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ORIGINAL RESEARCH ARTICLE

Clinical Outcomes and Prognostic Factors in Bullous Pemphigoid Patients: A 15-Year Review in China

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Abstract

Background There are limited data on clinical outcomes and prognosis factors for bullous pemphigoid (BP) at long-term follow-up.

Objective We aimed to investigate the clinical outcomes and prognostic factors in BP patients.

Methods This retrospective study was performed between January 1, 2009 and December 31, 2023 in Shandong Province, China. The primary outcomes were the rates and predictive factors of mortality, complete remission off-therapy (CROT), and relapse by Cox proportional hazards models or logistic regression analyses. Nomograms for BP mortality and CROT were also described.

Results Of the 1063 BP patients enrolled, 45 were excluded due to loss to follow-up. The cohort comprised 1018 BP patients to analyze. A total of 344 (33.8%) patients died, with cumulative 1-, 3-, and 5-year mortality rates of 22.8%, 31.2%, and 34.5%, respectively. Increased age at onset (HR = 1.08), body surface area (BSA) involvement 10–30%, BSA involvement > 30% (HR = 7.19; HR = 9.84, respectively), double-positive IgG and C3 on DIF (HR = 1.37), and systemic corticosteroid in combination with immunosuppressants treatments (HR = 0.50) were associated with mortality. A total of 321 (31.5%) patients achieved CROT. Cumulative CROT rates at 1, 3, and 5 years were 10.9%, 32.9%, and 47.5%, respectively. Shorter diagnosis delay time (HR = 1.01), baseline anti-BP180 antibody < 50 IU/mL (HR = 1.48) and systemic drugs other than corticosteroid treatment (HR = 1.68) were associated with CROT. Predictive models demonstrated outstanding performance in classifying mortality at 1, 3, and 5 years (AUCs 0.83, 0.86, 0.88), but moderate classification for CROT (AUCs 0.67, 0.62, 0.63). A total of 749 (73.6%) patients experienced relapses.

Conclusions This study, the first large cohort to examine long-term outcomes in BP patients, identifies risk factors for mortality and CROT, offering key insights for clinicians to improve prognosis and reduce relapse rates.

1 Introduction

Bullous pemphigoid (BP) stands as the most prevalent form of autoimmune bullous disease (AIBD) globally, targeting the antigens BP180NC16A and/or BP230. It falls within the pemphigoid group and clinically manifests as tense blisters and erosions on the skin or mucous membranes near the skin surface [1–3]. The global incidence of BP is around 0.0419 per 1000 person-years, with a clinic-based prevalence averaging approximately 0.79% [4]. With the increasing average life expectancy (LE) worldwide, BP's incidence and prevalence are notably rising [2, 5–7], posing a significant burden on healthcare systems.

BP typically onsets in the late 70s, necessitating long-term treatment with corticosteroid and/or immunosuppressants (IS) or other advanced treatment regimens with varying therapeutic effects [8, 9]. Hence, managing BP in the long term is challenging. Clinical practice suggests that most BP patients are treated for many years [10, 11]. Moreover, as it primarily affecting older individuals, BP is marked by a poor prognosis, owing to its high mortality rate ranging from 20.6% to 63.1% [7, 12, 13], and its tendency to relapse [14, 15]. Enhancing the management of BP requires understanding prognostic factors and clinical regression statistics to identify patients at high risk of disease progression and

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Key Points

Our 15-year cohort study identified clinical outcomes of mortality, complete remission off-therapy (CROT), and relapse in a large cohort (1018 patients) in the referral center (Dermatopathology Center in Shandong province) in China.

The cumulative mortality rates at 1, 3, and 5 years were 22.8%, 31.2%, and 34.5%, respectively. Predictors of mortality included age at onset, extent of body surface area involvement, deposition of IgG and C3 detected via direct immunofluorescence (DIF), and the treatment regimen.

The cumulative rates of CROT at 1, 3, and 5 years were 10.9%, 32.9%, and 47.5%, respectively. Predictors of CROT included delay in diagnosis, baseline levels of anti-BP180 antibodies (with a cutoff value of 50 IU/mL), and the treatment regimen. Additionally, 73.6% of patients with BP experienced relapses. Predictive models, nomograms for CROT and mortality outcomes, and risk factors for relapse were also identified.

its associated outcomes. However, few studies have reported the clinical outcomes of the entire disease post-treatment. Previous literature has predominantly focused on mortality, risk factors of mortality, or treatment analyses, with results varying by geographical region of BP [10, 12, 16–22]. Data on other clinical outcomes, such as rates of complete remission off-therapy (CROT), complete remission on minimal therapy, and relapse, remain unclarified.

Herein, we conducted a comprehensive and systematic analysis of clinical outcomes and prognostic factors of 1018 BP patients, extensively examining associated risk factors. The study's findings can directly inform clinical practice by providing clinicians with evidence-based guidance on managing and following up with BP patients. The development of predictive models, such as the nomograms for mortality and CROT, offer practical tools for risk assessment and decision making in clinical settings.

2 Methods

2.1 Study Design and Participants

This was a retrospective, observational, non-interventional study of BP patients. Eligible patients were diagnosed at the Hospital for Skin Diseases in Shandong Province (Shandong Provincial Institute of Dermatology and Venereology). This hospital serves as a referral alliance center for dermatology in Shandong province, catering to a population of 100 million in China. Patients with suspected AIBD are referred center for immunopathology confirmation. This cohort included all BP patients from January 1, 2009, until December 31, 2023. All patients in this study presented with characteristic clinical features of BP, including pruritus and predominantly tense blisters or non-bullous skin manifestations, along with histopathological findings consistent with the disease. The diagnosis was confirmed by positive direct immunofluorescence (DIF) results showing linear or n-serrated linear deposits of immunoglobulin G (IgG) and/or complement component 3 (C3) along the epidermal basement membrane zone, in conjunction with at least one positive serologic test of indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay (ELISA) examinations [23]. This study received approval from the Institutional Review Board at the Shandong Provincial Institute of Dermatology and Venereology (No. 20221223KYKTKS001). The findings are reported based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

