
Associations of pemphigus or pemphigoid with autoimmune disorders in US adult inpatients



Shanthi Narla, MD,^a and Jonathan I. Silverberg, MD, PhD, MPH^{b,c,d,e}
Chicago, Illinois

Background: The associations and predictors of the gamut of autoimmune conditions in pemphigus and pemphigoid have been examined in few large-scale controlled studies.

Objective: To examine associations of pemphigus or pemphigoid with autoimmune disorders and related outcomes in adults.

Methods: Data from the 2002-2012 National Inpatient Sample were analyzed, including an ~20% sample of all US hospitalizations (n = 72,108,077 adults).

Results: In multivariable logistic regression models, pemphigus (adjusted odds ratio 1.46, 95% confidence interval 1.30-1.63) and pemphigoid (adjusted odds ratio 1.35, 95% confidence interval 1.24-1.48) were associated with ≥ 1 autoimmune disorder. Pemphigus was associated with 9 of 29 and pemphigoid with 13 of 32 autoimmune disorders examined in bivariable models. Among pemphigus inpatients, unspecified autoimmune disease, vitiligo, eosinophilic esophagitis, and myasthenia gravis had the strongest effect sizes. Whereas, among pemphigoid inpatients, unspecified autoimmune disease, vitiligo, and chronic urticaria had the strongest effect sizes. There were significant differences of autoimmune comorbidities by age, sex, and race/ethnicity. The estimated excess annual costs of hospital care attributed to autoimmune disorders among inpatients with pemphigus was \$2,286,588 and pemphigoid \$4,301,681.

Limitation: Lack of treatment history data.

Conclusion: Inpatients with pemphigus or pemphigoid had increased odds of multiple cutaneous, extracutaneous, and systemic autoimmune disorders, which were associated with a considerable cost burden. (J Am Acad Dermatol 2020;82:586-95.)

Key words: autoimmune; hospitalization; inpatient; pemphigoid; pemphigus; systemic disorders.

Pemphigus and pemphigoid are autoimmune blistering disorders associated with pain and pruritus, impaired activities of daily living, and mortality.¹⁻³ Individuals with 1 autoimmune disorder are at an increased risk of other autoimmune disorders, a concept known as autoimmune diathesis.⁴⁻⁷

Previous case studies have reported associations between pemphigus and other autoimmune disorders, eg, rheumatoid arthritis (RA), diabetes mellitus

type 1, and systemic lupus erythematosus (SLE), and strong associations between pemphigus and myasthenia gravis, thymoma, or autoimmune thyroid disease.^{4,8-23} Other case reports reported associations between pemphigoid and multiple sclerosis (MS).^{3,24-27} A review of case reports and case series showed that pemphigus and pemphigoid were associated with autoimmune conditions, including myasthenia gravis, SLE, vitiligo, alopecia,

From the Department of Medicine, University of Illinois at Chicago^a; Department of Dermatology,^b Department of Preventive Medicine,^c and Department of Medical Social Sciences,^d Northwestern University Feinberg School of Medicine, Chicago; and Northwestern Medicine Multidisciplinary Eczema Center, Chicago.^e

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Correspondence to: Jonathan I. Silverberg, MD, PhD, MPH, Department of Dermatology, Northwestern University Feinberg School of Medicine, Ste 1600, 676 N. St. Clair St, Chicago, IL 60611. E-mail: jonathanisilverberg@gmail.com.

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polymyositis, and autoimmune thrombocytopenia.¹ However, some studies demonstrated conflicting results about such associations.¹⁶ The odds and predictors of a comprehensive set of autoimmune conditions in pemphigus and pemphigoid have been examined in few large-scale controlled studies. We hypothesized that adults with pemphigus or pemphigoid have significantly higher rates of a wide array of autoimmune disorders affecting the skin and other organ systems. We also hypothesized that autoimmune comorbidities indirectly contribute toward substantial excess costs in pemphigus and pemphigoid patients. In this study, we examined whether pemphigus and pemphigoid are associated with increased autoimmune disease in adults and the predictors and excess costs of autoimmune disease in pemphigus and pemphigoid inpatients.

METHODS

Data source

The 2002-2012 Nationwide Inpatient Sample (NIS) provided by the Healthcare Cost and Utilization Project from the Agency for Healthcare Research and Quality was analyzed. Each year of NIS data contains an ~20% stratified representative cross-sectional sample of all US hospitalizations. Sample weights were provided in NIS that factored in the sampling design of hospitals. These sample weights enable nationally representative estimations to be made of hospital discharges. All data were deidentified, and no attempts were made to identify any of the individuals in the database. All parties with access to NIS data were compliant with the Healthcare Cost and Utilization Project's data use agreement. This study was approved by the institutional review board at Northwestern University (Chicago, Illinois).

Identification of pemphigus, pemphigoid, and autoimmune disorders

The databases were searched for a primary or secondary diagnosis of pemphigus and pemphigoid by using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. In a previous study, the discharge diagnosis codes 694.4 (pemphigus) and 694.5 (pemphigoid) were validated in the inpatient setting for identifying these disorders.² Cases with both ICD-9-CM codes

694.4 and 694.5 were excluded. Autoimmune disorders were identified by using ICD-9-CM or clinical classification software codes provided in NIS (Supplemental Table 1; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>). The control group included all hospitalizations without a diagnosis of pemphigus or pemphigoid. To determine the autoimmune comorbidities of pemphigus and pemphigoid per se, hospitalizations with comorbid diagnoses of psoriasis, atopic dermatitis, eczema, hidradenitis, or dermatomyositis were excluded from the cases and controls.

