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ORIGINAL ARTICLE

Generalized pustular psoriasis: A nationwide population-based study using the National Health Data System in France

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Abstract

Background: GPP is a rare, chronic, neutrophilic skin disease, with limited real-world data characterizing patients with flares and the impact of flares on disease progression and morbidity.

Objective: Describe the clinical characteristics of patients with GPP, comorbidities, disease epidemiology and frequency and severity of flares, and compare patients with GPP with a matched severe psoriasis population.

Methods: In this population-based real-world cohort study an algorithm was developed to identify patients with GPP flares. Three cohorts were identified using the Système National des Données de Santé (SNDS) database covering almost the entire French population; a prevalent cohort (2010–2018), an incident cohort (2012–2015). A severe psoriasis cohort was compared with the GPP incident cohort using propensity score matching.

Results: The prevalent and incident cohorts comprised 4195 and 1842 patients, respectively. In both cohorts, mean age was 58 years; 53% were male. Comorbidities were significantly more common in the incident cohort versus matched psoriasis cohort, respectively, including hypertension (44% vs. 26%), ischaemic heart disease (26% vs. 18%) and hyperlipidaemia (25% vs. 15%). In the incident cohort, the flare rate was 0.1 flares/person-year and 0.4 flares/person-year among the 569 out of 1842 patients hospitalized with flares. These patients had a mean (±SD) stay of 11.6 ± 10.4 days; 25% were admitted to the intensive care unit. In 2017, the cumulative incidence and cumulative GPP age–sex standardized prevalence were 7.1 and 45.2 per million, respectively.

Conclusions: Patients with GPP had a distinct comorbidity profile compared to patients with severe psoriasis, and GPP flares were associated with long hospitalizations.

INTRODUCTION

Generalized pustular psoriasis (GPP), a rare autoinflammatory disease, primarily involves the skin, and can occur with or without systemic inflammation and be associated with or without plaque psoriasis.[1,2] Disease course varies greatly between patients, with relapsing, subacute and constantly flaring patterns reported.[2–4] Patients with GPP experience frequent flares that can impair their quality of life during the acute and post-flare periods.[5] GPP flares may involve extracutaneous organs and potentially lead to life-threatening complications, including sepsis and multisystem organ failure.[6,7] Patients experiencing a GPP flare make more outpatient visits than those with plaque psoriasis, and

are more likely to require inpatient hospitalization.[7] The European Rare and Severe Psoriasis Expert Network and the Japanese Dermatological Association have published guidelines on GPP diagnosis, but no global consensus exists on what constitutes a flare.[2,5,8] This lack of consensus limits the availability of real-world data characterizing patients with flares and the impact of flares on disease progression and morbidity, presenting a challenge to identifying GPP flares in administrative claims databases.

Some international studies aimed to evaluate GPP epidemiology and patient characteristics, including incidence, prevalence, sex, triggering/worsening factors, patterns of relapse and patient prognosis.[6,9–15] However, only two of these studies, which relied on limited case series, included a description of comorbidities in patients with GPP.[6,12] In addition, none of these studies allowed for characterization of GPP flares—the main driver of disease burden. Therefore, uncertainty remains regarding the evolution of GPP and disease severity, and its comorbidity burden in real life at a large population level.

This retrospective, longitudinal, population-based study aimed to analyse real-world data from the Système National des Données de Santé (SNDS)[16–20] to characterize the demographics and comorbidities of patients with GPP, describe GPP flare frequency and severity, and calculate prevalence and cumulative incidence of GPP.

METHODS

Data source

The SNDS database covers almost the entire French population (estimated coverage: 98%, representing ~66 million people).[20–22]

Study design and population

This population-based study used SNDS data to investigate two cohorts (prevalent and incident) of patients with GPP. The prevalent cohort comprised patients with ≥1 GPP-related hospital admission or long-term history of GPP. All patients with ≥1 inpatient claim with a primary, related or associated diagnosis of GPP (International Classification of Diseases, Tenth Revision (ICD-10) code L40.1) or GPP informed as a diagnosis in the chronic disease list (ALD) between 1 January 2010 and 31 December 2018 (index event) were included. This cohort was created to allow an estimated number of living patients with GPP in France in 2018. The incident cohort was analysed longitudinally and included patients with a GPP diagnosis between 1 January 2012 and 31 December 2015, and no GPP claim before the index date, ensuring a minimum of 2 years and a maximum of 5 years prior to their index date (from 2010 to year $N-1$). Patients in the incident cohort were followed from the index event date until death or 31 December 2018, allowing a minimum follow-up of 3 years and a maximum of 7 years (Figure S1). This cohort was used to estimate the number of new GPP cases in France in 2017 and enabled the identification and characterization of GPP flares longitudinally. Only inpatient and ALD claims contain ICD-10 codes; therefore, to be identified, all patients in the study had ≥1 inpatient event or were registered in the ALD.

Data reporting complies with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and Reporting of studies Conducted using Observational Routinely collected Data (RECORD) recommendations (checklists available as Data S1).

