Prevalence estimates for pyoderma gangrenosum in the United States: An age- and sex-adjusted population analysis

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Background: The disease burden of pyoderma gangrenosum (PG) is poorly understood.

Objective: To determine standardized overall and age-, sex-, and race-specific prevalence estimates for PG among adults in the United States.

Methods: Cross-sectional analysis of 1971 patients with PG identified using electronic health records data from a diverse population-based sample of more than 58 million patients.

Results: The age- and sex-standardized prevalence of PG among the study population was 0.0058%, or 5.8 PG cases (95% confidence interval [CI], 5.6-6.1) per 100,000 adults. Adjusted prevalence was nearly twice as high among women (7.1 cases [95% CI, 6.7-7.5] per 100,000) than men (4.4 cases [95% CI, 4.0-4.7] per 100,000). Patients between the ages of 70 and 79 years had the highest standardized prevalence (9.8 cases [95% CI, 8.8-10.9] per 100,000), with patients aged ≥50 years representing nearly 70% of all PG cases. Standardized prevalence was similar among white and African American patients. The female-to-male ratio of PG was >1.8 across all age groups.

Limitations: Analysis of electronic health records data may result in misclassification bias.

Conclusion: PG is a rare disease that most commonly affects women and those aged ≥50 years. (J Am Acad Dermatol 2020;83:425-9.)

Key words: epidemiology; female; prevalence; pyoderma gangrenosum.

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis characterized by rapidly expanding, suppurative ulcers that heal with cribriform scarring. More than half of patients with PG have an associated underlying systemic illness, most commonly inflammatory bowel disease (IBD), hematologic disorders, solid organ malignancy, and inflammatory arthritis.[1] Pathergy represents a prominent feature, because PG can arise after surgical intervention in the absence of predisposing conditions.[2-4] The pathogenesis of PG is poorly understood but may involve neutrophil dysfunction triggered by inflammatory or traumatic injury in susceptible individuals.[5-9]

Patients with PG experience considerable health-related reductions in quality of life. Severe pain, sleep disturbances, and poor appetite are common.[10] Chronic wounds with associated drainage likely account for the high rates of depression seen in patients with PG and can trigger feelings of anxiety and social isolation.[11,12] In addition, delays in diagnosis frequently expose patients to multiple disease-exacerbating débridements, unnecessary antibiotics, or other inappropriate therapies.[2,13]

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Although PG remains a debilitating condition with significant morbidity and mortality, the overall burden of disease is poorly understood. In this study, we sought to establish standardized overall and age-, sex-, and race-specific prevalence estimates for PG among adults in the United States (US).

METHODS

After approval by the Human Subjects Committee at the Feinstein Institute of Medical Research at Northwell Health, we performed a cross-sectional analysis using Explorys, a multi-institutional data analytics and research platform developed by IBM Watson Health (IBM, Armonk, NY). Clinical information from electronic medical records, laboratories, practice management systems, and claims systems are matched using a single set of Unified Medical Language System ontologies to create longitudinal data for individual patients. Data within Explorys are standardized according to common terms and classification systems, including International Classification of Diseases (ICD), Systemized Nomenclature of Medicine-Clinical Terms (SNOMED-CT), Logical Observation Identifiers Names and Codes, and RxNorm. The database currently comprises >58 million unique patients from 27 participating integrated health care organizations, representing >17% of the population across all 4 US Census regions.

CAPSULE SUMMARY

- The prevalence of pyoderma gangrenosum in the United States is poorly understood.
- Pyoderma gangrenosum is a rare disease that most commonly affects women and individuals aged ≥50 years. Our study provides an epidemiologic framework for further characterizing risk factors, clinical associations, and disease outcomes.

Study definitions

PG cases were identified by using ≥3 counts of the SNOMED-CT term "pyoderma gangrenosum," which is associated with the ICD-9 and ICD-10 codes for PG (686.01 and L08.0, respectively). This method was shown to have a positive predictive value of 76% for identifying cases of PG using an electronic health record database.[14]

Statistical analysis

We calculated overall prevalence of PG among patients aged ≥18 years who were active within the last 5 years in the database, as well as prevalence within age-, sex-, and race-stratified subgroups. *Active* signified that the patient had at least 1 encounter with a provider contributing to the database within the last 5 years. Race was categorized as white, African American, other, or unknown. Age in years was recorded as a categorical variable within 1 of 6 groups: 18 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years. Calculations were standardized according to the age and sex composition of the 2010 US Census population. Estimates were age-adjusted for comparison between men and women, sex-adjusted for age group comparisons, and both age- and sex-adjusted for race comparisons. Confidence intervals (CIs) for crude and standardized prevalences were computed on the basis of Poisson and gamma distributions, respectively. Standardized prevalences were compared assuming the prevalence ratio followed a log-normal distribution. A 2-sided α level of 0.05 was used to determine statistical significance. All analyses were performed using SAS 9.4 software (SAS Institute, Inc, Cary, NC).