After obtaining informed consent, trained physicians extracted clinical data from medical records using a standardized format. Follow-ups were conducted during outpatient visits via a standardized questionnaire and, for those unable to attend in person, through telephone interviews using the same questionnaire, covering the full treatment period. Data encompassed baseline demographics, clinical characteristics, laboratory examinations, therapeutic regimens, and follow-up clinical outcomes. Variables retrieved from the medical records included gender, age at onset, delay time of diagnosis (the interval between onset and diagnosis), medical history, associated comorbidities, body surface area (BSA) involvement (categorized as <10%, 10–30%, and > 30%, defined as mild, moderate, and severe, respectively) [24], mucosal involvement, DIF of C3, IgG, immunoglobulin M (IgM), immunoglobulin A (IgA) antibodies, IIF of IgG antibody, levels of circulating autoantibodies against anti-BP180 and anti-BP230 by ELISA (positive was defined as > 20 IU/mL). Therapeutic regimens prior to disease outcome consisted of systemic drugs other than corticosteroids (tetracyclines or minocycline with niacinamide), systemic corticosteroid monotherapy (typically initiated at a dose of 0.5–1 mg/kg/

day, with adjustments made based on the patient's response), and systemic corticosteroids in combination with immunosuppressive drugs. Patients used topical steroids as focal treatments. All patients were followed up until occurrence of CROT events or mortality, the end of follow-up time, or loss follow-up. For patients with regular follow-ups at our hospital, all baseline, clinical, and outcome data were obtained from the Hospital Information System. For those who sought follow-up care elsewhere, baseline and clinical data were retrieved from our system, while outcome data were collected via standardized questionnaires during scheduled visits or through active outreach efforts.

2.2 Outcomes

One significant outcome was mortality rate, defined as the percentage of patients who died at 1-, 3- and 5-year timepoints from the initial BP diagnosis.

Other significant outcomes examined [25], included CROT and non-CROT categories with complete remission on minimal therapy, partial remission on minimal therapy, partial remission off therapy, and relapse [26]. CROT was characterized by the absence of new or established lesions while the patient was off all BP therapy for at least 2 months [25]. Relapse rates and CROT were calculated for 1, 3, and 5 years. Time of CROT was defined by the interval between the date of initial BP diagnosis and the date of CROT. Additionally, patients who died were assessed based on whether they achieved CROT before mortality. Moreover, complete remission on minimal therapy referred to patients receiving prednisone (or equivalent) at ≤ 0.1 mg/kg/day and/or minimal adjuvant therapy for more than 2 months [24]. Partial remission on minimal therapy is the presence of transient new lesions that heal without scarring within 1 week while the patient is receiving minimal therapy for more than 2 months. Partial remission off-therapy was characterized by new lesions that heal within 1 week and off all BP therapy for more than 2 months [25].

Relapse was defined as the appearance over 3 new lesions within one month, which did not heal spontaneously within 1 week or as the extension of established lesions in patients who had previously achieved disease control [25].

2.3 Statistical Analysis

The categorical variables presented as frequency (percentage), and continuous variables as mean (standard deviation [SD]) or median (range). The median follow-up time was estimated with the reverse Kaplan-Meier method. Survival curves were estimated by the Kaplan-Meier method. Univariate and multivariate Cox regression was used to search for potential variables and CROT or mortality. Identified factors in univariate analysis and the important clinical variables were used to discover independent predicting factors in multivariate analysis. The results of Cox analyses are expressed as a hazard ratio (HR) and 95% confidence interval (95% CI). Besides, we developed a nomogram with the significant variable in the multivariate cox analyses to predict patients' 1-, 3-, and 5-year CROT and survival probability after BP diagnosis. The cutoff values for anti-BP180 and anti-BP230 antibody related to CROT or mortality were determined by X-tile software [27]. The nomogram's reliability and accuracy were assessed via the concordance index (C-index), area under the time-dependent receiver operating characteristic curve (AUC) by 5-fold cross-validation. The association between relative factors and BP relapse was estimated through logistic regression analyses.

Statistical analyses were conducted using RStudio, version 4.3.2 (R Foundation for Statistical Computing) with the 'survival,' 'survminer', 'foreign', 'timeROC', 'rms', 'riskRegression', and 'caret' packages. In all analyses, the level of significance was set at a 2-sided $p < 0.05$. We used the pairwise.t.test function and pairwise Nominal Independence function with Bonferroni correction method in R software for multiple comparisons. The flow diagram of study design is shown in Fig. 1.

3 Results

3.1 Characteristics of Study Population

Of the 1063 BP patient, 45 were excluded due to loss to follow-up. Consequently, the study cohort comprised 1018 BP patients, consisting of 589 (57.9%) males and 429 (42.1%) females, all of Chinese nationality. The mean age at BP onset was 69.7 years. The mean delay from onset of skin symptoms to diagnosis was 7.3 months. Comorbidities were present in 821 (80.6%) patients, with hypertension being the most common (496, 48.7%), followed by neurological diseases (175, 17.2%). Regarding disease severity, 462 (45.4%), 223 (21.9%), and 333 (32.7%) patients had mild BSA involvement (<10%), moderate BSA involvement (10–30%), and severe BSA involvement (> 30%), respectively. Mucosal involvement was observed in 260 (25.5%) patients with BP.

All patients tested positive for IgG and/or C3 antibodies by DIF. Of these, 35.6% showed double positivity for IgG and C3, while 64.4% showed single positivity. Additionally, IgM positivity was observed in only 23.8% of patients, double positivity for IgM and IgA in 5.1%, and positive IgA in only 1.0%, with the remaining 70.1% negative for IgM and IgA. A total of 78.2% (577/738) patients were IgG-positive by IIF with median IgG titers of 40.0 (0–2560.0). Additionally, 77.4% (652/842) patients were positive by anti-BP180 antibody and 37.3% (314/842) patients were

