p-value	aHR ^a (95% CI)	p-value
Any	3.27 (3.15–3.38)	<0.001	2.01 (1.92–2.10)	<0.001
Skin and soft tissue infections	3.86 (3.51–4.23)	<0.001	2.63 (2.37–2.92)	<0.001
Musculoskeletal infections	3.21 (2.51–4.11)	<0.001	1.86 (1.40–2.47)	<0.001
Upper respiratory tract infections	1.90 (1.41–2.57)	<0.001	1.02 (0.72–1.46)	0.90
Lower respiratory tract infections	2.57 (2.44–2.71)	<0.001	1.75 (1.65–1.87)	<0.001
Heart infections	1.53 (1.09–2.16)	0.01	1.16 (0.79–1.69)	0.44
Sepsis/septicaemia	3.85 (3.63–4.08)	<0.001	2.49 (2.32–2.67)	<0.001
Central nervous system infections	2.08 (1.30–3.32)	0.002	1.43 (0.81–2.54)	0.22
Gastrointestinal infections	1.75 (1.53–2.01)	<0.001	1.25 (1.06–1.47)	0.009
Urinary tract infections	2.64 (2.48–2.81)	<0.001	1.69 (1.57–1.82)	<0.001
Infections leading to ICU admission	2.76 (2.55–3.00)	<0.001	2.06 (1.86–2.29)	<0.001

^aAdjusted for age, sex, monthly premium, annual number of outpatient visits, annual number of hospitalizations, and comorbidities including diabetes mellitus, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, chronic hepatic disease or cirrhosis, chronic kidney disease or renal failure, nephrotic syndrome, connective tissue disease or systemic vasculitis, psoriasis, dementia, Parkinson's disease, depression, and malignancies.

aHR: adjusted hazard ratio; BP: bullous pemphigoid; CHR: crude hazard ratio; 95% CI: 95% confidence interval; ICU: intensive care unit.

Table IV. Risk factors of any serious infection in patients with bullous pemphigoid (N = 14,048)