RESULTS

We identified 1971 patients with PG, whose demographic characteristics are summarized in Table I. Patients were predominantly female (68.0%) and white (78.5%). Most patients were aged between 60 and 69 years (21.3%), with individuals aged ≥50 years representing nearly 70% of all patients with PG.

The standardized prevalence of PG among the entire study population was 0.0058%, or 5.8 PG cases (95% CI, 5.6-6.1) per 100,000 adults (Table II), and was nearly twice as high among women (7.1 cases [95% CI, 6.7-7.5] per 100,000) compared with men (4.4 cases [95% CI, 4.0-4.7] per 100,000). In addition, patients aged between 70 and 79 years had the highest standardized prevalence (9.8 cases [95% CI, 8.8-10.9] per 100,000). Standardized prevalence was similar among white and African American patients.

Table III summarizes the ratio of female to male patients with PG stratified by age group. Of note, women with PG outnumbered men with PG by more than 1.8-fold in all age groups, and the highest female-to-male ratio of 3.7 was observed in patients aged ≥80 years.

DISCUSSION

In this study, we estimated overall and group-specific prevalences for PG among patients in the US. The overall standardized point prevalence of PG was

Abbreviations used:

CI: confidence interval
IBD: inflammatory bowel disease
ICD: International Classification of Diseases
IL: interleukin
PG: pyoderma gangrenosum
SNOMED-CT: Systemized Nomenclature of Medicine—Clinical Terms
US: United States

0.0058%, or 5.8 patients with PG per 100,000 adults. Adjusted prevalence in women was nearly twice that of men, and most patients with PG were ≥50 years old. Standardized prevalence did not differ between white and African American patients.

Perhaps owing to disease rarity, epidemiologic studies of PG are sparse. Prior worldwide incidence, commonly quoted as 3 to 10 cases per million per year, was extrapolated from case reports, case studies, and cohort studies of patients with IBD. Several European studies have recently examined the incidence of PG on a regional or national level. A population analysis from the United Kingdom identified 313 patients with PG, with an observed standardized incidence rate of 0.63 cases per 100,000 person-years.[15] An Italian study identifying 64 patients with PG estimated the incidence to be 5.17 cases per million per year.[16] A Spanish study identifying 15 patients with PG estimated the incidence to be 3.26 cases per million per year.[17] In contrast, prevalence studies in PG have been limited primarily to cohorts with IBD, in which the prevalence of PG has ranged from 0.5% to 5%.[18-20] These figures likely overestimate true disease prevalence given the known association between IBD and PG, and indeed, represent a nearly 100- to 1000-fold increase in prevalence compared with our observations.

Several prior studies have demonstrated that PG more commonly affects women, with female-to-male ratios ranging from 1.2 up to 3.1.[12,21-24] Although the exact mechanism remains unclear, this sex distribution cannot be explained by contributions from underlying comorbidities, because several of these conditions—including ulcerative colitis, acute myeloid leukemia, and myelodysplastic syndrome—more commonly affect men.[25-29]

Interestingly, increasing evidence suggests that estrogen has wide-ranging and pleomorphic effects on the immune system.[30-32] Estrogen receptors are expressed on T cells, B cells, dendritic cells, neutrophils, macrophages, and natural killer cells, and after estrogen binding, translocate to the nucleus to modulate transcription of various gene programs.[33-37] A recent study showed that estrogen supplementation increases the absolute neutrophil number in the mouse spleen, peripheral blood, and bone marrow, resulting in functional increases in inflammatory molecules such as interleukin (IL)-1β, IL-6, IL-10, interferon-γ, tumor necrosis factor-α, and monocyte chemoattractant protein-1.[38] Notably, several of these cytokines—in particular IL-1β, IL-6, interferon-γ receptor, and tumor necrosis factor-α—are enriched several-fold in skin lesions of patients with PG compared with controls.[39,40] Estrogen signaling also appears to play a critical role in T-cell activation and proliferation and in augmenting B-cell antibody production.[31,41,42]

Overall, these findings suggest that sex-specific differences in hormone levels may contribute to immune dysregulation in PG, particularly in younger patients. Why the female predominance persists despite a reduction of endogenous estrogen production in postmenopausal women (eg, those aged ≥60) remains unclear.