Statistical analysis

Statistical analyses were performed by using survey procedures that included sample weights, strata, and clustering in SAS version 9.4 (SAS Institute, Cary, NC). The unit of analysis was an individual hospitalization. Weighted frequency and prevalence (95% confidence intervals [CIs]) of a primary or secondary diagnosis of an autoimmune disorder was determined for patients with pemphigus or pemphigoid and controls.

Summary statistics, including frequency, prevalence, and 95% CI, were generated for each disorder. The hospital cost for inpatient care was estimated on the basis of the total charge of the hospitalization and the cost-to-charge ratio estimated by the Healthcare Cost and Utilization Project. All costs were adjusted for inflation to 2014 according to the Consumer Price Index from the US Bureau of Labor Statistics. Excess length of stay (LOS) and cost of care for an autoimmune disorder indirectly related to pemphigus or pemphigoid were estimated by calculating the prevalence of that autoimmune disorder in patients with pemphigus or pemphigoid divided by the prevalence of that disorder in controls multiplied by the total hospitalization annual days or costs for that disorder in patients with pemphigus or pemphigoid. The proportion of inpatients who died were assessed in those with versus without pemphigus or pemphigoid.

Survey logistic regression models were used to determine the association of pemphigus and pemphigoid (independent variables) with autoimmune conditions (binary dependent variables). Crude odds ratios (ORs) and 95% CIs were estimated. Multivariable

CAPSULE SUMMARY

- This study found increased risk for autoimmune disorders of the skin, endocrine, gastrointestinal, neurologic, and musculoskeletal systems in adults with pemphigus and pemphigoid.
- Clinicians should consider increased screening for autoimmune disorders in patients with pemphigus and pemphigoid.

Abbreviations used:

aOR:	adjusted odds ratio
BP180:	bullous pemphigoid
CI:	confidence interval
EOE:	eosinophilic esophagitis
ICD-9-CM:	International Classification of Disease, 9th Edition, Clinical Modification
ITP:	idiopathic thrombocytopenic purpura
LOS:	length of stay
MG:	myasthenia gravis
MS:	multiple sclerosis
NIS:	Nationwide Inpatient Sample
OR:	odds ratio
PA:	pernicious anemia
RA:	rheumatoid arthritis
SLE:	systemic lupus erythematosus
TTP:	thrombotic thrombocytopenic purpura
UC:	ulcerative colitis

models included age (continuous), sex, race (white vs nonwhite), and insurance status (yes vs no).

To determine the associations of autoimmune disorders in inpatients with pemphigus or pemphigoid, multivariable logistic regression models were constructed with any autoimmune disorder as the dependent variable. Stepwise selection ($\alpha = 0.10$) was used from the available patient-level covariables: age (18-39, 40-59, 60-79, and ≥ 80 years), sex (female, male), race/ethnicity (white, black, Asian, Hispanic, other, or multiracial), median annual income of the hospital ZIP code (quartiles), insurance coverage (insured, uninsured), and number of chronic conditions (0-1, 2-5, and ≥ 6).

All statistical models included discharge trend weights, sample strata, and clustering by individual hospital. Comorbidities with a crude frequency of <5 in each cell were excluded from analyses. A 2-sided P value $< .05$ was considered statistically significant.

RESULTS

Population characteristics

There were 72,108,077 adult discharges captured in the NIS between 2002-2012, with 6256 (weighted frequency 29,804) and 13,009 (weighted frequency 62,315) admissions with pemphigus and pemphigoid, respectively. Adults hospitalized with versus without pemphigus were more likely to be older, male, nonwhite, and on Medicare. Whereas, adults hospitalized with versus without pemphigoid were more likely to be older, male, white, and on Medicare (Supplemental Table 2; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

Pemphigus and autoimmune disorders

In multivariable logistic regression models controlling for age, race/ethnicity, sex, and insurance

status, pemphigus was associated with significantly higher odds of having ≥ 1 autoimmune disorder (adjusted OR [aOR] 1.46, 95% CI 1.30-1.63). In particular, pemphigus was associated with 9 of 29 autoimmune disorders examined in bivariable regression models (Fig 1, A). Autoimmune disorders with the largest effect size included unspecified autoimmune disease (aOR 24.40, 95% CI 13.78-43.19), eosinophilic esophagitis (EOE; aOR 19.21, 95% CI 4.76-77.43), and vitiligo (aOR 4.20, 95% CI 1.28-13.78). Pemphigus was also associated with MG, pernicious anemia (PA), RA, SLE, unspecified connective tissue disease, and autoimmune hemolytic anemia. All the associations in bivariable models remained significant in multivariable models, except for PA.

In bivariable models stratified by age, pemphigus was significantly associated with MG, RA, SLE, autoimmune hemolytic anemia, and unspecified autoimmune disease in both adults <50 and ≥ 50 years of age (Table I, Supplemental Tables 3 and 4; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>). Whereas, Hashimoto disease, thyroiditis, Takayasu arteritis, ulcerative colitis (UC), Sjogren syndrome, vitiligo, and unspecified connective tissue disease were only associated with pemphigus in persons <50 years of age. EOE was only associated with pemphigus at age ≥ 50 years.

