Clinical Characteristics and Survival of Pemphigoid and Pemphigus Patients in a Thai Population

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ABSTRACT

Objective: Pemphigoid and pemphigus are skin diseases with high morbidity and mortality. The research aims to study the clinical presentations, comorbidities, and medications used prior to diagnosis, as well as the survival rates and prognostic factors for pemphigoid and pemphigus patients.

Materials and Methods: The cohort study was conducted on retrospective data of patients who were treated at Naresuan University Hospital between 1 October 2012 and 30 September 2022.

Results: There were 30 pemphigoid patients and 44 pemphigus patients. Pemphigoid patients were on average older than pemphigus patients (76 years vs 52 years), have more skin blisters, and less oral cavity lesions. Neurological disease increases risk of being diagnosed as a bullous pemphigoid (odds ratio=4.6, p-value =0.051). After adjustment by neurologic disease and age at diagnosis, pemphigoid was not significantly associated with the use of any medications. The survival rate of pemphigus was 91.1% at 1 year and 82.2% at 5 years, while the survival rate of pemphigoid was 69.9% at 1 year, and 47.7% at 5 years. In multivariable Cox regression analysis, there was worse prognosis among pemphigoid and pemphigus patients that have comorbidity disease (adjusted HR= 3.13, p-value=0.057) and were older than 70 years (adj HR= 6.93, p-value=0.015).

Conclusion: Clinical characteristics of bullous pemphigoid and pemphigus were different such as age of onset, presence of blister and oral lesion. Neurological disease was a risk factor for developing bullous pemphigoid than pemphigus. Survival of pemphigoid patients was worse than pemphigus patients. However, this finding could be confounded by older age of pemphigoid patients.

Keywords: Autoimmune bullous disease; pemphigoid; pemphigus; survival rate; prognostic factor (Siriraj Med J 2024; 76: 14-20)

INTRODUCTION

Bullous pemphigoid and pemphigus are autoimmune bullous diseases caused by the presence of autoantibodies targeting bullous pemphigoid antigen (BP180, BP230) and desmoglein (DSG1, DSG3), respectively. Though prevalence of bullous disorder is quite low as 30 per 100,000 population in a study of a primary care area in Thailand[1], these are severe and poor prognosis skin disease with some distinct patterns of lesion locations, clinical presentations, and laboratory findings. Bullous pemphigoid was commonly found in elderly and pemphigus tend to have more oral lesions. The disease pathogenesis was the interaction between predisposing factors, such as human leukocyte antigen (HLA) genes, comorbidities, aging, and trigger factors.[2]

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Neurological disease was found to be associated with pemphigoid. Some medications such as aldosterone antagonists, DPP-4 inhibitors, anticholinergics and dopaminergic were associated with pemphigoid patients.[3]

Both diseases are skin diseases with high morbidity and mortality. In a study, the first-year mortality rate of pemphigoid was 31% and pemphigus was 24%.[4] A meta-analysis showed the pooled estimate of 1-year mortality rate of pemphigoid was 23.5%.[5]

The purposes of this research are to study differences in clinical manifestations, underlying diseases, comorbidities, prior drug use, survival rates at 1- and 5-year, and prognostic factors of pemphigoid and pemphigus diseases.

MATERIALS AND METHODS

The retrospective cohort study was conducted on patients with bullous pemphigoid and pemphigus who were diagnosed and treated at Naresuan University Hospital between 1 October 2012 and 30 September 2022. Ethical approval was allowed by the Naresuan University Institute Review Board.

All diagnosis of pemphigoid and pemphigus was confirmed by immunological laboratory findings of either positive direct immunofluorescence (DIF) test or positive indirect immunofluorescence (IIF) test.

Data was obtained by reviewing medical records. The variables included gender, age of diagnosis, characteristic of skin blisters and oral cavity lesions, immunological laboratory results, prior drug use before diagnosis, comorbidity, treatment, and survival. Death status was confirmed by medical chart review and from the national death registration database.

