Original Article

Epidemiology and Factors Associated with Remission of Pemphigus Vulgaris and Foliaceus in Singapore

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Abstract

Background: Pemphigus is a chronic, relapsing immunobullous disease. There is limited data on the clinical course and prognostic factors of pemphigus in Asian patients. Methods: We conducted a retrospective cohort study of all newly diagnosed pemphigus vulgaris (PV) and pemphigus foliaceus (PF) patients seen at the National Skin Centre from 1 January 2004 to 31 December 2009. Demographic and clinical data on co-morbidities, treatment and remission were recorded. Mortality information was obtained from the National Registry of Diseases. Prognostic endpoint was overall remission at last visit. Results: Sixty-one patients (36 PV and 25 PF) were recruited. Among PV patients, higher initial prednisolone dose (*P* = 0.017) and the use of azathioprine (*P* = 0.028) were significantly associated with overall remission at last visit. However, higher desmoglein 1 antibody titres at diagnosis (*P* = 0.024) and the use of dapsone (*P* = 0.008) were negatively associated with overall remission at last visit. Among PF patients, only higher desmoglein 1 antibody titre at diagnosis (*P* = 0.041) was found to be associated with lower overall remission at last visit. There was no mortality during the 3-year follow-up period in both PV and PF. Conclusions: Higher initial prednisolone dose and the use of azathioprine in PV desmoglein 1 antibody titre at diagnosis in PV and PF might be prognostic markers for achieving remission. Use of dapsone was associated with lower overall remission in PV, but this might be confounded because dapsone was used as an adjuvant therapy in recalcitrant cases. Owing to study methodology and limitations, further evaluation is needed for better prognostication of pemphigus.

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Key words: Autoimmune blistering disease, Dermatology, Pemphigus foliaceus, Pemphigus vulgaris, Remission

Introduction

Pemphigus is an autoimmune disorder that causes immune-mediated blistering of the skin and mucous membranes. There are 2 major subtypes: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV and PF are characterised by intra-epidermal blister and acantholysis, resulting from damage caused by IgG autoantibodies directed against desmosomal glycoproteins, namely desmoglein 3 and/or desmoglein 1. On direct immunofluorescence (DIF), intercellular IgG deposits are found in the epidermis. PV is the most common intra-epidermal immunobullous disorder, with a variable incidence ranging from 0.76 per million per year in Finland[1] to 16.1 per million per year in Jerusalem.[2] PF is less common, occurring at 0.5 per million per year in Western Europe[3] to 6.7 per million per year in Tunisia.[4] In an earlier study from 1995 to 1997, PV and PF constitute 62% and 32%, respectively, of all pemphigus cases seen at the National Skin Centre, which is the major referral centre for immunobullous skin diseases in Singapore.[5]

Pemphigus has a chronic relapsing course, often requiring long-term immunosuppressants including systemic corticosteroids and other adjunctive

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agents. There are significant disease morbidity and mortality, with most data in Western and Middle Eastern countries.[1,4,6–10]

At present, there is limited data on the clinical course, prognostic factors and survival of Asian patients as compared to Western cohorts. w

Our primary aim was to describe and compare the demographics, clinical features, co-morbidities, treatment and disease outcomes of PV and PF in Singapore. We also sought to identify the prognostic factors affecting remission for PV and PF.

Methods

This was a retrospective cohort study. Our study cohort comprised all newly diagnosed Singaporean pemphigus patients seen at the National Skin Centre from 1 April 2004 to 31 December 2009. Patients with either PV or PF were recruited based on the following criteria: i) typical clinical findings of pemphigus; ii) histopathological findings of suprabasilar or subcorneal blister or acantholysis; iii) immunopathology – direct immunofluorescence (DIF) with intercellular deposition of IgG and/or complement 3 in the epidermis; iv) indirect immunofluorescence (IIF) findings with circulating intercellular IgG antibodies or v) positive serum desmoglein 3 and/or desmoglein 1 antibodies. Exclusion criteria included foreign patients as well as patients with other subtypes of pemphigus and any other immunobullous disorders. Desmoglein 3 and desmoglein 1 antibodies were measured by commercial enzyme-linked immunosorbent assay (ELISA) kits (MBL Co. Ltd, Japan). Antibody levels ≥ 20 U/ml were interpreted as positive ELISA results.