In this study, we identified 1971 patients with PG across a demographically heterogeneous population using a validated method of case identification. As such, our analysis, to our knowledge, includes the largest and likely the most heterogeneous group of PG patients ever described. The cohort includes patients with all types of insurance and self-pay patients who sought care in health care settings across all US Census regions. Given the size and

Table I. Demographic characteristics of adults with pyoderma gangrenosum

Characteristic	Patients (N = 1971), No. (%)
Sex	
Female	1341 (68.0)
Male	630 (32.0)
Age, y	
18-39	321 (16.3)
40-49	279 (14.2)
50-59	402 (20.4)
60-69	420 (21.3)
70-79	338 (17.1)
≥80	211 (10.7)
Race	
White alone	1548 (78.5)
African American alone	273 (13.9)
Other*	75 (3.8)
Unknown	75 (3.8)

*Includes patients whose race/ethnicity was recorded as Hispanic/Latino, Asian, multiracial, Chinese, Filipino, Japanese, Oriental, Samoan, Latin American, Native Hawaiian, Native American or Alaskan Native, Asian/Pacific Islander, or other, as well as patients with ≥2 races on record.

Table II. Crude and standardized prevalence estimates for pyoderma gangrenosum in the United States

Variable	PG cases, No.	Population size, No.	Prevalence per 100,000 (95% CI)	
			Crude	Standardized*†
Overall population	1971	30,940,953	6.4 (6.1-6.7)	5.8 (5.6-6.1)
Sex				
Female	1341	17,558,564	7.6 (7.2-8.1)	7.1 (6.7-7.5)
Male	630	13,382,389	4.7 (4.3-5.1)	4.4 (4.0-4.7)
Age, y				
18-39	321	10,456,218	3.1 (2.7-3.4)	3.0 (2.7-3.3)
40-49	279	4,602,997	6.1 (5.4-6.8)	5.9 (5.2-6.6)
50-59	402	5,111,878	7.9 (7.1-8.7)	7.7 (7.0-8.5)‡
60-69	420	4,948,670	8.5 (7.7-9.3)	8.4 (7.6-9.2)‡
70-79	338	3,387,476	10.0 (8.9-11.1)	9.8 (8.8-10.9)
≥80	211	2,433,714	8.7 (7.5-9.9)	8.1 (7.0-9.3)‡
Race				
White	1548	19,355,769	8.0 (7.6-8.4)	7.2 (6.8-7.5)
African American	273	3,256,047	8.4 (7.4-9.4)	8.1 (7.2-9.1)‡
Other	75	2,332,515	3.2 (2.5-4.0)	3.2 (2.5-4.0)
Unknown	75	5,996,622	1.3 (1.0-1.6)	1.1 (0.9-1.4)

CI, Confidence interval.

*Comparisons between males and females are adjusted for age. Age group comparisons are adjusted for sex. Race comparisons are adjusted for sex and age. The sex and age distribution of the 2010 United States Census population was used as the standard population, with 6 age groups: 18-39, 40-49, 50-59, 60-69, 70-79, and ≥80 years.

†All comparisons between standardized subgroups were significant with $P < .001$ unless otherwise noted. Reference groups for age and race comparisons were age group 70-79 years, and white respectively.

‡$P = .001$ for comparison of between ages 50-59 and 70-79 years. $P = .03$ for comparison between ages 60-69 and 70-79 years. $P = .03$ for comparison between ages ≥80 and 70-79 years. $P = .07$ for comparison between white and African American race.

Table III. Sex distribution of pyoderma gangrenosum by age group (N = 1971)

Age group, y	Male, No.	Female, No.	Female %	Female-to-male ratio
18-39	101	220	68.5	2.2
40-49	88	191	68.5	2.2
50-59	137	265	65.9	1.9
60-69	149	271	64.5	1.8
70-79	110	228	67.5	2.1
≥80	45	166	78.7	3.7

diversity of our cohort, we believe our prevalence analysis may be generalizable to the US population. Indeed, our findings recapitulate prior descriptive studies showing that most PG cases occur in elderly and female patients.[1,12]

Some limitations should be considered when interpreting the results of our analysis. Although the case cohort was identified using a previously validated method, we could not independently confirm the diagnosis of PG in each case. We could not include patients with PG who were undiagnosed or those who did not seek care in health systems included in the database. Further, owing to variations in geography, environmental triggers, and ethnic composition, our prevalence estimate may not be applicable to other nations.

CONCLUSION

We observe that PG is a rare disease that predominantly affects women and those aged ≥50 years. Nonetheless, morbidity in PG is significant, and this study may support future large-scale epidemiologic investigations of risk factors, associated comorbidities, and health outcomes.

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