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Remission Rate of Pemphigus Vulgaris and Pemphigus Foliaceus in the Institute of Dermatology: A 7 Years Retrospective Study

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Abstract

Pemphigus, an autoimmune blistering disease caused by autoantibodies targeting desmoglein 1, desmoglein 3, and desmosomal cadherins, is characterized by blister formation and can be a long-term condition with the possibility of relapse. This study aimed to evaluate the remission rates and compare them between pemphigus vulgaris (PV) and pemphigus foliaceus (PF) at the Institute of Dermatology. A retrospective analysis was conducted on 426 patients diagnosed and treated at the Institute of Dermatology in Bangkok, Thailand, between January 1, 2016, and December 31, 2022, for PV and PF. Patients were followed up for 1, 2, and 5 years to assess complete remission using Consensus statement criteria. The remission rates for PV and PF were 3.3%, 17.5%, and 48.4% at 1, 2, and 5 years, and 7.9%, 33.1%, and 61.6% at the same intervals, respectively. PF demonstrated significantly higher remission rates compared to PV at all time points ($p < .001$). The average time to remission was 60 months for PV and 36 months for PF. Prognostic factors associated with complete remission included age, age at onset, control of underlying disease, disease severity, primary site of involvement, and initial mucosal involvement. In conclusion, the remission rates for PV and PF at five years were 48.4% and 61.6%, respectively. PF achieved complete remission more frequently than PV. Good control of underlying disease, absence of initial mucosal involvement, and mild disease severity were associated with better prognosis for both PV and PF.

Keywords: *pemphigus vulgaris (PV); pemphigus foliaceus (PF); remission rate of pemphigus; oral prednisolone treatment; antiCD-20 monoclonal antibody; IVIG*

1. Introduction

Pemphigus is an autoimmune illness associated with IgG autoantibodies against desmogleins of epidermal keratinocytes, causing blisters to form on the skin and mucosal membrane in pemphigus. Types of pemphigus vary, but the most common types are Pemphigus vulgaris (PV) and Pemphigus foliaceus (PF) (Rosi-Schumacher et al., 2023). The incidence of PV is related to ethnicity, gender, age, and geographic site. In Asia, studies have shown that the incidence of pemphigus was 4.7 per million per year (Krain, 1974). The incidence of PF depends on environmental factors. The endemic area is Brazil, Colombia (Aoki et al., 2004; Warren et al., 2000; Sevadjian, 1979). PF is predominantly found in women, with a female-to-male ratio of 4:1 (Bastuji-Garin et al., 1995). Pemphigus typically manifests between the ages of 50 and 70 years (Bastuji-Garin et al., 1995; Salmanpour et al., 2004; Tsankov et al., 2000; Uzun et al., 2004) Pemphigus is a chronic blister disease that recurs and relapses. Factors influencing the prognosis of the disease include underlying disease, type of pemphigus, severity of disease, and

patient's age (Seidenbaum et al., 1988). In the past, doctors mainly used steroids to treat pemphigus disease. They discovered that steroids could improve the prognosis, the incidence of mortality rates increase because of the steroids' adverse effect (Pisanti et al., 1974). Now doctors use anti-CD20 monoclonal antibodies to treat pemphigus disease. In 2018, the Food and Drug Administration (FDA) approved targeted therapy including an anti CD20 monoclonal antibody, to be the first line of treatment pemphigus disease (Murrell et al., 2020). However, for cases where monoclonal antibodies are not an option, it is suggested to use a combination of immunosuppressants and steroids to mitigate steroid-related adverse effects without increasing the remission rate (Barthelemy et al., 1988; Lapidoth et al.,1994; Piamphongsant, 1979)

Currently, there are very few studies showing the remission rate of PV and PF in Thailand. The remission rate of pemphigus reflects the proportion of patients who recover from their illness. The factors influencing the remission rate prognosis are unknown. The target of this research was to evaluate the remission rate of PV and PF and prognostic factors.