Patients were identified through the National Skin Centre's electronic medical and histology records. Data collection was performed by reviewing the case records of the patients to obtain demographic data, medical history, clinical features, laboratory results, treatment details and disease status at last follow-up visit. Patients were then matched with the National Registry of Diseases Office (NRDO) death registry for verification of mortality status. This study was approved by the ethics committee of the National Healthcare Group, Singapore.

The disease status definition was based upon the consensus statement on definitions of disease activity and therapeutic response as proposed by the International Pemphigus Committee in 2008.[11] Remission status was defined at the last visit. Remission on minimal or off therapy was defined as the absence of new or established lesions, or presence of transient new lesions that healed within 1 week, while receiving minimal therapy (i.e. prednisolone ≤ 10 mg/day and/or minimal adjuvant therapy defined as half of the dose required to be defined as treatment failure), or off all systemic therapy, for at least 2 months. Remission during tapering of therapy was defined as the absence of new lesions that did not heal within one week while receiving more than minimal therapy for at least 2 months.

Statistical Analysis

Continuous variables were summarised using medians with ranges and were compared using Mann-Whitney U test. Categorical variables were summarised using counts with percentages and were compared using Fisher's exact test. Time to remission was examined using Cox proportional hazard model which is a time-to-event survival analysis that is able to deal with miss-to-follow-up data using censoring. Predictors with P-value < 0.2 from the univariate Cox proportional hazard model that did not cause convergence problem were included in the final multivariate model. Hazard ratios with 95% confidence intervals (CI) were reported. Significance was assessed at a level of 0.05. All statistical analyses were performed using IBM SPSS Statistics 24.

Results

Demographic and clinical features

A total of 36 patients with PV and 25 patients with PF were included in the study. There were 20 (55.6%) females and 16 (44.4%) males in the PV group, compared to 9 (36.0%) females and 16 (64.0%) males in the PF group (P = 0.193; Table 1). The median age at which PV was diagnosed was 53.7 years (range 22.3–86.9 years), similar to that of PF at 52.1 years (range 27.2–78.8 years). PV patients had a significantly longer median duration of follow-up (range) of 4.7 (0.2–8.4) years, compared to PF of 3.6 (0.0–8.5) years, P = 0.026. The ethnic distribution in patients with PV versus PF was similar: 24 (66.7%) versus 17 (68.0%) Chinese, 4 (11.1%) versus 3 (12.0%) Malay, 5 (13.9%) versus 4 (16.0%) Indian and 3 (8.3%) versus 1 (4.0%) of other ethnicities, P = 0.969. Generalised lesions (defined as affecting more than one body site, in contrast to localised pemphigus affecting only one body site) were predominant in both PV (94.4%) and PF (96.0%). Lesions were predominantly mucocutaneous (77.8%) in the PV group but cutaneous