Statistical analysis was done by using the STATA software version 18.0. Descriptive statistics were used to report demographic data, clinical characteristics, treatment, and treatment outcomes of pemphigoid and pemphigus patients. Prior medication use of pemphigoid and pemphigus patients were compared using univariable and multivariable logistic regression. The survival rate between pemphigoid and pemphigus patients was analyzed by the Kaplan-Meier method. The relationship between various factors and survival rates in patients with pemphigus and pemphigoid were analyzed with log-rank test statistics. Multivariable analysis for the effect of factors on survival was analyzed using Cox's proportional hazard model statistics presented by hazard ratio (HR).

RESULTS

Of 74 patients, there were 30 pemphigoid patients and 44 pemphigus patients. Pemphigus patients included 32 pemphigus vulgaris, 11 pemphigus foliaceus, and 1 pemphigus vegetans. There were 17 (57%) pemphigoid and 29 (63%) pemphigus female patients as shown in Table 1.

Pemphigoid patients were older than pemphigus patients on average. Approximately 76% of pemphigoid and 18% of pemphigus patients were 70 years or older than. The mean age of the pemphigoid patient was 75.3 years old (±13.9 SD) while for pemphigus was 52.4 years old (±18.8 SD), with a statistically significant difference at p-value 0.001. Skin vesicles appeared more in pemphigoid patients than pemphigus patients (75.8% versus 52.3%, p-value 0.043). Oral cavity lesions were more common in pemphigus patients than pemphigoid patients (40.9% versus 20.0%, p-value 0.051).

Neurologic diseases (cerebrovascular disease, dementia, Alzheimer, Parkinson) were present in 53% of pemphigoid and 9% of pemphigus patients. The odds ratio of neurologic disease for being pemphigoid was 11.42 (p-value <0.001) in univariable analysis and 4.64 (p-value=0.051) in multivariable analysis adjusted by age and gender.

Certain medications were more frequently used by pemphigoid patients than pemphigus patients, prior to their diagnosis. Some of those medications include angiotensin receptor blockers, calcium channel blockers, statins, biguanide, and non-steroidal anti-inflammatory drugs. However, in multivariable logistic regression analysis adjusted by age at diagnosis and neurologic disease, these were not statistically significant as shown in Table 2.

For the treatment, pemphigoid patients were treated with systemic corticosteroid in 23 cases (82.1%) and immunosuppressive therapy in 12 cases (40.0%). Pemphigus patients were treated with systemic corticosteroid in 41 cases (97.6%) and immunosuppressive therapy in 32 cases (72.7%). No patients were treated with biologic drug. Comorbidity disease (neurologic disease, diabetes mellitus, cancer, hypertension, and dyslipidemia) existed in 66% of pemphigoid patients and 25% of pemphigus patients.

In Table 3, the survival rate of pemphigoid patients at 1-year was 69.90% compared with 91.10 % for pemphigus patients as shown. While at 5-year, 47.7 % of pemphigoid patients and 82.2% of pemphigus patients survived. There was a statistically significant difference of survival rate between pemphigoid and pemphigus by log rank test. (p-value< 0.001). The Kaplan-Mier survival estimates curve was shown in Fig 1. The survival rate of autoimmune bullous disease (pemphigoid and pemphigus) also depends on age at diagnosis and the presence of comorbidity

TABLE 1. Characteristics of pemphigoid and pemphigus patients.

Characteristics	Pemphigoid (N=30)	Pemphigus (N=44)	Univariable Odds Ratio (pemphigoid as outcome)	p-value	Multivariable Odds Ratio	p-value
Gender						
Male	13 (43.3)	15 (34.1)	ref	0.42	ref	0.34
Female	17(56.7)	29 (65.9)	0.67(0.26-1.75)		0.54(0.15-1.92)	
Age						
Mean, SD	76.6, 12.4	52.4, 18.8				
Median	82.5,	54, 15-87				
Min-max	38-89					
Age group						
<60	4(13.3)	28(63.6)	Ref		Ref	0.833
60-69	3(10.0)	8(18.2)	1.28(.08-8.8)	0.801	1.23(.17-8.90)	0.001
>70	23(76.7)	8(18.2)	10.25(2.44-43.10)	0.001	11.25(2.57-49.22)	
Neurologic disease						
No	14(46.7)	40(90.9)	Ref	<0.001	Ref	0.051
Yes	16(53.3)	4(9.1)	11.42(3.26-40.02)		4.64(0.99-21.76)	

disease. The survival rate reduces from 96.8% among those less than 60 years old to 90.9% in 61–69-year group and 63.3% in those more than 70 years old. The presence of comorbidity reduces the 1-year survival of both diseases from 87.9% to 73.8%.