In models stratified by sex, pemphigus was significantly associated with MG, RA, vitiligo, autoimmune hemolytic anemia, and unspecified autoimmune disease in both male and female adults. Whereas, Hashimoto disease and SLE were only associated with pemphigus in female patients. EOE, PA, and unspecified connective tissue disease were only associated with pemphigus in male patients (Table I, Supplemental Tables 5 and 6; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

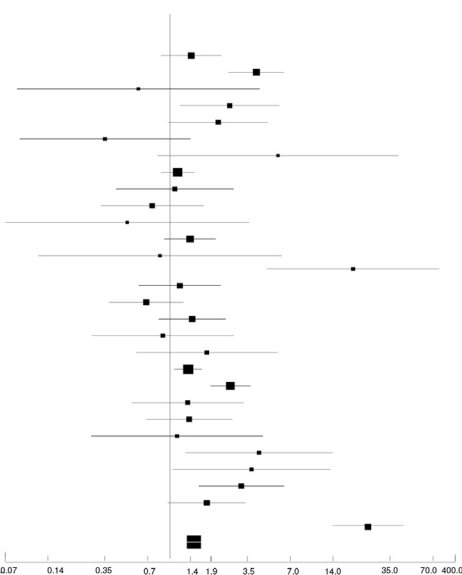
In models stratified by race, pemphigus was significantly associated with MG, RA, and SLE in all races. Whereas, Takayasu arteritis and vitiligo were significantly associated with pemphigus in nonwhite patients. EOE, autoimmune hemolytic anemia, and unspecified autoimmune disease were significantly associated with pemphigus in white patients (Table I, Supplemental Tables 7 and 8; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

Pemphigoid and autoimmune disorders

In multivariable regression models, pemphigoid was also associated with ≥ 1 autoimmune disorder (aOR 1.35, 95% CI 1.24-1.48). In particular, pemphigoid

A Associations between pemphigus and autoimmune disorders in adult inpatients

Autoimmune Comorbidity	Inpatient diagnosis of pemphigus					
	No			Yes		
	Wtd freq	% Prev [95% CI]	Wtd freq	% Prev [95% CI]	Crude OR [95% CI]	P
Multiple sclerosis	1,366,864	0.4 [0.4-0.4]	145	0.5 [0.3-0.7]	1.24 [0.81-1.89]	.3222
Myasthenia gravis	335,898	0.1 [0.1-0.1]	135	0.5 [0.3-0.7]	4.61 [2.97-7.17]	<.0001
Polymyositis	99,794	0.03 [0.03-0.03]	510	0.02 [0.00-0.05]	0.60 [0.09-4.21]	.6074
Hashimoto's disease	196,341	0.06 [0.06-0.06]	35	0.1 [0.0-0.2]	2.07 [0.98-4.34]	.0569
Thyroiditis	231,143	0.1 [0.1-0.1]	35	0.1 [0.0-0.2]	1.78 [0.86-3.70]	.1218
Giant cell arteritis	234,031	0.07 [0.07-0.07]	510	0.03 [0.00-0.08]	0.48 [0.12-1.84]	.2825
Takayasu's arteritis	12,070	0.004 [0.003-0.004]	510	0.02 [0.00-0.05]	4.34 [0.62-30.43]	.1398
Type 1 diabetes mellitus	4,857,291	1.4 [1.4-1.5]	383	1.3 [1.0-1.6]	0.91 [0.71-1.15]	.4257
Chronic glomerulonephritis	253,501	0.1 [0.1-0.1]	30	0.1 [0.0-0.2]	1.35 [0.62-2.95]	.4483
Polyarteritis nodosa	717,646	0.2 [0.2-0.2]	66	0.2 [0.1-0.4]	1.06 [0.53-2.14]	.8700
Primary biliary cirrhosis	111,319	0.03 [0.03-0.03]	510	0.02 [0.00-0.05]	0.52 [0.08-3.56]	.5021
Non-alcoholic steatohepatitis	1,304,943	0.4 [0.4-0.4]	145	0.5 [0.3-0.7]	1.28 [0.87-1.86]	.2100
Autoimmune hepatitis	20,656	0.006 [0.006-0.006]	510	0.02 [0.00-0.05]	0.85 [0.12-5.88]	.8696
Eosinophilic esophagitis	9,081	0.003 [0.003-0.003]	510	0.03 [0.00-0.07]	11.21 [2.78-45.15]	.0007
Pernicious anemia	349,359	0.1 [0.1-0.1]	62	0.2 [0.1-0.3]	2.04 [1.18-3.52]	.0104
Crohn's disease	1,682,447	0.5 [0.5-0.5]	76	0.3 [0.1-0.4]	0.52 [0.31-0.88]	.0153
Ulcerative colitis	960,195	0.3 [0.3-0.3]	101	0.3 [0.2-0.5]	1.23 [0.75-2.01]	.4218
Celiac disease	214,026	0.06 [0.06-0.06]	24	0.08 [0.01-0.15]	1.29 [0.54-3.04]	.5687
Ankylosing spondylitis	131,946	0.04 [0.04-0.04]	24	0.1 [0.0-0.2]	2.08 [0.58-7.47]	.2638
Rheumatoid arthritis	4,379,299	1.3 [1.3-1.3]	628	2.1 [1.7-2.5]	1.67 [1.36-2.06]	<.0001
Systemic lupus erythematosus	1,702,370	0.5 [0.5-0.5]	374	1.3 [0.9-1.6]	2.56 [1.91-3.42]	<.0001
Scleroderma	329,615	0.1 [0.1-0.1]	37	0.1 [0.0-0.2]	1.30 [0.52-3.20]	.5748
Sjogren's syndrome	131,229	0.1 [0.1-0.1]	47	0.2 [0.1-0.3]	1.75 [0.93-3.22]	.0720
Chronic urticaria	131,101	0.04 [0.04-0.04]	15	0.05 [0.00-0.11]	1.29 [0.42-4.01]	.6603
Vitiligo	51,234	0.02 [0.01-0.02]	24	0.1 [0.0-0.2]	5.33 [1.91-14.85]	.0014
Unspecified diffuse connective tissue disease	97,723	0.03 [0.03-0.03]	30	0.1 [0.0-0.2]	3.57 [1.17-10.92]	.0254
Autoimmune hemolytic anemia	135,447	0.04 [0.04-0.04]	43	0.1 [0.1-0.2]	3.68 [1.93-7.01]	<.0001
Idiopathic thrombocytopenic purpura	336,848	0.1 [0.1-0.1]	51	0.2 [0.1-0.3]	1.76 [0.95-3.27]	.0745
Unspecified autoimmune disease	36,115	0.01 [0.01-0.01]	71	0.2 [0.1-0.4]	22.64 [13.59-37.72]	<.0001
Any autoimmune disorder	10,358,034	5.7 [5.6-5.7]	2,381	8.0 [7.2-8.8]	1.45 [1.30-1.61]	<.0001

