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RESEARCH ARTICLE

Clinical characteristics and heterogeneity of generalized pustular psoriasis: A comparative study in a large retrospective cohort

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Abstract

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening skin disease and the clinical heterogeneity of which is largely unknown. Retrospective cohort analysis was conducted on hospitalized GPP patients between January 2010 and November 2022. A total of 416 patients with GPP and psoriasis vulgaris (PV) respectively were included, matched 1:1 by sex and age. The heterogeneity of GPP was stratified by PV history and age. Compared with PV, GPP was significantly associated with prolonged hospitalization (11.7 vs. 10.3 day, $p < 0.001$), elevated neutrophil lymphocyte ratio (NLR) (5.93 vs. 2.44, $p < 0.001$) and anemia (13.9% vs. 1.2%, $p < 0.001$). Moreover, GPP alone (without PV history) was a relatively severer subtype with higher temperature (37.6°C vs. 38.0°C, $p = 0.002$) and skin infections (5.2% vs. 11.4%, $p = 0.019$) than GPP with PV. For patients across different age, compared with juvenile patients, clinical features support a severer phenotype in middle-aged, including higher incidence of anaemia (7.5% vs. 16.0%, $p = 0.023$) and NLR score (3.83 vs. 6.88, $p < 0.001$). Interleukin-6 ($r = 0.59$), high density lipoprotein cholesterol ($r = -0.56$), albumin ($r = -0.53$) and C-reactive protein-to-albumin ratio ($r = 0.49$) were the most relevant markers of severity in GPP alone, GPP with PV, juvenile and middle-aged GPP, respectively. This retrospective cohort suggests that GPP is highly heterogeneous and GPP alone and middle-aged GPP exhibit severe disease phenotypes. More attention on the heterogeneity of this severe disease is warranted to meet the unmet needs and promote the individualized management of GPP.

KEYWORDS
autoinflammatory disease, generalized pustular psoriasis, heterogeneity, psoriasis vulgaris

1 | INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare autoinflammatory skin disease characterized by recurrent flares of sterile pustules that occur with systemic inflammation.[1] The irregular and relapsing pattern of disease flares, GPP-associated systemic complications and comorbidities make it challenging to manage the disease and pose a major clinical burden to patients.[2] GPP has been classified as a

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severe variant of psoriasis vulgaris (PV) before; however, accumulating evidence indicates that it is distinct from PV,[2] regarding the aetiology, histopathologic and dermatologic features, and comorbidities.[3] Emotional distress, seasonal changes, medication withdraw and infections such as COVID-19 are associated with GPP flares.[4,5] The pathogenesis of GPP involves in genetic and immunologic factors, including gene mutations of interleukin-36 receptor antagonist (*IL36RN*)[6] and a positive feedback loop of uncontrolled IL-36 signalling, which eventually leads to enhanced chemokine expression, neutrophil infiltration and pustule formation.[7–9] Recently, an IL-36R-specific antibody demonstrates superiority over placebo in treating GPP in a clinical trial.[10,11] To date, retinoids, cyclosporine and methotrexate are recommended as the first-line therapy for GPP.[12,13] With relatively limited options, rapid controlling of flares and long-term management of GPP remain major challenges and unmet needs for dermatologists.

Existing studies argue that GPP is clinically heterogeneous, according to PV history, age, flares or systemic inflammation.[14] For instance, some researches identify the aetiology differences between GPP alone and GPP concomitant with PV: *IL36RN* mutations are more common in GPP alone whereas caspase recruitment domain 14 gene (*CARD14*) mutations are common in GPP with PV.[15,16] The flare frequency of GPP also differs significantly, most patients are reported to experience at least 1 flare per year, and cases of more than 3 flares annually are not rare.[17,18] Therefore, the heterogeneity and characteristics of GPP need in depth elucidation for improving monitoring strategies.

In order to describe the heterogeneity of GPP and facilitate disease assessment and individualized therapy, we compared them in a large retrospective cohort and revealed the clinical differences between subgroups based on PV history and age. This study will improve our understanding of the uniqueness and heterogeneity of GPP, and help update our approaches to patient stratification and management.