Severe psoriasis cohort

Patients with any type of severe psoriasis, including plaque psoriasis (5.2%; 95 patients), excluding any kind of GPP diagnosis, were identified via a two-step process. Patients with a minimum enrolment of 1 year after the index date (except in case of death) were initially identified as having psoriasis by the prescription of at least two topical vitamin D derivatives during the index period, excluding patients with specific claims for a GPP or PPP diagnosis during the index period (see Table S1 for list of medications). Patients were excluded from the severe psoriasis cohort if they had a prescription for at least one of these medications during the pre-index period. Patients in the GPP incident cohort were matched to the severe psoriasis cohort in a 1:1 ratio using propensity score matching. This cohort was compared with the GPP incident cohort regarding patient characteristics, comorbidity burden and occurrence of events of interest.

Characterization of GPP flares

In the incident cohort, patients with GPP flares leading to hospitalization were identified from 2012 to 2015. To identify GPP flares, an algorithm was developed based on data on diagnosis and hospital stay duration within SNDS. The algorithm required an inpatient claim with a primary diagnosis of GPP (ICD-10 code L40.1) in the acute hospital setting (known in France as médecine, chirurgie et obstétrique) and ≥3 days' hospitalization. The criterion of ≥3 days' hospitalization was included based on dermatologist advice that hospitalizations for flares are usually at least this long[23,24]; it ensures that hospitalizations for reasons such as diagnostic investigation or drug infusion are not misclassified as a GPP flare. Time to first flare was calculated from the index date until the first flare event; if the index date met the definition of a flare, then the two dates coincided.

Primary outcomes

Primary study outcomes were (1) description of GPP patient demographic characteristics and comorbidities, (2)

flare characterization and (3) epidemiology as represented by prevalence and cumulative incidence. Patient demographics were described for the prevalent and incident cohorts at index event (the date of the first claim observed for the disease diagnosis): age, age group, sex and beneficiaries of aide médicale de l'État (AME). Details of comorbidities, Charlson comorbidity index (CCI) scores and events of interest were available only for the incident cohort. Selected comorbidities (Data S1) and the 20 most common comorbidities were described from index date to end of follow-up (except in case of death). Events of interest possibly related to GPP occurring during follow-up were retrieved using ICD-10 codes. The absolute number of patients who met the GPP case definition annually between 2010 and2018 was reported. As GPP is a chronic disease with primarily intermittent flares and not all patients will require inpatient care in a given year, the annual crude GPP prevalence was calculated from the number of cases identified from previous years minus patients who had died before the given year. Age–sex standardized estimated prevalence

TABLE 1 Patient baseline demographics from each study cohort.

	GPP prevalent cohort[a] (*n* = 4195)	GPP incident cohort[b] (*n* = 1842)	Severe psoriasis cohort[c] (*n* = 1842)	Absolute difference in % [95% CI] (GPP incident cohort vs. severe psoriasis cohort)[d]
Age				
Mean ± SD	57.6 ± 19.3	57.8 ± 19.5	57.8 ± 19.5	
Median (min, max)	59 (0, 103)	59 (0, 103)	59 (0, 103)	
Age group, *n* (%)				
0–12 years	93 (2.2)	42 (2.3)	42 (2.3)	
13–25 years	138 (3.3)	62 (3.4)	62 (3.4)	
26–60 years	1958 (46.7)	871 (47.3)	871 (47.3)	
≥61 years	2006 (47.8)	867 (47.1)	867 (47.1)	
Sex, *n* (%)				
Male	2242 (53.4)	981 (53.3)	981 (53.3)	
AME				
Yes	33 (0.8)	17 (0.9)	17 (0.9)	
CCI score				
Mean ± SD	–	0.7 ± 0.9	0.7 ± 0.9	
Median (min, max)	–	1 (0, 9)	1 (0, 1.1)	
Comorbidities, *n* (%)				
Hypertension	–	801 (43.5)	484 (26.3)	17.2 (14.2–20.2)
Ischaemic heart disease	–	472 (25.6)	333 (18.1)	7.5 (4.9–10.2)
Hyperlipidaemia	–	456 (24.8)	282 (15.3)	9.4 (6.9–12.0)
Congestive heart failure	–	443 (24.0)	156 (8.5)	15.6 (13.3–17.9)
Depression	–	366 (19.9)	123 (6.7)	13.2 (11.0–15.3)
Type 1 diabetes		251 (13.6)	95 (5.2)	8.5 (6.6–10.3)
Type 2 diabetes		120 (6.5)	110 (6.0)	0.5 (−1.0–2.1)
Psoriatic arthritis	–	79 (4.3)	50 (2.7)	1.6 (0.4–2.8)
Obesity	–	4 (0.2)	2 (0.1)	0.1 (−0.2–0.4)

Note: Empty cells indicate parameters for which data were not collected.

Abbreviations: AME, aide médicale de l'État (state medical aid); CCI, Charlson comorbidity index; CI, confidence interval; GPP, generalized pustular psoriasis; SD, standard deviation.

[a]Patients with ≥1 GPP-related hospital admission or long-term history of GPP from 2010 to 2018.

[b]Patients diagnosed with GPP between 1 January 2012 and 31 December 2015 with a minimum follow-up of 2 years post their index date and a maximum of 5 years prior to their index date. Patients in the incident cohort were followed from the index event date until death or 31 December 2018 with a minimum follow-up of 3 years and a maximum of 7 years. The mean (SD) duration of the follow-up period was 56 ± 17 months.