**B** Associations between pemphigoid and autoimmune disorders in adult inpatients

Autoimmune Comorbidity	Inpatient diagnosis of pemphigoid					
	No			Yes		
	Wtd freq	% Prev [95% CI]	Wtd freq	% Prev [95% CI]	Crude OR [95% CI]	P
Multiple sclerosis	1,366,864	0.4 [0.4-0.4]	682	1.1 [0.9-1.3]	2.75 [2.21-3.44]	<.0001
Myasthenia gravis	335,898	0.1 [0.1-0.1]	122	0.2 [0.1-0.3]	1.99 [1.17-3.38]	.0111
Polymyositis	99,794	0.03 [0.03-0.03]	16	0.03 [0.00-0.05]	0.89 [0.29-2.74]	.8328
Hashimoto's disease	196,341	0.06 [0.06-0.06]	39	0.06 [0.02-0.11]	1.11 [0.56-2.20]	.7744
Thyroiditis	231,143	0.1 [0.1-0.1]	39	0.06 [0.0-0.1]	0.94 [0.47-1.87]	.8531
Giant cell arteritis	234,031	0.07 [0.07-0.07]	134	0.2 [0.1-0.3]	3.14 [1.92-5.15]	<.0001
Takayasu's arteritis	12,070	0.004 [0.003-0.004]	510	0.008 [0.000-0.023a]	2.19 [0.31-15.48]	.4309
Type 1 diabetes mellitus	4,857,291	1.4 [1.4-1.5]	808	1.3 [1.1-1.5]	0.91 [0.76-1.10]	.3294
Chronic glomerulonephritis	253,501	0.1 [0.1-0.1]	63	0.1 [0.0-0.2]	1.36 [0.79-2.39]	.2785
Goodpasture's syndrome	23,005	0.007 [0.006-0.007]	510	0.008 [0.000-0.024]	1.20 [0.18-8.26]	.8526
Polyarteritis nodosa	717,646	0.2 [0.2-0.2]	105	0.2 [0.1-0.3]	0.80 [0.40-1.31]	.3743
Granulomatosis with polyangiitis	118,343	0.03 [0.03-0.04]	510	0.01 [0.00-0.03]	0.42 [0.10-1.65]	.2115
Primary biliary cirrhosis	111,319	0.03 [0.03-0.03]	510	0.01 [0.00-0.03]	0.38 [0.09-1.51]	.1665
Non-alcoholic steatohepatitis	1,304,943	0.4 [0.4-0.4]	125	0.2 [0.1-0.3]	0.53 [0.36-0.79]	.0018
Autoimmune hepatitis	20,656	0.006 [0.006-0.006]	510	0.02 [0.00-0.04]	0.82 [0.21-3.18]	.7743
Pernicious anemia	349,359	0.1 [0.1-0.1]	185	0.3 [0.2-0.4]	2.91 [2.03-4.17]	<.0001
Crohn's disease	1,682,447	0.5 [0.5-0.5]	158	0.3 [0.2-0.4]	0.52 [0.35-0.76]	.0008
Ulcerative colitis	960,195	0.3 [0.3-0.3]	265	0.4 [0.3-0.6]	1.52 [1.05-2.19]	.0258
Celiac disease	214,026	0.06 [0.06-0.06]	123	0.2 [0.1-0.3]	3.16 [2.13-4.69]	<.0001
Ankylosing spondylitis	131,946	0.04 [0.04-0.04]	32	0.05 [0.01-0.09]	1.32 [0.58-3.02]	.5061
Rheumatoid arthritis	4,379,299	1.3 [1.3-1.3]	1,257	2.0 [1.7-2.3]	1.59 [1.38-1.84]	<.0001
Erythema nodosum	20,656	0.006 [0.006-0.006]	510	0.02 [0.00-0.04]	2.59 [0.66-10.21]	.1741
Systemic lupus erythematosus	1,702,370	0.5 [0.5-0.5]	431	0.7 [0.5-0.9]	1.39 [1.05-1.84]	.0208
Scleroderma	329,615	0.1 [0.1-0.1]	91	0.1 [0.1-0.2]	1.52 [0.88-2.61]	.1334
Sjogren's syndrome	131,229	0.1 [0.1-0.1]	74	0.1 [0.1-0.2]	1.30 [0.74-2.28]	.3683
Chronic urticaria	131,101	0.04 [0.04-0.04]	108	0.2 [0.1-0.2]	4.52 [2.93-6.97]	<.0001
Vitiligo	51,234	0.02 [0.01-0.02]	63	0.1 [0.0-0.2]	6.78 [3.62-12.69]	<.0001
Unspecified diffuse connective tissue disease	97,723	0.03 [0.03-0.03]	29	0.05 [0.01-0.08]	1.62 [0.74-3.58]	.2296
Autoimmune hemolytic anemia	135,447	0.04 [0.04-0.04]	50	0.1 [0.0-0.1]	2.04 [1.01-4.11]	.0457
Idiopathic thrombocytopenic purpura	336,848	0.1 [0.1-0.1]	119	0.2 [0.1-0.3]	1.94 [1.25-3.01]	.0030
Thrombotic thrombocytopenic purpura	50,423	0.02 [0.01-0.02]	30	0.05 [0.00-0.10]	3.03 [0.99-9.29]	.0524
Unspecified autoimmune disease	36,115	0.01 [0.01-0.01]	117	0.2 [0.1-0.3]	17.81 [12.03-26.37]	<.0001
Any autoimmune disorder	19,537,211	5.7 [5.7-5.8]	4,936	7.9 [7.3-8.5]	1.42 [1.31-1.54]	<.0001

