REMISSION RATE OF PEMPHIGUS VULGARIS AND PEMPHIGUS FOLIACEUS IN THE INSTITUTE OF DERMATOLOGY: A 7 YEARS RETROSPECTIVE STUDY

BY

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Abstract

Pemphigus, an autoimmune blister disease caused by autoantibodies targeting desmoglein 1 and 3, as well as desmosomal cadherins, is characterized by blistering 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), together with prognostic factors in the Institution of Dermatology. A retrospective analysis was conducted on 426 patients diagnosed and treated at Institute of Dermatology (a tertiary skin hospital 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 the consensus statement criteria. The remission rate for PV was 3.3%, 17.5%, and 48.4% at 1, 2, and 5 years after diagnosis respectively. The remission rate of PF was 7.9%, 33.1%, and 61.6% at 1, 2, and 5 years following diagnosis. PF demonstrated significantly higher remission rates compared to PV at all time points ($P < .001$). The average timing of remission was 60 months for PV (95% confidence interval 58.6-61.3) and 36 months for PF (95% confidence interval 23.1-48.8). Prognostic factors associated with complete remission include age, age at onset, underlying disease control, disease severity, site of primary involvement and initial mucosal involvement. In conclusion, the remission rates of PV and PF at five years were 48.4% and 61.6% respectively. PF achieves complete remission more frequently than PV. Good control of underlying disease, absence of initial mucosal involvement, and mild severity disease were associated with better prognosis for both PV and PF.

(Total 28 pages)

Keywords: Pemphigus VULGARIS (PV), Pemphigus Foliaceus (PF), The Remission Rate of Pemphigus, Oral Prednisolone Treatment, Adjuvant Therapy, Anti-CD20 Monoclonal Antibody, IVIG

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Chapter 1

Introduction

1.1 Background and Significance of the Problem

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 were differentiated from many types but mostly were PV and PF (Rosi-Schumacher et al.,2023). PV's incidence was related to ethnicity, gender, age, and origin site. In Asia, the study revealed that incidence of pemphigus was 4.7 people per million per year (Krain, 1974; Huang et al., 2012). The incidence of PF depends on environmental factors. The endemic area is Brazil, Columbia (Aoki et al., 2004; Warren et al., 2000; Sevadjian et al.,1978; Tallab et al., 2001). Mostly PF was found in women, the ratio of female to male sex was 4:1 (Bastuji-Garin et al.,1995). Pemphigus typically manifested between the ages of 50 and 70 years (Bastuji-Garin et al.,1995; Salmanpour et al.,2004; Tsankov et al.,2000). Pemphigus is a chronic blister disease that has been recurrent and relapsed. The factors influencing the prognosis of disease depended on underlying disease, type of pemphigus, severity of disease, and patient's age (Seidenbaum et al.,1988). In the past, doctor used steroids that main to treat pemphigus disease. They discovered that steroids could improve the prognosis and the incidence of mortality rates increased because of the steroids' adverse effects (Pisanti et al.,1974). Now the doctor has used anti-CD20 monoclonal antibody for pemphigus disease. In 2017, FDA approved targeted therapy including anti-CD20 monoclonal antibody for to be the first line of treatment pemphigus disease (Murrell et al.,2008a) However, in cases, that limited to use of monoclonal antibodies, suggested the use of

immunosuppressants combination with steroids to reduce adverse effects of steroids but not increase remission rate (Barthélemy et al.,1988; Lapidoth et al.,1994; Piamphongsant.,1979)

Nowadays, very few studies have shown remission rate of PV and PF in Thailand. Remission rate of pemphigus reflects patients who recover from their illness. The prognosis of remission rate had unknown cause. The target of this research was to evaluate remission rate of PV and PF and prognostic factors.

1.2 Research objectives

1.2.1 Remission rate of PV and PF in the Institute of Dermatology

1.2.2 To compare remission rate between PV and PF

1.2.3 Prognostic factors of remission rate PV and PF

1.3 Research Questions

How much of remission rate PV and PF in the Institute of Dermatology?

1.4 Research Framework

Retrospective study, electrical medical record form of every patient with PV (ICD10 L10.1) and PF (ICD10 L10.2) were diagnosed at Institute of Dermatology between 1 January 2016 and 31 December 2022. The information was noted and analyzed such as age, sex, underlying disease, disease severity, type of pemphigus, site of primary involvement, initial mucosal involvement, treatment, and time to remission.

Independent Variables

1) Patient factors: age, sex, underlying diseases

2) Clinical factor: disease severity, type of pemphigus, site of primaryinvolvement,

initial mucosal involvement, treatment, duration of disease

Dependent Variables

1) Remission rate of PV and PF

1.4.1 Inclusion criteria

1) All patients who were diagnosed with PV and/or PF

2) Pemphigus vulgaris (ICD10 L10.1) and/or pemphigus foliaceus (ICD10 L10.2) patients were treated at the Institute of Dermatology between 1 January 2016 and 31 December 2022

3) Follow-up period at least 1 year from initial treatment

1.4.2 Exclusion criteria

Exclusion criteria PV and PF patients' incomplete data such as without photo or body surface area or severity of disease cannot be divided severity grading.

