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RESEARCH ARTICLE

Pustular psoriasis in Malaysia: A review of the Malaysian Psoriasis Registry 2007–2018

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Abstract

Pustular psoriasis (PP) is an uncommon subtype of psoriasis with distinct genetic features and clinical phenotypes. Patients with PP tend to experience frequent flares and significant morbidity. This study aims to determine the clinical characteristics, co-morbidities and treatment of PP patients in Malaysia. This was a cross-sectional study of patients with PP notified to the Malaysian Psoriasis Registry (MPR) between January 2007 and December 2018. Of 21 735 psoriasis patients, 148 (0.7%) had pustular psoriasis. Of these, 93 (62.8%) were diagnosed with generalized pustular psoriasis (GPP) and 55 (37.2%) with localized PP (LPP). The mean age for pustular psoriasis onset was 31.71 ± 18.33 years with a male to female ratio of 1:2.1. Patients with PP were more likely to have dyslipidaemia (23.6% vs. 16.5%, $p = 0.022$), severe disease (Body surface area >10 and/or Dermatology Life Quality Index [DLQI] >10) (64.8% vs. 50%, $p = 0.003$) and require systemic therapy (51.4% vs. 13.9%, $p < 0.001$) compared to non-PP patients. Patients with PP also suffered greater impairment to their quality of life (DLQI >10, 48.9% vs. 40.3%, $p = 0.046$), had more days off school/work (2.06 ± 6.09 vs. 0.5 ± 4.91, $p = 0.004$) and a higher mean number of hospitalizations (0.31 ± 0.95 vs. 0.05 ± 1.22, $p = 0.001$) in 6 months compared to non-PP patients. Overall, 0.7% of psoriasis patients in the MPR had pustular psoriasis. Patients with PP had a higher rate of dyslipidaemia, severe disease, greater impairment of quality of life and systemic therapy usage compared to other psoriasis subtypes.

KEYWORDS
dermatology quality of life, generalized pustular psoriasis, interleukin-36, localized pustular psoriasis, psoriasis

1 | INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects approximately 0.5%–11.4% of the global population.[1] Pustular psoriasis (PP) is an uncommon subtype of psoriasis that is characterized by widespread or localized pustular eruption. Pustular psoriasis can occur independently or in patients with a history of pre-existing psoriasis.[2] Although PP patients may have preceding plaque psoriasis, PP is a distinct entity, with distinct phenotypes, histological features and genetic profiles.[3]

Generalized pustular psoriasis (GPP) is a rare and unpredictable variant of PP, characterized by widespread sterile pustules on an erythematous base, with a relapsing–remitting course.[2] Acute GPP (von Zumbusch variant) is the most severe form of GPP with

systemic symptoms. Common triggers include infections, stress, pregnancy and withdrawal of systemic corticosteroids. Localized PP (LPP) primarily involves the palms, soles, digits or nail apparatus. Palmoplantar pustulosis (PPP) is characterized by pustular eruptions involving the palms and soles, while acrodermatitis continua of Hallopeau (ACH) typically involves the distal digits and nail apparatus.[3]

The prevalence of GPP was estimated to be 1.76 per million in the French population and 7.46 per million in the Japanese population.[4] Whereas, the estimated prevalence of PPP ranged from 0.01% to 0.05%.[5] Mutations in the IL36RN, AP1S3 and CARD14 genes are associated with GPP.[6] Due to the rarity of PP, studies on demography and clinical characteristics are lacking. The objective of this study was to describe the demography, clinical characteristics and treatment of pustular psoriasis patients in Malaysia.

2 | MATERIALS AND METHODS

This was a cross-sectional study of patients with PP notified to the Malaysian Psoriasis Registry (MPR) between January 2007 and December 2018. The MPR is a prospective collection of data of patients with psoriasis from 38 centres in Malaysia. Data were obtained from the first notification. This study was approved by the Malaysian Medical Research and Ethics Committee (MREC; NMRR-20-2658-57418). Pustular psoriasis was diagnosed clinically by dermatologists with or without histological confirmation.

Data on age, gender, ethnicity, family history, comorbidities, body surface area (BSA), nail, scalp and joint involvement were collected to determine the difference between patients with GPP, LPP and other subtypes of psoriasis. BSA involvement were recorded according to four scales only: <5%, 5%–10%, 11%–90% and >90%. Other subtypes of psoriasis included patients with plaque psoriasis, guttate psoriasis, inverse psoriasis and erythrodermic psoriasis. Obesity was defined as body mass index (BMI) ≥25 kg/m^2 according to the WHO Asia Pacific recommendation.[7] The Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (CDLQI) was used to measure the impact of psoriasis on the quality of life (QOL). A DLQI score of more than 10 or CDLQI score of more than 12 was considered as significant impairment of QOL. Severe disease was defined as BSA involvement of more than 10% and/or a DLQI score >10/CDLQI score >12.