[c]Patients with any type of severe psoriasis (including plaque psoriasis), excluding any kind of GPP diagnosis, were defined by at least two prescriptions of topical vitamin D derivatives and at least one prescription for systemic medication for psoriasis between 2012 and 2015.

[d]Patients in the GPP incident cohort were matched to the severe psoriasis cohort in a 1:1 ratio, using propensity score matching for statistical comparison.

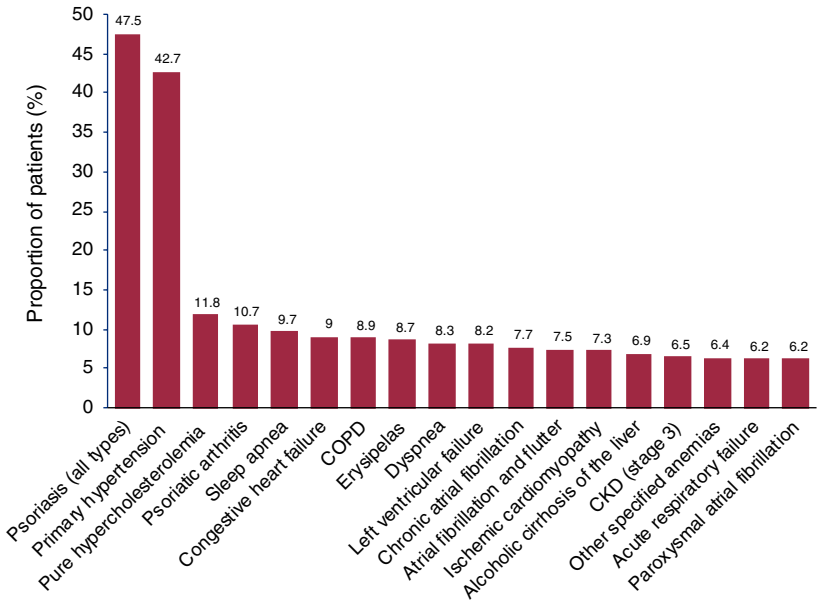

FIGURE 1 Frequency of the most common comorbidities[a] found during follow-up in patients with GPP from the GPP incident cohort[b]. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GPP, generalized pustular psoriasis. 'Psoriasis', 'psoriasis, unspecified' and 'other psoriasis' are pooled under 'psoriasis (all types)'. [a]All primary, linked and associated diagnoses that were coded in the hospital were examined to determine comorbidities. Therefore, comorbidities could also include reasons for discharge (primary or secondary). [b]Patients diagnosed with GPP between 1 January 2012 and 31 December 2015 with a minimum follow-up of 2 years post their index date and a maximum of 5 years prior to their index date ($n = 1842$). Patients in the incident cohort were followed from the index event date until death or 31 December 2018 with a minimum follow-up of 3 years and a maximum of 7 years. The mean (SD) duration of the follow-up period was 56 ± 17 months.

were calculated using the age and sex distribution of the European population as a reference,[25] to allow comparison with other European countries. GPP cumulative incidence was estimated yearly based on the number of patients with GPP diagnosed in France between 2012 and 2015 with no recorded GPP diagnosis for ≥2 years, and up to 5 years, prior to their index date (from 2010 to year $N-1$). Estimated GPP cumulative incidence was also represented by age group and sex. Data from the National Institute of Statistics and Economic Studies were used for the French population.[26]

Statistical analysis

Descriptive analyses were conducted for baseline and outcome measures of both cohorts. For continuous variables, the mean (standard deviation [SD]), median, interquartile range, minimum and maximum values were reported. Differences between matched groups were assessed using Student's *t*-tests and chi-squared tests. Categorical variables were described by the absolute number and proportion of patients in each category. Propensity score matching between the GPP incident and severe psoriasis cohorts was based on the following variables: age group, sex, region of residence and CCI score. SAS software Enterprise Guide (v7.15) was used for statistical analyses, with SAS 9.3 used to import/export data and tables.

RESULTS

Patient demographics

In total, 4195 patients were identified; this constituted the prevalent cohort (Figure S2). The incident cohort comprised 1842 patients with GPP, after excluding patients with any inpatient claim for GPP and patients with missing demographic data. Both cohorts had a mean age of 58 years and 53% were male (Table 1). In the incident cohort, 21.9% of patients with GPP also had plaque psoriasis.

Patient comorbidities

Baseline comorbidities of interest were significantly more common in the GPP incident cohort versus the matched severe psoriasis cohort: respectively, hypertension (44% vs. 26%), ischaemic heart disease (26% vs. 18%), hyperlipidaemia (25% vs. 15%) and congestive heart failure (24% vs. 9%). Rates of Type 2 diabetes and obesity were similar between the GPP incident and severe psoriasis cohorts (Table 1). During follow-up, the most frequently reported comorbidities in the GPP incident cohort were psoriasis (all types; 47.5%), hypertension (42.7%), hypercholesterolaemia (11.8%) and psoriatic arthritis (10.7%) (Figure 1).