Table 1. Clinical characteristics and treatment summary of PV and PF patients

	PV (n = 36)	PF (n = 25)	*P* value
Male	16 (44.4%)	16 (64.0%)	0.193
Female	20 (55.6%)	9 (36.0%)	
Median age of diagnosis, years	53.7 (22.3, 86.9)	52.1 (27.2, 78.8)	0.936
Median follow-up duration, years	4.7 (0.2, 8.4)	3.6 (0.0,8.5)	0.026
Race			
Chinese	24 (66.7%)	17 (68.0%)	0.969
Malay	4 (11.1%)	3 (12.0%)	
Indian	5 (13.9%)	4 (16.0%)	
Other	3 (8.3%)	1 (4.0%)	
Localised	2 (5.6%)	1 (4.0%)	1.000
Generalised	34 (94.4%)	24 (96.0%)	
Mucocutaneous involvement	28 (77.8%)	-	<0.00001
Cutaneous involvement	8 (22.2%)	25 (100%)	
Positive direct immunofluorescence	34 (94.4%)	25 (100%)	1.000
Missing	-	-	
Positive IIF	27 (87.1%)	18 (85.7%)	1.000
Missing	5	4	
IIF median titres	160 (20, 160)	160 (20, 160)	0.336
Dsg 1 antibody positivity at diagnosis	27 (87.1%)	21 (90.5%)	1.000
Missing	5	4	
Dsg 1 median antibody titre at diagnosis (IU/ml)	94 (4, 300)	137 (1, 283)	0.097
Dsg 3 antibody positivity at diagnosis	29 (93.5%)	2 (9.5%)	<0.00001
Missing	5	4	
Dsg 3 median antibody titre at diagnosis (IU/ml)	148 (1, 300)	36.25 (29, 43.5)	<0.00001
Co-morbidities	16 (44.4%)	11 (44.0%)	1.000
Hypertension	10 (27.8%)	5 (20.0%)	0.557
Hyperlipidemia	10 (27.8%)	3 (12.0%)	0.206
Diabetes mellitus	4 (11.1%)	2 (8.0%)	1.000
Stroke	2 (5.6%)	1 (4.0%)	1.000
Cardiovascular disease	3 (8.3%)	0 (0%)	0.262
Gastrointestinal disease	2 (5.6%)	0 (0%)	0.512
Prior malignancy	2 (5.6%)	0 (0%)	0.512
Renal disease	1 (2.8%)	1 (4.0%)	1.000
Lung disease	1 (2.8%)	0 (0%)	1.000
Thyroid disease	0 (0%)	0 (0%)	-
Remission during tapering of therapy at last visit	9 (25.0%)	5 (20.0%)	1.000
Remission on minimal/off therapy at last visit	23 (63.9%)	15 (60.0%)	
Corticosteroid only	12 (33.3%)	12 (48.0%)	0.294
Initial corticosteroid dose, mg/kg/day	0.7 (0.5, 1.0)	0.6 (0.4, 1.0)	
Median corticosteroid dose, mg/kg	40 (20,80)	30 (20,50)	
Use of other immunosuppressants	24 (66.7%)	13 (52.0%)	0.189
Azathioprine	19 (52.8%)	1 (4.0%)	<0.00001
Dapsone	10 (27.8%)	13 (52.0%)	0.175
Mycophenolate mofetil	3 (8.3%)	-	
Cyclophosphamide	2 (5.6%)	-	
Intravenous immunoglobulin	2 (5.6%)	-	
Rituximab	1 (2.8%)	-	

Results are presented as n (%) or median (minimum, maximum) Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus, IIF: indirect immunofluorescence, Dsg: desmoglein

in the PF group. There was no significant association between anti-desmoglein antibody titres and generalised versus localised disease, or mucocutaneous versus cutaneous disease.

Diagnosis

All patients had histological findings of suprabasilar and subcorneal blistering for PV and PF, respectively. In the PV group, 22 patients fulfilled all 5 diagnostic criteria (i–v) above, 13 fulfilled 4 criteria and 1 fulfilled 3 criteria. Almost all had positive DIF except for 2 PV patients who were diagnosed based on characteristic clinicopathological findings, positive IIF and desmoglein 3 titres. In the PF group, 16 patients fulfilled all 5 criteria, 7 fulfilled 4 criteria and 2 fulfilled 3 criteria.