2 | MATERIALS AND METHODS

2.1 | Patients and data extraction

All GPP and PV cases were obtained from our hospital. Clinical information and laboratory test information were extracted from the electronic medical record system. All patients were diagnosed on admission based on the 10th version International Classification of Diseases (ICD-10). We reviewed all patients with a diagnosis of GPP (ICD-10: L40.1), admissions between 1 January 2010 and 30 November 2022. After extracting the case information, all medical records were checked again according to 2017 ERASPEN criteria[14] and the following patients were excluded: pustules confined to the palmoplantar region; patients with an admission diagnosis of GPP but not admitted for GPP; inconsistent pathological diagnosis. Following the identification of GPP patients, we conducted a screening of individuals admitted for PV (ICD-10: L40.0) during the same time but without a prior diagnosis of GPP. Propensity score matching was performed to achieve 1:1 age and sex matching between the GPP and PV groups with a calliper value set at 0.02, followed by independent group analysis.

First, we compared the clinical differences between GPP and matched PV patients. Subsequently, we categorized GPP according to PV history and age, respectively. Those who were diagnosed with PV or had typical skin lesions of PV (well demarcated, salmon-pink plaques covered in silvery scales in white skin or grey plaques in black skin)[1] more than 6 months before GPP diagnosis were classified as GPP with PV, otherwise was GPP alone. Patients younger than 18 years, 19 to 54 years, and older than or equal to 55 years old were classified into juvenile, middle-aged and senior groups, respectively. The study protocol was approved by the Ethics Committee of our hospital, and participants provided informed agreement.

2.2 | Assessment of the generalized pustular psoriasis area and severity index

Given that the assessment of generalized pustular psoriasis area and severity index (GPPASI) is a subjective process, we have implemented measures to ensure objectivity and credibility throughout the assessment process. The assessment of GPPASI was based on the criteria of previous clinical trial[19] and completed independently by two well-trained researchers. The admission images, which meticulously documented and photographed the patient's entire body skin, were used for evaluation. The intraclass correlation coefficient (ICC, two-way random, absolute agreement and single measures) was used to evaluate the reliability of assessment. If the ICC value was higher than 0.750, then the mean of the GPPASI of the two researchers was taken as the final value; otherwise, a third researcher was introduced for assessment, and the median of the three researchers' results was taken as the final value. The ICC was 0.860 (95%CI = 0.640–0.929), and the mean value of two researchers was taken as the final value.

2.3 | Statistical analysis

Categorical variables were described using number (percentage) and assessed through chi-square test or Fisher exact probability method. Continuous variables which obedience normal distribution were described or assessed by mean (standard deviation) or t-test; others were described by median (interquartile range). Pearson correlation and spearman correlation were used to determine the relationship between GPPASI and laboratory tests. Significance levels were taken as two-sided 0.05. Analyses were conducted using SPSS version 26 (IBM) and GraphPad Prism software version 8 (GraphPad software).

3 | RESULTS

3.1 | Demographic and clinical characteristic of GPP in comparison with PV

After primary screening and recheck, 416 eligible patients with GPP were included in this study and 330 (79.2%) of them were confirmed by pathological and clinical images, as shown in Figure S1. We also identified 416 hospitalized PV patients during the same period for comparative analysis. In our cohort, the mean age of the GPP and PV was 30.5 and 33.8 years. However, the mean onset age of GPP was older (28.0 vs. 24.4 years, $p<0.001$) than PV (Table 1). The proportion of males was 50.2% and 50.7% in GPP and PV. Meanwhile, the hospitalization length of GPP was longer than PV (11.7 vs. 10.3 days, $p<0.001$). Smoking and alcohol consumption have been reported to be associated with psoriasis risk,[1,20] while the proportion of smokers (17.3% vs. 26.2%, $p=0.002$) and drinkers (8.4% vs. 13.9%, $p=0.011$) was lower in GPP than PV (Table 1).

Laboratory tests were also significantly different between GPP and PV. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are the systemic inflammation markers,[21,22] and we found they were all significantly higher in GPP than those in PV: (NLR, 5.93 vs. 2.44, $p<0.001$) and (PLR, 176 vs. 137, $p<0.001$) (Table 1). We recorded prevalent comorbidities in patients, with anaemia (13.9% vs. 1.2%, $p<0.001$), hypoproteinemia (10.6% vs. 7.2%, $p=0.088$) and skin infections (7.7% vs. 0.7%, $p<0.001$), all being more frequent in GPP than PV, while psoriatic arthritis (6.3% vs. 8.7%, $p=0.187$) and hypertension (4.1% vs. 7.7%, $p=0.027$) were more frequent in PV (Table 1). We conclude that GPP patients exhibit heavier inflammatory responses and disease burden than PV.