The occurrence of pre-selected events of interest during follow-up, including pneumonia, shock and sepsis, were

significantly higher in the GPP incident patients compared with the matched severe psoriasis cohort (Table S2). A comparison of treatment patterns during the follow-up period indicate a higher rate of immunosuppressant usage in the severe psoriasis cohort compared with the incident cohort (Table S3).

Characteristics of patients hospitalized with GPP flares

Among the 1842 patients in the GPP incident cohort, 569 with GPP flares leading to hospitalization for ≥3 days (30.9%) were identified, with a median of 1 flare and a mean of 1.4 flares/patient during the study period (Table 2). Annual follow-up data for number of patients with flare per year of follow-up, and total number of flares per year of follow-up are also presented in Table 2. The mean (SD) duration of the follow-up period was 56 ± 17 months. In total, 811 GPP flares resulted in hospitalization, corresponding to 0.4 flares/person-year in 569 patients. The flare rate for the entire incident cohort was 0.1 flares/person-year. For patients hospitalized with flares, the mean ± SD time to first flare was 35.7 ± 185.2 days, with an average hospitalization stay of 11.6 days (Table 3). A quarter of these patients (142 out of 569) were admitted to the ICU for 17.7 ± 24.1 days, not including additional days in the regular unit after the ICU. Most flares occurred within the first year of follow-up. Flares continued to occur throughout the follow-up period, but decreased over time.

Prevalence and incidence of GPP

Annual GPP cases identified between 2010 and 2018 are shown in Figure 2a and Table S4. Approximately, 570 patients with a GPP diagnosis were identified each year. Prevalence increased with age and were higher in males than females (Figure 2b,c). In 2017, the cumulative GPP prevalence was 45.2 per million population and estimated at 48.2 per million population after direct standardization using the age and sex distribution of the European population. The 9-year cumulative prevalence from 2010 to 2018 (period prevalence divided by mid-interval population from 2014 [66.1 per million population]) was 63.4 per million population. New cases of GPP identified each year from 2012 to 2015 were stable (Figure 2d and Table S5). Cumulative incidence increased with age and were higher in males than females (Figure S3).

DISCUSSION

This population-based study was conducted using a nationwide quasi-exhaustive database from the French health insurance system, and characterized patients who were identified as receiving a GPP diagnosis between 2010 and 2018. To our knowledge, this is the first study to develop an

TABLE 2 Characterization of patients hospitalized with GPP flares from the GPP incident cohort.[a]

	Patients hospitalized with GPP flares (*n* = 569)
Age	
Mean ± SD	57.9 ± 19.6
Median (min, max)	59 (0, 96)
Age group, *n* (%)	
0–12 years	13 (2.3)
13–25 years	22 (3.9)
26–60 years	271 (47.6)
≥61 years	263 (46.2)
Sex, *n* (%)	
Female	301 (52.9)
Number of patients with flare per year of follow-up (*n*%)	
1st year	554 (97.4)
2nd year	26 (4.6)
3rd year	19 (3.3)
4th year	18 (3.2)
5th year	11 (1.9)
6th year	6 (1.1)
7th year	2 (0.4)
Total number of flares per year of follow-up (*n*%)	
Overall	811
1st year	678 (83.6)
2nd year	50 (6.2)
3rd year	28 (3.5)
4th year	29 (3.6)
5th year	13 (1.6)
6th year	8 (1.0)
7th year	5 (0.6)
Number of flares per patient during the follow-up period	
Mean ± SD	1.4 + 1.2
Median (min, max)	1 (1, 12)
Number of flares during the follow-up period, *n* (%)	
1	452 (79.4)
2	70 (12.3)
3	22 (3.9)
4	8 (1.4)
≥5	17 (3.0)
Number of flares per person-year	
Number of flares	811
Number of flares per person-year	0.4
Time between study inclusion and first flare (days)	
Mean ± SD	35.7 ± 185.2
Median (min, max)	0 (0, 1928)

Abbreviations: GPP, generalized pustular psoriasis; SD, standard deviation.

[a]Patients diagnosed with GPP between 1 January 2012 and 31 December 2015 with a minimum follow-up of 2 years post their index date and a maximum of 5 years prior to their index date (*n* = 1842). Patients in the incident cohort were followed from the index event date until death or 31 December 2018, with a minimum follow-up of 3 years and a maximum of 7 years. The mean (SD) duration of the follow-up period was 56 ± 17 months.

TABLE 3 Hospitalizations and admissions to the ICU in patients with GPP flares from the GPP incident cohort.[a]

	Patients hospitalized with GPP flares (*n* = 569)
Duration of stay, days	
Mean ± SD	11.6 ± 10.4
Median (min, max)	8 (3, 99)
Duration of stay after first flare, days	
Mean ± SD	11.1 ± 10.2
Median (min, max)	8 (3, 99)
Duration of stay for second flare, days	
Mean ± SD	13.5 ± 12.9
Median (min, max)	8 (3, 57)
≥1 GP visit after the first flare, *n* (%)	556 (97.7)
≥1 dermatologist visit after the first flare, *n* (%)	276 (48.5)
Admission to the ICU, *n* (%)	142 (25.0)
Duration of stay in the ICU (days)	
Mean ± SD	19.7 ± 21.5
Median (min, max)	13 (3, 176)
Number of visits to the ICU	N_{icu} = 244[b]
Intensive care in a neurovascular unit, n_{icu} (%)	16 (6.6)
Intensive care in a non-neurovascular unit, n_{icu} (%)	117 (48.0)
Resuscitation in a non-paediatric unit, n_{icu} (%)	110 (45.1)
Resuscitation in a paediatric unit, n_{icu} (%)	1 (0.4)
Total number of flares	N_f = 811[c]
Number of flares in patients with available GHM codes, n_f (%)	783 (96.5)
Severity level of skin disease[d], n_f (%)	
1	223 (27.5)
2	240 (29.6)
3	256 (31.6)
4	64 (7.9)
Missing data	28 (3.5)