There was no significant difference in IIF positivity between PV and PF patients: 87.1% (27/31) versus 85.7% (18/21), $P = 1.000$. Out of 31 PV and 21 PF patients who had desmoglein serologies sent at diagnosis, 87.1% and 90.5% had desmoglein 1 positivity, respectively ($P = 1.000$). Their median desmoglein 1 titres at diagnosis were 94 IU/ml versus 137 IU/ml $P = 0.097$). The PV group had a median desmoglein 3 titre at diagnosis of 148 IU/ml.

Associated Diseases

The most common co-morbidities in PV compared to PF were: hypertension (27.8% versus 20.0%), hyperlipidemia (27.8% versus 12.0%), diabetes mellitus (11.1% versus 8.0%) and stroke (5.6% versus 5.0%). Cardiovascular disease (8.3%), gastrointestinal disease (5.6%) and prior malignancy (5.6%) were present in the PV patients, but absent in the PF group.

Treatment Regimes

Systemic treatment for PV included combination therapy of oral corticosteroid (100%) and non-steroidal immunosuppressants (94.4%), comprising azathioprine (52.8%), dapsone (27.8%), mycophenolate mofetil (11.1%), cyclophosphamide (5.6%), intravenous immunoglobulin (5.6%) and rituximab (2.8%). The majority were started on systemic non-steroidal immunosuppressants in addition to oral corticosteroid to control the disease activity. Of note was the significantly greater use of azathioprine found in PV (52.8% versus only 4.0% in PF, $P < 0.00001$). However, dapsone was used in both PF (48.0%, $P = 0.175$) and PV (27.8%).

Only 33.3% PV patients were on oral corticosteroid monotherapy for the entire duration of disease with moderate to high initial dose of prednisolone (0.5 to 1 mg/kg/day) used to treat PV, at a mean initial dose of 0.7 mg/kg/day. Within this group, 16.7% had localised disease and 25.0% had no mucosal involvement, whereas all PV patients who received combination therapy had generalised disease, with 20.8% having no mucosal involvement. Comparatively, 48.0% of PF patients received prednisolone monotherapy for the entire duration of disease with a mean initial dose at 0.6 mg/kg/day (range 0.4 to 1 mg/kg/day). Ninety six percent of all PF patients had generalised cutaneous disease at presentation.

Remission Outcomes

There was no significant difference in time to overall remission at last visit between PF (median time to remission 3.95 years, 95% CI 3.27–5.45) and PV (median time to remission 4.91 years, 95% CI 4.14–6.18) ($P = 0.30$). The majority of PV and PF patients achieved disease control (Table 2). Four PV patients (11.1%) and 5 PF patients (20.0%) remained with active disease at the last follow-up. Amongst the PV patients with active disease, 3 (75.0%) were treated with combination therapy (2 with prednisolone and azathioprine, 1 with prednisolone, azathioprine, dapsone, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin, rituximab sequentially) and 1 with prednisolone monotherapy (1.1 kg/mg/day). In contrast, all 5 PF patients with active disease were treated with oral prednisolone monotherapy.

Twenty-three PV patients (63.9%) attained remission on minimal or off therapy at last visit compared to 15 PF patients (60.0%). Seventeen of these PV patients (73.9%) received combination therapy, most commonly with azathioprine (76.5%, n=13), followed by dapsone (41.2%, n=7), mycophenolate mofetil (11.8%, n=2), cyclophosphamide (5.9%, n=1) and intravenous immunoglobulin (5.9%, n=1). Nine of the above PF patients (60.0%) received combination therapy, most commonly with prednisolone and dapsone (88.9%, n=8) and 1 patient with prednisolone and azathioprine.

Survival

Using data from the national registry of deaths, we had complete verification of the death status of all patients. At 3 years of follow-up, all PV and PF patients were alive.