Data analyses were performed using IBM® Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 24.0. IBM Corp. Descriptive analyses were conducted for sociodemographic characteristics, co-morbidities, clinical pattern and treatment modalities. Continuous variables were expressed as means and standard deviations (SD). Categorical variables were presented as frequencies and percentages. The Chi-square test and Fisher's exact test were used to analyse categorical data. Analysis of continuous variables was done with the independent *t*-test. A p value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Demographic characteristics

Of the 21 735 patients with psoriasis, 148 (0.7%) patients had pustular psoriasis. Of these, 95 (64.2%) had GPP and 53 (35.8%) had LPP. Fifteen patients (10.1%) belonged to the paediatric group (≤18 years). The mean age of onset for PP was 31.71 ± 18.33 years (Table 1). The male to female ratio was 1:2.1. Bimodal age of onset was observed among PP patients, with both GPP and LPP having the first peak at >18 to 30 years. The second peak for GPP was at >50 to 60 years and for LPP was at >60 to 70 years (Figure 1).

Most of the PP patients were Malays (63.5%), followed by Chinese (19.6%) and Indians (5.4%). Overall, PP patients reported a lower rate of family history of psoriasis compared to non-PP patients (13.1% vs. 23% $p = 0.005$).

3.2 | Co-morbidities

The most common co-morbidities among PP patients were hypertension (24.1%), dyslipidaemia (23.6%) and diabetes mellitus (19.2%) (Table 1). There were more PP patients with dyslipidaemia compared to non-PP patients (23.6% vs. 16.5%, $p = 0.022$). There was no significant difference between the prevalence of obesity among PP and non-PP patients.

3.3 | Clinical characteristics

The aggravating factors reported by our PP cohort were infection (11.1%), medications (8.3%) and pregnancy (5.9%). Whereas among the GPP patients, the triggering factors most reported were infection (14.4%), medication (10%) and pregnancy (7.8%). Patients with PP had a lower rate of scalp involvement compared to non-PP patients (61.1% vs. 81.5%, $p < 0.001$). The rate of scalp involvement was higher in GPP patients compared to LPP patients (71.7% vs. 42.3%, $p = 0.001$; Table 2). Face and neck involvement were similar among PP and non-PP patients (47.9% vs. 51.6%, $p = 0.378$), however, it was more common in GPP patients compared to localized PP patients (59.1% vs. 27.5%, $p < 0.001$).

PP patients had a higher rate of erythroderma (BSA >90%) compared to non-PP patients (11.1% vs. 2.5%). All PP patients with erythroderma were patients with GPP. More PP patients had severe disease (BSA >10 and/or DLQI >10) compared to non-PP patients (64.8% vs. 50%, $p = 0.003$; Table 1).

Nail disease was reported in around half of the PP and non-PP patients (54.1% vs. 56.4%, $p = 0.562$). The most common nail manifestations in PP patients were pitting (66.3%) followed by onycholysis (43.8%) and discolouration (23.8%). More non-PP patients had psoriatic arthropathy compared to PP patients (13.1% vs. 10.1%, $p = 0.292$). The most common joint manifestation was symmetrical

TABLE 1 Comparison of demography, clinical characteristics, quality of life and treatment between pustular psoriasis and non-pustular psoriasis.

Characteristic	Pustular psoriasis *n* (%)	Non-pustular psoriasis *n* (%)	*p*-Value
Age of onset (years)[a]			
Mean (SD)	31.71 (18.33)	33.37 (16.91)	0.248
Min, Max	1, 84	1, 88	
0–10	3 (2)	359 (1.8)	
>10–18	12 (8.1)	1311 (6.4)	
>18–30	36 (24.3)	4512 (22.2)	
>30–40	26 (17.6)	3529 (17.4)	
>40–50	19 (12.8)	3542 (17.4)	
>50–60	26 (17.6)	3770 (18.6)	
>60–70	20 (13.5)	2396 (11.8)	
>70	6 (4.1)	903 (4.4)	
Male: Female	**1:2.1**	1.26:1	**<0.001**
Ethnicity[b]			
Malay	94 (63.5)	10968 (54)	–
Chinese	29 (19.6)	3868 (19)	
Indian	8 (5.4)	3370 (16.6)	
Others	17 (11.5)	2110 (10.4)	
Family history of psoriasis[c]	19 (13.1)	**4595 (23)**	**0.005**
Comorbidities			
Dyslipidaemia[d]	**34 (23.6)**	3240 (16.5)	**0.022**
Hypertension[e]	35 (24.1)	4735 (23.9)	0.920
Diabetes mellitus[f]	28 (19.2)	3153 (15.9)	0.284
Ischaemic heart disease[g]	4 (2.8)	972 (4.9)	0.237
Cerebrovascular accident[h]	2 (1.4)	290 (1.5)	0.939
HIV infection[i]	0	98 (0.5)	0.769
Body mass index (kg/m^2) (%)[j]			
<25	64 (48.9)	8075 (44.5)	0.315
≥25	67 (51.1)	10082 (55.5)	
Aggravating factors[k]			
Infection	**16 (11.1)**	1319 (6.6)	**0.031**
Drugs	**12 (8.3)**	422 (2.1)	**<0.001**
Pregnancy[†]	**6 (5.9)**	294 (3.3)	**0.008**
Body surface area (BSA) (%)[l]			
<5	49 (41.9)	7097 (44.7)	–
5–10	24 (20.5)	4994 (31.5)	
11–90	31 (26.5)	3374 (21.3)	
>90	13 (11.1)	408 (2.5)	
Face and neck involvement[m]	69 (47.9)	10049 (51.6)	0.378
Scalp involvement[n]	88 (61.1)	**16045 (81.5)**	**<0.001**
Severe psoriasis[o]	**68 (64.8)**	7286 (50)	**0.003**
Nail disease[p]	80 (54.1)	11336 (56.4)	0.562
Nail feature[‡]			
Pitting	53 (66.3)	8300 (73.2)	
Onycholysis	35 (43.8)	5268 (46.5)	
Subungual hyperkeratosis	10 (12.5)	1420 (12.5)	
Total nail dystrophy	11 (13.8)	552 (4.9)	
Discoloration	19 (23.8)	3178 (28)	
Psoriatic arthropathy[q]	15 (10.1)	2623 (13.1)	0.292
Types[§]			
Oligo-/monoarthropathy	6 (40)	1047 (39.9)	
Distal hand joints arthropathy	4 (26.7)	822 (31.3)	
Symmetrical polyarthropathy	4 (26.7)	747 (28.5)	
Spondylitis/sacroiliitis	1 (6.7)	213 (8.1)	
Arthritis mutilans	0	85 (3.2)	
DLQI >10[r]	**64 (48.9)**	7458 (40.3)	**0.046**
Mean DLQI (SD)	10.68 (6.7)	9.61 (6.74)	0.069
Mean CDLQI (SD)	8.67 (5.35)	9.07 (5.93)	0.791
DLQI domain, mean (SD)			
Symptoms and feelings[s]	2.71 (1.57)	2.86 (1.55)	0.272
Daily activities[t]	**2.46 (1.79)**	2.12 (1.73)	**0.038**
Leisure[u]	**2.70 (1.96)**	2.26 (1.86)	**0.018**
Work and school[v]	**1.21 (1.14)**	0.76 (0.97)	**0.008**
Personal relationship[w]	1.49 (1.53)	1.32 (1.55)	0.277
Treatment[x]	0.95 (0.89)	0.94 (0.94)	0.962
Mean no. days off work/school (SD) in 6 months	**2.06 (6.09)**	0.51 (4.91)	**0.004**
Mean no. of hospitalizations (SD) in 6 months	**0.31 (0.95)**	0.05 (1.22)	**0.001**
No. of patients with hospitalization in 6 months[y]			
0 hospitalization	105 (76.6)	18792 (97.7)	**<0.001**
≥1 hospitalization	**32 (23.4)**	437 (2.3)	
Treatment			
Topical[z]	139 (95.9)	18906 (94.9)	**<0.001**