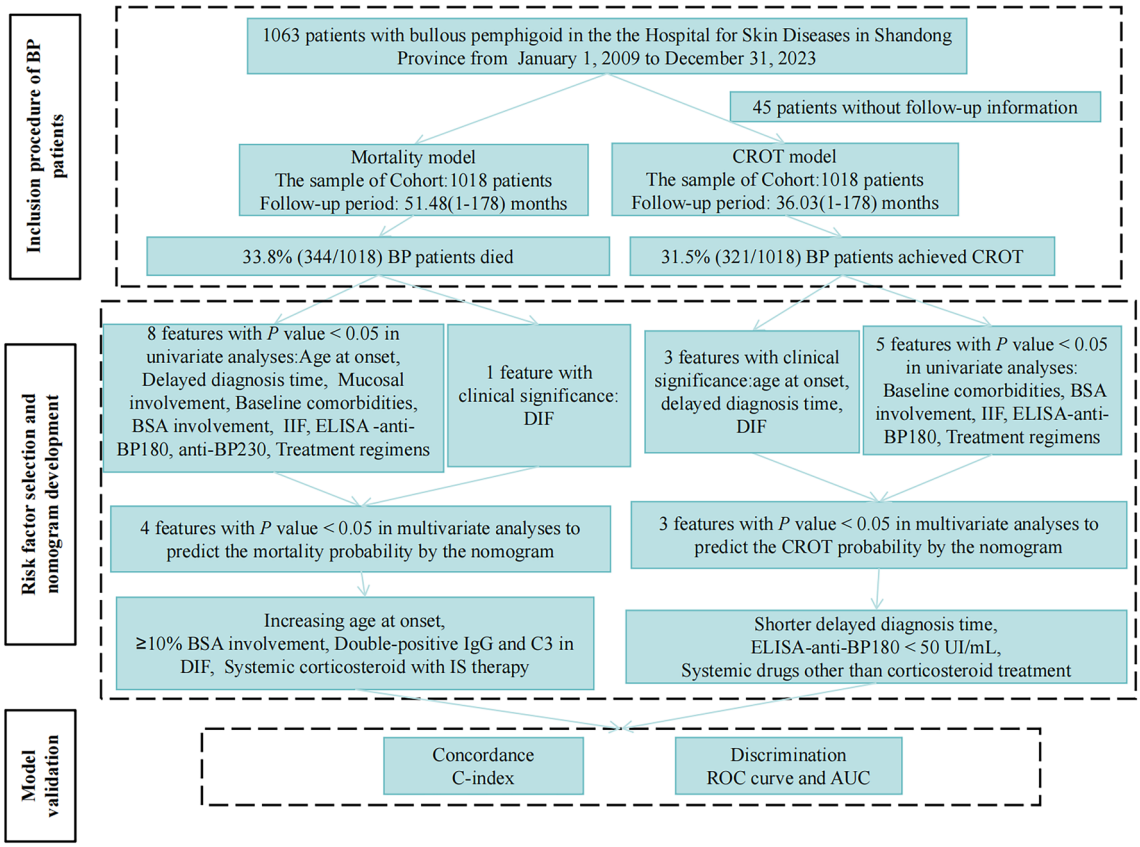

Fig. 1 The flow chart of study design

positive by anti-BP230 antibody; the median anti-BP180 antibody and anti-BP230 antibody were 191.8 (0–246.0) and 2.0 (0–209.9). Therapeutic regimens included systemic corticosteroid with IS treatments (492, 48.3%), systemic corticosteroid monotherapy (335, 32.9%), and systemic drugs other than corticosteroid therapy (191, 18.8%). The IS medications consisted of cyclophosphamide (372, 75.6%), mycophenolate mofetil (83, 16.9%), methotrexate (26, 5.3%), cyclosporine (6, 1.2%), and azathioprine (5, 1.0%). Further details of clinical characteristics at baseline are provided in Table 1.

3.2 Mortality Analysis

With a median (range) follow-up period of 51.48 (1–178) months, 344 (33.8%) patients with BP had passed away and 674 (66.2%) had survived. The 1-, 3-, and 5-year mortality rates were 22.8%, 31.2%, and 34.5%, respectively (Fig. 2a). Of the patients who died, 123 (35.8%) died of known diseases including cardiovascular diseases (43, 35.0%), neurological diseases (32, 26.0%), COVID-19 infection (19, 15.4%), cancer (15, 12.2%), renal failure (13, 10.6%), and accidents (1, 0.8%). Among 32 patients who died of neurological diseases, including stroke (27 cases), cerebral hemorrhage (4 cases), and Parkinson's disease (1 case). Among the three treatment groups, mortality rates were highest in the systemic drugs other than corticosteroid group (40.8%), followed by the systemic corticosteroid group (34.6%) and the systemic corticosteroid combined with IS therapy group (30.5%) (Supplementary Table S1).

After both the univariate and multivariate Cox regression analyses, we identified three significant factors increasing mortality with increasing age at onset (HR = 1.08; 95%CI 1.06–1.10; $p < 0.0001$), > 10% BSA involvement (10–30%, HR = 7.19; 95%CI 4.35–11.86; $p < 0.0001$; > 30%, HR = 9.84; 95%CI 6.30–15.40; $p < 0.0001$), and double-positive for IgG and C3 antibodies on DIF (HR = 1.37; 95%CI 1.0–1.87; $p = 0.049$). Notably, systemic corticosteroid in combination with IS treatments (HR = 0.50; 95%CI 0.33–0.75; $p = 0.00080$) significantly decreased the risk of mortality compared to systemic drugs other than corticosteroid group (Table 2).

A predictive model for mortality was formulated, utilizing these significant risk factors, including age at onset, BSA involvement, positive antibodies on DIF, and treatment regimens. This model demonstrates excellent predictive abilities for 1-, 3-, and 5-year mortality rates, with AUC values (0.83, 0.86, and 0.88, respectively) (Fig. 2b). The C-index of

Table 1 Baseline demographics and clinical characteristics of 1018 patients with bullous pemphigoid

Characteristic	Patients, no. (%)
Age at onset, mean ± SD, y	69.7 ± 13.8
Sex	
Male	589 (57.9)
Female	429 (42.1)
Diagnosis delay time, mean ± SD, m	7.3 ± 15.0
Associated comorbidities	821/1018 (80.6)
Hypertension	496/1018 (48.7)
Neurological diseases	175/1018 (17.2)
Diabetes	170/1018 (16.7)
CVD	166/1018 (16.3)
Tumors	63/1018 (6.2)
BSA involvement[a]	
Mild (< 10%)	462/1018 (45.4)
Moderate (10–30%)	223/1018 (21.9)
Severe (> 30%)	333/1018 (32.7)
Mucosal involvement	260/1018 (25.5)
DIF[b]	
IgG or C3 antibodies	
IgG^+ and $C3^+$	362/1018 (35.6)
IgG^+ or $C3^+$	656/1018 (64.4)
IgM or IgA antibodies[c]	
IgM^+ and/or IgA^+	304/1018 (29.9)
IgM^- and IgA^-	714/1018 (70.1)
IIF[d]	577/738 (78.2)
Positive ELISA antibody	
Anti-BP180 antibody	652/842 (77.4)
Anti-BP230 antibody	314/842 (37.3)
Treatment regimens[e]	
Systemic drugs other than corticosteroid[f]	191/1018 (18.8)
Systemic corticosteroid monotherapy	335/1018 (32.9)
Systemic corticosteroid with IS	492/1018 (48.3)

BSA body surface area, *CVD* cardiovascular disease, *C3* complement component 3, *DIF* direct immunofluorescence, *ELISA* enzyme linked immunosorbent assay, *IgA* immunoglobulin A, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *IIF* indirect immunofluorescence, *IS* immunosuppressants

[a] BSA involvement including three types of mild (<10%), moderate (10–30%), severe (> 30%)

[b] IgG, C3, IgM and IgA antibodies with DIF

[c] Positive antibodies with for IgM and/or IgA along with C3 and/or IgG

[d] Positive for IgG antibody titer with IIF

[e] Treatment regimens prior to disease outcome

[f] Tetracyclines or minocycline with niacinamide

survival predictive model is 0.81 ± 0.01. For further validation, the results of a 5-fold cross-validation, including AUC and C-index, were described in Supplementary Table S2.