Table 2. Remission outcomes at last visit in PV and PF patients

	PV (n = 36)	PF (n = 25)
Median time to overall remission	4.91 years (95% CI: 4.14, 6.18)	3.95 years (95% CI: 3.27, 5.45)
Active disease	4 (11.1%)	5 (20.0%)
Corticosteroid monotherapy	1 (25.0%)	5 (100%)
Use of other immunosuppressants	3 (75.0%)	-
Azathioprine	2 (66.7%)	-
Azathioprine, dapsone, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin, rituximab sequentially	1 (33.3%)	-
Remission on minimal/off therapy	23 (63.9%)	15 (60.0%)
Corticosteroid monotherapy	6 (26.1 %)	6 (40.0%)
Use of other immunosuppressants	17 (73.9%)	9 (60.0 %)
Azathioprine	13 (76.5%)	1 (11.1%)
Dapsone	7 (41.2%)	8 (88.9%)
Mycophenolate mofetil	2 (11.8%)	-
Cyclophosphamide	1 (5.9%)	-
Intravenous immunoglobulin	1 (5.9%)	-

Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus
Median time to remission is the average time when 50% patients reach remission.

Factors Associated with Remission at Last Visit

In patients with PV, higher initial prednisolone dose (mg/kg/day) (hazard ratio 1.1, 95% CI 1.01–1.15, $P = 0.017$) and use of azathioprine (hazard ratio 10.05, 95% CI 1.28–78.64, $P = 0.028$) were predictive of attaining overall remission (Table 3). However, higher desmoglein 1 antibody titres at diagnosis (hazard ratio 0.98, 95% CI 0.95–0.99, $P = 0.024$) and the use of dapsone (hazard ratio 0.04, 95% CI 0.003–0.412, $P = 0.008$) were negatively associated with overall remission.

Among PF patients, only higher desmoglein 1 antibody titre at diagnosis (hazard ratio 0.97, 95% CI 0.94–0.99, $P = 0.041$) was negatively associated with achieving overall remission (Table 4). Although IIF titre was found to have a statistically significant P value = 0.014, both the hazard ratio and 95% CI closely overlapped with null.

Generalised versus localised disease (as a proxy marker of clinical severity) was not significantly associated with attaining overall remission in both PV and PF patients. Similarly, the presence of mucosal lesions in PV patients was not significantly associated with attaining overall remission.

Discussion

In the present study, we report on the clinical course, co-morbidities, treatment regimes and prognostic factors of pemphigus. PV was the more common subtype found in patients (56.2%), versus PF (43.8%), consistent with reported studies.[4–6,8–9,12–17] The mean age of diagnosis for PV (53.1 years) and PF (54.5 years) in our study was comparable to other studies in both Asian and western cohorts.[1,4,7–9,12–14,16–18] The female-to-male ratio of 1.3 among patients with PV was similar to that reported from China, Korea, India, Israel, Tunisia, Turkey, UK, France and Finland with an overall female predominance.[1,4–7,9–10,12–17,19–22] However, we noted a male preponderance (female-to-male ratio of 0.6) in patients with PF, which was evident in an earlier study of pemphigus in Singapore.[5] Several studies of PF in Israel, Brazil and India also had a female-to-male ratio of 0.5, 0.3 and 0.16, respectively.[9,17,23] Other studies have, however, reported a female predilection.[8,10,13,14] The reason for this female predominance is largely unexplained, although a female predominance is seen in other autoimmune diseases. In both PV and PF, there was no particular

Table 3. Results of univariate and multivariate analyses on attaining overall remission at last visit in PV