3.2 | Phenotypic heterogeneity between GPP with PV and GPP alone

As GPP with or without PV may have some clinical differences,[14] we further performed a comparison according to their PV history. We observed that GPP patients with PV were older at onset (31.3 vs. 23.0 years, $p<0.001$) and with higher proportion of family history of psoriasis (23.2% vs. 11.4%, $p=0.003$) (Table 2) than GPP

TABLE 1 The phenotype of GPP in a comparison with PV.

	GPP ($n=416$)		PV ($n=416$)		p-value
Age, year	30.5	17.7	33.8	17.0	0.007
Age of GPP or PV onset, year	28.0	18.1	24.4	14.3	<0.001
Male sex	209	50.2%	211	50.7%	0.890
Length of hospitalization, day	11.7	5.3	10.3	3.7	<0.001
BMI, kg/m^2[a]	22.0	4.9	23.4	5.0	0.004
Ever or currently smoking	72	17.3%	109	26.2%	0.002
Ever or currently consuming alcohol	35	8.4%	58	13.9%	0.011
Family history of psoriasis	77	18.5%	98	23.6%	0.074
Comorbidities					
Anaemia	58	13.9%	5	1.2%	<0.001
Hyperlipidemia	44	10.6%	30	7.2%	0.088
Skin infections	32	7.7%	3	0.7%	<0.001
Psoriatic arthritis	26	6.3%	36	8.7%	0.187
Diabetes mellitus	20	4.8%	18	4.3%	0.740
Hypertension	17	4.1%	32	7.7%	0.027
Laboratory tests					
Neutrophils, 10^9/L[b]	8.90	6.65	4.22	1.89	<0.001
Lymphocytes, 10^9/L[c]	1.90	1.16	1.97	0.72	0.358
NLR[c]	5.93	5.02	2.44	1.59	<0.001
Platelets, 10^9/L[d]	278	98	242	76	<0.001
PLR[e]	176	91	137	63	<0.001

Note: Data are presented as mean (SD) or *n* (%). A 1:1 matching of age and sex between the GPP and PV groups was performed using the propensity score matching (calliper value = 0.02), followed by independent group analysis.

Abbreviations: BMI, body mass index; GPP, generalized pustular psoriasis; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PV, psoriasis vulgaris.

[a]Data were available in 143 and 378 cases in GPP and PV.

[b]Data were available in 412 and 290 cases in GPP and PV.

[c]Data were available in 409 and 290 cases in GPP and PV.

[d]Data were available in 413 and 290 cases in GPP and PV.

[e]Data were available in 408 and 290 cases in GPP and PV.

TABLE 2 Comparison of demographic and clinical characteristics of GPP with PV and GPP alone.

	GPP with PV ($n=250$)		GPP alone ($n=166$)		p-value
Age, year	32.2	16.9	28.0	18.6	0.020
Age of GPP onset, year	31.3	17.0	23.0	18.6	<0.001
Male sex	126	50.4%	83	50.0%	0.936
Length of hospitalization, day	11.6	4.8	12.0	6.0	0.506
BMI, kg/m^2[a]	21.7	4.5	22.4	5.6	0.395
Ever or currently smoking	50	20.0%	22	13.3%	0.075
Ever or currently consuming alcohol	23	9.2%	12	7.2%	0.478
Family history of psoriasis	58	23.2%	19	11.4%	0.003
Maximum temperature, °C[b]	37.6	1.1	38.0	1.3	0.002
Available pathological or clinical images	190	76.0%	140	84.3%	
GPPASI[c]	27.4	11.8	25.0	13.1	0.124
Comorbidities					
Anaemia	26	10.4%	32	19.3%	0.010
Hyperlipidemia	27	10.2%	17	10.2%	0.856
Skin infections	13	5.2%	19	11.4%	0.019
Psoriatic arthritis	16	6.4%	10	6.0%	0.877
Diabetes mellitus	15	6.0%	5	3.0%	0.163
Hypertension	10	4.0%	7	4.2%	0.928
Acral pustular psoriasis	1	0.4%	13	7.8%	<0.001
Laboratory tests					
Neutrophils, $10^9/L$[d]	8.35	4.96	9.72	8.53	0.063
Lymphocytes, $10^9/L$[e]	1.80	1.08	2.05	1.26	0.042
NLR[e]	5.89	5.09	5.99	4.94	0.854
Platelets, $10^9/L$[f]	263	95	299	100	<0.001
PLR[g]	174	87	180	97	0.482

Note: Data are presented as mean (SD) or *n* (%). GPP patients with a diagnosis of PV or had typical skin lesions of PV more than 6 months before GPP diagnosis were classified as GPP with PV, otherwise was GPP alone.