Abbreviations: GHM, groupe homogène de malades (French healthcare system disease-related group); GP, general practitioner; GPP, generalized pustular psoriasis; ICU, intensive care unit; SD, standard deviation.

[a]Patients diagnosed with GPP between 1 January 2012 and 31 December 2015 with a minimum follow-up of 2 years post their index date and a maximum of 5 years prior to their index date (*n* = 1842). Patients in the incident cohort were followed from the index event date until death or 31 December 2018 with a minimum follow-up of 3 years and a maximum of 7 years. The mean (SD) duration of the follow-up period was 56 ± 17 months.

[b]The number of intensive care unit (ICU) visits was calculated across all visits, including the index hospital stay and potential subsequent hospitalizations. N_{icu} and n_{icu} describe the numbers of visits to the ICU.

[c]N_f and n_f describe numbers of flares.

[d]Severity level of skin disease during hospitalization was calculated according GHM codes, from the least severe (Level 1) to the most severe (Level 4).

algorithm to identify GPP flares in an administrative claims database, providing comprehensive coverage of a large population and the first study to use SNDS data, a health insurance administrative claims database (covering virtually the whole population from a large European country) to focus on GPP.

The most common comorbidities of interest at baseline in the GPP cohort were indicative of chronic disease, including hypertension, ischaemic heart disease, hyperlipidaemia and congestive heart failure. Obesity, which has been reported in patients with GPP,[5] and was prevalent in a population of patients predominantly with psoriasis within SNDS (16%),[18] appeared uncommon here (<1%); potentially due to under-coding and therefore could have been under-reported.[25] GPP was characterized by a higher comorbidity burden compared with severe psoriasis, at baseline and during the follow-up period. Similarly, psoriatic arthritis has previously been reported in a higher proportion of patients with GPP (12%–35%),[27,28] compared to 4.3% (79 out of 1842) of patients from the GPP incidence cohort here. Such coding is dependent on individual rheumatologist's discretion and perhaps highlights a need for clearer guidelines on how to define arthritis in the context of GPP.

The increased prevalence of pre-selected comorbidities, including pneumonia, shock and sepsis, observed in the GPP incident cohort during follow-up are indicative of a higher rate of infections. While this is unlikely to be caused by immunosuppressant treatment usage, with lower rates observed in the GPP incident cohort compared with the severe psoriasis cohort, this possibility cannot be fully excluded as the effects of treatments such as systemic corticosteroids may differ between patients with GPP and psoriasis. This apparent increase in sepsis in the GPP incident cohort might have potentially resulted from miscoding; very severe GPP flares leading to ICU care due to cytokine-release syndrome-related shock may be interpreted as sepsis due to the presence of skin pustules.[29]

Hospital admissions were common in patients experiencing flares, with a relatively long median duration of stay of 8 days in hospital (mean: 11.0, SD: 10.2), and 12 days in the ICU, compared with an average duration of stay of around 5.5 days in acute hospital settings in France.[30] These findings are in accordance with previous studies demonstrating that GPP is a life-threatening disease requiring hospitalization.[6,7] The high ICU admission rate reported here may be due to only the most severely affected patients being admitted, with a delay in their treatment another potentially contributing factor. The comorbidities associated with GPP may have contributed to the observed hospitalization rates; however, this study was not designed to test a causal relationship between outcomes.

The algorithm used should be considered conservative as it may underestimate the actual number of flares, because hospitals may use different diagnosis codes to those used for