Furthermore, incorporating these aforementioned significant indicators, we have constructed a nomogram to simplify the practical application of mortality prediction (Fig. 2c). For instance, consider a 70-year-old patient with BP, BSA involvement exceeding 20%, and both IgG and C3 positive on DIF. According to the nomogram, this patient's total score would be 95 points (70 points for age, 22.5 points for BSA involvement, and 2.5 points for both IgG and C3 positivity on DIF. Based on this score, the predicted one-year mortality rate with a treatment regimen of systemic corticosteroid combined with IS would be 25%, with a projected mortality rate of 45% by the fifth year. In comparison, if the patient receives systemic drugs other than corticosteroid therapy, the one-year mortality rate rises significantly to 45%, with a long-term mortality rate of 70%. Conversely, with systemic corticosteroid monotherapy, the one-year mortality rate is 35%, and the long-term mortality rate is 55%.

3.3 Complete Remission Off-Therapy Analysis

A total of 321 (31.5%) achieved CROT and 697 (68.5%) patients were non-CROT. The cumulative rates of CROT at 1, 3, and 5 years were 10.9%, 32.9%, and 47.5%, respectively (Fig. 3a). The median time to achieve CROT was 66.0 months. Among non-CROT patients, 233 (22.9%) achieved complete remission on minimal therapy, 380 (37.3%) achieved partial remission on minimal therapy, and 84 (8.3%) achieved partial remission off therapy. Among three treatment groups, the percentages of patients achieving CROT were 39.8% (systemic drugs other than corticosteroid treatment group), 31.7% (systemic corticosteroid combined with IS therapy group), and 26.6% (systemic corticosteroid treatment group) in the Supplementary Table S1, respectively.

Through univariate and multivariate Cox regression analyses, patients with a shorter diagnosis delay time, baseline anti-BP180 antibody (< 50 IU/mL) and systemic drugs other than corticosteroid treatment had a 1.01-fold (HR = 1.01; 95%CI 1.0–1.03; p = 0.0069), a 1.48-fold (HR = 1.48; 95%CI 1.06–2.07; p = 0.020), and a 1.68-fold (HR = 1.68; 95%CI 1.12–2.52; p = 0.013) chance of achieving CROT (Table 3). This model demonstrates medium predictive abilities for 1-, 3-, and 5-year CROT rates, achieving AUC values of 0.67, 0.62, and 0.63, respectively (Fig. 3b). The C-index of CROT predictive model was 0.65 ± 0.02. The 5-fold cross-validation's AUC and C-index were described in Supplementary Table S3.

A CROT predictive model was depicted as a nomogram for practical application with these aforementioned significant indicators, including diagnosis delay time, baseline anti-BP180 antibody, and treatment regimens (Fig. 3c). For example, consider a 65-year-old BP patient with a diagnosis delay of less than 20 months and an anti-BP180 antibody

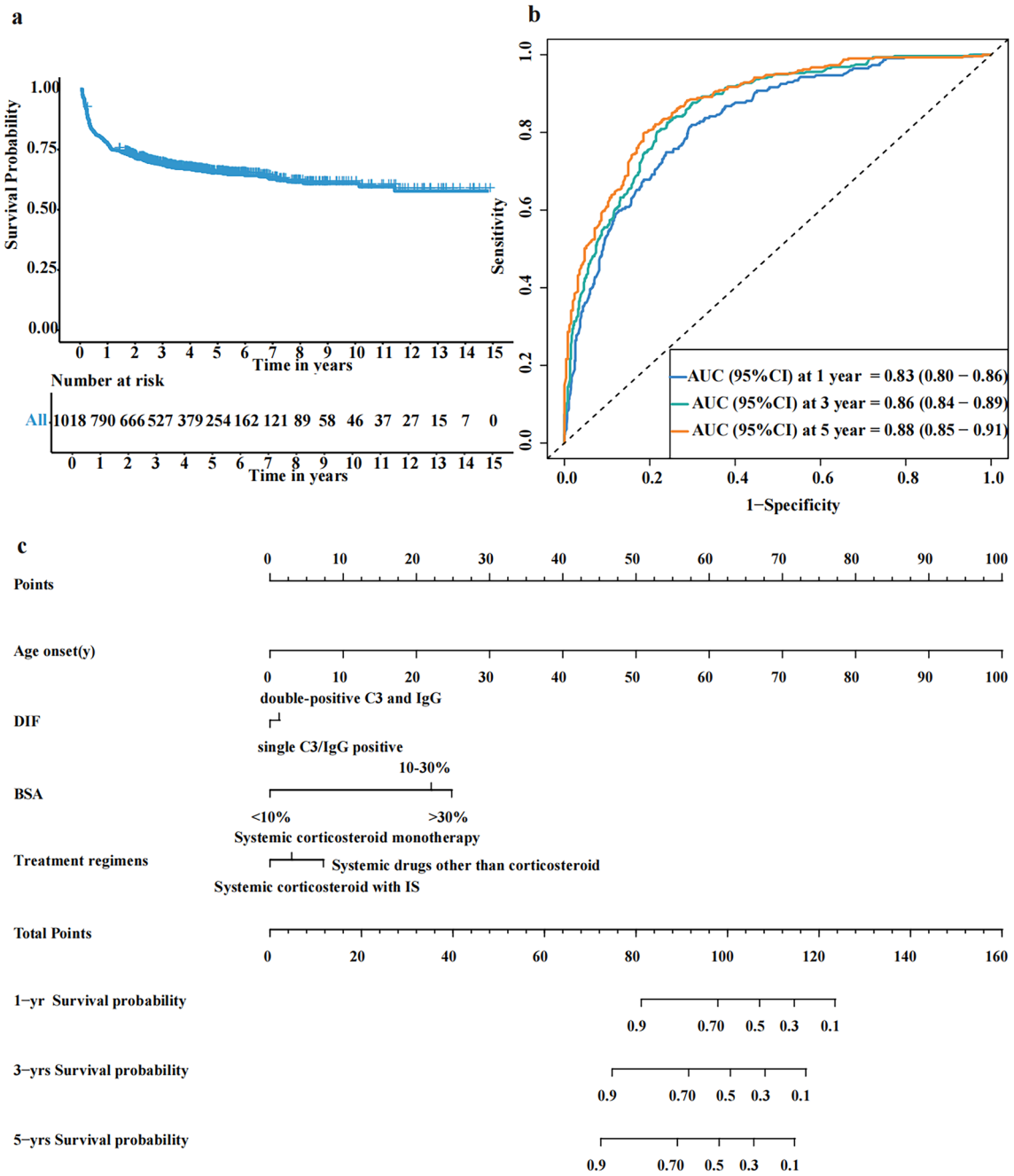

Fig. 2 Mortality outcome and prediction of bullous pemphigoid (BP): **a** Survival probability of BP; **b** Receiver operating characteristic curve with survival prediction model in the 1 year (blue), 3 years (green) and 5 years (orange); **c** The nomogram of mortality prediction

