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Clinical characteristics, mortality, and prognostic factors for bullous pemphigoid in a Thai population

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Abstract

Bullous pemphigoid is an uncommon, autoimmune, blistering disease. Clinical features, associated conditions, and outcomes differ according to country. We aimed to determine the mortality rate and clinical characteristics of Thai patients and to evaluate the risk factors associated with survival.

A retrospective analysis was conducted on 119 patients, over a ten-year period, at Songklanagarind Hospital, the largest tertiary university hospital in Southern Thailand.

The median age of onset was 82 years [interquartile range 72, 90], and 60 (50.4%) patients were men. The underlying diseases were hypertension (53.8%), neurological disease (42.8%), and diabetes mellitus (31.9%). Fifty-eight patients (48.7%) experienced pruritus, and 61.3% of patients had mild cutaneous lesions (less than 10% of the body surface area) on the day of diagnosis. Nine percent of patients presented with mucosal involvement. Complete blood counts showed anemia (32.8%), neutrophilia (30.3%), and eosinophilia (42.9%). The 1-, 3- and 5-year overall mortality rates were 28.1% [95% confidence interval (CI), 7.8–36.6], 55.7% (95% CI, 44.4–64.7) and 71.9% (95% CI 59.9–80.2), respectively. On multivariate analysis, high neutrophil/lymphocyte ratio [odds ratio (OR) 5.55, $P < .001$] and anemia (OR 2.93, $P = .025$) were found to be independently associated with mortality rate, whereas disease remission (OR 0.25, $P = .003$) was demonstrated to be a good prognostic factor.

This is the first study to analyze the mortality rate of Bullous pemphigoid in Thailand. Mortality was associated with high neutrophil/lymphocyte ratio and anemia.

Abbreviations: BP = bullous pemphigoid, CI = confidence interval, IQR = interquartile range, LR = likelihood ratio, NLR = neutrophil/lymphocyte ratio, OR = odds ratio.

Keywords: bullous pemphigoid, mortality rate, neutrophil-to-lymphocyte ratio, prognostic factor, Thailand

1. Introduction

Bullous pemphigoid (BP) is a blistering, autoimmune disease of the skin and mucous membranes that typically occurs in elderly patients. The disease mechanism is mediated by the development of autoantibodies against the hemidesmosome proteins BP180 and BP230, causing blister formation.[1] The clinical presentation is characterized by pruritus, tense bullae, or urticarial plaque, and only 10% of patients present with mucous membrane involvement.[2]

Although BP patients could experience clinical remission in some cases, high morbidity and mortality rates have been reported. A recent meta-analysis showed that the pooled estimate for the 1-year mortality rate was 23.5%.[3] In European countries, the 1-year mortality rate has been reported in the range of 13.0% to 31.0% .[4–9] In contrast, data from the United States showed a lower 1-year mortality range of 11.0% to 15.0%.[10–12] However, little data regarding the mortality rate of BP patients have been reported for Asian countries, with 1-year mortality rates of 13%, 19%, 24%, 27%, and 30% reported for China, Korea, Israel, Singapore, and Kuwait, respectively.[13–19] In Thailand, only 1 study has described the clinical features of BP; however, mortality rate data was not reported.[20]

Previous studies have reported that certain comorbidities, including neurological diseases, particularly dementia, Parkinson's disease, and stroke, and modalities of treatment, such as the use of corticosteroids or immunosuppressive drugs, and high serum anti-BP180 IgG levels may affect the mortality rate.[6,21–24] Due discrepancies in the mortality rates reported among various countries and the lack of studies regarding the mortality rate among the Thai population, we aimed to determine the mortality rate among patients with BP in a representative Thai cohort, from the largest tertiary academic center in Southern Thailand, to identify the factors affecting survival.

Editor: Xin Yang.

Funded by the Faculty of Medicine, Prince of Songkla University.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files.