Risk factor	Univariate Analysis (Cox Regression)		Multivariate Analysis[1,2] (Cox Regression)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	1.01 (0.48, 2.15)	0.97	0.22 (0.02, 2.08)	0.19
Female				
Age, years	1.00 (9.97, 1.03)	0.87	1.05 (0.96, 1.15)	0.32
Ethnicity				
Chinese	0.82 (0.38, 1.79)	0.62	0.37 (0.07, 2.02)	0.25
Others				
Lesion distribution				
Localised	2.83 (0.65, 12.44)	0.17	3.40 (0.09, 130.98)	0.51
Generalised				
Mucosal lesions				
Present	1.45 (0.62, 3.40)	0.39	2.58 (0.22, 30.29)	0.45
Absent				
IIF titre	1.00 (0.99, 1.01)	0.55	1.00 (0.97, 1.02)	0.85
Initial corticosteroid dose (mg/day)	1.01 (0.98, 1.03)	0.68	**1.08 (1.01, 1.15)**	**0.017**
Desmoglein 1 titre at diagnosis (IU/ml)	1.00 (0.99, 1.01)	0.84	**0.98 (0.95, 0.99)**	**0.024**
Desmoglein 3 titre at diagnosis (IU/ml)	1.00 (1.00, 1.01)	0.59	1.02 (1.00, 1.04)	0.036
Azathioprine				
Yes	1.68 (0.81, 3.50)	0.17	**10.05 (1.28, 78.64)**	**0.028**
No				
Dapsone				
Yes	0.51 (0.23, 1.16)	0.11	**0.04 (0.003, 0.41)**	**0.008**
No				
Mycophenolate mofetil				
Yes	0.92 (0.22, 3.94)	0.91	17.44 (0.99 – 306.57)	0.05
No				
Hypertension				
Yes	0.88 (0.40, 1.93)	0.76	2.55 (0.11, 59.02)	0.56
No				
Diabetes				
Yes	0.50 (0.15, 1.69)	0.26	4.13 (0.11, 157.27)	0.45
No				

[1]Variables significant *at* $P < 0.2$ in the univariate analysis were considered for inclusion in the final multivariate analysis
[2]For each risk factor, the last group is the reference group for calculating the hazard ratio in the Cox regression analysis
Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus, IIF: indirect immunofluorescence

Table 4. Results of univariate and multivariate analyses on attaining overall remission at last visit in PF

Risk factor	Univariate Analysis (Cox Regression)		Multivariate Analysis (Cox Regression) [1,2]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender				
Male	1.41 (0.56, 3.52)	0.47	0.23 (0.02, 3.03)	0.27
Female				
Age, years	1.02 (0.98, 1.05)	0.34	1.05 (0.95, 1.17)	0.34
Ethnicity				
Chinese	0.49 (0.17 to 1.42)	0.19	-	-
Others				
Lesion distribution				
Localised	1.28 (0.17, 10.00)	0.81	-	-
Generalised				
IIF titre	1.01 (1.00, 1.02)	0.01	1.04 (1.00, 1.07)	0.014
Initial corticosteroid dose (mg/day)	0.96 (0.92, 1.01)	0.08	1.08 (0.94, 1.24)	0.304
Desmoglein 1 titre at diagnosis (IU/ml)	1.00 (0.99, 1.01)	0.85	**0.97 (0.94, 0.99)**	**0.041**
Azathioprine				
Yes	0.04 (0.00, 21.77)	0.31	-	-
No				
Dapsone				
Yes	1.55 (0.60, 3.97)	0.36	0.85 (0.08, 9.74)	0.90
No				
Hypertension				
Yes	1.23 (0.44, 3.46)	0.70	0.71 (0.06, 8.32)	0.79
No				
Diabetes				
Yes	3.92 (0.79, 17.60)	0.10	-	-
No				
Hyperlipidemia				
Yes	5.07 (1.18, 21.77)	0.03	-	-
No				

[1]Variables significant *at* $P < 0.2$ in the univariate analysis were considered for inclusion in the final multivariate analysis
[2]For each risk factor, the last group is the reference group for calculating the hazard ratio in the Cox regression analysis
Abbreviations: PV: pemphigus vulgaris, PF: pemphigus foliaceus, IIF: indirect immunofluorescence

racial predilection, with the distribution similar to the national racial demographics. Mucocutaneous involvement was seen in 77.8% patients with PV at initial presentation, in keeping with earlier studies.[9–10,12–13,15–16,19–20]

We note that Indians (13.9% in PV and 16.0% in PF) may be over-represented in our study. The ethnic composition of Singapore's resident population from 2008 to 2018 was about 74% Chinese, 13% Malays, 9% Indians and 3% Others. The reason for this is unclear, but we postulate that this may be due to our small sample size.