level of 100 IU/mL (> 50 IU/mL). According to the nomogram, this patient's total score would be 85 points (85 points for diagnosis delay and 0 point for anti-BP180 antibody levels). Based on this score, the predicted one-year CROT rate with a treatment regimen of systemic drugs other than corticosteroid is over 10%, with a projected CROT rate over 55% by the fifth year. In contrast, if the patient receives systemic corticosteroid combined with IS therapy, the one-year CROT rate is less than 10%, with a long-term CROT rate of 40%. With corticosteroid monotherapy, the one-year CROT rate is less than 10%, and the long-term CROT rate is less than 40%.

Table 2 Multivariate Cox regression analyses of mortality factors with bullous pemphigoid

Characteristic, no. (%)	Survival ($n = 674$)	Mortality ($n = 344$)	Univariate analyses		Multivariate analyses	
			HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at onset, mean ± SD, y	65.8 ± 13.8	77.5 ± 10.0	1.08 (1.07–1.09)	**<0.0001**	1.08 (1.06–1.10)	**<0.0001**
Sex						
Male	387/674 (57.4)	202/344 (58.7)	1.04 (0.84–1.29)	0.70	NA	NA
Female	287/674 (42.6)	142/344 (41.3)	1 [Reference]	NA	NA	NA
Diagnosis delay time, mean ± SD, m	8.3 ± 17.1	5.1 ± 9.1	0.98 (0.97–0.99)	**0.0019**	1.0 (0.99–1.02)	0.68
Mucosal involvement						
Yes	192/674 (28.5)	68/344 (19.8)	0.68 (0.52–0.88)	**0.0041**	0.71 (0.49–1.03)	0.075
No	482/674 (71.5)	276/344 (80.2)	1 [Reference]	NA	1 [Reference]	NA
Baseline comorbidities						
Yes	525/674 (77.9)	296/344 (86.0)	1.66 (1.22–2.25)	**0.0011**	1.09 (0.66–1.78)	0.74
No	149/674 (22.1)	48/344 (14.0)	1 [Reference]	NA	1 [Reference]	NA
BSA involvement						
Mild (<10%)	406/674 (60.2)	56/344 (16.3)	1 [Reference]	NA	1 [Reference]	NA
Moderate (10–30%)	119/674 (17.7)	104/344 (30.2)	4.46 (3.22–6.18)	**< 0.0001**	7.19 (4.35–11.86)	**< 0.0001**
Severe (> 30%)	149/674 (22.1)	184/344(53.5)	6.05 (4.48–8.16)	**< 0.0001**	9.84 (6.30–15.40)	**< 0.0001**
DIF[a]						
IgG or C3 antibodies						
IgG^+ and $C3^+$	243/674 (36.1)	119/344(34.6)	0.99 (0.79–1.23)	0.90	1.37 (1.0–1.87)	**0.049**
IgG^+ or $C3^+$	431/674 (63.9)	225/344(65.4)	1 [Reference]	NA	1 [Reference]	NA
IgM or IgA antibodies[b]						
IgM^+ and/or IgA^+	196/674 (29.1)	108/344(31.4)	1.01 (0.81–1.28)	0.91	1.34 (0.93–1.93)	0.12
IgM^- and IgA^-	478/674 (70.9)	236/344(68.6)	1 [Reference]	NA	1 [Reference]	NA
IIF[c]	40.0 (0–2560.0)	160.0 (0–2560.0)	1.27 (1.13–1.43)[d]	**< 0.0001**	1.03 (0.88–1.20)[d]	0.70
ELISA antibody						
Anti-BP180 antibody[e]	176.7 (0–231.0)	200 (0–246.0)	1.61 (1.27–2.05)[e]	**0.00011**	1.04 (0.77–1.41)[e]	0.79
Anti-BP230 antibody[f]	0 (0–209.9)	15 (0–209.9)	1.40 (1.10–1.77)[f]	**0.0058**	0.84 (0.61–1.16)[f]	0.30
Treatment regimens[g]						
Systemic drugs other than corticosteroid[h]	113/674 (16.8)	78/344 (22.7)	1 [Reference]	NA	1 [Reference]	NA
Systemic corticosteroid monotherapy	219/674 (32.5)	116/344 (33.7)	0.83 (0.62–1.11)	0.21	0.68 (0.46–1.02)	0.060
Systemic corticosteroid with IS	342/674 (50.7)	150/344 (43.6)	0.67 (0.51–0.88)	**0.0037**	0.50 (0.33–0.75)	**0.00080**

Bold indicates significant values ($p < 0.05$)

BSA body surface area, *CI* confidence interval, *C3* complement component 3, *DIF* direct immunofluorescence, *ELISA* enzyme linked immunosorbent assay, *HR* hazard ratio, *IIF* indirect immunofluorescence, *IgA* immunoglobulin A, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *IS* immunosuppressants, *NA* not applicable

[a]Antibodies with C3, IgG, IgM and IgA antibodies with DIF

[b]Positive for IgM and/or IgA along with C3 and/or IgG with DIF

[c]Positive for IgG antibody titer with IIF

[d]The unit of IIF is $\log_{10}$ conversion of original value in the regression model

[e]ELISA-anti-BP180 antibody cutoff value 200 IU/mL

[f]ELISA-anti-BP230 antibody cutoff value 40 IU/mL

[g]Treatment regimens prior to disease outcome

[h]Tetracyclines or minocycline with niacinamide

3.4 Relapse Analysis

Remarkably, a total of 749 (73.6%) patients had experienced relapses, including 233 (31.1%) patients after achieving CROT and 516 (68.9%) during non-CROT, with cumulative rates at 1-, 3-, and 5-years of 21.9%, 46.6%, and 60.9%, respectively. Most relapses were attributed to patients adjusting their medication themselves (606, 80.9%). The