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How to cite this article: Amonchaisakda N, Aiempanakit K. Clinical characteristics, mortality, and prognostic factors for bullous pemphigoid in a Thai population. Medicine 2020;99:43(e22850).

Received: 15 May 2020 / Received in final form: 14 September 2020 / Accepted: 22 September 2020

http://dx.doi.org/10.1097/MD.0000000000022850

2. Methods

2.1. Study design and setting

We comprehensively reviewed the electronic medical records of all BP cases who were diagnosed at the Division of Dermatology, Songklanagarind Hospital, Prince of Songkla University, Southern Thailand, between January 2007 and December 2016. The patients were identified based on the International Classification of Diseases 10, coded as L120 bullous pemphigoid. Inclusion criteria included all patients who were diagnosed and followed up at the hospital. The diagnosis of BP was based on the combination of clinical presentation and laboratory evidence, including any of the following:

(1) skin histopathology, consistent with BP, or
(2) direct or indirect immunofluorescence studies.[11]

Assessed comorbidities included the following:

(1) cardiovascular diseases;
(2) neurological diseases, including stroke, Parkinson's disease, and dementia;
(3) diabetes mellitus;
(4) hypertension;
(5) chronic renal insufficiency; and
(6) malignancy.

Disease severity was defined by the percent of body surface area involvement, as follows: less than 10% was classified as mild, 10% to 30% as moderate, and greater than 30% as severe. Laboratory investigation data were also collected: anemia was defined as hemoglobin levels < 12 g/dL, in women, and < 13 g/dL, in men; neutrophilia was defined when the absolute neutrophil counts were greater than 7700 cells/μL; eosinophilia was defined when the absolute eosinophil counts were greater than 4000 cells/μL; and lymphocytosis was defined when the absolute lymphocyte counts were greater than 4000 cells/μL.[25] The neutrophil-to-lymphocyte ratio (NLR) was used to indicate an inflammatory response, according to the cut-off value of NLR > 4.[26–28] The therapeutic outcome was defined based on criteria established by the International Pemphigus Committee.[29] Disease control was defined as the time during which no new lesions developed and existing lesions began to heal. Remission was defined as being lesion-free for at least 2 months, after the discontinuation of all systemic therapies. Disease relapse was defined as any time at which patients experience 3 or more new lesions per month that do not heal spontaneously within 1 week. Patients' names and social security numbers were used to verify mortality status and the cause of mortality, as reported in the national registration database. The study was approved by the Research Ethics Committee, Faculty of Medicine, Prince of Songkla University, in accordance with the Declaration of Helsinki (REC 59–356–14–4).

2.2. Statistical analysis

The primary outcomes were the overall survival and mortality rates of BP patients after 1, 3, and 5 years following the diagnosis, which were calculated using the Kaplan–Meier survival analysis method. The secondary outcome focused on prognostic factors that influenced the 3-year mortality rates among BP patients. All quantitative data were analyzed using the mean or median and standard deviation, whereas all qualitative data were analyzed as percentages and ratios. The variables were undergone the normality test by Shapiro-Wilk Test. For non-normally distributed data, those were reported as the median and interquartile range (IQR). Univariate analysis was performed to assess the association between each particular prognostic factor and the mortality rate, using logistic regression analysis. Multivariate analysis was performed by logistic regression analysis. Variables showing some evidence of association with mortality from univariate analysis ($P < 0.2$) were included in initial multivariate analysis, which was then refined by using backward stepwise regression to remove the variables not contributing statistically significant. All of the Logistic regression analysis are using Wald's test and Likelihood ratio to prove the hypothesis. Statistical significance was set at $P \leq 0.05$. All analyses were performed using R Program 3.5.1 (R Foundation for Statistical Computing, Vienna, Australia, 2018).

3. Results

3.1. Clinical characteristics

A total of 119 patients were included in the study, and their clinical characteristics can be observed in Table 1. The median age of onset was 82 years (IQR, 72, 90). Patients included 60 (50.4%) males and 59 (49.6%) females. Half of the patients presented with comorbidities, including hypertension (53.8%), diabetes mellitus (31.9%), and dyslipidemia (20.2%). Forty-two

Table 1

Demographic data and clinical characteristics of bullous pemphigoid patients.

