Prevalence estimates for pemphigoid in the United States: A sex-adjusted and age-adjusted population analysis

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Background: The burden of the pemphigoid group of autoimmune blistering diseases is poorly understood.

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

Methods: Cross-sectional analysis of electronic health records data for a demographically heterogeneous population-based sample of >55 million patients across all 4 census regions.

Results: Overall pemphigoid prevalence was 0.012%, or 12 pemphigoid patients/100,000 adults. Prevalence of pemphigoid among those aged ≥60 years was 0.038%, or 37.7 cases/100,000 adults. Prevalence increased ~2-fold within each successive age group and was highest among patients aged ≥90 years (123.6 [95% CI 115.2-132.5] cases/100,000 adults). Adjusted prevalence in women was 12.7 (95% CI 12.3-13.2) cases/100,000 adults, slightly more than that in men (11.0 [95% CI 10.5-11.6] cases/100,000 adults). Adjusted prevalences were similar for blacks (15.4 [95% CI 14.0-17.0] cases/100,000 adults) and whites (13.5 [95% CI 13.0-13.9] cases/100,000 adults).

Limitations: Analysis of electronic health data might result in disease misclassification.

Conclusion: Pemphigoid is rare in the United States. Patients aged ≥60 years comprise the majority of cases. (J Am Acad Dermatol 2019;80:655-9.)

Key words: bullous pemphigoid; epidemiology; pemphigoid; prevalence.

The pemphigoid group of diseases forms a subset of autoimmune blistering disorders characterized by autoantibodies against antigenic proteins at the dermal-epidermal junction. Clinically this translates to patients presenting with pruritus or pain, along with tense blisters and erosions of the skin and, in some cases, the mucous membranes.[1] Although some forms of pemphigoid might be self-limited, the most common variant bullous pemphigoid (BP) generally follows a chronic course characterized by disease exacerbations and remissions.[2]

Abbreviations used:

BP:	bullous pemphigoid
CI:	confidence interval
ICD:	International Classification of Diseases
SNOMED-CT:	Systemized Nomenclature of Medicine—Clinical Terms

Patients with pemphigoid experience significant health-related reductions in quality of life. Sleep disturbances, fatigue, and irritability due to pruritus

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and pain might account for higher scores on indices of depression for BP patients when compared with controls. The visible eruption of blisters might also influence mood and limit social relationships and contact, contributing to loneliness expressed by patients.[3] BP is also associated with increased numbers of chronic medical conditions, higher hospital mortality rates, and significant health care–associated costs.[4]

Although it is evident that pemphigoid results in significant morbidity and mortality, the overall burden of disease is poorly understood. The purpose of this study was to establish standardized prevalence estimates for pemphigoid among adults in the United States.

CAPSULE SUMMARY

- The burden of pemphigoid in the United States is poorly understood. Our findings demonstrate that patients in the United States with pemphigoid are commonly women aged ≥60 years, with whites and blacks equally affected.
- This study provides a population-based structure for better understanding pemphigoid risk factors, associated comorbidities, and potential treatment outcomes.

METHODS

This was a cross-sectional analysis using a multisystem data analytics and research platform Explorys (IBM Watson Health, Cambridge, MA).[5] Clinical information from electronic medical records, laboratories, practice management systems, and claims systems are matched by using a single set of Unified Medical Language System ontologies to create longitudinal records for unique patients. The data are standardized and curated according to common controlled vocabularies and classifications systems, including International Classification of Diseases (ICD), Systemized Nomenclature of Medicine–Clinical Terms (SNOMED-CT), Logical Observation Identifiers Names and Codes, and RxNorm.[6-9] At present, the database encompasses 27 participating integrated health care organizations. Over 55 million unique lives representing ~17% of the population across all 4 census regions of the United States are captured. Patients with all types of insurance, as well as those who self-pay are represented. Population counts are reported by the database to the nearest 10 or represented as <10 if population count is 0-9 to prevent patient identification.

The case cohort was established by using ≥2 counts of the SNOMED-CT term pemphigoid, which is associated with ICD-9 code for bullous pemphigoid (694.5) and includes bullous pemphigoid and benign mucous membrane pemphigoid. Cases with the concomitant SNOMED-CT term pemphigus, which has one-to-one mapping with ICD-9 code for pemphigus (694.4), were excluded. This method has been validated previously and shown to have a positive predictive value of 99% for identifying cases of bullous pemphigoid.[10]

Statistical analysis

We calculated overall prevalence of pemphigoid among patients aged ≥18 years who were active in the Explorys database during 2013-2018, as well as prevalence of pemphigoid within subgroups according to age, sex, and race. Patients were categorized into 1 of 4 race categories: white, black, other, and unknown. Prevalence estimates were based on records for which age and sex information was available. Direct standardization was used to account for differences in sex and age distributions when comparing pemphigoid prevalence across subgroups. The age and sex composition of the 2010 US Census population was used as the standard population, with 8 age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, and ≥90 years.[11] Estimates were age adjusted for comparison between males and females, sex-adjusted for age group comparisons, and sex-adjusted and age-adjusted for race comparisons. Confidence intervals for crude and standardized prevalences were computed on the basis of the Poisson and gamma distributions,[12] respectively. Standardized prevalences were compared assuming the prevalence ratio followed a log-normal distribution. A 2-sided α level of 0.05 was applied to determine statistical significance. All analyses were performed by using SAS version 9.4 (SAS Institute Inc, Cary, NC). The Human Subjects Committee at the Feinstein Institute for Medical Research at Northwell Health approved this study.