1.4.3 Diagnosis PV and PF (Joly et al.)

Pemphigus vulgaris (PV)

1) Clinical presentation. Always start with oral lesions; buccal and/or gingival mucosa with painful and disturbed eating. The appearance of cutaneous involvement is characterized with flaccid bullae with clear fluid. The lesions may be localized or generalized and main at chest, face, and scalp region. Positive Nikolsky sign

2) Histopathology of pemphigus vulgaris. Suprabasal blister with acantholysis "row of tombstones" appearance

3) Direct immunofluorescence (DIF). IgG bound to surface of keratinocytes (intercellular pattern)

4) Indirected immunofluorescence test (IIF) and/or ELISA Desmoglein1 and Desmoglein 3. IIF Monkey esophagus substrate ideal IgG in cell surface pattern. ELISA Desmogleins 1, 3 (mucosal and skin involvement), Desmoglein 3 (mucosal dominant)

Pemphigus foliaceus (PF)

1) Clinical presentation. The appearance of cutaneous involvement: transient, flaccid bullae in seborrheic areas

2) Histopathology of pemphigus foliaceus. Early lesions show eosinophilic spongiosis; histopathology demonstrates acantholysis below stratum corneum; epidermis under the granular layer normal; subcorneal pustules containing neutrophils and acantholytic in the cavity.

3) Direct immunofluorescence (DIF). IgG bound to surface of keratinocytes (intercellular pattern)

4) Indirected immunofluorescence test (IIF) and/or ELISA. pig esophagus or human skin substrate ideal IgG in intercellular pattern. ELISA Desmoglein 1 Diagnosis of pemphigus. Clinical features were used to make the diagnosis, which was then confirmed by immunofluorescence examination and histology.

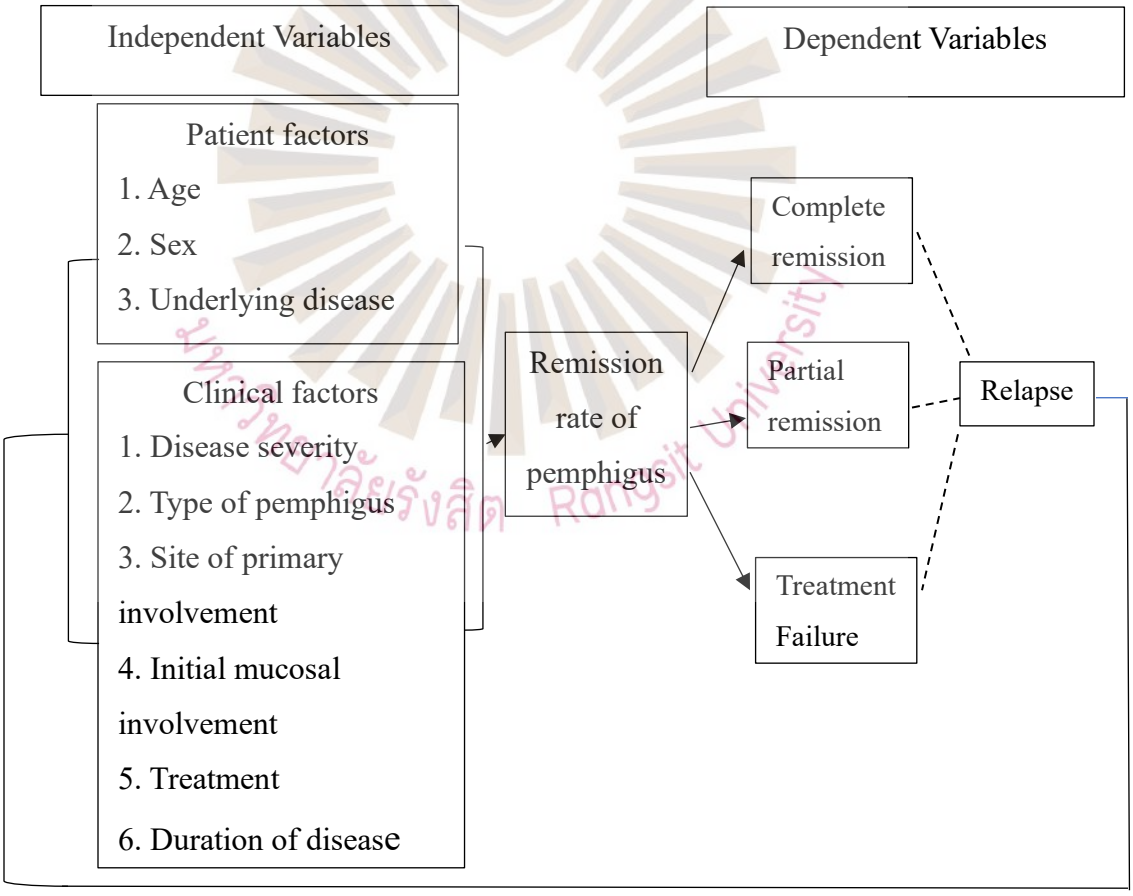

Figure 1.1 Variable of Remission rate of pemphigus

1.5 Definition of Term (Murrell et al.)

1) Complete remission off therapy = Absence of new lesions while the patient is off all systemic therapy for at least two months.