Characteristic	Bullous pemphigoid patients N = 119
Age of onset; median (IQR), yr	82 (72, 90)
Sex; number of patients (%)	
Male	60 (50.4)
Female	59 (49.6)
Underlying disease; number of patients (%)	
Hypertension	64 (53.8)
Diabetes Mellitus	38 (31.9)
Dyslipidemia	24 (20.2)
Cardiovascular disease	15 (12.6)
Chronic kidney disease	13 (10.9)
Neurological disease	51 (42.8)
Cerebrovascular disease	35 (29.4)
Parkinson's disease	8 (6.7)
Others	8 (6.7)
Malignancy	13 (10.9)
Solid tumor	10 (8.4)
Brain	2 (1.7)
Cervix	2 (1.7)
Prostate	2 (1.7)
Others	4 (3.3)
Hematologic malignancy	3 (2.5)
Skin morphology; number of patients (%)	
Vesicle/bullae	110 (92.4)
Wheal	5 (4.2)
Ulcer/erosion	45 (37.8)
Mucosal involvement; number of patients (%)	11 (9.2)
Pruritus; number of patients (%)	58 (48.7)
Severity on the day of diagnosis; number of patients (%)	
Mild (< 10%)	73 (61.3)
Moderate (10%–30%)	39 (32.8)
Severe (> 30%)	7 (5.9)

IQR = interquartile range.

percent of patients presented with neurological diseases, particularly cerebrovascular accident (68.6%) and Parkinson's disease (15.7%). Thirteen patients presented with malignancies, including solid tumors (76.9%) and hematologic malignancies (23.1%)

The onset of the disease was 30 days (IQR, 14, 90) before the diagnosis. Fifty-eight patients (48.7%) experienced pruritus. The majority of patients (61.3%) had cutaneous involvement of less than 10% of the body surface area on the day of diagnosis. Only 11 patients (9.2%) presented with mucosal involvement. Complete blood counts showed anemia (32.8%), leukocytosis (28.6%), and eosinophilia (42.9%). Eighty patients (67.2%) were treated with topical corticosteroids. Sixty-one patients (51.2%) were treated with oral prednisolone alone, and in only 4 patients (3.3%) received adjuvant azathioprine. The median dose of oral prednisolone was 30 grams per day.

3.2. The mortality rate and associated factors

The median duration of follow-up for all patients was 20 months. The 1-, 3-, and 5-year overall mortality rates were 28.1% [95% confidence interval (CI), 7.8–36.6], 55.7% (95% CI, 44.4–64.7), and 71.9% (95% CI, 59.9–80.2), respectively. The median survival time was 27 months; therefore, our study focused on the factors that affected the mortality rate 3 years after BP diagnosis. In the univariate analysis (Table 2), several variables associated with mortality were identified, including older age, underlying neurological disease, mucosal involvement, anemia, hypoalbuminemia, high NLR, and patients without disease remission. In the multivariate analysis (Table 3), patients with anemia [odds ratio (OR) 2.93, p = 0.025] and high NLR values (OR 5.55, $P < .001$) were found to be independently associated with the mortality rate (Fig. 1A and 1B). In contrast, disease remission (OR 0.25, $P = .003$) was demonstrated to be a good prognostic factor (Fig. 1C).