RESULTS

Table I lists demographic characteristics of adult pemphigoid patients in the population-based sample. We identified 5095 cases of pemphigoid. Patients aged ≥60 years comprised 86% of cases. The ratio of women to men with pemphigoid was 1.5 to 1. Pemphigoid patients were most frequently white (77.5%).

Crude and standardized group-specific prevalences of pemphigoid are listed in Table II. We observed an overall standardized point prevalence of 0.012% or 11.9 (95% confidence interval [CI] 11.5-12.2) cases/100,000 adults. Among adults aged ≥60 years, standardized prevalence was 0.038%

Table I. Demographics for adults with pemphigoid (N = 5095)

Characteristic	n (%)
Age group, y	
18-29	70 (1.4)
30-39	110 (2.2)
40-49	160 (3.1)
50-59	375 (7.4)
60-69	760 (14.9)
70-79	1230 (24.1)
80-89	1530 (30.0)
≥90	860 (16.9)
Sex	
Female	3040 (59.7)
Male	2055 (40.3)
Race	
White	3950 (77.5)
Black	460 (9.0)
Other*	235 (4.6)
Unknown	450 (8.8)

*Other includes Asian, Hispanic/Latino, Filipino, Chinese, Japanese, Samoan, Oriental, Latin American, Native Hawaiian, Multiracial, and other.

(37.7 [95% CI 36.6-38.9] cases/100,000 adults). Standardized prevalence increased ~2-fold within each successive age group. The highest prevalence (0.124%) was observed in the ≥90-year age group. Standardized prevalence was slightly greater among women (0.13%) than men (0.11%). Standardized prevalence was similar among white persons, black persons, and persons of other racial groups.

Table III lists age-specific prevalences by sex. Women had a slightly greater prevalence of pemphigoid across all age groups, except the 80—89-year and ≥90-year age groups. The highest prevalence of pemphigoid among women was in the ≥90-year age group [111.6 (95% CI 102.2-121.6) cases/100,000 adults]. The highest prevalence overall was observed among men aged ≥90 years [136.3 (95% CI 122.2-151.6) cases/100,000 adults].

DISCUSSION

In this study, we have estimated overall and group-specific standardized prevalence estimates for pemphigoid among adults in the United States. Overall standardized point prevalence of pemphigoid was 0.012%, or 11.9 pemphigoid patients/100,000 adults. The prevalence was increased 3-fold (0.038% or 37.7 cases/100,000 adults) among adults aged ≥60 years. Women have slightly greater disease prevalence up to age 80 years, after which the burden appears to be higher among men. Standardized prevalence increased 2-fold within each successive age group and peaked in patients aged ≥90 years.

The propensity for particular autoimmune skin diseases to afflict the elderly population might be due in part to senescence of the dermatologic immune system.[13] Immunologic senescence in the elderly manifests as a paradoxical combination of immunodeficiency and increased autoimmunity.[14-16] Increased autoimmunity in the elderly might be due to selection of T cells with increased affinity to self-antigens and proinflammatory characteristics.[17] Accordingly, with aging, there is loss of CD28, a key molecule responsible for $CD4^+$ and $CD8^+$ T-cell activation. Without CD28 expression, these T cells become more resistant to apoptosis and, thus, might promote a proinflammatory state with autoreactive T cells that expand clonally.[18,19] Taken together, this might provide an explanation for the increased pemphigoid prevalence estimates we observed among the elderly in our study.

Epidemiologic studies estimating disease burden for pemphigoid are sparse. Moreover, existing studies are limited by sample size, nonvalidated methods of data extraction from claims databases, and nonstandardization of prevalence estimates to the national reference population. Reports of worldwide prevalence estimates for pemphigoid range 0.012%-0.038%.[20,21] In a German claims-based analysis, a combined standardized point prevalence for BP and mucous membrane pemphigoid was estimated to be 0.028% with both BP and mucous membrane pemphigoid observed more frequently among women and among patients aged 70-89 years. However, this study only included patients with insurance and might have underestimated disease burden.[20] Prevalence of pemphigoid was estimated to be 0.012% by using the national Danish registry over the period 1977-2006. However, age and sex information was not reported in the Danish study.[21] Neither of the aforementioned studies provided information on race. It is interesting to note that the prevalence rates of pemphigoid in Europe appear higher than those observed in our US cohort; yet, these observations might be driven by limitations in our methods as well as potential ethnic and genetic risk factors inherent in these geographic populations.[22]