2) Complete remission on therapy = Absence of new lesions while the patient is receiving prednisolone <10mg/kg/day or the equivalent.

3) Partial remission off therapy = The presence of transient new lesions that heal within one week without treatment

4) Partial remission on minimal therapy = The presence of transient new lesions that heal within one week while the patient is receiving prednisolone <10mg/kg/day or the equivalent

5) Relapse/flare is the appearance of >3 new lesions per month that don't spontaneously heal within 1 week, or the extension of established lesions, in a patient who has achieved disease control.

6) Treatment failure = The failure to control disease activity with full therapeutic dose of systemic treatment.

Severity assessment of PV and PF

In this study, the severity of pemphigus is divided using body surface area (BSA), picture (rule of nine), or OPD record.

Mild types of PV and PF.

1) PF associated with less than 5% BSA

2) PV associated with less than 5% BSA and restricted oral lesions do not disturb food intake or require analgesics.

Moderate to severe PV and PF.

1) Many mucosal involvements of PV: oral, nasopharyngeal, conjunctival, genital

2) Severe oral lesions or difficultly swallowing and significant weight loss

3) Severe pain

4) And/or skin lesions more than 5% BSA.

Treatment of mild PF recommended (Figure 1.2)

1) Dapsone: start with 50 to 100 mg/day, adjusted to clinical response up to 1.5 mg/kg body weight. Dapsone is mostly combined with topical steroids.

2) Topical corticosteroids: alone if there are only very limited lesions.

3) Systemic corticosteroids therapy prednisolone 0.5-1.0 mg/kg/day

4) Rituximab alone, or associated with topical or oral corticosteroids

Treatment of mild PV recommended (Figure 1.2)

1) Systemic steroid therapy: prednisolone 0.5-1.0 mg/kg/day with or without AZA (2.0mg/kg/day), or MMF 2g/day or mycophenolate sodium 1,440 mg/day.

2) Only rituximab or combination with oral corticosteroids

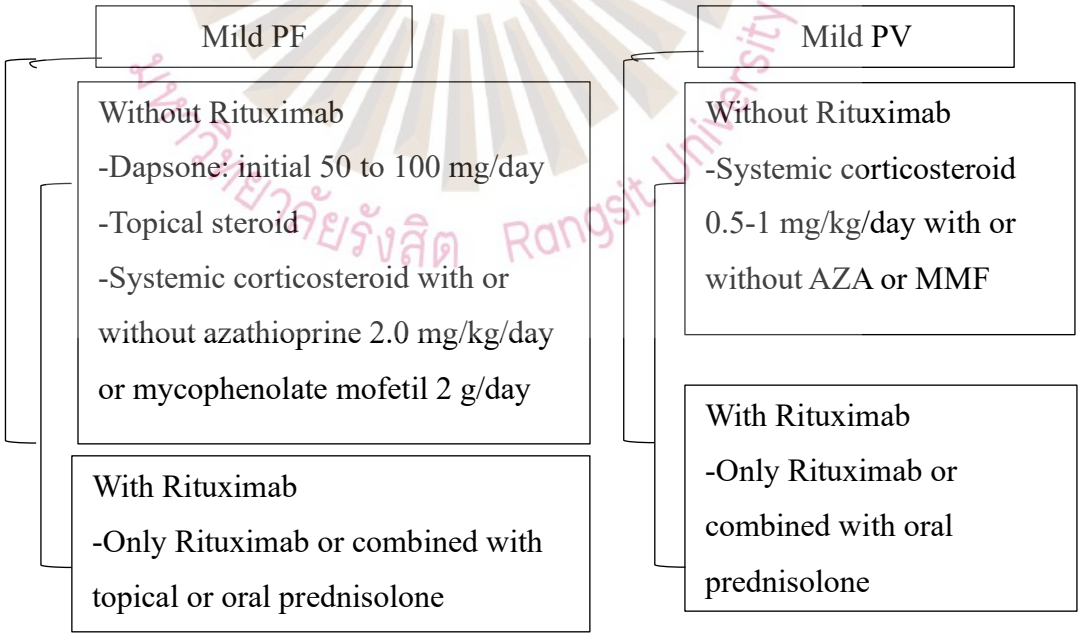

Figure 1.2 Treatment of mild PV and PF

Source: Joly, 2011

Treatment of moderate-to-severe PV and PF recommended (Figure 1.3)

1) Only systemic steroid therapy (oral prednisolone 1 to 1.5 mg/kg/day) or combined with an immunosuppressant drug (AZA, MMF, or mycophenolate sodium), Especially in patients who are more experience severe adverse effects from prolonged use of steroids, or in case, there is no option to treat with rituximab.

2) Rituximab (two infusions of 1 g two weeks apart) combined with systemic steroids (prednisolone 1 mg/kg/day)

After treatment divide to disease can or can't be controlled at three to four weeks.

3) If Disease can't be controlled at 3-4 weeks. Patients was treated with rituximab and prednisolone. Recommended rise prednisolone up to 1.5 mg/kg/day or intravenous (IV) corticosteroid pulse: methylprednisolone 0.5-1 g/day.