2. Objectives

The objective is to assess the remission rate of PV and PF using the consensus statement at the Institute of Dermatology and to compare the remission rates between PV and PF. Moreover, the study seeks to identify prognostic factors that increase the remission rate of PV and PF.

3. Methodology

A retrospective study compared the remission rates of PV and PF and identified prognostic factors using the medical records of every patient diagnosed with PV and PF at the Institute of Dermatology, a tertiary skin hospital in Bangkok, Thailand, between January 1, 2016, and December 31, 2022. Ethical approval number IRB/IEC 024/2566 was obtained. The information was noted and analyzed: age, sex, underlying disease, disease severity, type of pemphigus, site of primary involvement, initial mucosal involvement, treatment, time to remission. Clinical features were used to make the diagnosis, which was then confirmed by immunofluorescence examination and histology. Patients who had at least 1 year of follow-up from initial treatment were included. Exclusion criteria included incomplete data for PV and PF patients, such as missing photos, body surface area, or severity of disease that cannot be determined.

Severity of diseases was assessed using criteria by the European academy of dermatology and venereology (EADV) (Joly et al., 2020), that divided PV and PF patients into mild, moderate to severe categories. Mild PV and PF consisted of patients whose body surface areas (BSA) were less than 5% and restricted oral lesions no significant weight loss, impairing food take or requiring analgesics. Moderate to severe PV and PF whose body surface area (BSA) is >5% or/and oral mucosa involves, severe pain, and weight loss. In this study, the severity of pemphigus is divided using body surface area, picture (rule of nine), or OPD record. Severity grading was noted at the first visit and every follow-up. When patients received multiple treatments, the last treatment received was analyzed. The doctors evaluated and followed up with patients at 1, 2, and 5 years and used the consensus statement according to the activity of disease (Murrell et al., 2008).

The final result of the retrospective study analysis showed that 426 patients with PV and PF were separated into 2 groups based on severity grading (mild and moderate to severe). Every group's patient received medication according to treatment guideline. Mild grading severity of patients that initial treatment only systemic corticosteroid. However, for patients with moderate-to-severe or mild grading severity who did not respond to prednisolone therapy for six to eight weeks, doctors also add immunosuppressive agents such as azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide, dapsone to control the disease. For patients who could not tolerate the above medications, doctors treated them with Intravenous immunoglobulin (IVIG) combined with immunosuppressive agents and prednisolone therapy. Rituximab was administered for patients who were diagnosed with severe grading and no responder patient for more than ten weeks. Rituximab was used in combination with prednisolone and immunosuppressive agents.

The term mean, standard deviation, median, interquartile range, minimum, maximum, and percentages were used to represent descriptive statistics. The Fisher's Exact or Chi-square test were used for statistical analysis of categorical data. The Independent t-test and Mann-Whitney U test were used to compare continuous data between two

groups. Time to remission were conducted with Kaplan-Meier (KM) presented by Survival plot. P-values <0.05 was considered statistically significant. The statistical software SPSS (SPSS Inc., Chicago, IL, USA) version 22.0 was used for all calculations and analyses.

4. Results and Discussion

4.1 Results

Over the 7 years period, the study included 426 patients (264 female and 162 male). The types of pemphigus included: PV, n=275 (64.6%); PF, n=151 (35.4%). The patients' average age was 56±15 years. The average age at onset for was 51±15 years. In total, 194 patients had underlying diseases, with 180 (92.8%) in good control and 14 (7.2%) in poor control. In total, 156 patients with PV and PF had primary mucosal area involvement, five of them had only mucosal involvement, while 153 had both cutaneous and mucosal involvement. According to severity grading of EADV (Joly et al., 2020), 278 patients (65.3%) had moderate to severe grading pemphigus (PV, n=192: PF, n=86) and 148 patients (34.7%) had mild grading pemphigus (PV, n=83: PF, n=65). The distribution of disease severity of pemphigus is shown in Table 1.