(Continues)

(Continues)

TABLE 1 (Continued)

Characteristic	Pustular psoriasis *n* (%)	Non-pustular psoriasis *n* (%)	*p*-Value
Phototherapy[Ω]	2 (1.4)	522 (2.6)	0.349
Systemic therapy[∂]	**74 (51.4)**	2749 (13.9)	**<0.001**
Acitretin	**41 (28.5)**	508 (2.6)	**<0.001**
Methotrexate	**24 (16.7)**	2162 (10.9)	**0.028**
Systemic corticosteroids	**9 (6.3)**	165 (0.8)	**<0.001**
Cyclosporin	**7 (4.9)**	129 (0.7)	**<0.001**
Biologics	0	78 (0.4)	0.450
Hydroxyurea	0	23 (0.1)	0.682

Note: Severe psoriasis = BSA >10 and/or DLQI >10; [a]PP $n = 148$, non PP $n = 20322$; [b]PP $n = 148$, non-PP $n = 21579$; [c]PP $n = 145$, non-PP = 19985; [d]PP $n = 144$, non-PP = 19620; [e]PP $n = 145$, non-PP = 19826; [f]PP $n = 146$, non-PP = 19808; [g]PP $n = 144$, non-PP $n = 19797$; [h]PP $n = 144$, non-PP = 19791; [i]PP $n = 144$, non-PP = 19921; [j]PP $n = 131$, non-PP $n = 18157$; [k]PP $n = 144$, non-PP = 19921; [l]PP $n = 117$, non-PP $n = 15873$; [m]PP $n = 144$, non-PP $n = 19475$; [n]PP $n = 144$, non-PP $n = 19691$; [o]PP $n = 105$, non-PP $n = 14583$; [p]PP $n = 148$, non-PP $n = 20090$; [q]PP $n = 148$, non-PP $n = 20079$; [r]PP $n = 131$, non PP $n = 18527$; [s]PP $n = 131$, non-PP $n = 18464$; [t]PP $n = 125$, non-PP = 17644; [u]PP $n = 115$, non-PP = 16132; [v]PP $n = 103$, non-PP = 14710; [w]PP $n = 94$, non-PP = 13748; [x]PP $n = 129$, non-PP = 17511; [y]PP $n = 137$, non-PP = 19229; [z]PP $n = 145$, non-PP $n = 19914$; [Ω]PP $n = 144$, non-PP $n = 19914$; [∂]PP $n = 144$, non-PP $n = 19802$.

Bold font indicates statistical significance.

Abbreviations: BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; HIV, human immunodeficiency virus; SD, standard deviation.

[†]These percentages were calculated by dividing the number of patients with female patients.

[‡]These percentages were calculated by dividing the number of patients with nail involvement in each group and multiplying by 100.