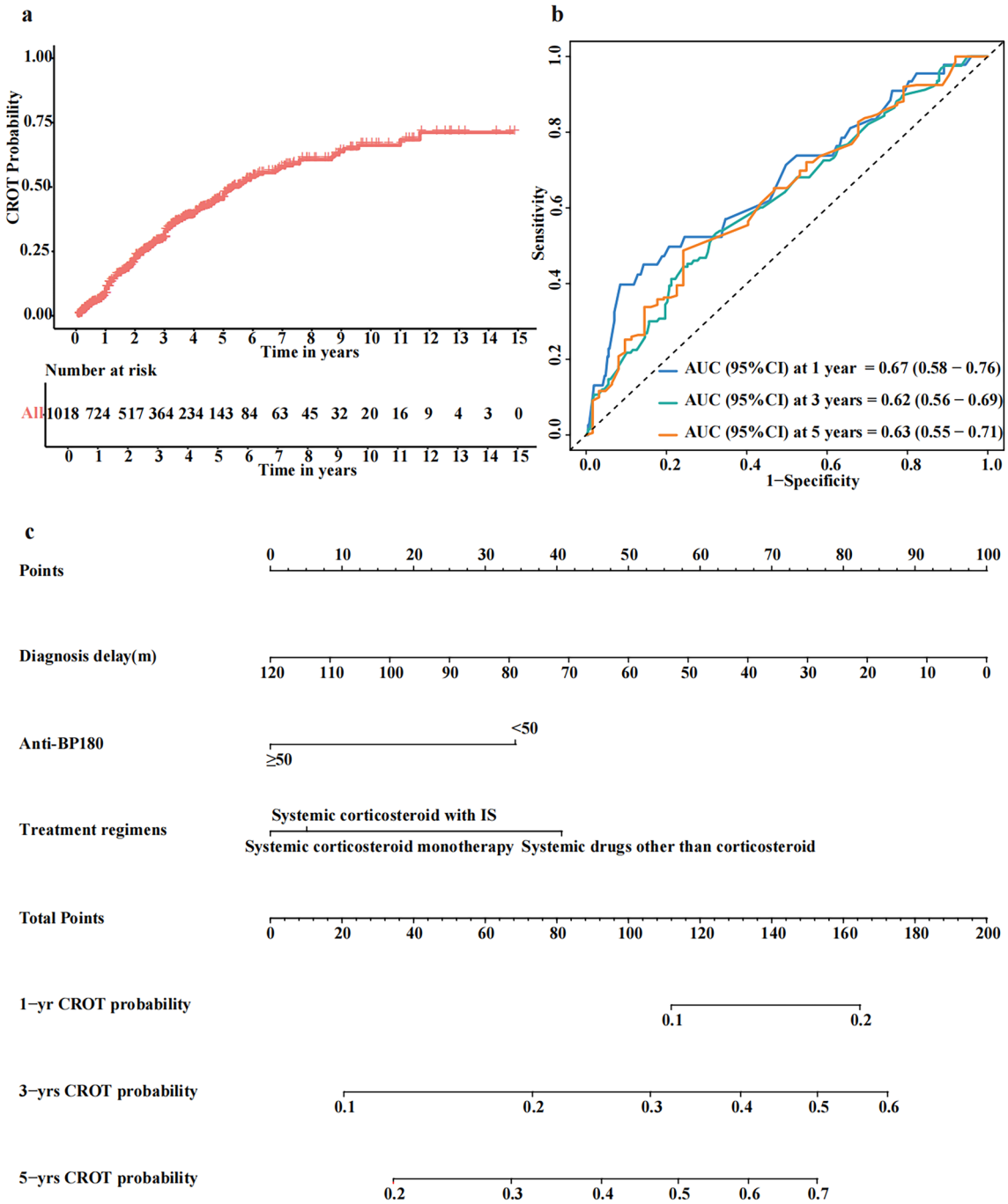

Fig. 3 Complete remission off-therapy regression (CROT) and prediction of bullous pemphigoid (BP): **a** CROT probability of BP; **b** Receiver operating characteristic curve with CROT prediction model in 1 year (blue), 3 years (green) and 5 years (orange); **c** The nomogram of CROT prediction

remaining factors of relapses were linked to exhaustion (65, 8.7%), trauma (3, 0.4%), and other unspecified causes (75, 10.0%).

Patients with baseline comorbidities, ≥10% BSA involvement, and higher anti-BP180 antibody level had a 1.81-fold (relative risk [RR], 1.81; 95%CI 1.09–2.96; $p = 0.020$), 4.83-fold (10–30% BSA, RR, 4.83; 95%CI 2.17–12.90; $p = 0.00042$), 2.51-fold (> 30% BSA, RR, 2.51; 95%CI 1.45–4.55; $p = 0.0015$), and 1.006-fold (RR, 1.006; 95%CI 1.003–1.009; $p < 0.0001$) higher likelihood of occurring a clinical relapse, as detailed in Supplementary Table S4.

Table 3 Multivariate Cox regression analyses of complete remission off-therapy factors associated with patients of bullous pemphigoid

Characteristic, no. (%)	CROT ($n = 321$)	Non-CROT ($n = 697$)	Univariate analyses		Multivariate analyses	
			HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at onset, mean ± SD, y	65.2 ± 14.8	71.8 ± 12.8	1.01 (0.99–1.01)[d]	0.23	1.0 (0.99–1.02)[d]	0.27
Sex						
Male	188/321 (58.6)	401/697 (57.5)	1.00 (0.80–1.25)	0.98	NA	NA
Female	133/321 (41.4)	296/697 (42.5)	1 [Reference]	NA	NA	NA
Delayed diagnosis time, mean ± SD, m	6.6 ± 12.4	8.6 ± 19.2	1.00 (0.99–1.01)[d]	0.51	1.01 (1.0–1.03)[d]	**0.0069**
Mucosal involvement						
Yes	89/321 (27.7)	171/697 (24.5)	1 [Reference]	NA	NA	NA
No	232/321 (72.3)	526/697 (75.5)	0.94 (0.74–1.20)	0.64	NA	NA
Baseline comorbidities						
Yes	235/321 (73.2)	586/697 (84.1)	1 [Reference]	NA	1 [Reference]	NA
No	86/321 (26.8)	111/697 (15.9)	1.42 (1.11–1.82)	**0.005**	1.19 (0.83–1.72)	0.35
BSA involvement[a]						
Mild (< 10%)	194/321 (60.4)	268/697 (38.5)	1.36 (1.04–1.78)	**0.025**	1.37 (0.93–2.04)	0.12
Moderate (10–30%)	52/321 (16.2)	171/697 (24.5)	0.84 (0.59–1.19)	0.32	0.80 (0.47–1.36)	0.40
Severe (> 30%)	75/321 (23.4)	258/697 (37.0)	1 [Reference]	NA	1 [Reference]	NA
DIF[a]						
IgG or C3 antibodies						
IgG^+ and $C3^+$	117/321 (36.4)	245/697 (35.2)	0.92 (0.73–1.16)	0.47	1.20 (0.86–1.68)	0.28
IgG^+ or $C3^+$	204/321 (63.6)	452/697 (64.8)	1 [Reference]	NA	1 [Reference]	NA
IgM or IgA antibodies[b]						
IgM^+ and/or IgA^+	99/321 (30.8)	210/697 (30.1)	1.15 (0.90–1.46)	0.26	1.49 (0.99–2.25)	0.058
IgM^- and IgA^-	222/321 (69.2)	487/697 (69.9)	1 [Reference]	NA	1 [Reference]	NA
IIF[c]	40.0 (.0–2560.0)	40.0 (0–2560.0)	1.18 (1.05–1.32)[e,d]	**0.0071**	1.12(0.97–1.29)[e,d]	0.11
ELISA antibody						
Anti-BP180 antibody	140.7 (0–231.0)	200 (0–246.0)	1.66 (1.28–2.15)[f]	**0.0001**	1.48 (1.06–2.07)[f]	**0.020**
Anti-BP230 antibody	0 (0–209.9)	4.37 (0–209.9)	1.23 (0.95–1.59)[g]	0.11	NA	NA
Treatment regimens[h]						
Systemic drugs other than corticosteroid[i]	76/321 (23.7)	115/697 (16.5)	1.76 (1.30–2.40)	**0.0003**	1.68 (1.12–2.52)	**0.013**
Systemic corticosteroid monotherapy	89/321 (27.7)	246/697 (35.3)	1 [Reference]	NA	1 [Reference]	NA
Systemic corticosteroid with IS	156/321 (48.6)	336/697 (48.2)	0.98 (0.75–1.27)	0.88	1.15 (0.81–1.63)	0.45