Abbreviations: Acral pustular psoriasis, palmoplantar pustulosis or acrodermatitis continua of hallopeau; GPP, generalized pustular psoriasis; GPPASI, generalized pustular psoriasis area and severity index; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PV, psoriasis vulgaris.

[a]Data were available in 89 and 54 cases in GPP with PV and GPP alone.

[b]Data were available in 246 and 156 cases in GPP with PV and GPP alone.

[c]Data were available in 139 and 106 cases in GPP with PV and GPP alone.

[d]Data were available in 247 and 165 cases in GPP with PV and GPP alone.

[e]Data were available in 245 and 164 cases in GPP with PV and GPP alone.

[f]Data were available in 248 and 165 cases in GPP with PV and GPP alone.

[g]Data were available in 244 and 164 cases in GPP with PV and GPP alone.

alone. Meanwhile, the maximum temperature was lower in GPP with PV than GPP alone (37.6°C vs. 38.0°C, $p=0.002$). The incidence of anaemia (10.4% vs. 19.3%, $p=0.010$), skin infections (5.2% vs. 11.4%, $p=0.019$) and acral pustular psoriasis (0.4% vs. 7.8%, $p<0.001$) was relatively low in GPP with PV compared to GPP alone (Table 2).

As the triggering and exacerbating factors are significant for disease management, we also compared them in Figure S2A. In brief, GPP alone patients were more likely to be triggered by several factors, including upper respiratory tract infections (30.7% vs. 16.4%), specific seasons or season changes (10.2% vs. 2.6%), and pregnancy (7.8% vs. 1.6%), compared to GPP with PV. Besides, higher proportion of the palmoplantar region was affected in GPP alone (Figure S3B). The differences in NLR, PLR (Table 2), albumin, lipids (Figure S4A) and inflammatory markers (Figure S5A) were not significant. In terms of treatment options, GPP patients with PV were more likely to accept retinoids (43.2% vs. 35.3%) and less to accept cyclosporine (17.6% vs. 29.3%) than GPP alone (Figure S6A). Furthermore, flares of patients were obtained by follow-up for those admitted

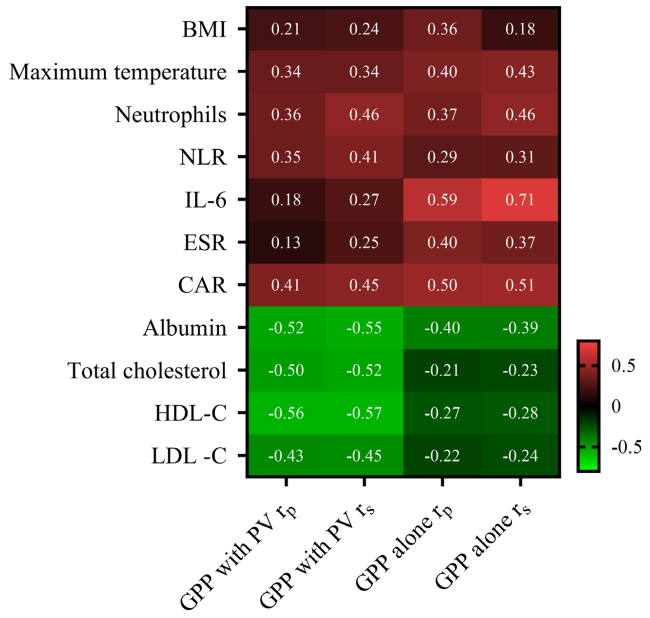

FIGURE 1 Relationship between GPPASI and laboratory tests in GPP alone and GPP with PV. The brightness and corresponding correlation coefficient (*r*) represent the strength of association. r_p, Pearson correlation coefficient; r_s, Spearman correlation coefficient. The *p*-value and the number of cases for each analysis are shown in the Table S1. GPP patients with a diagnosis of PV or had typical skin lesions of PV more than 6 months before GPP diagnosis were classified as GPP with PV, otherwise was GPP alone. BMI, body mass index; CAR, C-reactive protein-to-albumin ratio; ESR, erythrocyte sedimentation rate; GPP, generalized pustular psoriasis; GPPASI, generalized pustular psoriasis area and severity index; HDL-C, high density lipoprotein cholesterol; IL-6, interleukin-6; LDL-C, low density lipoprotein cholesterol; PV, psoriasis vulgaris; NLR, neutrophil lymphocyte ratio.

after January 2017 and before January 2022 (80 cases). 52.9% (27 cases) of GPP with PV and 62.1% (18 cases) of GPP alone patients experienced flares after initial admission (Figure S7A).