Prognostic factors of survival in pemphigoid and pemphigus patients were analyzed using univariable and multivariable cox regression as shown in Table 4. In univariable analysis, diagnosis of pemphigoid, age more than 70 and presence of comorbidity disease were associated with increasing hazard of death. However, in multivariable analysis, only age more than 70 years old was statistically significant associated with increasing hazard of death (hazard ratio= 4.57, p-value 0.015).

DISCUSSION

In our study, we found bullous pemphigoid patients slightly less frequent than pemphigus patients (30 cases versus 44 cases). It showed increase proportion of bullous pemphigoid when compare to the study in 2009 at Siriraj Hospital in Bangkok which found diagnosed pemphigoid (29.6% of autoimmune bullous disease) compared to pemphigus (63.3%).[6] A study in Singapore showed the relative incidence of pemphigoid versus pemphigus was 4:1.[4] The difference may reflect patient data coverage, referral bias, and aging structure with a rising incidence in bullous pemphigoid in older population. The age distribution of patients with both diseases significantly differed, with pemphigoid patients exhibiting a higher age than pemphigus patients. Clinical symptoms such as vesicles and oral lesions varied between the diseases. Vesicles were more pronounced in pemphigoid, while oral lesions were more common in pemphigus.

Previous study found some factors independently associated with pemphigoid such as major cognitive impairment, bedridden condition, Parkinson's disease, unipolar or bipolar disorder, and use of spironolactone or phenothiazines with aliphatic side chains.[7,8] In our study, we use pemphigus patients as a control. After controlling for age and gender, neurologic disease might increase risk of being diagnosed as pemphigoid versus pemphigus (odds ratio= 4.64, 95% CI 0.99-21.76, P-value=0.051). Previous studies found neurological disease were associated with BP.[8,9] A meta-analysis showed neurological disease increase risk of pemphigoid (RR 4.93, 95% CI: 3.62-6.70).[9] This is consistent with the finding of a study in Bangkok which showed pemphigoid patients had a significantly higher chance of having neurologic diseases compared

TABLE 2. Medications used prior to diagnosis in pemphigoid and pemphigus patients: frequency and odds ratio of being bullous pemphigoid by logistic regression.

Drug	Pemphigoid N= 30 n(%)	Pemphigus N= 44 n(%)	Univariable Odds Ratio (pemphigoid as outcome)	p-value	Multivariable Odds Ratio (adjusted by age and neurologic disease)	p-value
Angiotensin-converting -enzyme inhibitors (ACEi)	1 (3.3)	0 (0.0)	-	0.405	-	-
Angiotensin receptor blockers (ARBs)	7 (23.3)	1 (2.3)	13.08(1.51-12.9)	0.019	5.27 (0.54-50.89)	0.150
Calcium channel blockers (CCBs)	8 (26.7)	3 (6.8)	4.96(1.19-20.65)	0.027	1.82 (0.33-10.04)	0.490
Beta blocker	6 (20.0)	5 (11.4)	1.95(0.53-7.09)	0.331	0.63 (0.12-3.31)	0.589
Proton pump inhibitors	6 (20.0)	7 (15.9)	1.32(0.39-4.41)	0.650	0.37 (0.63-2.16)	0.271
Statins	12(40.0)	6(13.6)	4.22(1.36-13.05)	0.012	1.92 (0.48-7.72)	0.188
Warfarin	3(10.0)	1(2.3)	4.77 (0.47-8.31)	0.185	3.54(0.21-58.59)	0.318
Aspirin	6(20.0)	3(6.8)	3.41(0.78-14.92)	0.102	1.09 (0.168-7.17)	0.524
Clopidogrel	3(10.0)	0(0.0)	-	0.032	-	-
Anticholinergic	0(0.0)	0(0.0)	-	-	-	-
L-DOPA bromocriptine	2(6.7)	1(2.3)	3.07(0.265-35.49)	0.369	0.21(0.01-3.44)	0.275
Hypnotic sedative	2(6.7)	3(6.8)	0.97(0.153-6.22)	0.980	0.10 (0.01-1.03)	0.053
Sulfonylurea	3(10)	1(2.7)	4.77(0.47-48.31)	0.185	2.67 (0.089-79.64)	0.571
Thiazolidinediones	1(3.3)	0(0)	-	0.405	-	-
Biguanide	7(23.3)	2(4.6)	6.39(1.23-33.33)	0.028	5.17 (0.61-43.51)	0.130
DDP-4 inhibitor	2(6.7)	0(0)	-	0.161	-	-
Loop diuretics	0(0)	1(2.3)	-	1.000	-	-
NSAIDs	8(26.7)	3(6.8)	4.96(1.19-20.65)	0.027	2.69(0.45-16.08)	0.276
Alpha blocker	1(3.3)	1(2.7)	1.48(0.08-24.66)	0.784	0.13(0.01-3.27)	0.218
Anticonvulsant	2(6.6)	3(6.8)	0.97(0.15-6.22)	0.980	0.15 (0.02-1.48)	0.106