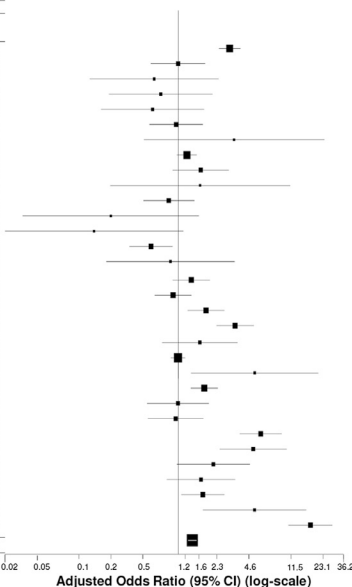


Fig 1. Associations of pemphigus (**A**) and pemphigoid (**B**) with autoimmune disorders. Survey logistic regression models were constructed with pemphigus or pemphigoid as the independent variable and the respective autoimmune disorder as the dependent variable. Multivariable models included age, sex, race/ethnicity, and insurance status as covariables. Adj ORs and 95% CIs were estimated. Forest plots of adj ORs and 95% CIs from model 1 are presented. *Adj*, Adjusted; *CI*, confidence interval; *freq*, frequency; *OR*, odds ratio; *wtd*, weighted.

was associated with 13 of 32 autoimmune disorders examined in bivariable regression models (Fig 1, B). Autoimmune disorders with the largest effect size included unspecified autoimmune disease (aOR 17.57, 95% CI 10.90-28.32), vitiligo (aOR 5.08, 95% CI 2.46-10.52), and chronic urticaria (aOR 5.96, 95% CI 3.78-9.41). Pemphigoid was also associated with MS, MG, giant cell arteritis, pernicious anemia, UC, celiac

disease, RA, SLE, autoimmune hemolytic anemia, and idiopathic thrombocytopenic purpura (ITP) (Fig 1, B). Most associations in bivariable models remained significant in multivariable models, except MG, giant cell arteritis, PA, RA, and autoimmune hemolytic anemia.

In bivariable models stratified by age, pemphigoid was associated with MS, PA, RA, chronic urticaria,

Table I. Summary of comorbid autoimmune conditions in adult patients with pemphigus and pemphigoid stratified by age, sex, and race

Autoimmune comorbidity	Pemphigus							Pemphigoid						
	Age, y			Sex		Race		Age, y			Sex		Race	
	All patients							All patients						
	≥18	18-49	≥50	M	F	White	Nonwhite	≥18	18-49	≥50	M	F	White	Nonwhite
Multiple sclerosis								+	+	+	+	+	+	+
Myasthenia gravis	+		+	+	+	+	+	+	+			+		
Hashimoto disease					+				+					
Thyroiditis		+							+					
Takayasu arteritis		+					+		+					
Giant cell arteritis								+		+		+		
Chronic glomerulonephritis									+					
Eosinophilic esophagitis	+		+	+		+								
Polyarteritis nodosa									+					
Pernicious anemia	+			+				+	+	+	+	+	+	+
Crohn's disease														
Ulcerative colitis		+						+	+					
Celiac disease								+		+	+	+	+	+
Rheumatoid arthritis	+	+	+	+	+	+	+	+	+	+		+	+	+
Erythema nodosum									+					
Systemic lupus erythematosus	+	+	+		+	+	+	+	+		+	+		
Scleroderma									+					
Sjogren syndrome		+							+					
Chronic urticaria								+	+	+	+	+	+	+
Vitiligo	+	+		+	+		+	+	+	+	+	+	+	+
Unspecified diffuse connective tissue disease	+	+		+					+					
Autoimmune hemolytic anemia	+	+	+	+	+	+		+						+
Idiopathic thrombocytopenic purpura								+	+	+	+		+	
Thrombotic thrombocytopenic purpura										+	+	+	+	
Unspecified autoimmune disease	+	+	+	+	+	+		+	+	+	+	+	+	+
Any autoimmune disorder	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+, Yes; blank, no.

vitiligo, ITP, and unspecified autoimmune disease in both adults <50 and ≥ 50 years of age. Whereas, MG, Hashimoto disease, thyroiditis, Takayasu arteritis, chronic glomerulonephritis, polyarteritis nodosa, UC, erythema nodosum, SLE, scleroderma, Sjogren syndrome, and unspecified connective tissue disease were only associated with pemphigoid in persons <50 years of age. Giant cell arteritis, celiac disease, and thrombotic thrombocytopenic purpura (TTP) were only associated with pemphigoid in patients ≥50 years of age (Table I, Supplemental Tables 9 and 10; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

In models stratified by sex, pemphigoid was associated with MS, PA, celiac disease, chronic urticaria, vitiligo, and unspecified autoimmune disease in both male and female adults. Whereas, MG, giant cell arteritis, RA, SLE, TTP, and any autoimmune disorder were only associated with pemphigoid in female patients. ITP was only significantly associated with

pemphigoid in male adults (Table I, Supplemental Tables 11 and 12; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