In addition to the analysis of the general clinical features, we also assessed the correlation between GPPASI and laboratory tests. In GPP patients with PV, HDL-C (high density lipoprotein cholesterol) ($r_p = -0.56$, $p < 0.001$) and albumin ($r_p = -0.52$, $p < 0.001$) were negatively correlated with GPPASI, whereas in GPP alone, IL-6 ($r_p = 0.59$, $p = 0.003$) and C-reactive protein-to-albumin ratio (CAR) ($r_p = 0.50$, $p < 0.001$) levels were positively correlated with GPPASI (Figure 1 and Table S1). The above data suggest that GPP patients with or without PV are highly heterogeneous and GPP alone patients exhibit severe disease phenotype.

3.3 | Phenotypic heterogeneity of GPP in different age groups

Apart from focusing on the history of PV, we also paid attention to the clinical phenotype of GPP in special populations, juvenile and senior patients, and observed significant heterogeneity between them. The mean age was 9.5, 35.4 and 62.6 years for juvenile, middle-aged and senior groups. Most patients were male in juvenile group (64.2%), while mainly female in middle-aged (55.9%) and senior (52.5%) (Table 3). The PsV(+)/PsV(−) ratio was higher in middle-aged (1.84) and senior patients (2.33) than that in juvenile patients (0.88). Juvenile patients had a higher temperature (38.1°C vs. 37.6°C, $p = 0.002$) than middle-aged (Table 3). Senior patients showed a lower proportion of family history of psoriasis (7.5% vs. 21.1%, $p = 0.043$) and GPPASI (21.5 vs. 27.1, $p = 0.010$) compared with middle-aged (Table 3). Besides skin infections (10.8% vs. 6.6%, $p = 0.162$), the incidence of most comorbidities was lower in the juvenile than middle-aged group, including anaemia (7.5% vs. 16.0%, $p = 0.023$), hyperlipidemia (3.3% vs. 13.3%, $p = 0.003$) and psoriatic arthritis (0.8% vs. 8.6%, $p = 0.043$). As a common disease of senior population,[23] the incidence of hypertension was higher in senior patients than middle-aged (15.0% vs. 3.9%, $p = 0.012$) (Table 3). The variation in laboratory tests was confined between juvenile and middle-aged patients: NLR (3.83 vs. 6.88, $p < 0.001$), and PLR scores (139 vs. 190, $p < 0.001$) were lower in the juvenile group (Table 3).

As for triggering factors, most triggers except upper respiratory tract infection (25.8% vs. 21.8%) were more common in middle-aged GPP, whereas all triggers were fewer in the senior group compared to juvenile and middle-aged together (Figure S2A). In addition, the lesions of juvenile were likely to occur in face or neck (66.7%), scalp (30.6%) and perineum (36.1%) (Figure S3B). The differences in albumin and lipids were not significant (Figure S4B), and the level of inflammatory markers was lower in juvenile than middle-aged (Figure S5B). In terms of treatment options, cyclosporine (42.5%) in juvenile and retinoids (48.0% and 69.2%) in middle-aged and senior groups were the most frequently administered with efficiency (Figure S6B). In addition, 64.3% (18 cases) of juvenile, 51.2% (22 cases) of middle-aged and 55.5% (5 cases) of senior patients experienced flares after initial admission (Figure S7B).

Finally, we found that markers of GPP severity were not completely consistent between age groups. In juvenile group, albumin ($r_p = -0.53$, $p < 0.001$) and IL-6 ($r_p = 0.52$, $p = 0.023$) were most strongly correlated with GPPASI, whereas in middle-aged group, this indicator is CAR ($r_p = 0.49$, $p < 0.001$) and albumin ($r_p = -0.47$, $p < 0.001$) (Figure 2 and Table S2). For senior patients, LDL-C (low density lipoprotein cholesterol) ($r_p = -0.58$, $p = 0.002$) and total cholesterol ($r_p = -0.49$, $p = 0.012$) were significant correlated with GPPASI (Figure 2 and Table S2). In conclusion, obvious phenotypic variation was observed between juvenile and middle-aged patients and middle-aged present a severer phenotype than juvenile. Consequently, clinicians should provide personalized care based on their clinical characteristics.