[§]These percentages were calculated by dividing the number of patients with joint involvement in each group and multiplying by 100.

polyarthropathy (rheumatoid-like) among the GPP patients (44.5%) and oligo-/monoarthropathy among the LPP patients (66.7%).

3.4 | Quality of life and disease burden

More patients with PP had a DLQI of >10 compared to non-PP patients (48.9% vs. 40.3%, $p = 0.046$; Table 1). A higher proportion of PP patients (9.2%) reported a DLQI of >20 (extremely large effect on quality of life) compared to non-PP patients (7.7%) (Figure 2). Although the mean DLQI score among PP patients was higher than non-PP, it was not statistically significant (10.68 ± 6.7 vs. 9.61 ± 6.74, $p = 0.07$). Patients with PP had significantly higher mean scores compared to non-PP patients in DLQI domains such as "daily activities," "leisure" and "work and school" (Table 1). As shown in Figure 3, "work and school" was the most affected domain with 20.4% of PP patients reporting a significant impairment in this area. The mean DLQI score were 10.72 ± 6.81 and 10.62 ± 6.54 among patients with GPP and localized PP patients respectively ($p = 0.93$; Table 2).

Our PP cohort reported a higher mean number of days off school/work compared to the non-PP cohort (2.06 ± 6.09 vs. 0.5 ± 4.91, $p = 0.004$). Patients with PP also had a higher mean number of hospitalizations compared to the non-PP patients (0.31 ± 0.95 vs. 0.05 ± 1.22, $p = 0.001$). More PP patients had at least one hospitalization in the past 6 months compared to non-PP patients (23.4% vs. 2.3%, $p < 0.001$). Among the PP patients with at least one hospitalization, 65.6% were GPP patients and 34.3% were LPP patients.

3.5 | Treatment

More PP patients received systemic therapy compared to non-PP patients (51.4% vs. 13.9%, $p < 0.001$). The most prescribed systemic therapies for PP patients were acitretin, followed by methotrexate, systemic corticosteroids and cyclosporine. Eight patients with PP (5.4%) were on combination therapy, of which four were on methotrexate and systemic corticosteroids, two were on methotrexate and acitretin and two on acitretin and systemic corticosteroids. Only two PP patients (1.4%) were treated with phototherapy. None of the PP patients were treated with biological agents.

4 | DISCUSSION

The prevalence of pustular psoriasis among psoriasis patients was reported to be 2.1% in Japan[8] and 1.2% in Thailand.[9] Our study reported a lower rate (0.7%) of pustular psoriasis among the psoriasis patients. This is probably due to underreporting of cases to the Malaysian Psoriasis Registry (MPR) as notification is not mandatory. In previous studies, GPP occurred more among women,[10,11] which is similar to our findings.

Twelves et al.[12] found that GPP patients had a lower mean age of onset compared to LPP patients. Although not statistically significant, we observed a younger age of onset among patients with GPP. We detected a bimodal peak age of onset in both our GPP and LPP patients. A bimodal age distribution was described among psoriasis patients, with two peaks at the age group of 16–22 and 55–60 years.[13] Fujita et al found that GPP male patients had two peaks of age of onset, 30–39 and 50–69 years, as with female patients with two peaks at 25–34 and 50–64 years.[14] Interestingly, our cohort showed a later second peak of disease onset for LPP which has not been described before. Previous studies showed 7.5%–29% of GPP patients had a family history of psoriasis.[9,15] Solmaz et al.[16] showed that plaque psoriasis was more common than pustular psoriasis among patients with a family history of psoriasis. Our cohort with family history was comparable with previous studies.

Increasing evidence demonstrates that the interleukin (IL)-36 cytokine plays a crucial role in the autoinflammatory response in GPP.[6] Mutations in the IL36RN gene were detected in nearly a quarter

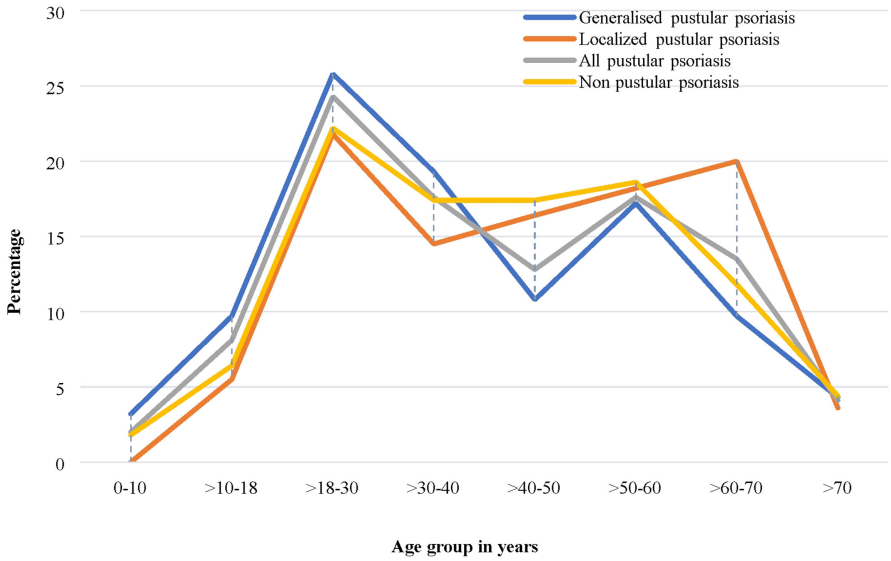

FIGURE 1 Age of onset of patients with pustular psoriasis and other subtypes of psoriasis.