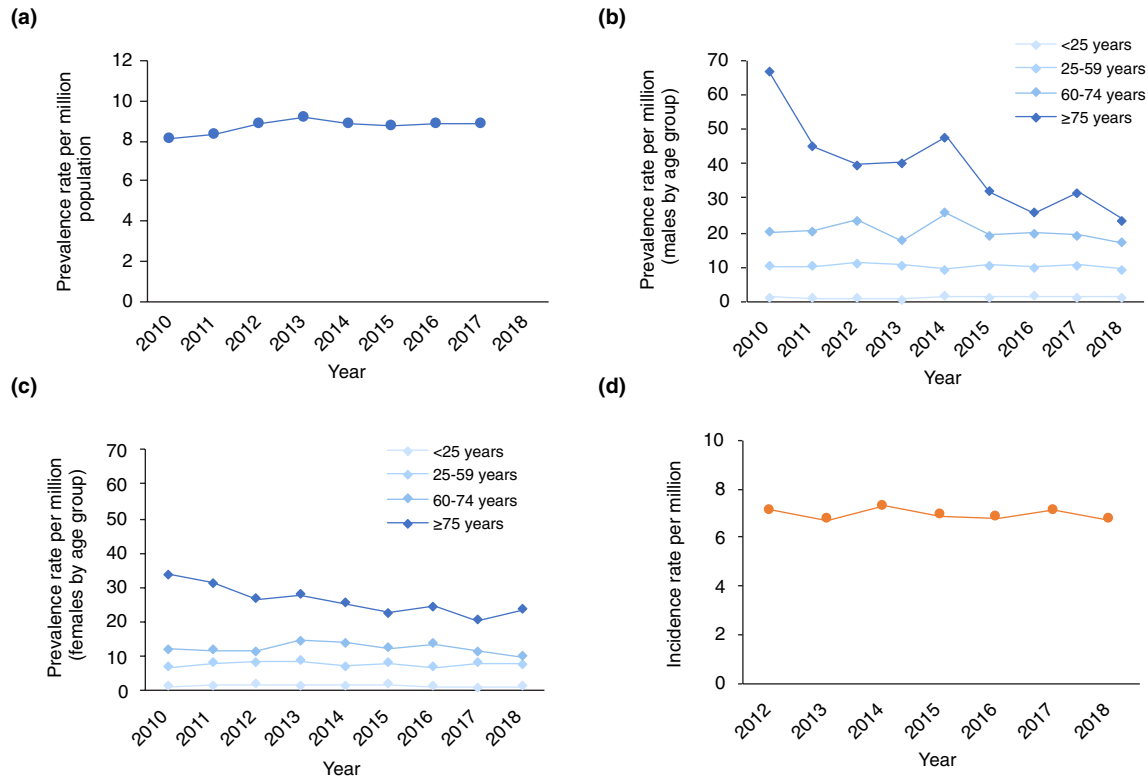

FIGURE 2 Prevalence and cumulative incidence of GPP from the GPP prevalent cohort[a]. (a) Crude annual prevalence of GPP from 2010 to 2018. Prevalence of GPP per million population, grouped by age in males (b) and females (c). (d) Crude annual cumulative incidence of GPP per million population from 2012 to 2018. GPP, generalized pustular psoriasis. [a]Patients with ≥1 GPP-related hospital admission or long-term history of GPP from 2010 to 2018.

the algorithm. Furthermore, it does not capture any flares that may be managed with an inpatient admission of <3 days or anywhere in the outpatient setting. Evaluation of GPP flare severity on patient entry into the SNDS preceded recent clinical guidelines and may not have been accurate, and data on factors that may influence flare severity (i.e. body mass index, alcohol consumption and smoking status) were not included. It should be noted that the criteria for patient inclusion differed between the two cohorts; with the GPP incidence cohort defined using inpatient claims of GPP diagnosis, while the severe psoriasis cohort was classified by outpatient prescriptions for vitamin D derivatives and specific systemic medications. Caution should also be taken when interpreting cumulative incidence; as GPP is a chronic disease, characterized as relapsing or persistent,[2] some patients may have had a diagnosis of GPP before the beginning of the 2-year pre-index period and were therefore counted as new cases. The similar mean ages of patients in the prevalent and incident cohorts also suggests that true incidence was not captured. Furthermore, as there are no data prior to 2010, inferences cannot be made about historical rates.

The extensive coverage of the SNDS national database allowed 569 patients hospitalized with GPP flares to be identified from the incident cohort. So far, few studies have been published on GPP epidemiology, and it is difficult to compare estimates of prevalence and incidence across studies due to differences in methodologies, diagnosis and coding behaviour and a lack of disease awareness. Indeed, an analysis of the Swedish general population reported considerable variation in both prevalence (32–91 per million) and incidence (28–82 cases per million) of GPP in 2015, depending on the stringency of criteria used to identify cases.[11] Our data revealed an age–sex standardized period prevalence of GPP of 52.0 per million population in 2018, placing GPP as a rare disease according to the European Medicines Agency definition.[31] Analyses showed that, although prevalence increased with age, the onset of GPP can occur at any age, and is a lifelong disease. Data from a questionnaire sent to 121 inpatient and outpatient dermatological wards in France in 2004 estimated a prevalence of 1.76 per million population.[9] The prevalence reported here may be higher than the 2004 study due to ward-based (therefore non-comprehensive) sampling in the latter, as well as changes in diagnostic criteria.

Studies using real-world administrative or claims data have several limitations, including inaccuracies of data input that may result in a lack of reproducibility in pharmacoepidemiologic studies.[32] However, the SNDS diagnostic codes are widely used in France for patient identification, therefore it is unlikely that errors were common. Few studies have analysed or validated ICD-10 codes in the SNDS, as

the process can be long and laborious. An inherent limitation of studies using French public health data is that collection of information on ethnicity is not permitted under French law, meaning analysis of disease characteristics by ethnicity was not possible in this dataset. In addition, patients' date of confirmed first GPP diagnosis were not available, meaning an estimation of incidence was not possible. Furthermore, information on concomitant GPP and plaque psoriasis was lacking. It should also be noted that this study and its findings reflect real-world treatment during the period between 2010 and 2018. Changes in the utilization of existing treatments are likely over time. For example, reductions in the use of systemic corticosteroids (which may induce GPP flares when withdrawn) and which may be associated with worse mortality and morbidity outcomes compared to biologics during hospitalization for a flare.[33] In addition, new, more targeted treatments that have recently been approved or are seeking approval,[34,35] or are in clinical development,[36] may improve outcomes in patients with GPP in the future. The expected enrichment of the database could enable further studies to assess the robustness of these current findings, identifying any changing patterns over time.[21]