Table 1 Demographic characteristics of subject and factors associated with remission in patient with pemphigus (n = 426)

Characteristics	Total (n=426)		Remission (n=396)		No Remission (n= 30)		p-value
	n	%	n	%	n	%	
Gender							0.847
Male	162	38.0%	150	37.9%	12	40.0%	
Female	264	62.0%	246	62.1%	18	60.0%	
Age (years)							0.046*
≥ 60	173	40.6%	166	41.9%	7	23.3%	
< 60	253	59.4%	230	58.1%	23	76.7%	
Mean±SD.	56.48	±15.33	56.96	±15.29	50.13	±14.70	0.032*
Age at onset (year) Mean±SD.	51.95	±15.59	52.47	±15.51	45.03	±15.21	0.012*
Underlying							0.801
Yes	194	45.5%	181	45.7%	13	43.3%	
no	232	54.5%	215	54.3%	17	56.7%	
DM	58	13.6%	53	13.4%	5	16.7%	0.613
HT	110	25.8%	103	26.0%	7	23.3%	0.747
DLP	63	14.8%	57	14.4%	6	20.0%	0.404
Other	93	21.8%	85	21.5%	8	26.7%	0.506
UD duration (year) Mean±SD.	7.32	±2.98	7.33	±2.81	7.15	±4.86	0.403
UD process (n=194)							<0.001*
good control	180	92.8%	173	95.6%	7	53.8%	
poor control	14	7.2%	8	4.4%	6	46.2%	
Current medication							0.991
yes	185	43.4%	172	43.4%	13	43.3%	
no	241	56.6%	224	56.6%	17	56.7%	
Diagnosis							0.067
PV	275	64.6%	251	63.4%	24	80.0%	
PF	151	35.4%	145	36.6%	6	20.0%	
Severity disease							<0.001*
Mild BSA<5%	148	34.7%	148	37.4%	0	0%	
Moderate to Severe >5%	278	65.3%	248	62.6%	30	100%	
PV (n=275)							
Severity disease							0.001*
Mild BSA<5%	83	30.2%	83	33.1%	0	0%	
Moderate to Severe >5%	192	69.8%	168	66.9%	24	100%	
PF (n=151)							
Severity disease							0.037*
Mild BSA<5%	65	43.0%	65	44.8%	0	0%	
Moderate to Severe >5%	86	57.0%	80	55.2%	6	100%	

Table 1 Cont.

Characteristics	Total (n=426)		Remission (n=396)		No Remission (n= 30)		p-value
	n	%	n	%	n	%	
Site of primary involvement							
Mucosal	5	1.2%	5	1.3%	0	0%	1.000
Cutaneous	268	62.9%	255	64.4%	13	43.3%	0.021*
Both	153	35.9%	136	34.3%	17	56.7%	0.014*
Initial mucosal involvement							0.018*
Present	156	36.6%	139	35.1%	17	56.7%	
Absent	270	63.4%	257	64.9%	13	43.3%	
Treatment							
Prednisolone	126	29.6%	125	31.6%	1	3.3%	0.001*
Prednisolone + Azathioprine	235	55.2%	212	53.5%	23	76.7%	0.014*
Prednisolone + MMF	11	2.6%	11	2.8%	0	0%	0.355
Prednisolone+Cyclophosphamide	16	3.8%	16	4.0%	0	0%	0.262
Rituximab	24	5.6%	22	5.6%	2	6.7%	0.799
IVIG	12	2.8%	8	2.0%	4	13.3%	<0.001*
plasmapheresis	2	0.5%	2	0.5%	0	0%	1.000

p values for mean data were calculated with the use of independent t-test or Mann-Whitney U-test, for percentages with the use of Chi-square test or Fisher's Exact test, * significant at p-value < 0.05
PV= Pemphigus vulgaris, PF= Pemphigus foliaceus