of GPP patients.[12] Homozygous mutations of IL36RN was discovered among consanguineous Tunisian families. Heterozygous mutations of IL36RN from non-consanguineous family have also been reported.[17] Sustained activation of IL-1 and IL-36 cytokines lead to hyperactivation of pro-inflammatory cytokines, neutrophil infiltration and pustule formation.[6] Patients with IL36RN mutations tend to present without concomitant plaque psoriasis, have more severe disease and an earlier age of onset.[18]

The precipitating factors for GPP were withdrawal of corticosteroids, pregnancy and infections in previous studies.[10,19] These findings were similar to our cohort, however, the type of medications that precipitated GPP were not available. GPP in pregnancy is characterized by erythematous plaques with pustules and systemic symptoms. It can present anytime during pregnancy or during the postpartum period, but typically occurs in the last trimester of pregnancy. Recurrences in subsequent pregnancies may be earlier in onset or greater in severity.[20] Other than significant effects on maternal outcome, it could also lead to poor fetal outcomes, including stillbirth, intrauterine growth retardation, placental insufficiency and fetal anomalies.[21] Jin et al.[11] reported two GPP patients in pregnancy, one had a spontaneous abortion and the other died during the course of the disease.

As with previous studies, the most common co-morbidities among PP patients in our study were hypertension, dyslipidaemia and diabetes mellitus.[10,12] A study in the United States found that patients with GPP had a higher rate of dyslipidaemia compared to patients with plaque psoriasis.[22] Systemic inflammation is the common pathogenesis in both pustular psoriasis and dyslipidaemia. The inflammatory cytokines implicated in pustular psoriasis such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1 β) and IL-6 play important roles in the dysregulation of serum lipids.[23] TNF-α induces the production of low-density lipoprotein (LDL) and reduces the level of high-density lipoprotein (HDL). Interleukin-6 and IL-1ß increase very low-density lipoprotein (VLDL) and reduce triglyceride (TG) clearance.[24] Among our pustular psoriasis cohort with dyslipidaemia, 15 patients (44%) were on acitretin. A higher proportion of PP patients on acitretin could contribute to a higher rate of dyslipidaemia among PP patients. A study in Chinese GPP patients found more patients with dyslipidaemia after acitretin treatment.[15] Acitretin increases triglyceride concentration, very low-density lipoprotein (VLDL) and/or LDL, which lead to hyperlipidaemia in 10%–30% of patients on acitretin. In addition, acitretin also decreases the HDL fraction in 40% of patients.[25] High LDL/HDL ratio and hypertriglyceridemia are associated with cardiovascular risk.[25,26] Lipid abnormalities caused by acitretin typically reverses within 4–8 weeks after discontinuation.[25]

Previous studies found that 28%–54% of GPP patients had scalp involvement.[11,15] We noted a greater number of GPP patients with scalp involvement compared to LPP patients. This is possibly due to it being a localized disease. Around 42%–85% of GPP patients reported a history of plaque psoriasis.[11] A study of PPP patients revealed 25% had concomitant plaque psoriasis.[5] A higher rate of concomitant plaque psoriasis among GPP patients compared to LPP patients could contribute to a higher rate of scalp involvement in GPP patients. However, data on concomitant plaque psoriasis in our PP patients were not captured.

Nail involvement was observed in 33%–42% of GPP patients[11,15] and one third of PPP patients.[27] The most common nail manifestations of patients with GPP were nail bed changes (onycholysis, subungual hyperkeratosis and oil spots).[9] Whereas the most common nail manifestations of patients with PPP were subungual pustules, followed by pitting and onycholysis.[28] In ACH, nail involvement typically starts with subungual or periungual pustules and later involves the nail bed which may lead to onychodystrophy, anonychia and resorption of the distal phalanx.[29] A Korean study found that patients with localized PP had more severe nail psoriasis than patients with plaque psoriasis, with high Nail Psoriasis Severity Index (NAPSI) scores and frequent involvement

TABLE 2 Comparison of demography, clinical characteristics, quality of life and treatment between generalized pustular psoriasis and localized pustular psoriasis patients.