Bold indicates significant values ($p < 0.05$)

BSA body surface area, *CI* confidence interval, *CROT* complete remission off-therapy, *C3* complement component 3, *DIF* direct immunofluorescence, *ELISA* enzyme linked immunosorbent assay, *HR* hazard ratio, *IgA* immunoglobulin A, *IgG* immunoglobulin G, *IgM* immunoglobulin M, *IIF* indirect immunofluorescence, *IS* immunosuppressants, *NA* not applicable, *Non-CROT* including CR on minimal therapy, partial remission (PR) on minimal therapy, and PR off therapy subgroups

[a] Antibodies with C3, IgG, IgM and IgA antibodies with DIF

[b] Positive for IgM and/or IgA along with C3 and/or IgG with DIF

[c] Positive for IgG antibody titer with IIF

[d] The reference is the older age or the longer delay diagnosis time or the larger IIF titer

[e] The unit of IIF is $\log_{10}$ conversion of original value in the regression model

[f] ELISA-anti-BP180 antibody cutoff value 50 IU/mL

[g] ELISA-anti-BP230 antibody cutoff value 40 IU/mL

[h] Treatment regimens prior to disease outcome

[i] Tetracyclines or minocycline with niacinamide

3.5 Side Effects

In our cohort, 573 (56.3%) experienced side effects which need to be treated. The most common side effects were hypertension (207, 36.1%), hyperlipidemia (204, 35.6%), elevated blood glucose (183, 31.9%), leukopenia (150, 26.2%) and neutropenia (143, 25.0%). A particularly concerning side effect was severe femoral head avascular bone necrosis, which was found in 13.3% of BP patients.

4 Discussion

We conducted a large retrospective cohort study involving 1018 BP patients over a 15-year period to identify prognostic factors and develop predictive models, including nomograms, for CROT and mortality outcomes, as well as risk factors for relapse. Our study offers valuable insights into the long-term management of BP, aiding clinicians in promptly devising targeted interventions and optimal treatments based on predictive outcomes.

The mortality of BP remains a significant clinical concern. As BP predominantly affects the elderly population, it is difficult to distinguish between BP-related mortality and all-cause mortality. However, a large cohort study, consisting of 2639 BP patients and 10463 matched controls, reported that the 1-year mortality rate for individuals with BP was nearly triple that of disease-free individuals (20.36% compared to 7.03%) [2], indicating that BP significantly increases mortality rates in the affected population. Several retrospective studies have reported the 1-year mortality rate of BP in different populations, ranging from 3.2% to 38.0%. Furthermore, a meta-analysis study reported that the pooled estimate of 1-year mortality rate among BP patients stands at 23.5% worldwide (Supplementary Table S5) [6, 7, 12, 16–18, 20–22, 27–38]. In our cohort, we observed a 1-year mortality rate of 22.8% in BP patients, consistent with previous studies [16, 17, 20]. It is notable that the lowest 1-year mortality rate (3.2%, 3.7%) was seen in a follow-up of BP patients from Italy and China [12, 22]. The reason for this low mortality rate was that only outpatients, with had fewer comorbidities, were included in the results [12, 22]. Our study primarily included hospitalized patients, with 80.6% having comorbidities at baseline. Additionally, 32.7% of BP patients had > 30% BSA involvement. Additionally, the mean age of our cohort (69.7 years) is younger than that reported in US and European studies (74.0–81.0 years) [16, 30, 35, 39], reflecting potential regional differences in disease presentation. While our mortality rate aligns with studies reporting 19.2–25.0% mortality [16, 30, 35, 39], lower rates in other cohorts, such as Bardazzi et al (3.2%) and Gual et al (12.9%), likely reflect differences in inclusion criteria, and sample size [12, 34, 40].

Age, baseline comorbidities (multi-morbidities, dementia, Parkinson's disease), and disease severity, anti-BP180 antibody, treatment regimens were related to BP mortality in previous studies [12, 16–18, 30]. Our cohort of BP patients included older age of onset, ≥ 10% BSA involvement with increased mortality. Interestingly, patients with double-positive IgG and C3 on DIF were first reported to have a higher risk of mortality compared to single-positive staining for either marker. Although IgM and/or IgA deposition was not significantly associated with mortality, we provided a comprehensive analysis of IgM and IgA deposition patterns in BP, contributing to a broader understanding of BP-related DIF profiles. We further evaluated the impact of the three treatment regimens on patient mortality and observed that a significant difference in mortality was found only between the corticosteroid with IS therapy group and the systemic drugs other than corticosteroid group (30.5% vs 40.8%, $p = 0.0008$). The lower mortality observed in patients treated with corticosteroids combined with IS agents may be attributed to the enhanced therapeutic efficacy of this regimen. This combination disrupts DNA replication, induces cell death, suppresses lymphocyte proliferation, and reduces the production of pathogenic autoantibodies, thereby effectively managing BP [41, 42]. Consistent with previous studies, IS use was associated with a significant reduction in BP-related mortality, particularly in patients aged <70 years [43]. While tetracyclines, minocycline and niacinamide demonstrated anti-inflammatory and immune-modulating effects [42, 44–46], their mechanisms are less comprehensive and potent compared to corticosteroids with IS. Delayed diagnosis of BP remains a clinical challenge, with reported diagnostic delays ranging from 6.1 to 15.91 months across different cohorts, and up to 22.7 months for non-bullous pemphigoid (NBP) [47–49]. In our study, the average diagnostic delay for BP was 7.3 months, not associated with increased mortality. The reasons for delayed diagnosis, particularly in mild cases, are primarily attributed to patients postponing medical consultation due to the mild nature of their condition or misdiagnosis during initial evaluations. These findings underscore the importance of enhanced health education and increased clinical awareness to recognize atypical presentations of BP earlier, thereby minimizing diagnostic delays.