There are limitations that warrant consideration when interpreting the results of our analysis. We could not capture patients who did not seek care in health systems included in the database. The extent to which our analysis might underestimate prevalence of pemphigoid is unknown. In addition, although the case cohort was identified by using a validated method, use of administrative data for case

Table II. Crude and standardized prevalence estimates for pemphigoid

Category	Pemphigoid cases, n*	Population size*	Crude prevalence per 100,000 adults (95% CI)	Crude prevalence, %	Standardized prevalence per 100,000 adults (95% CI)†	Standardized prevalence, %
Overall population	5095	29,396,600	17.3 (16.9-17.8)	.017	11.9 (11.5-12.2)	.012
Population aged ≥60 y	4380	10,270,430	42.6 (41.4-43.9)	.043	37.7 (36.6-38.9)	.038
Age group, y						
18-29	70	5,179,440	1.4 (1.1-1.7)	.001	1.3 (1.0-1.7)	.001
30-39	110	4,702,070	2.3 (1.9-2.8)	.002	2.3 (1.9-2.7)	.002
40-49	160	4,355,030	3.7 (3.1-4.3)	.004	3.6 (3.1-4.2)	.004
50-59	375	4,889,630	7.7 (6.9-8.5)	.008	7.6 (6.8-8.4)	.008
60-69	760	4,627,480	16.4 (15.3-17.6)	.016	16.2 (15.1-17.4)	.016
70-79	1230	3,150,390	39.0 (36.9-41.3)	.039	38.9 (36.7-41.1)	.039
80-89	1530	1,777,240	86.1 (81.8-90.5)	.086	86.3 (82.0-90.7)	.086
≥90	860	715,320	120.2 (112.3-128.5)	.120	123.6 (115.2-132.5)	.124
Sex						
Female	3040	16,608,300	18.3 (17.7-19.0)	.018	12.7 (12.3-13.2)	.013
Male	2055	12,788,300	16.1 (15.4-16.8)	.016	11.0 (10.5-11.6)	.011
Race						
White	3950	18,346,330	21.5 (20.9-22.2)	.022	13.5 (13.0-13.9)	.014
Black	460	2,907,470	15.8 (14.4-17.3)	.016	15.4 (14.0-17.0)	.015
Other	235	2,030,330	11.6 (10.1-13.2)	.012	10.2 (8.9-11.7)	.010
Unknown	450	6,112,470	7.4 (6.7-8.1)	.007	5.4 (4.9-5.9)	.005

Prevalence estimates are based on records for which age and sex information was available.
CI, Confidence interval.
*Sum of group-specific counts might not equal total N since the database rounds counts to the nearest 10.
†Sex comparisons 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 US Census population was used as the standard population, with 8 age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, and ≥90 years.

Table III. Age-specific prevalence of pemphigoid by sex

	Male		Female	
Age group, y	Pemphigoid cases, n	Prevalence per 100,000 adults (95% CI)	Pemphigoid cases, n	Prevalence per 100,000 adults (95% CI)
18-29	25	1.1 (0.7-1.7)	45	1.5 (1.1-2.0)
30-39	35	1.8 (1.3-2.5)	75	2.7 (2.1-3.4)
40-49	60	3.2 (2.4-4.1)	100	4.0 (3.3-4.9)
50-59	145	6.6 (5.6-7.8)	230	8.5 (7.4-9.7)
60-69	270	12.8 (11.3-14.4)	490	19.4 (17.8-21.2)
70-79	510	35.4 (32.4-38.6)	720	42.1 (39.1-45.3)
80-89	670	87.9 (81.4-94.9)	860	84.7 (79.1-90.6)
≥90	340	136.3 (122.2-151.6)	520	111.6 (102.2-121.6)

CI, Confidence interval.

identification is an imperfect standard that could result in misclassification bias. Moreover, although mucous membrane pemphigoid is rare and might not account for a significant number of cases in our cohort, the grouping under 1 ICD-9 code limits our ability to understand the distinct prevalence of this disease variant.

This study also has several strengths. This prevalence estimate of pemphigoid is based on the largest and most ethnically diverse population sample reported in the world, and represents the first such population-based analysis in the United States. The cohort is also drawn from patients with all insurance types and self-pay patients across various types of health care settings and from all census regions. For these reasons, we believe these results might be generalizable in the United States.

In summary, pemphigoid is a rare disease that predominantly affects patients aged ≥60 years. This analysis of pemphigoid burden in the United States provides an epidemiologic framework for the validation of potential disease associations—namely

neurologic diseases, such as cerebrovascular disease,[23-25] Parkinson disease,[25,26] dementia,[23-26] multiple sclerosis,[23-26] and epilepsy[25]—that might provide further insight into pemphigoid pathogenesis, risk, and prognosis.

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