Risk factors	Serious infections (n = 5,006) n (%)	No serious infections (n = 7,294) n (%)	CHR (95% CI)	p-value	aHR ^a (95% CI)	p-value	aHR ^b (95% CI)	p-value
Age, years								
≥81	2,848 (56.9)	3,568 (48.9)	1.30 (1.22–1.37)	<0.001	1.13 (1.07–1.19)	<0.001	1.15 (1.09–1.22)	<0.001
<81	2,158 (43.1)	3,726 (51.1)	Ref		Ref		Ref	
Sex								
Female	2,451 (49.0)	3,505 (48.1)	1.03 (0.97–1.09)	0.32	1.05 (1.00–1.11)	0.04	1.06 (1.01–1.12)	0.02
Male	2,555 (51.0)	3,789 (51.9)	Ref		Ref		Ref	
Monthly premium, USDs								
≥730	2,364 (47.2)	4,073 (55.8)	0.78 (0.740–0.83)	<0.001	0.83 (0.78–0.87)	<0.001	0.82 (0.78–0.87)	<0.001
<730	2,642 (52.8)	3,221 (44.2)	ref		ref		ref	
Diabetes mellitus								
Present	2,700 (53.9)	3,513 (48.2)	1.22 (1.16–1.29)	<0.001	1.16 (1.10–1.22)	<0.001	1.16 (1.10–1.23)	<0.001
Absent	2,306 (46.1)	3,781 (51.8)	Ref		Ref		Ref	
Heart failure								
Present	1,619 (32.3)	1,899 (26.0)	1.24 (1.17–1.31)	<0.001	1.07 (1.07–1.13)	0.03	1.07 (1.01–1.13)	0.02
Absent	3,387 (67.7)	5,395 (74.0)	Ref		Ref		Ref	
CVD								
Present	2,460 (49.1)	2,964 (40.6)	1.29 (1.22–1.36)	<0.001	1.18 (1.12–1.25)	<0.001	1.19 (1.13–1.25)	<0.001
Absent	2,546 (50.9)	4,330 (59.4)	Ref		Ref		Ref	
COPD								
Present	1,655 (33.1)	1,897 (26.0)	1.26 (1.19–1.34)	<0.001	1.13 (1.06–1.19)	<0.001	1.11 (1.05–1.18)	<0.001
Absent	3,351 (66.9)	5,397 (74.0)	Ref		Ref		Ref	
CLD or cirrhosis								
Present	797 (15.9)	1,229 (16.8)	0.94 (0.87–1.02)	0.12	0.96 (0.90–1.04)	0.32	0.97 (0.90–1.04)	0.36
Absent	4,209 (84.1)	6,065 (83.2)	Ref		Ref		Ref	
CKD or renal failure								
Present	1,114 (22.3)	1,412 (19.4)	1.15 (1.07–1.22)	<0.001	1.10 (1.03–1.17)	0.003	1.12 (1.05–1.19)	<0.001
Absent	3,892 (77.7)	65,882 (80.6)	Ref		Ref		Ref	
Nephrotic syndrome								
Present	80 (1.6)	100 (1.4)	1.18 (0.95–1.47)	0.14	1.15 (0.94–1.41)	0.18	1.16 (0.94–1.42)	0.16
Absent	4,926 (98.4)	7,194 (98.6)	Ref		Ref		Ref	
CTD or systemic vasculitis								
Present	105 (2.1)	191 (2.6)	0.84 (0.69–1.02)	0.08	1.00 (0.83–1.21)	0.97	0.98 (0.82–1.18)	0.84
Absent	4,901 (97.9)	7,103 (97.4)	Ref		Ref		Ref	
Psoriasis								
Present	121 (2.4)	230 (3.2)	0.80 (0.67–0.96)	0.02	0.88 (0.74–1.04)	0.13	0.86 (0.73–1.02)	0.08
Absent	4,885 (97.6)	7,064 (96.8)	Ref		Ref		Ref	
Dementia								
Present	2,523 (50.4)	3,012 (41.3)	1.31 (1.24–1.38)	<0.001	1.17 (1.10–1.24)	<0.001	1.17 (1.11–1.24)	<0.001
Absent	2,483 (49.6)	4,282 (58.7)	Ref		Ref		Ref	
Parkinson's disease								
Present	849 (17.0)	1,046 (14.3)	1.15 (1.07–1.24)	<0.001	1.07 (1.00–1.15)	0.05	1.07 (1.00–1.15)	0.05
Absent	4,157 (83.0)	6,248 (85.7)	Ref		Ref		Ref	
Depression								
Present	246 (4.9)	377 (5.2)	0.97 (0.85–1.10)	0.60	0.95 (0.85–1.08)	0.45	0.95 (0.85–1.08)	0.45
Absent	4,760 (95.1)	6,917 (94.8)	Ref		Ref		Ref	
Malignancy								
Present	442 (8.8)	716 (9.8)	0.92 (0.83–1.01)	0.07	0.94 (0.86–1.03)	0.20	0.95 (0.86–1.04)	0.25
Absent	4,564 (91.2)	6,578 (90.2)	Ref		Ref		Ref	
Regimens of systemic SISs ^c								
SCSs +other SISs	299 (6.0)	4,30 (5.9)	1.88 (1.66–2.12)	<0.001	1.80 (1.60–2.03)	<0.001		
SCSs alone	3,666 (73.2)	4,070 (55.8)	2.21 (2.07–2.36)	<0.001	1.96 (1.83–2.10)	<0.001		
SISs other than SCSs	17 (0.3)	48 (0.7)	0.97 (0.61–1.54)	0.89	1.10 (0.70–1.73)	0.67		
No SISs ^d	1,024 (20.5)	2,746 (37.6)	Ref		Ref			
Mean dose of SCSs ^e								
≥1 DDD/day	1,990 (39.8)	1,901 (26.1)	2.63 (2.45–2.82)	<0.001			2.33 (2.16–2.52)	<0.001
≥0.5, <1 DDD/day	1,017 (20.3)	1,126 (15.4)	2.16 (1.99–2.35)	<0.001			1.97 (1.81–2.14)	<0.001
<0.5 DDD/day	958 (19.1)	1,473 (20.2)	1.62 (1.49–1.76)	<0.001			1.53 (1.41–1.66)	<0.001
No SCSs	1,041 (20.8)	2,794 (38.3)	Ref				Ref	