Patients were treated with only systemic steroids (prednisolone, 1.0 mg/kg/day). suggested rise prednisolone to 1.5 mg/kg/day and add rituximab or addition immunosuppressant (azathioprine, or mycophenolate mofetil or mycophenolate sodium)

Patients were treated only systemic steroids (start prednisolone, 1.5 mg/kg/day). In the event, rituximab can't possibility treat patient advice to add an immunosuppressant (azathioprine or mycophenolate mofetil or mycophenolate sodium).

Diseases can be controlled at 3-4 weeks. Maintenance therapy following a rituximab cycle. Patients's status six months after the first cycle of rituximab (month 6). If patients start presented with a severe pemphigus and/or still have a high rate of anti-Dsg antibodies at three months, suggested to administer an infusion of 500 mg or 1 g of rituximab at month six.

Patients without complete remission on/off therapy at month 6, recommended to perform two infusions of one gram two weeks apart.

Month twelve and eighteen after the 1st cycle. Rituximab 500 mg is advised in patients who complete remission on/off therapy at month twelve and eighteen, Especially, in patients with positive anti-Dsg antibodies.

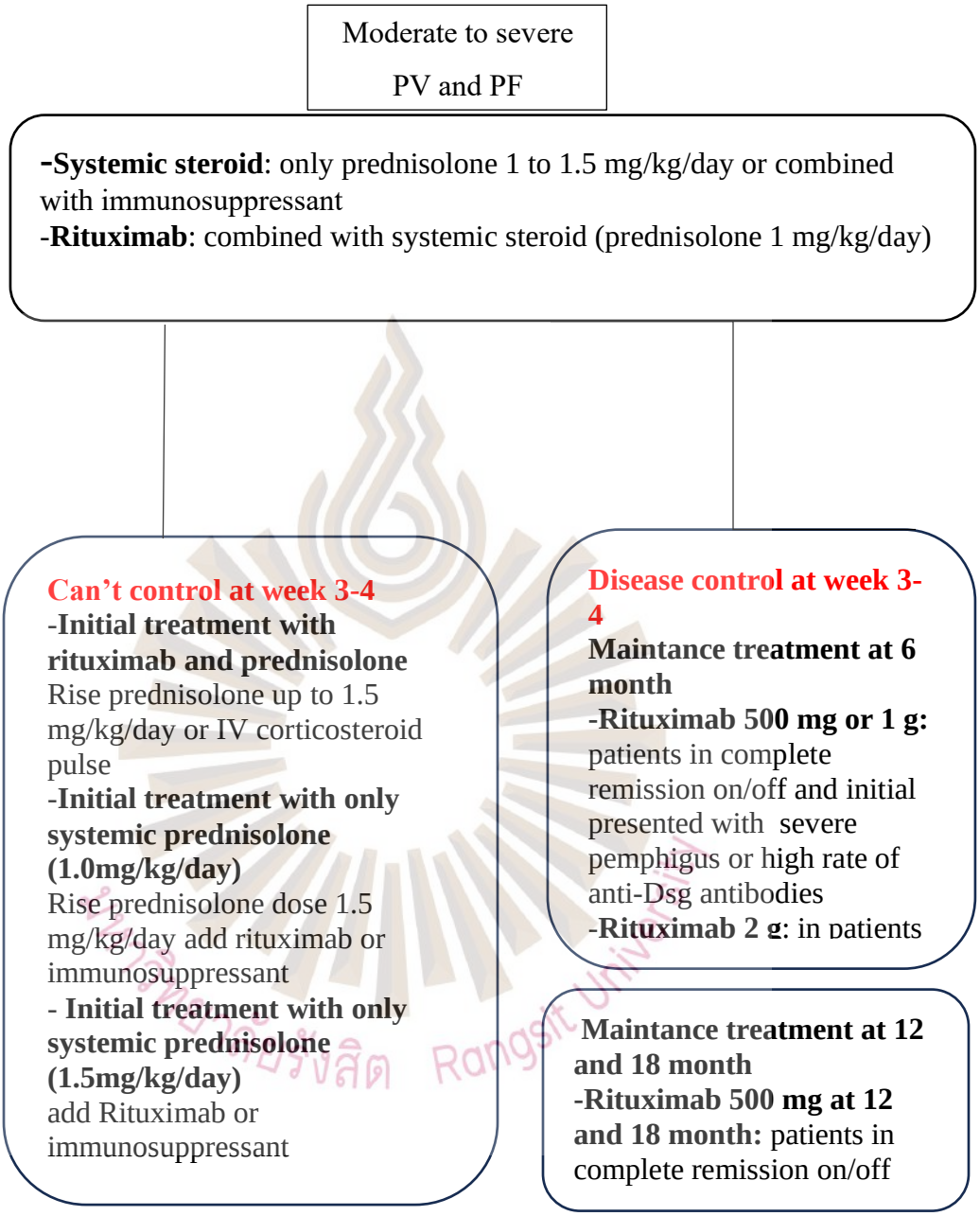

Figure 1.3 Treatment of moderate to severe PV and PF
Source: Joly, 2011

Chapter 2

Literature Review

Pemphigus is an intermittent disease, there was a period of relapse and remission. Moreover, pemphigus requires long-term treatment and usually destroys patient's appearance. Clinical features were used to make the diagnosis, which was then confirmed by immunofluorescence examination and histology. There are two common types of pemphigus; pemphigus vulgaris (PV) and pemphigus foliaceus (PF) (Rosi-Schumacher, Baker, Waris, Seiffert-Sinha, & Sinha, 2023). PF is characterized by a superficial scaly crusted patches at seborrheic area, while PV is usually preceded by blisters, followed by crusted patches, usually has mucosal involvement with more severity compared to PF. Study by Mi ri Kim et al (Kim, Kim, & Kim, 2011) complete and partial remission rate of PV was 77% and 94% at five and ten years after diagnosis respectively. Complete and partial remission rates of PF were 87% and 98% at five and ten years after the diagnosis respectively. Almost all patients receive remission at 10 years. In America, studies have shown (Herbst, & Bystryn, 2000) that PV was 40 patients treated with steroid and immunosuppressant drugs. Studies have shown completed remissions of PV were 25%, 50%, and 75% at 2, 5, and 10 years after diagnosis respectively. In Asia, studies have shown (Kulthanan, & Chularojanamontri, 2011) that complete remission both of PV and PF that 31.6%. Both PV and PF are predominantly found in women, with a female-to-male ratio of 2:1. PV and PF typically manifest the ages of 45.4 and 57.4 years respectively. Moreover, Studies from the National Skin Centre (Rosi-Schumacher et al.,2023) major treatment using prednisolone and azathioprine have showed remission rate of pemphigus was 63.9% and 60.0% of PV and PF patients. Retrospective. Study from (Baum, Scope, Barzilai, Azizi & Trau, 2006) in severe PV were treated with IVIG. The

study revealed that 83% of responses to 6 cycles of IVIG, the patients had 50% complete remission and 33% partial remission. Now doctor use anti-CD20 monoclonal antibodies to treat severe pemphigus disease. Study from (Miše, Jukić, & Marinović, 2022) shown remission rate of severe pemphigus treated with rituximab is 31.8%, 85.7%, and 100% in first dose, second dose, third dose rituximab and 44.4% relapse at first cycle of rituximab. Pemphigus is a chronic blister disease that recur and relapses. Factors influencing remission include ethnicity, gender, age, and pemphigus type (Saha et al., 2014). Moreover, study from (Seidenbaum et al., 1988) shown underlying disease, severity of disease affected to remission