	GPP	Localized PP	
Characteristics	***n* (%)**	***n* (%)**	***p*-Value**
Age of onset (years)[α]			
Mean (SD)	29.46 (18.43)	35.7 (17.62)	0.054
Min, Max	1, 84	8, 74	
0–10	3 (3.2)	0	
>10–18	9 (9.7)	3 (5.5)	
>18–30	24 (25.8)	12 (21.8)	
>30–40	18 (19.3)	8 (14.5)	
>40–50	10 (10.8)	9 (16.4)	
>50–60	16 (17.2)	10 (18.2)	
>60–70	9 (9.7)	11 (20)	
>70	4 (4.3)	2 (3.6)	
Male: Female	1:2.3	1:1.9	0.667
Ethnicity[β]			
Malay	59 (62.1)	35 (66)	–
Chinese	17 (17.9)	12 (22.6)	
Indian	7 (7.4)	1 (2)	
Others	12 (12.6)	5 (9.4)	
Family history of psoriasis[χ]	13 (13.7)	6 (11.3)	0.629
Co-morbidities			
Dyslipidaemia[δ]	21 (22.8)	13 (25)	0.768
Hypertension[ε]	21 (22.6)	14 (26.9)	0.558
Diabetes mellitus[ϕ]	18 (19.1)	10 (19.2)	0.860
Ischaemic heart disease[η]	3 (3.3)	1 (1.9)	0.639
Cerebrovascular accident[ι]	1 (1.1)	1 (1.9)	0.705
Body mass index (BMI) (kg/m^2)[θ]			
<25	41 (50)	23 (46.9)	0.734
≥25	41 (50)	26 (53.1)	
Body surface area (BSA)[π]			
<5	22 (29.7)	27 (62.8)	–
5–10	13 (17.6)	11 (25.6)	
11–90	26 (35.1)	5 (11.6)	
>90	13 (17.6)	0	
Face and neck involvement[ρ]	**55 (59.1)**	14 (27.5)	**<0.001**
Scalp involvement[τ]	**66 (71.7)**	22 (42.3)	**0.001**
Severe psoriasis[ξ]	**47 (72.3)**	21 (52.5)	**0.039**
Nail disease[σ]	50 (52.6)	30 (56.6)	0.642
Nail features[a]			
Pitting	33 (66)	20 (66.7)	
Onycholysis	17 (34)	18 (60)	
Subungual hyperkeratosis	3 (6)	7 (23.3)	
Total nail dystrophy	1 (2)	10 (33.3)	
Discolouration	9 (18)	10 (33.3)	
Psoriatic arthropathy[υ]	9 (9.5)	6 (11.3)	0.810

TABLE 2 (Continued)

Characteristics	GPP *n* (%)	Localized PP *n* (%)	*p*-Value
Types[b]			
Oligo-/monoarthropathy	2 (22.2)	4 (66.7)	
Distal hand joints arthropathy	2 (22.2)	2 (33.3)	
Symmetrical polyarthropathy	4 (44.5)	0	
Spondylitis/sacroiliitis	1 (11.1)	0	
Arthritis mutilans	0	0	
DLQI >10[ϖ]	40 (49.4)	24 (48)	0.878
Mean DLQI (SD)	10.72 (6.81)	10.62 (6.54)	0.929
Mean CDLQI (SD)	8.75 (5.85)	8.33 (3.51)	0.909
No. of patients with hospitalization in 6 months[ϒ]			
0 hospitalization	63 (75)	42 (79.2)	0.567
≥1 hospitalization	21 (25)	11 (20.8)	
Treatment			
Topical[Ψ]	91 (96.8)	48 (94.1)	0.437
Phototherapy[ζ]	1 (1.1)	1 (1.9)	0.686
Systemic therapy[∞]	48 (51.6)	26 (51)	0.942
Acitretin	28 (30.1)	13 (25.5)	0.557
Methotrexate	15 (16.1)	9 (17.6)	0.815
Systemic corticosteroids	4 (4.3)	5 (9.8)	0.192
Cyclosporin	6 (6.5)	1 (2)	0.231
Biologics	0	0	–
Hydroxyurea	0	0	–

Note: Severe psoriasis = BSA >10 and/or DLQI >10; [α]GPP *n* = 93, localized PP *n* = 55; [β]GPP *n* = 95, localized PP *n* = 53; [χ]GPP *n* = 95, localized PP *n* = 53; [δ]GPP *n* = 92, localized PP *n* = 52; [ε]GPP *n* = 93, localized PP *n* = 52; [ϕ]GPP *n* = 94, localized PP *n* = 52; [η]GPP *n* = 92, localized PP *n* = 52; [ι]GPP *n* = 92, localized PP *n* = 52; [θ]GPP *n* = 84, localized PP *n* = 47; [π]GPP *n* = 74, localized PP *n* = 43; [ρ]GPP *n* = 93, localized PP *n* = 51; [τ]GPP *n* = 92, localized PP *n* = 52; [ξ]GPP *n* = 65, localized PP *n* = 40; [σ]GPP *n* = 95, localized PP *n* = 53; [υ]GPP *n* = 95, localized PP *n* = 53; [ϖ]GPP *n* = 81, localized PP *n* = 50; [ϒ]GPP *n* = 84, localized PP *n* = 53; [Ψ]GPP *n* = 94, localized PP *n* = 51; [ζ]GPP *n* = 91, localized PP *n* = 52; [∞]GPP *n* = 93, localized PP *n* = 51.

Bold font indicates statistical significance.

Abbreviations: BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; GPP, generalized pustular psoriasis; PP, pustular psoriasis; SD, standard deviation.

[a]These percentages were calculated by dividing the number of patients with nail involvement in each group and multiplying by 100.

[b]These percentages were calculated by dividing the number of patients with joint involvement in each group and multiplying by 100.