The study included a total of 426 patients, among whom 126 (29.6%) received treatment with prednisolone alone. Among these, remission was observed in 125 cases, with a significant association noted (p=.0001). Additionally, 235 patients (55.2%) were treated with a combination of prednisolone and azathioprine, resulting in remission in 212 cases (p=.014). Treatment with prednisolone and mycophenolate mofetil was administered to 11 patients (2.6%), with remission observed in 11 cases, although the association was not statistically significant (p=.355). Similarly, treatment with prednisolone and cyclophosphamide was provided to 16 patients (3.8%), resulting in remission in 16 cases (p=.262). Rituximab treatment was administered to 24 patients (5.6%), leading to remission in 22 cases, with no significant association observed (p=.799). Notably, intravenous immunoglobulin (IVIG) treatment was provided to 12 patients (2.8%), predominantly those with moderate-to-severe PV, and resulted in remission in 8 cases, demonstrating a highly significant association (p<.001). Plasma-pheresis treatment was administered to 2 patients (0.5%), resulting in remission in both cases, although the association was not statistically significant (p=1.000). The analysis revealed a significant association between certain treatments, including prednisolone, prednisolone and azathioprine, and IVIG, and remission rates (Table 1). Particularly, IVIG treatment emerged as the most significant factor associated with pemphigus remission (p<.001). The distribution of disease severity according to treatment is outlined in Table 2.

The remission rates of pemphigus were assessed over varying durations post-diagnosis. In the initial year, 21 patients (4.9%) achieved complete remission, with nine cases attributed to PV and 12 to PF, yielding statistically significant outcomes (p<.001). Concurrently, 382 patients (89.7%) experienced partial remission, while 23 patients (5.4%) encountered relapse within this period (p< .001). Progressing to the second year, 98 patients (23.0%) attained complete remission, comprising 48 PV and 50 PF cases, demonstrating a notable improvement (p<.001). Meanwhile, 280 patients (65.7%) achieved partial remission, yet 48 patients (11.3%) experienced relapse (p< .001). By the fifth year, 226 patients (53.0%) achieved complete remission, including 133 PV and 93 PF cases, showcasing a statistically noteworthy trend (p=.009). Moreover, 170 patients (39.9%) attained partial remission, while 27 patients (6.3%) faced relapse during this period (p=.034). Remarkably, only three patients experienced treatment failure throughout the study duration.

Table 2 Severity of disease according to treatment

Treatment	PV (n=275)		PF (n=151)		Total
	Mild BSA<5%	Moderate to Severe >5%	Mild BSA<5%	Moderate to Severe >5%	
Prednisolone	45	7	59	15	**126**
Prednisolone + Azathioprine	31	134	6	64	**235**
Prednisolone + MMF	1	10			**11**
Prednisolone + Cyclophosphamide	1	9		6	**16**
Rituximab	4	19		1	**24**
IVIG		12			**12**
plasmapheresis	1	1			**2**
Total	**83**	**192**	**65**	**86**	**426**

The rates of complete remission for PV were 3.3%, 17.5%, and 48.4% at 1, 2, and 5 years post-diagnosis, respectively, while for PF, they were 7.9%, 33.1%, and 61.6% during the same intervals. Notably, PF demonstrated a significantly higher rate of complete remission compared to PV (p< .001) (Table 3). The average duration until remission was 60 months for PV and 36 months for PF (Figure 1).

The primary prognostic factors influencing the complete remission of both PV and PF were identified as follows: age (p=.046), indicating a higher likelihood of remission in younger patients; underlying disease control (p<.001), with better remission rates observed in cases where underlying disease control was optimal; disease severity (p= .001), with a greater likelihood of remission in cases of moderate to severe pemphigus; and initial mucosal involvement (p=.018), which indicated a worse prognosis when mucosal involvement was present at the onset of the disease. Additionally, the site of primary involvement (p=.021) was found to influence prognosis, with a better prognosis observed in cases where only cutaneous involvement was present. Multiple variate analysis confirmed the positive associations of age, age at onset, underlying disease control, disease severity, site of primary involvement, and initial mucosal involvement with the remission rate.