^aAdjusted for age, sex, monthly premium, comorbidities listed in Table I, and therapeutic regimens of systemic immunosuppressants, excluding the factor used for categorization in individual analyses. ^bAdjusted for age, sex, monthly premium, comorbidities listed in Table I, and mean dose of systemic corticosteroids, excluding the factor used for categorization in individual analyses. ^cSystemic immunosuppressant use for bullous pemphigoid within 12 weeks before the study endpoint; these immunosuppressants included corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, cyclophosphamide, and chlorambucil. ^dAmong these patients, 75.4% (2,841/3,770) had prescription records of topical corticosteroids. ^eMean dose of systemic corticosteroids within 12 weeks before the study endpoint; the defined daily dose is prednisolone 10 mg/day or equivalent doses of other corticosteroid compounds.

aHR: adjusted hazard ratio; BP: bullous pemphigoid; CHR: crude hazard ratio; 95% CI: 95% confidence interval; CKD: chronic kidney disease; CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; CTD: connective tissue disease; CVD: cerebrovascular disease; DDD: defined daily dose; SCSs: systemic corticosteroids; SISs: systemic immunosuppressants; USDs: US dollars.

Susceptibility to infections in patients with BP is probably multifactorial. Recent exposure to systemic corticosteroids was the strongest risk factor identified in the current study, a finding supported by previous findings that treatment with systemic corticosteroids is associated with an increased risk of infectious complications in patients with BP (8, 13, 23). The current study found a dose-dependent relationship between the daily dose of corticosteroids and the risk of serious infections, suggesting that treatment with the lowest effective dose and early tapering of systemic corticosteroids are important in the management of BP. Notably, the risk even increased in those who received prednisolone equivalent doses of 5 mg or less daily. A previous study reported an additional risk of infection in patients with BP complicated by Cushing syndrome, implying that the duration of corticosteroid exposure might also play a role (23). However, the duration-dependent effect of systemic corticosteroids on the risk of serious infections was not easily explored in the current study because of survivor treatment selection bias that potentially occurs in survival analysis (26). In addition to systemic corticosteroids, whole-body application of high-potency topical corticosteroids is also considered first-line treatment for BP, since it is equally effective and could lead to lower morbidity and mortality (24, 27). The current findings add evidence to this perspective, since those who did not use systemic immunosuppressants in our BP cohort had a significantly lower risk of serious infections, and most were treated with topical corticosteroids.

The use of systemic immunosuppressants other than corticosteroids was not an independent predictor of serious infections in the current study. This finding is in agreement with our previous analysis in which BP patients treated with corticosteroid-sparing immunosuppressants for more than 3 consecutive months had a significantly lower mortality rate than those treated with systemic corticosteroids alone (17), since serious infection is among the leading causes of mortality in these patients (7–11). Furthermore, corticosteroid use is associated with an increased risk of severe bacterial infections in patients with rheumatoid arthritis vs those solely treated with corticosteroid-sparing immunosuppressants, many of which are also commonly used as adjuvant therapy for BP (28, 29). Besides, several non-immunosuppressive agents with anti-inflammatory properties (e.g. doxycycline, omalizumab, and dupilumab) have been reported to be as effective as systemic corticosteroids for treating BP (30–32). Given these findings, adding corticosteroid-sparing agents to the therapeutic regimen with early withdrawal of corticosteroids may be crucial in preventing serious infections in patients with BP.

Strength and limitations

The strengths of this study include analysis of population-based cohorts with detailed treatment information, which

allowed for adequate statistical power and less susceptibility to both selection and attrition bias compared with previous single-centre studies. The study also has certain limitations. First, disease severity was unavailable in the NHIRD, and hence was not evaluated in the current study. However, since patients with severe BP tend to receive more intensive immunosuppressive therapy, it would have been difficult to separate the effects of disease severity and immunosuppressant use on the risk of serious infections. Second, our analyses focused on infections that were severe enough for hospitalization. Minor infections that could be managed in outpatient departments were not analysed. Lastly, although we controlled for the most important factors, potential confounders associated with infections, such as smoking, alcohol, obesity, and nutritional status, remained uncontrolled because of lack of relevant data in the NHIRD.

Conclusion

Patients with BP had an increased risk of developing serious infections requiring hospitalization. Systemic corticosteroid use was the most significant factor in predicting serious infections, while advanced age, female sex, low income, and comorbidities also played a role. These findings highlight the importance of adopting topical corticosteroids or corticosteroid-sparing therapies in the treatment of BP, especially for patients with multiple risk factors for serious infection.

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The authors have no conflicts of interest to declare.

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