4 | DISCUSSION

Our study analysed the heterogeneity of GPP in a large cohort, including 416 GPP patients and a matched group of 416 PV patients. The GPP diagnoses in our study were strongly supported by

TABLE 3 Comparison of demographic and clinical characteristics of GPP in different age groups.

			Juvenile ($n=120$)			Senior ($n=40$)		
	Middle-aged ($n=256$)				p-value[h]			p-value[h]
Age, year	35.4	10.0	9.5	4.8	<0.001	62.6	7.2	<0.001
Male sex	113	44.1%	77	64.2%	<0.001	19	47.5%	0.691
History of PV	166	64.8%	56	46.7%	<0.001	28	70.0%	0.523
PV(+)/PV(−)	1.88		0.88			2.33		
Length of hospitalization, day	11.9	5.5	11.3	4.6	0.302	11.8	5.9	0.870
BMI, kg/m^2[a]	23.1	4.5	19.0	4.8	<0.001	23.9	3.9	0.591
Ever or currently smoking	59	23.0	1	0.8	<0.001	12	30.0	0.338
Ever or currently consuming alcohol	27	10.5	0	0	<0.001	8	20.0	0.145
Family history of psoriasis	54	21.1%	20	16.7%	0.314	3	7.5%	0.043
Maximum temperature, °C[b]	37.6	1.1	38.1	1.3	0.001	37.6	1.1	0.847
GPPASI[c]	27.1	12.8	26.7	12.3	0.814	21.5	9.4	0.010
Comorbidities								
Anaemia	41	16.0%	9	7.5%	0.023	8	20.0%	0.528
Hyperlipidemia	34	13.3%	4	3.3%	0.003	6	15.0%	0.767
Skin infections	17	6.6%	13	10.8%	0.162	2	5.0%	1.000
Psoriatic arthritis	22	8.6%	1	0.8%	0.003	3	7.5%	1.000
Diabetes mellitus	15	5.9%	0	0.0%	0.007	5	12.5%	0.165
Hypertension	10	3.9%	1	0.8%	0.185	6	15.0%	0.012
Acral pustular psoriasis	12	4.7%	1	0.8%	0.070	1	2.5%	1.000
Laboratory tests								
Neutrophils, 10^9/L[d]	9.26	7.57	8.41	4.86	0.261	8.03	4.68	0.331
Lymphocytes, 10^9/L[e]	1.58	0.70	2.72	1.56	<0.001	1.47	0.81	0.392
NLR[e]	6.88	5.65	3.83	2.70	<0.001	6.28	4.12	0.549
Platelets, 10^9/L[f]	262	90	315	103	<0.001	266	109	0.802
PLR[g]	190	93	139	67	<0.001	203	113	0.469

Note: Data are presented as mean (SD) or *n* (%). Middle-aged: 19–54 years old; juvenile: 0–18 years old; senior: ≥55 years old.

Abbreviations: Acral pustular psoriasis, palmoplantar pustulosis or acrodermatitis continua of hallopeau; GPP, generalized pustular psoriasis; GPPASI, generalized pustular psoriasis area and severity index; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; PV, psoriasis vulgaris.

[a]Data were available in 42, 89, 12 and cases in juvenile, middle-aged and senior GPP group.

[b]Data were available in 114, 249, 39 and cases in juvenile, middle-aged and senior GPP group.

[c]Data were available in 72, 146, 27 and cases in juvenile, middle-aged and senior GPP group.

[d]Data were available in 120, 254, 38 and cases in juvenile, middle-aged and senior GPP group.

[e]Data were available in 120, 254, 35 and cases in juvenile, middle-aged and senior GPP group.

[f]Data were available in 119, 254, 40 and cases in juvenile, middle-aged and senior GPP group.

[g]Data were available in 119, 254, 35 and cases in juvenile, middle-aged and senior GPP group.

[h]*p* value compared with middle-aged group.

pathological or clinical evidence in 79.3% of cases, largely avoiding the selection bias of retrospective cohort. Although it is assumed to be heterogeneous,[3,14] the clinical manifestation of heterogeneity has not been reported in large cohorts due to the rarity of GPP. Therefore, we conducted this study and observed that GPP alone and middle-aged GPP exhibit severe phenotypes. In addition, we found significant differences in markers of severity among subgroups. The above results indicate the heterogeneity of GPP.