Table 3 Compare remission rate of pemphigus vulgaris and foliaceus

	Total (n=426)		PV (n=275)		PF (n=151)		p-value
	n	%	n	%	n	%	
Outcome year 1							<0.001*
Complete remission	21	4.9%	9	3.3%	12	7.9%	0.033*
Partial remission	382	89.7%	243	88.4%	139	92.1%	0.231
Relapse	23	5.4%	23	8.4%	0	0%	<0.001*
Outcome year2							<0.001*
Complete remission	98	23.0%	48	17.5%	50	33.1%	<0.001*
Partial remission	280	65.7%	184	66.9%	96	63.6%	0.488
Relapse	48	11.3%	43	15.6%	5	3.3%	<0.001*
Outcome year 5							0.034*
Complete remission	226	53.1%	133	48.4%	93	61.6%	0.009*
Partial remission	170	39.9%	118	42.9%	52	34.4%	0.088
Relapse	27	6.3%	21	7.6%	6	4.0%	0.138
Treatment failure	3	0.7%	3	1.1%	0	0%	0.555

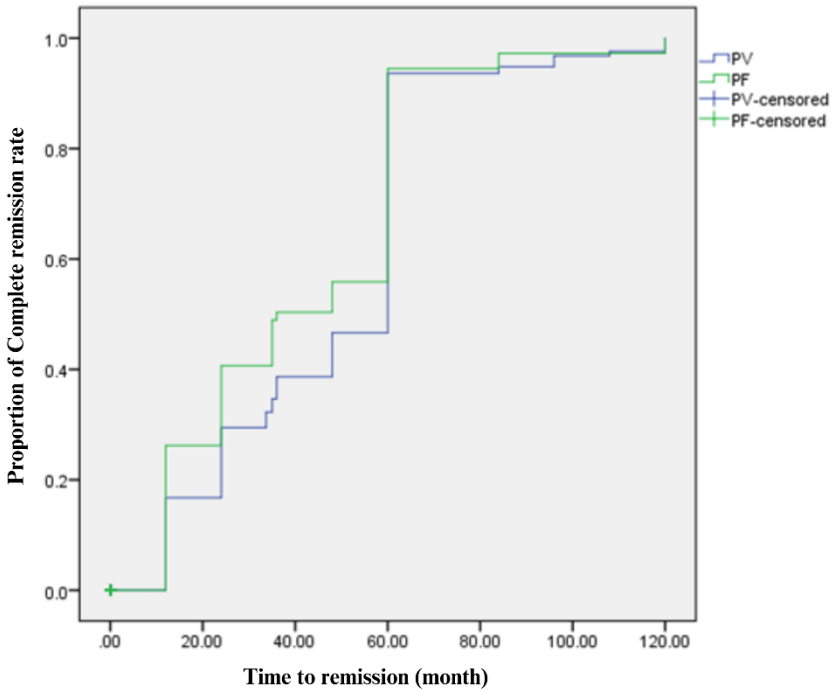

Figure 1 Time to remission of pemphigus vulgaris and foliaceus

4.2 Discussion

Pemphigus, classified as a rare autoimmune blistering disorder, exhibits a variable incidence rate of 0.5-3.2 cases per 100,000 individuals annually, as reported by Ahmed (1983). Predominantly affecting females, our investigation corroborates this gender predisposition with a female to male ratio of 1.6:1. The demographic distribution predominantly includes middle-aged individuals, with our study documenting the oldest and youngest patients at 92 and 17 years, respectively, and an average age of onset at approximately 51.95 years.

The therapeutic landscape of pemphigus has undergone significant evolution since the 1950s when corticosteroids were introduced, markedly reducing the mortality rate to an average of 30%, as highlighted by Bystryn (1984). This mortality rate experienced a further decline to below 10% following the integration of adjuvant therapies, including immunosuppressive drugs during the 1960s and 1970s (Ahmed, 1983). The introduction of Rituximab, a monoclonal antibody targeting CD20 antigens on B-lymphocytes, in 2017, marked a pivotal advancement in pemphigus treatment, demonstrating effective outcomes.