TABLE 3. 1- and 5-year survival probability in pemphigoid patients and pemphigus Patients.

	Survival probability				P-value
	1-year	95%CI	5-year	95%CI	(Log-rank test)
Pemphigoid	0.691	0.489 - 0.826	0.427	0.227- 0.613	<0.001
Pemphigus	0.907	0.770 -0.964	0.813	0.642 - 0.907	
Age					<0.001
<60	0.968	0.798- 0.995	0.827	0.598- 0.932	
61-69	0.909	0.508-0.986	0.818	0.447-0.951	
>=70	0.633	0.435-0.778	0.436	0.247-0.610	
Comorbidity					0.006
Present	0.738	0.544-0.859	0.4595	0.260-0.638	
Absent	0.879	0.734-0.948	0.8173	0.650-0.909	

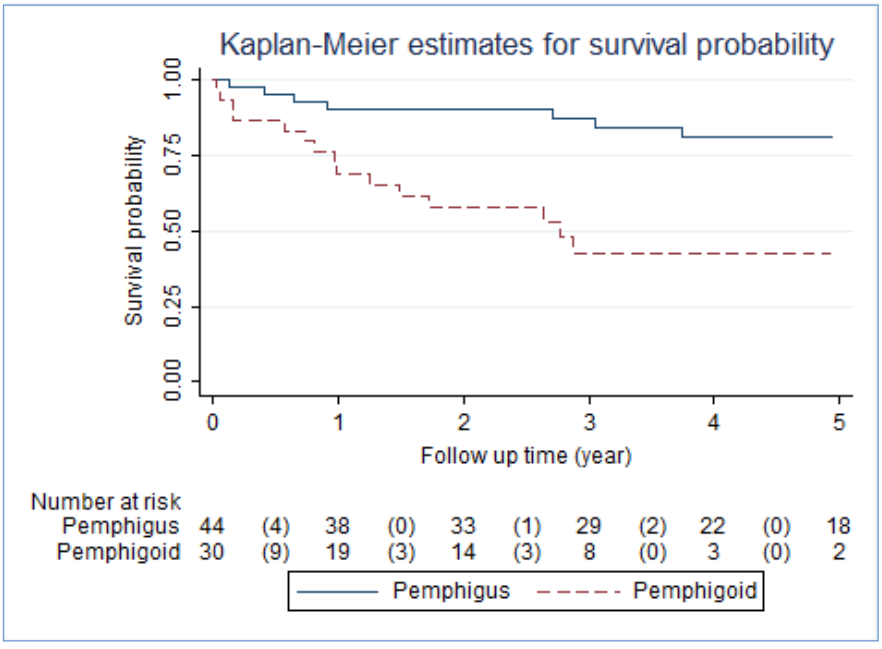

Fig 1. Survival curve of pemphigoid patients compared to pemphigus patients.