In models stratified by race, pemphigoid was associated with MS, pernicious anemia, celiac disease, RA, chronic urticaria, vitiligo, and unspecified autoimmune disease in all races. Whereas, autoimmune hemolytic anemia was only associated with pemphigoid in nonwhite patients. SLE, ITP, and TTP were associated with pemphigoid in white adults (Table I, Supplemental Tables 13 and 14; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

In models comparing the prevalence of autoimmune conditions in patients with pemphigoid versus those with pemphigus, pemphigoid was associated with a higher risk of MS, giant cell arteritis, Goodpasture syndrome, granulomatosis with polyangiitis, erythema nodosum, chronic urticaria, and TTP. Whereas, MG, nonalcoholic steatohepatitis, SLE, and EOE were

Table II. Associations of autoimmune disorders in US adult inpatients with pemphigus or pemphigoid

Variable	Pemphigus		Pemphigoid	
	aOR (95% CI)	P value	aOR (95% CI)	P value
Age, y				
18-39	1.00 (Referent)	—	1.00 (Referent)	—
40-59	1.00 (0.84-1.19)	.9832	0.82 (0.68-0.99)	.0807
60-79	0.51 (0.43-0.61)	<.0001	0.28 (0.24-0.34)	<.0001
≥80	0.26 (0.21-0.31)	<.0001	0.13 (0.11-0.16)	<.0001
Sex				
Female	1.64 (1.50-1.79)	<.0001	2.05 (1.92-2.18)	<.0001
Male	1.00 (Referent)	—	1.00 (Referent)	—
Race/ethnicity				
White	1.00 (Referent)	—	1.00 (Referent)	—
Black	1.17 (1.05-1.30)	.0188	0.93 (0.85-1.01)	.1372
Hispanic	0.59 (0.51-0.68)	<.0001	0.81 (0.71-0.93)	.0097
Asian	0.84 (0.64-1.09)	.2629	0.69 (0.58-0.81)	.0003
Other	0.73 (0.57-0.94)	.0412	0.60 (0.48-0.74)	<.0001
Insurance				
Insured	1.45 (1.19-1.76)	.0023	2.31 (1.81-2.94)	<.0001
Not Insured	1.00 (Referent)	—	1.00 (Referent)	—
No. chronic conditions*				
0-1			1.00 (Referent)	—
2-5			22.86 (10.70-48.86)	<.0001
≥6			40.67 (19.03-86.92)	<.0001

aOR, Adjusted odds ratio; CI, confidence interval; —, reference category.

*A chronic condition was defined as having lasted for at least 12 months and either placing limitations on self-care or requiring continuous therapy/treatment.

inversely associated with pemphigoid when compared with pemphigus (Supplemental Table 15; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

Associations of autoimmune disorders

Multivariable models with stepwise selection were used to identify associations of autoimmune disorders among inpatients with pemphigus or pemphigoid. Among inpatients with pemphigus, autoimmune disorders were associated with female sex (aOR 1.64, 95% CI 1.50-1.79), black race/ethnicity (aOR 1.17, 95% CI 1.05-1.30), and being insured (aOR 1.45, 95% CI 1.19-1.76) but inversely associated with increasing age (60-79 years aOR 0.51, 95% CI 0.43-0.61, and ≥80 years aOR 0.26, 95% CI 0.21-0.31), Hispanic race/ethnicity (aOR 0.59, 95% CI 0.51-0.68), and multiracial or other race/ethnicity (aOR 0.73, 95% CI 0.57-0.94; Table II).

Among pemphigoid inpatients, autoimmune disorders were associated with female sex (aOR 2.05, 95% CI 1.92-2.18), increasing number of chronic conditions (2-5 conditions aOR 22.86, 95% CI 10.70-48.86, and ≥6 conditions aOR 40.67, 95% CI 19.03-86.92) and being insured (aOR 2.31, 95% CI 1.81-2.94) but inversely associated with increasing age (60-79 years aOR 0.28, 95% CI 0.24-0.34, and ≥80 years aOR 0.13, 95% CI 0.11-0.16), nonwhite race/ethnicity (Hispanic aOR 0.81, 95% CI 0.71-0.93; Asian aOR

0.69, 95% CI 0.58-0.81; and multiracial or other race/ethnicity aOR 0.60, 95% CI 0.48-0.74) (Table II).

LOS and cost

There were no significant differences in geometric mean LOS or cost of care between inpatients who had pemphigus with versus without an autoimmune disorder (LOS $P = .7749$, cost $P = .9630$) or between inpatients who had pemphigoid with versus without an autoimmune disorder (LOS $P = .5171$, cost $P = .0523$) (Tables III and IV). However, owing to the higher prevalence of autoimmune disorders, the estimated excess annual costs of hospital care attributed to autoimmune disorders among inpatients with pemphigus was \$2,286,588 and pemphigoid \$4,301,681 (Tables III and IV).

Inpatient mortality

Inpatient mortality was generally low among adult inpatients with pemphigus or pemphigoid. However, MG, pernicious anemia, autoimmune hemolytic anemia, ITP, and unspecified autoimmune disease were associated with numerically higher inpatient mortality rates among pemphigus patients. MG, polymyositis, giant cell arteritis, type 1 diabetes mellitus, UC, ankylosing spondylitis, unspecified diffuse connective tissue disease, autoimmune hemolytic anemia, TTP, and unspecified autoimmune

Table III. Costs of care and LOS of adults with pemphigus with and without autoimmune disorders