Our research revealed that a combination of prednisolone and azathioprine served as the principal therapeutic regimen in 55.2% of pemphigus cases (p= .014). Treatment strategies were tailored according to the disease subtype, severity, and the presence of comorbidities such as diabetes mellitus, renal dysfunction, and hepatic failure. For cases of mild severity, monotherapy with prednisolone was often sufficient, whereas moderate to severe cases necessitated a combination of prednisolone with immune-suppressive agents like azathioprine, mycophenolate mofetil, or cyclophosphamide.

Initial diagnoses revealed that Pemphigus Vulgaris (PV) predominantly presented with moderate-to-severe disease, while Pemphigus Foliaceus (PF) was more commonly classified as mild-to-moderate in severity. A significant 61.6% of both PV and PF cases were managed with a combination of prednisolone and immune-suppressive drugs. The study identified a notable difference in the treatment to remission rates among patients administered solely prednisolone, those treated with a combination of prednisolone and azathioprine, and those receiving Intravenous Immunoglobulin (IVIG), with respective p-values of .001, .014, and < .001. Moreover, a significant correlation was observed between the control of underlying diseases and remission rates (p<.001).

Prognostic factors for remission in PV and PF included age, age at onset, control of underlying disease, disease severity, site of primary involvement, and initial mucosal area involvement, echoing findings from Almugairen et al. (2013) and Cura et al. (2020) which identified mucosal involvement and younger age as predictors of complete remission. The rate of complete remission at 1, 2, and 5 years post-diagnosis was contrastingly lower in our study compared to the rates of 25%, 50%, and 75% at 2, 5, and 10 years, respectively, reported by Herbst, & Bystryn (2000). This discrepancy could be attributed to the study's setting in a tertiary skin hospital in Bangkok, Thailand, potentially leading to an overrepresentation of severe cases. Nevertheless, Kulthanan et al. (2011) reported a 31.6% complete remission rate in both PV and PF over a decade post-diagnosis, suggesting improvements in therapeutic outcomes, potentially due to the incorporation of more effective treatments like rituximab.

Our analysis also highlighted a differential in complete remission rates between PF and PV, with PF exhibiting significantly higher rates of complete remission at 1, 2, and 5 years post-diagnosis ($p < .001$). This difference underscores the variable clinical courses and responses to treatment between these pemphigus subtypes. Furthermore, the time to remission was notably longer in PV than in PF, with median durations of 60 and 36 months, respectively.

The study's limitations include its retrospective nature, the absence of long-term clinical follow-up, and a restricted timeframe for data collection, which may influence the generalizability and interpretation of the findings.

5. Conclusion

In conclusion, our investigation presents a detailed comparative analysis of the remission rates within pemphigus vulgaris (PV) and pemphigus foliaceus (PF) cohorts over a span of 1, 2, and 5 years post-diagnosis. The findings indicate that the complete remission rates for PV were 3.3%, 17.5%, and 48.4% at the respective intervals, whereas PF demonstrated higher remission rates of 7.9%, 33.1%, and 61.6%. This differential outcome underscores the inherently variable natural histories and therapeutic responses between these two subtypes of pemphigus, with PF patients exhibiting a notably greater propensity towards achieving complete remission compared to their PV counterparts. Critical prognostic factors identified include age, age at onset, effective control of underlying diseases, severity of the disease at presentation, the primary site of disease involvement, and the extent of primary mucosal involvement. These factors collectively contribute to the likelihood of remission and the overall prognosis, emphasizing the necessity for a personalized, comprehensive approach to treatment planning and management.

Moreover, the duration to remission further delineates the clinical course of these conditions, with PF patients typically reaching remission at a median of 36 months, compared to 60 months for PV patients. This variance not only highlights the differential disease progression and response to therapy between PV and PF but also necessitates the consideration of these timelines in the therapeutic decision-making process.

6. Acknowledgements

This study enhances our understanding of the remission rates of PV and PF at the Institute of Dermatology, as well as the time to remission and prognostic factors for pemphigus patients. The author wishes to thank the College of Medicine, Rangsit University, and the Institute of Dermatology for their assistance in collecting information.

7. Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that had no conflict of interest.

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