TABLE 4. Prognostic factors of survival in pemphigoid and pemphigus patients, univariable and multivariable cox regression

Characteristics	Univariable hazard ratio	p-value	Multivariable hazard ratio	p-value
Type of bullous disease				
Pemphigus	Ref.		Ref.	
Pemphigoid	4.10 (1.76- 9.58)	0.001	1.51 (0.54-4.26)	0.427
Age				
<60	Ref.		Ref	
61-69	1.59(0.29-8.75)	0.589	0.95(0.16-5.49)	0.955
>=70	6.93 (2.34-20.48)	<0.001	4.57 (1.34-15.51)	0.015
Comorbidity				
Absent	Ref.		Ref	
Present	3.13 (1.33-7.33)	0.008	2.46 (0.97-6.22)	0.057

with other autoimmune vesiculobullous disease patients (adjusted odd ratios =4.00 , 95% CI 2.00-13.30).[6] It was postulated that genetic background, regulatory T cell dysfunction, aging and triggering factors such as trauma, irradiation, infection, neurological diseases, hematological malignancies, and certain drugs synergistically induce the breakdown of immune tolerance to BP180/COL17, and result in the production of autoantibodies and the onset of pemphigoid.[10]

A meta-analysis suggested that aldosterone antagonists, dipeptidyl peptidase 4 inhibitors, anticholinergics, and dopaminergic medications are associated with bullous pemphigoid.[11] Drug intake, which may potentially induce pemphigus, includes D-penicillamine[12], angiotensin-converting enzyme inhibitors, angiotensin receptor blockers[13], beta blockers, cephalosporins, phenylbutazone, pyritinol, and thiopronine.[14] In our study, drug use prior to diagnosis: ARBs, CCBs, statins, clopidogrel, biguanides, and NSAIDs pemphigoid were more frequently used in pemphigoid patients than in pemphigus patients. However, after adjustment by cerebrovascular disease and age, there are no drugs that were statistically significant at p-value less than 0.05. This negative finding of association may be due to small sample size or adjustment with confounding effects by age.

In our study the mortality rate after diagnosis of pemphigoid was higher than pemphigus (at one-year 31.9% vs 9.7%: at 5-year 57.2% vs 19.7%). A study in Singapore found the 1-year mortality of pemphigoid and pemphigus were nearly similar at 31% and 24%.[4] A prospective study in Switzerland found the 1-year, 2-year and 5-year probabilities of death in pemphigoid patients were 26.7%, 37.1%, and 60.8%.[15] A study in Songkhla, Thailand found that the 1-year, 3-year and 5-year overall mortality rates of pemphigoid patients were 28.1% , 55.7% and 71.9%.[16] The 1-year, and 3-year overall mortality rates of pemphigoid patients were 25.8% and 43.0% from a study in Morocco.[17] For pemphigus, the 1-, 2-, and 5-year overall survival rates were 92%, 88%, and 77% in a French multicenter study with 249 patients.[18]

In our analysis for prognostic factor of survival in pemphigoid and pemphigus patients, being diagnosed as pemphigoid, older age of initial diagnosis at 75 years old or more and having comorbidity disease were the prognostic factors that increase death in pemphigoid and pemphigus patients in univariable cox regression analysis. In multivariable analysis only the age of diagnosis more than 75 years old was statistically significant. This could explain that pemphigoid is not more severe than pemphigus but rather confounded by older age. A cohort study in France found the prognosis of patients with pemphigoid is influenced by age and Karnofsky score.[19]

There are some limitations of the study due to the small sample size. The comparison drawn between pemphigoid and pemphigus patients in our study might not fully capture the comparative of pemphigoid cases with the general population. The retrospective nature of the study relying on medical records could introduce information bias by missing information.

Overall, this research provides insights into the attributes, prognoses, and associated factors for survival of pemphigoid and pemphigus patients. Bullous pemphigoid incidence should increase as society becomes older. The treatment outcome is still unfavorable especially for pemphigoid. The new treatment such as biologic and topical treatment might reduce the mortality.[20,21] The findings highlight the need for further study of the pathogenesis of disease, novel treatment, and larger population studies with more comprehensive controls for confounding variables.

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