4. Discussion

BP is the most common autoimmune, blistering disease among the elderly. The median age of onset during the present study was 82 years, which was comparable with those reported in French and UK populations, which were 82 and 81 years, respectively.[4–5] However, most previous studies have reported a lower median age of onset, ranging from 70 to 80 years.[6–19] The previous study, from central Thailand, reported a median age of onset of 69 years, which was lower than that in the present study.[20]

In our study, 92.4% of patients had vesicles/bullae at diagnosis, whereas only 4.2% of patients had wheals/urticarial plaques. Although BP lesions primarily occur on the skin, 9.2% of our patients also presented with lesions of the oral mucosa, which is lower than the percentage reported by the previous study from central Thailand (15.5%).[20]

We found that patients with BP presented with the following underlying diseases: hypertension, 53.8%; neurological disease, 42.8%; cerebrovascular disease, 29.4%; diabetes, 31.9%; and malignancy, 10%. These results are comparable with those in the study by Kulthanan et al, who reported associated diseases including hypertension, 41.4%; cerebrovascular disease, 24.1%; diabetes, 19%; and malignancy, 8.6%.[20]

This study found identified a 1-year mortality rate of approximately 28.1%, which was similar to those reported by studies from other Asian countries. Cai et al, from Singapore, revealed 1-year mortality of 26.7%, whereas Zhang et al reported a 1-year mortality rate of 23.4%, although the latter study included only hospitalized patients.[14,18] Lee et al, from Korea,

Table 2

Univariate analysis among patients with bullous pemphigoid to identify factors that affect the 3-year mortality rate.

Variable	OR (95% CI)	*P*-value (Wald test)	*P*-value (LR-test)
Age; yr			.017*
<72	Reference		
72-82	3.29 (1.08, 9.95)	.035	
82-90	3.29 (1.1, 9.81)	.033	
90-100	5.59 (1.77, 17.67)	.003	
Smoking			
No	Reference		
Yes	4.94 (0.54, 45.59)	.159	.113
Mucosal involvement			
No	Reference		
Yes	0.23 (0.05, 1.12)	.068	.041*
Diabetes mellitus			
No	Reference		
Yes	0.94 (0.58, 1.54)	.809	.808
Hypertension			
No	Reference		
Yes	1.21 (0.76, 1.92)	.423	.422
Neurological disease			
No	Reference		
Yes	2.69 (1.24, 5.84)	.012	.011*
Anemia			
No	Reference		
Yes	2.98 (1.34, 6.59)	.007	.006*
Neutrophilia			
No	Reference		
Yes	1.76 (0.78, 3.97)	.173	.074
High NLR (≥ 4)			
No	Reference		
Yes	4.96 (2.16, 11.38)	< .001	<.001*
Hypoalbuminemia (< 3.5 mg/dl)			
No	Reference		
Yes	3.03 (1.25, 7.14)	.014	.013*
Oral corticosteroids			
No	Reference		
Yes	1.28 (0.62, 2.63)	.507	.506
Disease remission			
No	Reference		
Yes	0.42 (0.18, 1.00)	.05	.045*

* P < .05 indicates statistically significant. CI = confidence interval, LR = likelihood ratio, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio.

Table 3

Multivariate analysis among patients with bullous pemphigoid to identify factors that affect the 3-year mortality rate.

Variable	Adjusted OR (95% CI)	*P*-value (Wald test)	*P*-value (LR-test)
Anemia			
No	Reference		
Yes	2.93 (1.12, 7.64)	.028	.025*
High NLR (≥ 4)			
No	Reference		
Yes	5.55 (2.23, 13.84)	<.001	<.001*
Disease remission			
No	Reference		
Yes	0.25 (0.09, 0.69)	.007	.003*

* P < .05 indicates statistically significant. CI = confidence interval, LR = likelihood ratio, NLR = neutrophil-to-lymphocyte ratio, OR = Odds ratio.