In terms of co-morbidities, we noted more patients with PV having hyperlipidaemia (27.8%) compared to patients with PF (17.9%), although this was not statistically significant. The prevalence of hypercholesterolemia in Singapore was reported to be 17.4% in 2010.[24] Other studies have also reported similar associations with hypertension, diabetes and hyperlipidaemia.[5,8,12,15,25–26] None of the pemphigus patients in our study was reported to have thyroid disorders, contrary to previous reports.[9,15,19,25,26] Two PV patients had prior malignancy of nasopharyngeal cancer and breast ductal carcinoma in situ, respectively. Although previous studies[27] had suggested an association of PV with internal malignancy, no significant association was found in our study.

The overall remission on minimal or off therapy at last visit was 63.9% for PV patients and 60.7% for PF patients in our study, comparable to between the 50% rate reported for complete remission off therapy[6,28] and the 70–80% reported for complete remission on minimal therapy.[29] Another study reported higher remission on minimal or off therapy at 70% and 83% for PV and PF patients, respectively.[17]

There was no significant difference in the initial median corticosteroid dose or remission between PV and PF in our study, although PV patients had a significantly longer follow-up period. This is in contrast to the earlier study in Singapore where PV was shown to be a more severe disease than PF, as indicated by the higher dose of corticosteroids required for disease control, longer duration to achieve complete remission and longer follow-up period.[5] However, other studies have reported that PV and PF follow a similar clinical course and prognosis.[8,10,14,20] Significantly, more than half of PV patients were treated with azathioprine compared to only 7.1% of PF patients. Azathioprine is a well-established choice of adjuvant treatment for management of PV.[30–31]

All patients in our study had completed 3 years of survival as verified with the national registry of death records. An earlier study conducted at the National Skin Centre, Singapore, from 1995 to 1997 saw a 12% mortality in the 3-year period.[5] A French study reported 1-, 2- and 5-year survival at 90%, 85% and 82%, respectively.[6] However, other studies have found lower mortality. A Korean study showed mortality to be 6.5% among 199 PV and PF patients during a 16-year follow-up period from 1993 to 2008,[13] with the commonest cause of death being sepsis. In a study in Thailand, there was only 2.4% mortality from 1993 to 1999 (only among the PV patients), resulting from sepsis as a complication of high-dose corticosteroids.[14] Another study in Israel[7] also found mortality rate to have decreased from 22% during 1960 to 1980, to 10% during 1976 to 2004, and none of the deaths was directly related to pemphigus or complication of treatment (mainly cancer (occurring years after diagnosis of pemphigus) and ischemic heart disease). It was suggested that the increased use of adjuvant therapy[32] and improved management of disease and treatment side-effects contributed to this finding. The better survival rate in our study may be attributed to the use of moderate dose of corticosteroids and increased use of adjuvant non-steroid immunosuppressants prescribed in our centre. The trend for improved survival is also corroborated by a recent study in India, which observed only 1 death from pulmonary embolism, over an average of 2.7 years of follow-up (0.01% mortality) during 1991–2013.[17]

We have tried to evaluate factors associated with remission in this study. However, as this was a retrospective study, definitive documentation of certain endpoints of pemphigus (for instance, transient new lesions healing within a week), which are primarily derived for use in prospective trials, was not possible in all cases. Thus, the following discussion regarding prognostic factors needs to be considered in this light.

We found that age,[8,17] gender,[8,17,20] ethnicity and mucosal involvement[17,20] were not prognostic factors for remission, similar to various studies, although some other groups have found that age,[6,7,20,22] ethnicity,[7,20,33] and initial mucosal involvement[6,7,8,21,32,34] had an impact on prognosis.