In conclusion, this real-world database study is one of the first to characterize the hospitalization of patients with GPP and their comorbidity profile in a large population. A novel claims-based algorithm designed to identify GPP flares revealed that patients with GPP have distinct comorbidities, report a higher disease burden compared with patients with severe psoriasis and experience flares associated with long hospitalizations, of which a quarter required ICU admittance. These findings improve understanding of the clinical characteristics of patients with GPP, comorbidities, flare patterns and disease epidemiology.

AUTHOR CONTRIBUTIONS

The authors met criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). MB, JA and PM conducted the data acquisition, with MB and JA also contributing to data analysis. MB, JA, TG, CT and PM contributed to the study design. All authors were involved in the data interpretation, critically revised the manuscript content, provided their approval of the final manuscript version and provided their agreement to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors did not receive payment related to the development of this manuscript. MV declares paid activities as an advisor, speaker or consultant for AbbVie, Almirall, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, Medac, Bristol Myers Squibb, Biogen and Novartis. MB was an employee of Cerner Enviza at the time of the study but is currently an employee of Gilead Sciences. JA and PM are employees of Cerner Enviza. GdP is a member of the scientific board of research at Boehringer Ingelheim. TG, BL and CT are employees of Boehringer Ingelheim. JM declares paid consulting activities for Boehringer Ingelheim. HB declares paid consulting activities for AbbVie, Almirall, BIOCAD, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermavant Sciences, Eli Lilly, Janssen, Kyowa Kirin, LEO Pharma, Mylan, Novartis, UCB and Xion Pharmaceuticals; grant support from Boehringer Ingelheim, Bristol Myers Squibb, Janssen, LEO Pharma, Novartis and Pfizer; and participation on a data safety monitoring board/advisory board from Avillion.

DATA AVAILABILITY STATEMENT

Due to the nature of the claims database that was used, with data at individual patient level, the source data for this study are only available through a highly secured portal accessible only to a limited number of individuals involved in the project. The data are managed by the French National Health Insurance Fund (CNAM) and the French Health Data Hub. Authors cannot share the data with any third parties or make the data publicly available.

PATIENT CONSENT

Not applicable.

REFERENCES

1. Benjegerdes KE, Hyde K, Kivelevitch D, Mansouri B. Pustular psoriasis: pathophysiology and current treatment perspectives. Psoriasis (Auckl). 2016;6:131–44.
2. Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Köks S, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol. 2017;31(11):1792–9.
3. Bachelez H. Pustular psoriasis: the dawn of a new era. Acta Derm Venereol. 2020;100(3):adv00034.
4. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol. 1968;80(12):771–93.
5. Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and economic burden of generalized pustular psoriasis: a structured review. Expert Rev Clin Immunol. 2020;16(3):239–52.
6. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2014;53(6):676–84.
7. Okubo Y, Kotowsky N, Gao R, Saito K, Morita A. Clinical characteristics and health-care resource utilization in patients with generalized pustular psoriasis using real-world evidence from the Japanese Medical Data Center database. J Dermatol. 2021;48(11):1675–87.