There are very few studies showing the remission rate of PV and PF in Thailand and the factors influencing the remission rate prognosis are unknown

Chapter 3

Research Methodology

3.1 Population and samples

A retrospective study compare 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. The information was noted and analyzed: age, gender, underlying disease, severity of disease, type of pemphigus, site of primary involvement, initial mucosal involvement, treatment, and 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. When a patient received multiple treatments, the results of the latest treatment were analyzed.

3.2 Data collection

Severity of diseases was assessed using criteria by EADV 2020 (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 taken, or requiring analgesics. Moderate to severe PV and PF whose body surface area (BSA) is more than 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 patient received multiple treatments, the last treatment received was analyzed

3.3 Evaluation

The doctor 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, show that 426 patients with PV and PF were separated into 2 groups based on severity grading . Mild grading severity of patients that initial treatment only systemic corticosteroid. However, for patients with moderate-to-severe or mild grading severity who didn't respond to prednisolone therapy for six to eight weeks, doctors also add immunosuppressive drugs such azathioprine , mycophenolate mofetil , cyclophosphamide, dapsone to control the disease. For the patients who could not tolerate the above medications, doctors treated them with IVIG combined with immunosuppressive agents and prednisolone therapy. Rituximab was administered for patients who were diagnosed with severe grading and no responder patients for more than ten weeks. Rituximab was used in combination with prednisolone and immunosuppressive agents.

3.4 Statistic analysis

The term mean, standard deviation, median, interquartile range, minimum, maximum, and percentages were used to represented descriptive statistics. Chi-square test or Fisher's Exact test were used for categorical data. The independent t-test and Mann-Whitney U test 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. All the statistical calculations and analysis were performed by using SPSS (SPSS Inc., Chicago, IL, USA) version 22.0 statistical software.

Chapter 4

Research Results

4.1 Result and discussion

Patient population

Over the 7 years, the study included four hundred twenty-six 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 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, 153 patients with PV and PF had both cutaneous and mucosal involvement, 268 had only cutaneous involvement, while five of them had only mucosal involvement. According to severity grading by EADV (Joly et al.,2020), 278 patients (65.3%) had moderate to severe pemphigus (PV, n=192; PF, n=86) and 148 patients (34.7%) had mild pemphigus (PV, n=83; PF, n=65). The clinical characteristic of patients with pemphigus are shown in Table 1

Table 4.1 Demographic and clinical characteristics of patients with pemphigus

	Total n=426	PV n=275 (64.6%)	PF n=151 (35.4%)
Gender			
Male	162 (38.0%)	107 (38.9%)	55 (36.4%)
Female	264 (62.0%)	168 (61.1%)	96 (63.6%)

Table 4.1 Demographic and clinical characteristics of patients with pemphigus (Cont.)