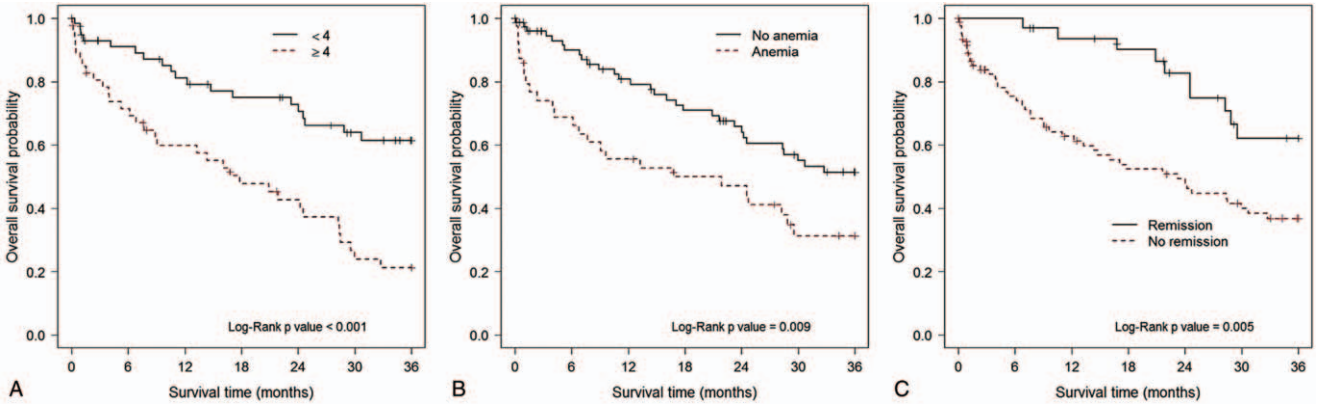

Figure 1. Kaplan-Meier curve comparing the 3-year survival rate of bullous pemphigoid patients with (A) neutrophil-to-lymphocyte (NLR) ratio [low NLR (< 4) and high NLR (≥ 4)], (B) anemia, and (C) disease remission.

reported a 1-year mortality rate of 19%, and research from China indicated a mortality rate as low as 12.9%.[13,15] The patients in the Korean and Chinese studies had a mean ages of 69.2 and 67 years, respectively, which were nearly 10 years younger than the patients in our study; therefore, age may represent a possible risk factor affecting the mortality rate, as was found in previous studies.[17,22,30] Although the present study found that older age was significant, based on the univariate analysis, this variable was not significant during the multivariate analysis.

We analyzed the prognostic factors associated with a 3-year mortality rate and found that high NLR and anemia were independent risk factors. NLR is a simple parameter for the prompt assessment of inflammatory status. NLR has previously been associated with mortality in major cardiac events and can act as a strong prognostic factor when associated with several types of cancers, or as a predictor and a marker of inflammatory or infectious pathologies.[27] In bullous pemphigoid, the association between NLR and disease prognosis can be explained by the inflammatory process associated with blister formation, as the mechanism requires the binding of an autoantibody with an antigen, causing both complement activation and mast cell degranulation. Then, neutrophils are recruited and proteolytic enzymes and reactive oxygen species are released, leading to subepidermal blistering.[31]

No previous studies have reported anemia as a prognostic factor associated with poor mortality rate. Although no known mechanism can currently explain this relationship, we hypothesize that the associated anemia primarily due to anemia of inflammation. However, no data were collected during this study that would allow this hypothesis to be tested. However, a case report describing pernicious anemia associated with BP was suggested to be associated with the autoimmune phenomenon.[32]

Our study has some limitations that should be noted. First, this was a single-center study that represents a small geographic area of Southern Thailand. Second, missing data and inaccurate measurements, based on self-reported history, and the nature of retrospective studies limited our analyses. Additionally, the potential risk of observational bias must be considered.

In conclusion, this is the first study to analyze the mortality rate of BP in Thailand. High NLR and anemia were found to be significantly associated with mortality rate, whereas disease remission was demonstrated to be associated with a good prognosis. Additional studies should perform a detailed analysis of the underlying causes of anemia, and useful data from the present study may lead to the development of a clinical prediction model to evaluate disease prognosis.

Acknowledgments

The authors are indebted to Ms Nannapat Pruphetkaew, Epidemiology Unit, Faculty of Medicine, Prince of Songkla University for providing help in statistical analysis. We would like to thank the Enago (www.enago.com) for English language editing.

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