8. Fujita H, Terui T, Hayama K, Akiyama M, Ikeda S, Mabuchi T, et al. Japanese guidelines for the management and treatment of generalized pustular psoriasis: the new pathogenesis and treatment of GPP. J Dermatol. 2018;45(11):1235–70.
9. Augey F, Renaudier P, Nicolas JF. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol. 2006;16(6):669–73.
10. Jin H, Cho HH, Kim WJ, Mun JH, Song M, Kim HS, et al. Clinical features and course of generalized pustular psoriasis in Korea. J Dermatol. 2015;42(7):674–8.
11. Löfvendahl S, Norlin JM, Schmitt-Egenolf M. Prevalence and incidence of generalised pustular psoriasis in Sweden – a population-based register study. Br J Dermatol. 2022;186(6):970–6.
12. Noe MH, Wan MT, Mostaghimi A, Gelfand JM, Pustular Psoriasis in the US Research Group, Agnihothri R, et al. Evaluation of a case series of patients with generalized pustular psoriasis in the United States. JAMA Dermatol. 2022;158(1):73–8.
13. Ohkawara A, Yasuda H, Kobayashi H, Inaba Y, Ogawa H, Hashimoto I, et al. Generalized pustular psoriasis in Japan: two distinct groups formed by differences in symptoms and genetic background. Acta Derm Venereol. 1996;76(1):68–71.
14. Wu X, Li Y. Clinical analysis of 82 cases of generalized pustular psoriasis. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2017;42(2):173–8.
15. Zelickson BD, Muller SA. Generalized pustular psoriasis. A review of 63 cases. Arch Dermatol. 1991;127(9):1339–45.
16. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017;26(8):954–62.
17. Grodner C, Sbidian E, Weill A, Mezzarobba M. Epidemiologic study in a real-world analysis of patients with treatment for psoriasis in the French national health insurance database. J Eur Acad Dermatol Venereol. 2021;35(2):411–6.
18. Poizeau F, Nowak E, Kerbrat S, le Nautout B, Droitcourt C, Drici MD, et al. Association between early severe cardiovascular events and the initiation of treatment with the anti-interleukin 12/23p40 antibody ustekinumab. JAMA Dermatol. 2020;156(11):1208–15.
19. Thereaux J, Lesuffleur T, Czernichow S, Basdevant A, Msika S, Nocca D, et al. Long-term adverse events after sleeve gastrectomy or gastric bypass: a 7-year nationwide, observational, population-based, cohort study. Lancet Diabetes Endocrinol. 2019;7(10):786–95.
20. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. Rev Epidemiol Sante Publique. 2017;65(Suppl 4):S149–S167.
21. Scailteux LM, Droitcourt C, Balusson F, Nowak E, Kerbrat S, Dupuy A, et al. French administrative health care database (SNDS): the value of its enrichment. Therapie. 2019;74(2):215–23.
22. Caisse nationale de l'Assurance Maladie des travailleurs salariés. Améliorer la qualité du système de santé et maîtriser les dépenses: propositions de l'Assurance Maladie pour 2016. 2015. Available from: https://www.vie-publique.fr/sites/default/files/rapport/pdf/275504.pdf?msclkid=d9dd9debd14e11ec8b17787315195e19. Accessed 27 July 2022.
23. Sobell JM, Gao R, Golembesky AK, Kotowsky N, Garry EM, Comerford EO, et al. Healthcare resource utilization and baseline characteristics of patients with generalized pustular psoriasis: real-world results from a large US database of multiple commercial medical insurers. J Psoriasis Psoriatic Arthritis. 2021;6(3):143–50.
24. Choon SE, Lebwohl MG, Turki H, Zheng M, Burden AD, Li L, et al. Clinical characteristics and outcomes of generalized pustular psoriasis (GPP) flares. Dermatology. 2023;239:345–54. https://doi.org/10.1159/000529274
25. eurostat. Database. 2022. Available from: https://ec.europa.eu/eurostat/data/database. Accessed 27 July 2022.
26. Institut National de la Statistique et des Études Economiques. Les résultats des recensements de la population. 2022. Available from: https://www.insee.fr/fr/information/2008354. Accessed 27 July 2022.
27. Prinz JC, Choon SE, Griffiths CEM, Merola JF, Morita A, Ashcroft DM, et al. Prevalence, comorbidities and mortality of generalized pustular psoriasis: a literature review. J Eur Acad Dermatol Venereol. 2023;37(2):256–73.
28. Löfvendahl S, Norlin JM, Schmitt-Egenolf M. Comorbidities in patients with generalized pustular psoriasis: a nationwide population-based register study. J Am Acad Dermatol. 2023;88(3):736–8.
29. Strober B, Leman J, Mockenhaupt M, Nakano de Melo J, Nassar A, Prajapati VH, et al. Unmet educational needs and clinical practice gaps in the Management of Generalized Pustular Psoriasis: global perspectives from the front line. Dermatol Ther (Heidelb). 2022;12(2):381–93.
30. Français R. Les dépenses de santéen 2018. Résultats des comptes de la santé édition 2019. 2019. Available from: https://dreessolidarites-santegouvfr/sites/default/files/2020-07/cns2019.pdf. Accessed 27 July 2022.
31. European Medicines Agency. Development of medicines for rare diseases. Available from: https://www.ema.europa.eu/en/news/development-medicines-rare-diseases#:~:text=A%20disease%20is%20considered%20rare,means%20one%20in%2017%20people. Accessed 27 July 2022.
32. Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and reproducibility of observational cohort studies using large healthcare databases. Clin Pharmacol Ther. 2016;99(3):325–32.
33. Miyachi H, Konishi T, Kumazawa R, Matsui H, Shimizu S, Fushimi K, et al. Treatments and outcomes of generalized pustular psoriasis: a cohort of 1516 patients in a nationwide inpatient database in Japan. J Am Acad Dermatol. 2022;86(6):1266–74.
34. Bachelez H, Choon SE, Marrakchi S, Burden AD, Tsai TF, Morita A, et al. Trial of Spesolimab for generalized pustular psoriasis. N Engl J Med. 2021;385(26):2431–40.
35. Morita A, Strober B, Burden AD, Choon SE, Anadkat MJ, Marrakchi S, et al. Efficacy and safety of subcutaneous spesolimab for the prevention of generalised pustular psoriasis flares (Effisayil 2): an international, multicentre, randomised, placebo-controlled trial. Lancet. 2023;402(10412):1541–51.
36. Warren RB, Reich A, Kaszuba A, Placek W, Griffiths CEM, Zhou J, et al. Imsidolimab, an anti-interleukin-36 receptor monoclonal antibody, for the treatment of generalized pustular psoriasis: results from the phase II GALLOP trial. Br J Dermatol. 2023;189(2):161–9.

SUPPORTING INFORMATION

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

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