Patients with PV and PF who had higher desmoglein 1 antibody levels at diagnosis in our study had significantly lower overall remission at last visit.

A previous study of survival prognosis demonstrated that PV patients with higher anti-desmoglein 1 antibodies achieved a lower overall survival, although this was not reflected among patients with PF.[22] We postulate that increased desmoglein 1 titres may reflect increased disease severity, with higher resistance to therapy and longer time to attain remission. Desmoglein 3+/1+ profile in PV patients has been associated with more severe disease, with additional desmoglein 1 predicting severe cutaneous involvement in additional to mucosal involvement.[35]

In another study, high desmoglein 3 antibody levels at baseline (>100), as compared to 0–29 (negative) and 30–100 (low-medium level), were indeed associated with a longer total disease duration.[20] However, our study did not demonstrate an association between desmoglein 3 antibody levels and remission at last visit, possibly because most of our PV patients (86.2%) had high absolute desmoglein 3 antibody levels (>100) at diagnosis, so this may have restricted the evaluation of a relationship. Further studies are needed to evaluate the roles of desmoglein 3 and 1 as prognostic markers.

Our data also indicated that an initial higher prednisolone dose and use of azathioprine were associated with achieving overall remission at last visit for PV patients. However, we did not control for the tapering schedule of corticosteroids and disease duration in our analysis. Hence, their prognostic impact on remission might be confounded. One study comparing high dose oral prednisone versus low dose prednisone plus azathioprine did report significantly longer time for disease control and remission with the latter group.[36] However, other studies revealed no improvement in disease duration or time to remission with high doses of prednisolone, possibly owing to the associated morbidity.[17,20,32] Co-administration of azathioprine was found to reduce the cumulative corticosteroid dose and displayed a superior steroid-sparing effect compared to mycophenolate mofetil.[30, 37, 38] However, another study showed that prednisolone alone allowed earlier complete remission than prednisolone with adjuvant treatment among patients with PF,[13] although this was confounded by the difference in initial disease severity.

The use of dapsone among PV patients was negatively associated with overall remission at last visit in our study. However, this association might be confounded because dapsone was used as an adjuvant treatment in recalcitrant cases, in combination with other agents, instead of being first-line therapy. Out of the 8 PV patients who received dapsone (whilst on concomitant oral corticosteroid), 3 had received azathioprine earlier (2 of whom had recalcitrant disease requiring subsequent use of other adjuvant therapy) and 3 had received dapsone as an initial steroid-sparing treatment before requiring azathioprine.

The strengths of this study include comprehensive patient data capture at a national dermatology referral centre, detailed recorded information including co-morbidities, long-term follow-up and complete verification of 3-year mortality status with the national registry of deaths.

The limitations include the small sample size and retrospective nature of the study, in which specific impact of disease severity or combination of immunosuppressive agents on prognosis could not be evaluated. Disease severity was not assessed as this was a retrospective study and there was no published validated severity scoring system at the time of study initiation. While treatment protocols were standardised as far as possible, selection bias of treatment including physician preference, patient characteristics and co-morbidities would be expected. Factors including the tapering schedule of corticosteroids and disease duration were also not controlled for in our analysis.

In conclusion, this is a long-term follow-up study illustrating the clinical characteristics and their influence on prognosis of Asian PV and PF patients. Higher initial prednisolone dose and use of azathioprine in PV as well as lower desmoglein 1 antibody titre at diagnosis in PV and PF might be prognostic markers for achieving remission. The use of dapsone was associated with lower overall remission in PV but this might be confounded because dapsone was used as an adjuvant therapy in recalcitrant cases, instead of being first-line therapy. Overall, owing to the study methodology and limitations, further evaluation is needed for better prognostication of pemphigus.

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