Age (years)			
>60	173 (40.6%)	93 (33.8%)	80 (52.9%)
<60	253 (59.4%)	182 (66.2%)	71 (47.1%)
Age Mean (years)	56.48±15.33	54.24±14.48	58.72±16.91
Age at onset (years)	51.95±15.59	49.42±13.47	54.48±16.94
Underlying disease	194 (45.4%)	117(42.5%)	77 (51.0%)
-Good control	180 (92.8%)	106(90.6%)	74 (96.1%)
-Poor control	14 (7.2%)	11 (9.4%)	3 (3.9%)
No UD	232 (54.5%)	158 (57.5%)	74 (49.0%)
Disease severity			
-mild BSA<5%	148 (34.7%)	83 (30.2%)	65 (43.0%)
-moderateBSA >5%	278 (65.3%)	192 (69.8%)	86 (57.0%)
Site of primary involvement			
-Mucosal	5 (1.2%)	4 (1.4%)	1 (0.7%)
-Cutaneous	268 (62.9%)	119 (43.3%)	149 (98.6%)
-Both	153 (35.9%)	152 (55.3%)	1 (0.7%)

PV= Pemphigus vulgaris, PF= Pemphigus foliaceus, BSA= Body surface area

Treatment

From our study shown seven treatment modularities were used to treat pemphigus patients. Prednisolone monotherapy, prednisolone with azathioprine, prednisolone with mycophenolate mofetil, prednisolone with cyclophosphamide, rituximab, IVIG and plasmapheresis. Prednisolone with azathioprine was the major treatment modularity used (55.2%). Prednisolone monotherapy was used 45 (10.5%) of mild PV and 59 (13.8%) of mild PF. Two hundred thirty-five patients (55.2%) were treated prednisolone and

azathioprine were used almost in moderate to severe PV and PF. Eleven patients (2.6%) were treated prednisolone and mycophenolate mofetil, including 1 case of mild PV and 10 cases of moderate-to-severe PV. Sixteen patients (3.8%) were treated with prednisolone and cyclophosphamide, including 1 case mild PV, 9 cases moderate-to-severe PV and 6 cases moderate to severe PV. Rituximab, IVIG, and plasmapheresis were used mostly in moderate to severe PV and PF. Treatment modularities in pemphigus patients shown in Table 4.2

Table 4.2 Treatment modularities in pemphigus patients

	PV (n=275)		PF (n=151)		
Treatment	Mild BSA<5%	Moderate to Severe >5%	Mild BSA<5%	Moderate to Severe >5%	**Total**
Prednisolone	45	7	59	15	**126 (29.6%)**
Prednisolone -AZA	31	134	6	64	**235 (55.2%)**
-MMF	1	10			**11 (2.6%)**
-Cy	1	9		6	**16 (3.8%)**
Rituximab	4	19		1	**24 (5.6%)**
IVIG		12			**12 (2.8%)**
plasmapheresis	1	1			**2 (0.5%)**
Total	**83**	**192**	**65**	**86**	**426**

AZA= Azathioprine, MMF= Mycophenolate mofetil, Cy= Cyclophosphamide, IVIG= Intravenous immunoglobulin

Remission rate of pemphigus

Remission rate of pemphigus were analyzed across multiple outcome years. In the first year, 21 patients (4.9%) achieved complete remission, comprising 9 patients with PV and 12 patients with PF demonstrating statistically significant outcome ($p < .001$).

Furthermore, 328 patients (89.7%) experienced partial remission, while 23 patients (5.4%) faced relapsed during this period ($p < .001$). Moving to the second year, 98 patients (23.0%) attained complete remission, with 48 PV patients and 50 PF patients, again demonstrating significant improvement ($p < .001$). Alongside, 280 patients (65.7%) achieved partial remission, but 48 patients (11.3%) experienced relapse ($p < .001$). By the fifth year, 226 patients (53.0%) achieved complete remission, including 133 PV patients and 93 PF patients, with a noteworthy statistical trend ($p = .009$). Additionally, 170 patients (39.9%) reached partial remission, while 27 patients (6.3%) encounter relapse during this period ($p = .034$). Only 3 patients experienced treatment failure in study period

The rate of complete remission for PV was 3.3%, 17.5%, and 48.4% at 1, 2, and 5 years post diagnosis, respectively, whereas for PF, they were 7.9%, 33.1%, and 61.6% during the same time frames. Notably, PF exhibited a significantly higher rate of complete remission compared to PV at 1, 2, and 5 years ($p < .001$) (Table 3.). Survival plot showed at 60 months remission rate was 91.3% of PV and 96% of PF (Figure 4.4). The average duration until remission was 60 months for PV and 36 months for PF.