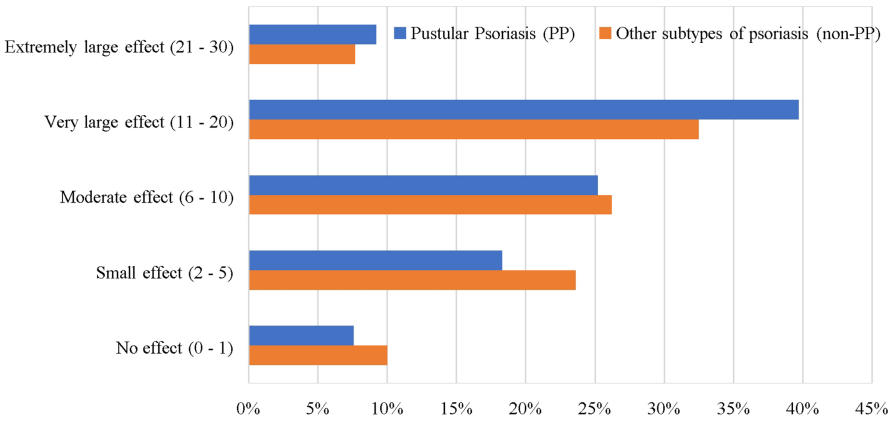

FIGURE 2 Dermatology Life Quality Index (DLQI) score of patients with pustular psoriasis and other subtypes of psoriasis.

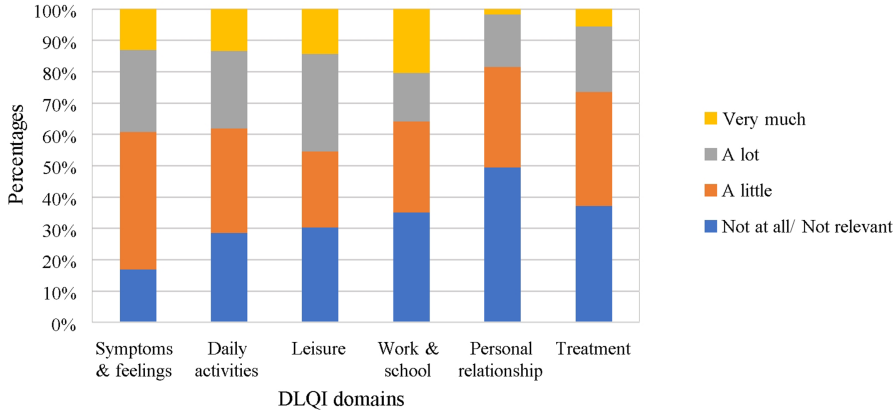

FIGURE 3 Quality of life impairment of patients with pustular psoriasis based on the Dermatology Life Quality Index (DLQI) domains.

of both nail bed and matrix.[30] The prevalence of arthritis among GPP patients were 10.9%–34.7%.[15,19] Around 28% of PPP patients had psoriatic arthritis.[5] All types of psoriatic arthritis including distal arthritis, symmetrical polyarthritis, asymmetric oligoarthritis, spondyloarthritis and arthritis mutilans were observed among GPP patients.[19]

There is a lack of consensus for severity assessment in GPP patients.[18] Body surface area (BSA) involvement was used in the severity assessment for our cohort. Severity assessment by BSA has not been validated for GPP and PP patients. The Japanese Dermatological Society Association Severity Index of GPP (JDA-GPPSI) was developed to assess GPP severity based on skin symptoms and systemic involvement. The Generalized Pustular Psoriasis Area and Severity Index (GPPASI) and Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) were developed recently specifically for GPP severity assessment and has been used in clinical trials. These assessment tools however have not been validated. Using these GPP-specific disease severity assessment tools may improve clinical assessment and treatment monitoring among our GPP cohort.[18]

The majority of our GPP patients had severe disease. Patients with GPP may experience recurrent flares and around 50% of GPP flares require hospitalization. The mortality rate of GPP and its associated treatment was demonstrated to be 2%–16%.[31] In a US study of 95 GPP patients, 35.8% were hospitalized at a median rate of 0.5 hospitalizations per year (IQR, 0.4–1.6).[32] Morita et al.[33] described a higher proportion of GPP patients needing hospitalization and a longer duration of hospitalization compared to patients with plaque psoriasis which was also seen in our GPP patients.

Pustular psoriasis has a substantial impact on patients' quality of life (QoL). More than half of our PP patients were treated with systemic therapy and nearly half of them reported significant impairment in their quality of life (DLQI >10). A study in Japan of 98 GPP patients demonstrated a decline in QoL in 84.7% of patients.[14] In a survey of 66 patients with GPP in the United States, 58% reported their daily activities were affected by GPP flares and 21% reported an impact on daily activities even in the absence of flares.[34] A study of 77 patients with PPP reported a mean DLQI score of 12.2 ± 7.7.[5]

Our study found that more PP patients received systemic therapy compared to non-PP patients. Morita et al reported more patients with GPP received a combination of topical steroids and systemic therapy compared to those with plaque psoriasis (42.3% vs. 23.9%).[33] The type of systemic therapy used in our PP cohort, was similar with previous studies.[9,15,33] Systemic therapy was however underutilized in our cohort compared with other studies.[9,15,33] Multiple factors may have contributed to this, which include prescription preference by dermatologists with a tendency to avoid systemic therapies and patient's reluctance due to fear of potential adverse effects.