GPP is distinct from PV and represents a severer disease with activated autoinflammatory response. Historically, GPP has often been described as a rare subtype of PV; however, accumulating evidence indicates that GPP is distinct from PV and associated with inpatient burden and systemic comorbidities,[3,24] consistent with our observations, GPP exhibited longer hospital stays and higher incidence of comorbidities than PV. As a biomarker conjugates innate and adaptive immune system,[25] significantly elevated NLR in GPP patients compared to PV may be a manifestation of pathogenesis distinction: autoinflammation involving the innate immune system and neutrophils is the predominant driver of GPP, whereas autoimmunity motivated by the adaptive immune system and lymphocytes is linked

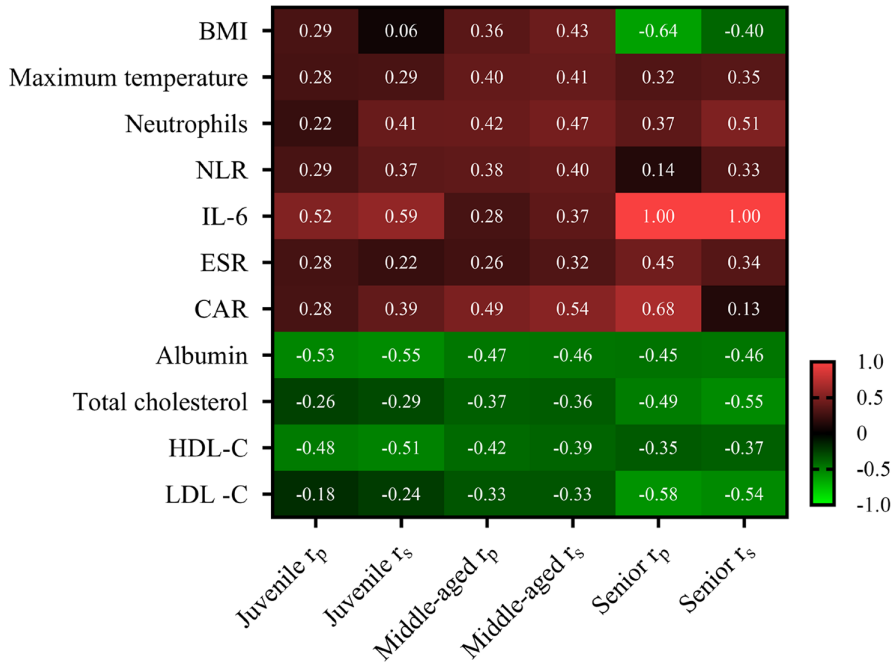

FIGURE 2 Relationship between GPPASI and laboratory tests in GPP in different age groups. The brightness and corresponding correlation coefficient (*r*) represent the strength of association. r_p, Pearson correlation coefficient; r_s, Spearman correlation coefficient. The *p*-value and the number of cases for each analysis are shown in the Table S2. For the senior group, *r*-values for BMI and CAR were large but *p*-values were greater than 0.05; only two patients had IL-6 values that could be included in the analysis. Middle-aged: 19–54 years old; juvenile: 0–18 years old; senior: older than 54 years old. BMI, body mass index; CAR, C-reactive protein-to-albumin ratio; ESR, erythrocyte sedimentation rate; GPP, generalized pustular psoriasis; GPPASI, generalized pustular psoriasis area and severity index; HDL-C, high density lipoprotein cholesterol; IL-6, interleukin-6; LDL-C, low density lipoprotein cholesterol; NLR, neutrophil lymphocyte ratio; PV, psoriasis vulgaris.

to PV pathogenesis.[26] In comparison of comorbidities, we observed the incidence of anaemia was elevated in GPP patients. Because of the extensive systemic inflammation of GPP and the low incidences of severe comorbidities in our cohort, it is reasonable to speculate that this is anaemia of inflammation caused by prolonged immune activation.[27,28] In addition, as inflammation and severity markers of psoriasis,[21,22] the differences of NLR and PLR support the conclusion that GPP represents a severer disease.

GPP is a clinically heterogeneous disease, as reflected in patients with or without PV. In our study, we found that GPP patients with PV were older at onset than GPP alone which aligns with previous research.[29] Besides, GPP alone seems to be a more severe subtype, as indicated by higher temperature, comorbidities incidence and inflammatory markers. The incidence of skin infections was significant higher in GPP alone than GPP with PV. Since most GPP patients are febrile, so determining the cause of fever is important for subsequent treatment: with or without infection. Considering the immunosuppressive effect of cyclosporine, the first-line treatment for GPP[30] and the high incidence of skin infections in GPP alone patients, we should evaluate the possibility of infection before treatment selection.