Autoimmune comorbidity	Autoimmune comorbidity					
	No			Yes		
	Cost, USD, geometric mean (95% CI)	Cost, USD, geometric mean (95% CI)	Excess annual cost, USD	LOS, d, geometric mean (95% CI)	LOS, d, geometric mean (95% CI)	Excess annual LOS, d
Multiple sclerosis	9107 (8840-9382)	9364 (7113-12,327)	144,012	4.9 (4.8-5.1)	4.5 (3.6-5.7)	59.6
Myasthenia gravis	9087 (8820-9362)	14,972 (12,251-18,298)	52,958	4.9 (4.8-5.1)	6.7 (5.3-8.5)	23.5
Polymyositis	9108 (8841-9382)	11,839 (NE)	—	4.9 (4.8-5.1)	6.0 (NE)	—
Hashimoto disease	9106 (8840-9381)	10,758 (NE)	29,577	4.9 (4.8-5.1)	4.9 (NE)	11.5
Thyroiditis	9106 (8840-9381)	10,758 (NE)	—	4.9 (4.8-5.1)	4.9 (NE)	—
Giant cell arteritis	9106 (8840-9381)	16,193 (NE)	—	4.9 (4.8-5.1)	12.2 (NE)	—
Takayasu arteritis	9103 (8837-9378)	227,872 (NE)	18,922	4.9 (4.8-5.1)	95.0 (NE)	7.9
Type 1 diabetes mellitus	9092 (8825-9367)	10,396 (8059-13,409)	—	4.9 (4.8-5.0)	5.9 (4.7-7.4)	—
Chronic glomerulonephritis	9113 (8846-9388)	5744 (378-87,333)	—	4.9 (4.8-5.1)	3.7 (0.1-117.7)	—
Polyarteritis nodosa	9119 (8851-9394)	5539 (4046-7582)	—	5.0 (4.8-5.1)	3.1 (2.5-3.9)	—
Primary biliary cirrhosis	9108 (8841-9383)	9201 (NE)	—	4.9 (4.8-5.1)	6.0 (NE)	—
Nonalcoholic steatohepatitis	9097 (8830-9371)	11,609 (7607-17,717)	199,019	4.9 (4.8-5.1)	5.3 (3.6-8.0)	83.2
Autoimmune hepatitis	9109 (8842-9383)	6275 (NE)	856	4.9 (4.8-5.1)	3.0 (NE)	0.4
Eosinophilic esophagitis	9107 (8841-9382)	12,286 (NE)	1031	4.9 (4.8-5.1)	4.8 (NE)	0.5
Pernicious anemia	9114 (8847-9389)	6704 (6394-7029)	22,532	4.9 (4.8-5.1)	5.0 (2.8-9.2)	15.9
Crohn's disease	9110 (8843-9385)	8217 (6420-10,516)	—	4.9 (4.8-5.1)	3.5 (1.5-8.0)	—
Ulcerative colitis	9102 (8836-9376)	10,882 (7165-16,527)	—	4.9 (4.8-5.1)	5.7 (3.9-8.4)	—
Celiac disease	9109 (8842-9383)	8498 (NE)	17,543	4.9 (4.8-5.1)	6.7 (NE)	13.0
Ankylosing spondylitis	9109 (8842-9383)	8578 (NE)	12,069	4.9 (4.8-5.1)	3.3 (NE)	4.1
Rheumatoid arthritis	9112 (8845-9387)	8946 (7653-10,458)	422,578	4.9 (4.8-5.1)	5.1 (4.5-5.9)	237.6
Systemic lupus erythematosus	9140 (8871-9416)	6890 (5916-8024)	149,985	5.0 (4.8-5.1)	3.9 (3.4-4.4)	75.4
Scleroderma	9106 (8840-9381)	11,290 (NE)	—	4.9 (4.8-5.1)	6.5 (3.7-11.5)	—
Sjogren syndrome	9108 (8842-9382)	9225 (5124-16,608)	26,725	4.9 (4.8-5.1)	3.4 (2.0-6.0)	12.4
Chronic urticaria	9108 (8842-9383)	9193 (NE)	41,855	4.9 (4.8-5.1)	6.8 (NE)	15.1
Vitiligo	9107 (8840-9381)	11,404 (2699-48,192)	4491	4.9 (4.8-5.1)	6.2 (0.4-110.9)	3.1
Unspecified diffuse connective tissue disease	9113 (8846-9388)	4879 (NE)	3604	4.9 (4.8-5.1)	5.7 (NE)	4.9
Autoimmune hemolytic anemia	9102 (8836-9376)	13,862 (3617-53,127)	66,789	4.9 (4.8-5.1)	6.6 (2.7-15.9)	20.9
Idiopathic thrombocytopenic purpura	9101 (8835-9376)	14,141 (NE)	45,588	4.9 (4.8-5.1)	6.8 (NE)	17.3
Unspecified autoimmune disease	9110 (8843-9384)	8455 (8265-8650)	3172	4.9 (4.8-5.1)	4.7 (2.4-9.3)	4.9
Any autoimmune disorder	9106 (8835-9386)	9127 (8353-9973)	2,286,588	4.9 (4.8-5.1)	5.0 (4.6-5.4)	1187.4

CI, Confidence interval; LOS, length of stay; NE, not estimable; USD, US dollar; —, no excess cost or LOS.