Based on the Japanese guidelines and Medical Board of The National Psoriasis Foundation, the first-line therapies for patients with GPP typically involves acitretin, methotrexate and cyclosporine.[14,35] Data on the efficacy of acitretin, methotrexate and cyclosporine were limited to case reports, retrospective studies and small single-arm studies. Acitretin is a non-immunosuppressive agent that has been shown to clear skin lesions of GPP patients within 4–6 weeks. Methotrexate has a slower onset of action with clearance of skin lesions occurring within 3–5 months for GPP.[36] Cyclosporine is the first-line therapy in treating GPP in pregnant women due to its fast onset of action and its non-teratogenic properties. However, long-term use is associated with renal dysfunction and hypertension.[36]

Systemic corticosteroids have been used as a first-line therapy in patients with GPP in pregnancy.[35] It has also been used during the acute phase of GPP, in patients with systemic symptoms.[14] In addition, it also can be used in patients with arthritis for initial control of severe joint symptoms.[14] Systemic corticosteroids should be used with caution as tapering may induce a rebound of GPP. It should be discontinued when other steroid sparing systemic agents take effect as long-term use is associated with various irreversible side effects.[14]

Palmoplantar pustular psoriasis (PPP) and acrodermatitis continua of Hallopeau (ACH) are known to be recalcitrant to topical therapy and require systemic therapy. In a study of 172 patients with PPP, the most frequently used systemic therapy were corticosteroids (40.1%), followed by acitretin (37.8%) and methotrexate (27.9%).[5] Whereas in a study of 39 patients with ACH, methotrexate, acitretin and cyclosporine were the most frequently used systemic therapy.[37]

Both psoralen plus ultraviolet A phototherapy (PUVA) and narrow-band ultraviolet B (NB-UVB) are second-line treatments for GPP and

LPP. Due to its delayed onset of action, it is used in chronic pustular psoriasis in combination with systemic therapy. Narrow-band ultraviolet B is utilized in pregnant patients, but PUVA is contraindicated in pregnancy.[14] In a study of eight patients with GPP, PUVA phototherapy resulted in complete clearance of GPP and remission of up to 1.5 years with maintenance phototherapy.[38] Treatment with UVA1 and NB-UVB phototherapy led to significant improvement in 64 patients with PPP.[39] Only a small number of our cohort with PP (1.4%) were treated with phototherapy. Underutilization of phototherapy could be due to lack of access to phototherapy and compliance issues.

None of our PP patients were treated with biologics. There has been no therapeutic agent approved for GPP by the Food and Drug Administration (FDA) until recently, where spesolimab was the first treatment approved.[40] The prohibitive cost of biological therapy is another contributing factor. Several biological agents have been approved in Japan for the treatment of GPP since 2010, including tumor necrosis factor (TNF)-α inhibitors (infliximab, adalimumab and certolizumab pegol); interleukin (IL)-17 inhibitors (secukinumab, ixekizumab and brodalumab) and IL-23 inhibitors (risankizumab and guselkumab).[14] Brodalumab was approved in Thailand and Taiwan for the treatment of GPP.[36] An analysis of 1516 GPP patients in Japan concluded that patients who received biologics (19%) had a better outcome, and lower in-hospital mortality rates compared to patients on other systemic agents.[41] A retrospective German study examining 86 GPP patients, revealed that the biologic-treated group showed higher efficacy and higher median drug survival than the non-biologic group.[42] In China, 15 of 110 GPP patients who received biologics (80%) achieved skin clearance. However, there was no significant difference when compared to the acitretin group.[15] The identification of the IL36RN gene mutation among GPP patients has led to the development of novel therapies targeting the IL-36 receptor. A phase 2 randomized placebo-controlled trial of GPP patients treated with spesolimab, an IL-36 receptor inhibitor demonstrated pustule clearance in 54% of patients on spesolimab compared to 6% of patients on placebo at the end of week-1.[43] Biologics such as (TNF)-α inhibitors, anti-IL 12/23 or anti-IL-17 have also been used in severe recalcitrant PPP patients.[28]

4.1 | Limitations

Data on the subtypes of localized PP, preceding or concomitant plaque psoriasis, and GPP in pregnancy were not collected by the MPR. This is due to the nature of the MPR clinical research form which captures the predominant type of psoriasis only at the point of data collection. Assessment of severity was based on BSA which did not consider the pustular component of PP. Data on frequency of flares and duration of remission were not available. In addition, the DLQI scores were collected during both GPP flares and on follow-up in different patients. This made it difficult to ascertain the actual impact of GPP on the quality of life.

We propose the development of a registry specific for pustular psoriasis to ensure accurate, relevant and comprehensive data collection. Prospective studies and randomized placebo-controlled trials on the treatment of PP would be valuable to determine the safety and efficacy of treatment. Treatment guidelines specific for pustular psoriasis should be established.

5 | CONCLUSION

The prevalence of pustular psoriasis patients in the MPR was 0.7% with 63% being GPP. Our PP cohort were more likely to have dyslipidaemia, severe disease, receive systemic treatment and require hospitalization compared to the non-PP cohort. Nearly half of the PP patients reported significant impairment in their quality of life indicating the unmet need and treatment gap in the management of pustular psoriasis. Early initiation of systemic therapy to achieve rapid control of cutaneous and systemic symptoms, reducing the frequency of flares and management of PP comorbidities are important in improving patients' quality of life.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception, design, data curation and analysis. Material preparation and article writing was performed by Teoh Xin Yun. All authors were involved in the review and correction of the article. All authors read and approved the final article.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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