Furthermore, we constructed a risk prediction model for BP mortality using these risk factors and also developed a nomogram using mortality risk factors to guide clinical practice. However, since BP is more prevalent among the elderly, it is important to consider the influence of current LE when interpreting the nomogram results. The average LE in China is 78.6 years [50], and the disability-adjusted life year for BP is approximately 7.1 years [51]. This suggests that when the onset age of BP is <71.5 years, the nomogram may offer a

more accurate mortality estimate. The nomogram aids clinicians in the early evaluation of a BP patient's risk enabling the optimization of management strategies.

Most patients with BP require long-term treatment with corticosteroids, necessitating ongoing management. Therefore, it is crucial to obtain accurate information on the timing and achievement of CROT during prolonged treatment, which is essential for the effective management of BP. However, data on this subject were limited and often derived from small sample sizes. A single-center study involving 23 BP patients found that only 2 patients achieved CROT after one year of follow-up [52]. Another recent study of 100 BP patients treated with omalizumab reported that 11.7% of patients achieved CROT, with 57.1% in complete remission on minimal therapy [53]. In our cohort, 10.9% and 47.5% of BP patients achieved CROT within the 1-year and 5-year timeframe, respectively.

Significantly, we identified several meaningful indicators associated with achieving CROT. With particular emphasis on the role of shorter diagnosis time as a partial remission off therapy predicted factor for assessing the likelihood of CROT. We found no association between mucosal involvement and CROT, consistent with previous studies [54], although the BP tends to be more difficult to control in patients with mucosal involvement [55, 56]. The observed result may be attributed to the comparatively low proportion of patients exhibiting mucosal involvement (25.5%). Additionally, a level of baseline anti-BP180 antibody < 50 IU/mL was also associated with higher likelihood of achieving CROT. Systemic drugs other than the corticosteroid therapy group had a higher CROT rate, which was related to the milder disease severity compared to the other two treatment groups (Supplementary Table S1). Our results also illustrated that even after 5 years, 52.5% of BP patients cannot achieve CROT, indicating an unmet need for BP treatment. Overall, these insights underscore the importance of considering various factors in the management of BP and highlight the potential utility of predictive models in informing treatment decisions and optimizing patient outcomes.

The propensity for relapse in BP is considered a poor prognostic indicator [14]. Previous research has reported a 1-year relapse rate for BP ranging from 27.9% to 53.0% [14, 15]. Our findings revealed a relatively lower 1-year relapse rate of 21.9%. Most relapses were attributed to patients self-adjusting their medication, underscoring the importance of health education and long-term management. Furthermore, anti-BP180 antibody, comorbidities, and disease severity (≥10% BSA involvement) at baseline were identified as a risk factor for relapse, consistent with previous studies [14, 56]. Remarkably, in the relapses patients, approximately 31.1% experienced recurrence after achieving CROT, indicating that attention should also be paid to those individuals free of BP. Therefore, a comprehensive guidance program for relapse prevention and long-term management is imperative and urgent.

Previous studies have revealed that adverse effects of systemic corticosteroid and/or IS therapies commonly include short-term side effects and long-term side effects of femoral head avascular bone necrosis, and even mortality [1, 22]. In our cohort, we observed all the aforementioned adverse effects associated with BP treatment. Notably, we observed higher rates of femoral head avascular bone necrosis (13.3%), which underscores the importance of vigilance by physicians with regard to the development of femoral head necrosis during the long-term management of BP. It is imperative for clinicians to take proactive measures in a timely manner, to prevent these complications from occurring.

This study had several notable strengths and limitations. First, it comprehensively presented the disease mortality, CROT, and relapse rates over long-term follow-up, along with related risk prediction factors. Notably, we constructed predictive models for mortality and CROT for the first time to aid clinicians in evaluating and managing BP patients over the long term. Second, as the referral center for dermatopathology in Shandong Province, our hospital receives BP patients referred from 189 hospitals across the province. The follow-up data represents the long-term course of BP in this province, which has a population of 100 million. This provides baseline data and guidance for the long-term chronic management of the disease, as well as for the development of subsequent improvement plans and strategies.

There were some limitations to consider. First, the data were primarily sourced from hospital records and family-reported information, which could introduce recall bias. Second, most patients in our cohort received systemic corticosteroid and/or IS therapy, but biological treatments such as rituximab, dupilumab, and omalizumab were not included in the analysis of clinical outcomes. This omission was due to the relatively short duration of use of these treatments in the Chinese population, which did not meet the required follow-up time for analysis.

5 Conclusions

This 15-year retrospective cohort study provides valuable insights into the prognosis and management of BP in China. We comprehensively identified risk factors associated with mortality, CROT, and relapse, and systematically compared the impact of different treatment regimens on mortality and CROT. Our predictive models for mortality and CROT serve as practical tools to guide individualized treatment strategies and improve clinical outcomes, offering valuable support to clinicians in optimizing BP management.

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Declarations

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Conflict of Interest/Competing Interests All authors have completed the ICMJE uniform disclosure form and no conflicts of interest to declare.

Ethics Approval The study protocol was reviewed and approved by the Institutional Review Board at the Shandong Provincial Institute of Dermatology and Venereology (No. 20221223KYKTKS001).

Consent to Participate Verbal informed consent was obtained prior to the interview.

Consent for Publication Verbal informed consent was obtained prior to the interview.

Availability of Data And Material The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Hospital for Skin Diseases, Shandong First Medical University.

Code Availability Not applicable.

Authors' Contributions HL, and FRZ conceived the work. SC, PCH, HDL, TSC, and PYX followed the patients and contributed to data collection. WCL, SC and ZZW performed the statistical analyses. YXL, GZZ, and SLC performed pathology studies. BQY, YHS, QY, MW, ZXS, TSC, HL, and FRZ performed clinical studies. SC, WCL, ZZW and HL wrote and revised the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Finally, all authors critically revised the manuscript.

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