The heterogeneity of GPP is also represented by the clinical variations in different age. Patients in our study were younger, compared to studies conducted in other regions,[31,32] which may attribute to the profile of population age in different regions and we only described patients' clinical features at first admission. The higher prevalence of positive PV history in GPP patients across different age groups may be partly due to genetic mutations, as evidenced by a previous study linking IL36RN gene mutations to early-onset GPP without PV history.[29] The low comorbidity incidence in juvenile patients represents a lower disease burden compared to middle-aged. However, the lesions of juvenile GPP were likely to occur in specific sites such as face or neck and perineum, which may increase their psychological burden. Combined with the psychological vulnerability of juvenile, additional psychological support is needed when treating juvenile GPP.[33] Concerning the triggers, we observed there were often no clear triggers for exacerbation in senior GPP patients, which imposed challenges in disease prevention and management. For differences in laboratory tests, as indicators of inflammation severity in psoriasis,[21,22] NLR and PLR combined with IL-6, hs-CRP and ESR, all of them were lower in the juvenile than middle-aged, which may indicate lower inflammation in paediatric GPP. However, due to high lymphocyte counts in juvenile group, no significant difference in GPPASI and missing data on inflammation-related indicators, this conclusion requires further confirmation. In our cohort, a higher proportion of juvenile patients present without PV history. Due to the potential side effects of retinoids on children, such as growth disorders like early epiphyseal closure and teratogenicity, we tend to avoid their use in this population and instead opt for cyclosporine.[12,13] This could explain why GPP alone patients have a higher

rate of using cyclosporine and a lower rate of using retinoids compared to those with PV. Overall, clinicians should offer individualized care for juvenile and senior patients based on their clinical features. The correlation of other inflammatory markers with GPP severity warrants in depth investigation for developing managing or predicting methods.

Although genetic information is not available in our study, the genetics of GPP are also heterogeneous. Only about 40% of GPP patients have mutations in the *IL36RN*[34] or *CARD14*[16] genes, and other patients have no known causative gene. Genotype–phenotype associations were also reported in partial studies, such as the association of *IL36RN* mutations with early onset and severity in some studies,[35,36] while others have not found this association.[37,38] In our cohort, we observed a weaker correlation between GPP and environmental factors than PV in our cohort, including smoking and alcohol consumption.

Apart from the clinical phenotype, GPP severity indicators were also heterogeneous across subgroups. It has been confirmed that HDL-C and LDL-C are correlated with psoriasis area and severity index (PASI) in PV,[39,40] and our study generalizes this conclusion in GPP: for GPP with PV and juvenile GPP, HDL-C is significantly negatively correlated with GPPASI; for senior GPP, the most reliable indicator is LDL-C. IL-6 is linked to vascular inflammation and can induce the expression of neutrophils IL-36 receptor (IL-36R),[35,41] which synergizes with IL-36 to promote the inflammatory responses and neutrophil influx.[1] Correspondingly, we have observed a strong correlation between IL-6 and disease severity in GPP alone and juvenile GPP. Our study found that CAR, a known marker of inflammation in psoriasis,[42] is correlated with GPPASI in GPP patients, with the strongest correlation seen in GPP alone and middle-aged GPP. Overall, these indicators can be used to assess the severity of GPP in clinical practice. Although we have established a database of standardized and high-definition images of patients' lesions, there is still a possibility of missing or inaccurate data due to the retrospective nature of the GPPASI assessment.

Although GPP is characterized by skin pustules, its widespread systemic impact should not be overlooked due to impairment of patients' quality of life and healthcare burden.[3] Our study reports the clinical characteristics of GPP in a large cohort and indicates that GPP with different PV background or ages is heterogeneous, especially in comorbidities and inflammation-related indicators. Prospective phenotype–genotype and multi-omics studies are warranted to better define the respective mechanisms in each subgroup. Our research will facilitate future effective assessment, stratification and management of the disease.

AUTHOR CONTRIBUTIONS

Zhongrui Xu: data acquisition, data analysis, statistical analysis and manuscript preparation; **Yanhua Liu**, **Huanhuan Qu**, **Yaxing Bai**, **Jingyi Ma** and **Junfeng Hao**: data acquisition and data analysis; **Chen Yu** and **Erle Dang**: literature search and manuscript editing; **Gang Wang** and **Shuai Shao**: concept, design, manuscript editing and manuscript review.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that no conflict of interest exists. All authors have read and approved the submitted manuscript, and each author believes that the manuscript represents honest work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1. Supporting information

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