Table 4.3 Treatment outcome of pemphigus patients at 1, 2, and 5 years

	Total (n=426)		PV	PF	p-value
	n	%	n	n	
Outcome year 1					<0.001
Complete remission	21	(4.9%)	9	12	0.033*
Partial remission	382	(89.7%)	243	139	0.231
Relapse	23	(5.4%)	23	0	<0.001*
Outcome year2					<0.001*
Complete remission	98	(23.0%)	48	50	<0.001*
Partial remission	280	(65.7%)	184	96	0.488
Relapse	48	(11.3%)	43	5	<0.001*
Outcome year 5					0.034*

Table 4.3 Treatment outcome of pemphigus patients at 1, 2, and 5 years (Cont.)

Complete remission	226	(53.1%)	133	93	0.009*
Partial remission	170	(39.9%)	118	52	0.088
Relapse	27	(6.3%)	21	6	0.138
Treatment failure	3	(0.7%)	3	0	0.555

P-values for mean data were calculated with the use of Mann-Whitney U-test, for percentages with the use of Chi-square test, * Significant at p-value < 0.05 PV= Pemphigus vulgaris, PF= Pemphigus foliaceus

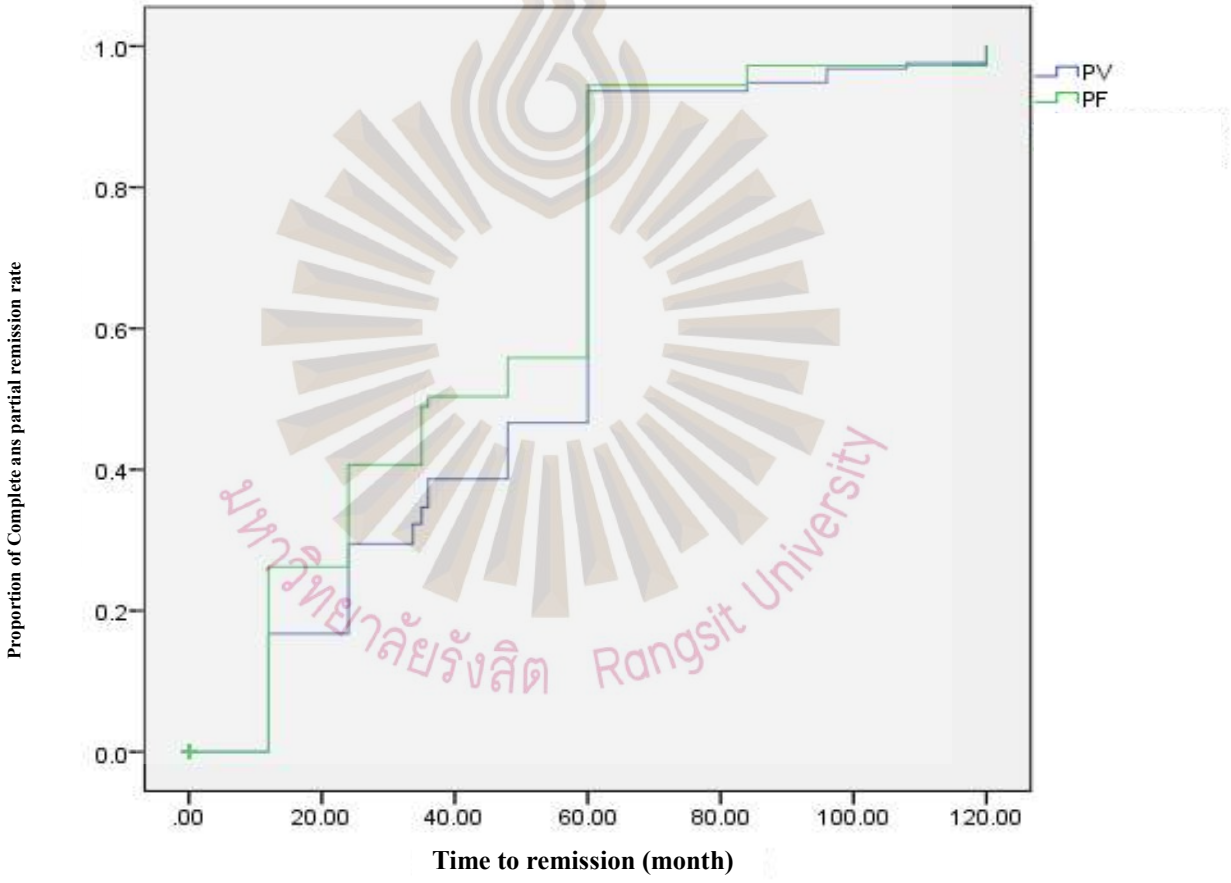

Figure 4.4 Survival plot of PV and PF

Factors affecting for remission rate of PV and PF

The factors influencing the complete remission of both PV and PF were identified as follows: age (p = .046), indicating a higher likelihood of remission in older patients from subgroup analysis found that the majority of young age (<60 years) had moderate to severity but in older patients (>60 years) were mostly in mild to moderate severity; underlying disease control (p < .001), with better remission rates observed in case where underlying disease control was optimal; disease severity (p = .001), with a greater likelihood of remission in cases of mild severity pemphigus. Site of primary involvement which indicated a worse prognosis in initial mucosal involvement compare with cutaneous involvement. Multiple variate analysis confirmed the positive associations of age, age at onset, underlying disease control, severity of disease, site of primary involvement and initial mucosal involvement positively with remission rate. Factors affecting for remission rate of PV and PF is shown in Table 4.4.

Table 4.4 Factors affecting for remission rate of PV and PF (n = 426)

Characteristics	Remission (n=396)		No Remission (n= 30)		p-value
	n	%	n	%	
Gender					0.847
Male	150	37.9%	12	40.0%	
Female	246	62.1%	18	60.0%	
Age (years)					0.046*
≥ 60	166	41.9%	7	23.3%	
< 60	230	58.1%	23	76.7%	
Mean±SD.	56.96	±15.29	50.13	±14.70	0.032*
Age at onset (year) Mean±SD.	52.47	±15.51	45.03	±15.21	0.012*

Table 4.4 Factors affecting for remission rate of PV and PF (n = 426) (cont.)

Underlying					0.801
yes	181	45.7%	13	43.3%	
no	215	54.3%	17	56.7%	
Underlying process (n=194)					<0.001*
good control	173	95.6%	7	53.8%	
poor control	8	4.4%	6	46.2%	
Diagnosis					0.067
PV	251	63.4%	24	80.0%	
PF	145	36.6%	6	20.0%	
PV (n=275)					
Severity disease					0.001*
-Mild BSA<5%	83	33.1%	0	0%	
-Moderate to Severe >5%	168	66.9%	24	100%	
PF (n=151)					
Severity disease					0.037*
-Mild BSA<5%	65	44.8%	0	0%	
-Moderate to Severe >5%	80	55.2%	6	100%	
Site of primary involvement					
Mucosal	5	1.3%	0	0%	1.000
Cutaneous	255	64.4%	13	43.3%	0.021*
Both	136	34.3%	17	56.7%	0.014*
Initial mucosal involvement					0.018*
Present	139	35.1%	17	56.7%	
Absent	257	64.9%	13	43.3%	

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, UD= Underlying disease, BSA= Body surface area

4.2 Discussion

Pemphigus, classified as a rare autoimmune blister disorder, exhibits a variable incidence rate of 0.5-3.2 cases per 100000 individuals annually, as reported by Ahmed (Ahmed, 1983). Predominantly affecting female, 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 patient at 92 and 17 years, respectively and an average age of onset at proximately 51.95 years.

The therapeutic landscape of pemphigus has undergone significant evolution since the 1950s when corticosteroid was introduced, markedly reducing the mortality rate to an average of 30%. the 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 targeted against the CD20 antigen on B-lymphocyte, 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 patients. Treatment strategies were tailored, According to type of disease, disease severity, and the presence of comorbidities, such as diabetes mellitus, renal dysfunction, and hepatic failure. For case of mild severity, monotherapy with prednisolone was often sufficient, whereas moderate to severe case necessitated a combination of prednisolone with immunosuppressant agents like azathioprine, mycophenolate mofetil, cyclophosphamide.

Initial diagnoses revealed that pemphigus vulgaris (PV) predominated presented with moderate-to-severe disease while pemphigus foliaceus (PF) was more commonly classified as mild-to-moderate severity. A 61.6% of both PV and PF cases were managed with a combination of prednisolone and immunosuppressive drugs. The study identified a notable difference in the treatment to remission rate among patients administered solely

prednisolone, those treated with a combination of prednisolone and azathioprine, and those receiving Intravenous Immunoglobulin (IVIG). Moreover, a significant correlation was observed between the control of underlying disease and remission rates ($p < .001$)

Prognostic factors for remission in PV and PF included age, age at onset, control underlying disease, disease severity, site of primary involvement, initial mucosal area involvement, echoing finding from Naif Almugairen et al (Almugairen et al.,2013) which identified mucosal involvement and younger age as predictors of complete remission. our study showed old age (>60 years) achieve higher remission because analysis subgroup that founded young age group (<60 years) had moderate to severe more than mild severity. Moreover, further statistical analysis, Age over 60 years is a factor associated with higher remission although, cutting out severity diseases For our study, the complete remission of PV was 3.3%, 17.5% and 48.4% of at 1, 2 and 5 years after diagnosis respectively which 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 and Bystryn (Herbst, & Bystryn, 2000). The 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. Moreover, our research showed which complete remission of PF was 7.9%, 33.1% and 61.6% at 1, 2 and 5 years after diagnosis respectively, 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 after 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 PF, with median durations of 60 and 36 months respectively.

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

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

In conclusion, our investigation presents a detailed comparative analysis of remission rate within pemphigus vulgaris (PV) and pemphigus foliaceus (PF) cohorts over a span of 1, 2, and 5 years after diagnosis. The finding eindicates 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 history 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. Prognostic factors identified include old age, good control of underlying disease, mild severity of the disease, only cutaneous involvement, and absent primary mucosal involvement were higher remission rate. 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 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.

5.2 Recommendation

This study improves our knowledge of remission rate of PV and PF patients at Institute of dermatology, time to remission and prognostic factors of pemphigus patients. Patients with moderate to severe pemphigus should receive prompt treatment and control of their underlying diseases to shorten the time to remission, increase quality of life and increase survival rate.

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