Table IV. Cost of care and LOS of adults with pemphigoid with and without autoimmune disorders

Autoimmune comorbidity	Autoimmune comorbidity					
	No			Yes		
	Cost, USD, geometric mean (95% CI)	Cost, USD, geometric mean (95% CI)	Excess annual cost, USD	LOS, d, geometric mean (95% CI)	LOS, d, geometric mean (95% CI)	Excess annual LOS, d
Multiple sclerosis	8880 (8696-9068)	9060 (8213-9995)	258,378	5.1 (5.1-5.2)	5.7 (5.1-6.4)	160.8
Myasthenia gravis	8875 (8693-9061)	13,301 (11,973-14,777)	134,047	5.2 (5.1-5.2)	6.2 (5.6-6.9)	56.0
Polymyositis	8882 (8699-9068)	11,744 (NE)	—	5.2 (5.1-5.2)	4.1 (NE)	—
Hashimoto disease	8884 (8701-9070)	7015 (4556-10,800)	—	5.2 (5.1-5.2)	5.3 (4.7-5.9)	—
Thyroiditis	8884 (8701-9070)	7015 (4556-10,800)	—	5.2 (5.1-5.2)	5.3 (4.7-5.9)	—
Giant cell arteritis	8881 (8699-9067)	9215 (7164-11,855)	51,881	5.2 (5.1-5.2)	4.5 (3.7-5.4)	25.0
Takayasu arteritis	8882 (8700-9068)	—	NE	5.2 (5.1-5.2)	3.0 (NE)	0.6
Type 1 diabetes mellitus	8872 (8688-9060)	9710 (8522-11,064)	—	5.1 (5.1-5.2)	5.6 (5.0-6.4)	—
Chronic glomerulonephritis	8883 (8701-9069)	8026 (1720-37,460)	—	5.2 (5.1-5.2)	4.7 (2.1-10.6)	—
Goodpasture syndrome	8882 (8700-9068)	—	NE	5.2 (5.1-5.2)	2.0 (NE)	0.8
Polyarteritis nodosa	8878 (8696-9065)	11,220 (8171-15,406)	—	5.2 (5.1-5.2)	6.0 (4.4-8.1)	—
Granulomatosis with polyangiitis	8882 (8699-9068)	13,091 (NE)	—	5.2 (5.1-5.2)	5.6 (NE)	—
Primary biliary cirrhosis	8882 (8700-9068)	8074 (NE)	—	5.2 (5.1-5.2)	4.0 (NE)	—
Non-alcoholic steatohepatitis	8878 (8695-9064)	11,405 (7526-17,284)	—	5.2 (5.1-5.2)	5.3 (3.5-8.2)	—
Autoimmune hepatitis	8883 (8700-9069)	5941 (NE)	1764	5.2 (5.1-5.2)	3.9 (NE)	1.1
Pernicious anemia	8885 (8702-9071)	8024 (6597-9758)	59,498	5.2 (5.1-5.2)	5.5 (4.5-6.8)	38.9
Crohn's disease	8884 (8701-9071)	8067 (5897-11,035)	—	5.2 (5.1-5.2)	3.7 (2.9-4.9)	—
Ulcerative colitis	8878 (8696-9065)	9812 (7608-12,655)	238,064	5.2 (5.1-5.2)	4.7 (4.2-5.4)	110.3
Celiac disease	8882 (8700-9069)	8800 (6076-12,745)	37,950	5.2 (5.1-5.2)	5.0 (4.2-5.9)	22.9
Ankylosing spondylitis	8880 (8698-9067)	14,385 (NE)	46,734	5.2 (5.1-5.2)	5.2 (NE)	13.9
Rheumatoid arthritis	8881 (8697-9069)	8935 (8110-9843)	966,742	5.2 (5.1-5.2)	5.2 (4.7-5.7)	541.0
Erythema nodosum	8883 (8701-9069)	4845 (NE)	1580	5.2 (5.1-5.2)	5.2 (NE)	1.5
Systemic lupus erythematosus	8888 (8706-9074)	8099 (6952-9435)	287,545	5.2 (5.1-5.2)	4.4 (3.7-5.2)	168.0
Scleroderma	8882 (8700-9069)	8758 (5355-14,321)	—	5.2 (5.1-5.2)	4.7 (3.0-7.4)	—
Sjogren syndrome	8881 (8698-9067)	10,306 (8076-13,152)	—	5.2 (5.1-5.2)	5.7 (4.3-7.6)	—
Chronic urticaria	8883 (8701-9069)	8106 (NE)	17,892	5.2 (5.1-5.2)	4.5 (0.9-22.6)	10.7
Vitiligo	8881 (8699-9067)	9965 (76-1,307,694)	16,269	5.2 (5.1-5.2)	5.6 (3.7-8.4)	8.5
Unspecified diffuse connective tissue disease	8883 (8701-9069)	7583 (3561-16,148)	11,875	5.2 (5.1-5.2)	3.9 (0.2-87.1)	7.8
Autoimmune hemolytic anemia	8878 (8695-9064)	16,506 (1212-224,767)	34,454	5.2 (5.1-5.2)	6.6 (4.4-9.9)	13.4
Idiopathic thrombocytopenic purpura	8875 (8693-9061)	13,103 (9766-17,581)	94,749	5.1 (5.1-5.2)	7.0 (5.0-9.6)	49.0
TTP	8877 (8694-9063)	87,257 (NE)	57,525	5.2 (5.1-5.2)	10.1 (NE)	20.7
Unspecified autoimmune disease	8884 (8702-9071)	7765 (5301-11,375)	5350	5.2 (5.1-5.2)	4.9 (4.0-5.9)	3.3
Any autoimmune disorder	8842 (8654-9034)	9360 (8877-9869)	4,301,681	5.1 (5.1-5.2)	5.2 (5.0-5.5)	2388.2

CI, Confidence interval; LOS, length of stay; NE, not estimable; TTP, thrombotic thrombocytopenic purpura; USD, US dollar; —, reference category.

disease were associated with numerically higher inpatient mortality rates among pemphigoid patients (Supplemental Table 16; available at <https://data.mendeley.com/datasets/368wwn8n9t/1>).

DISCUSSION

Hospitalized adults with pemphigus or pemphigoid had higher rates of comorbid cutaneous, extracutaneous, and systemic autoimmune disorders. Pemphigus and pemphigoid were associated with MG, PA, SLE, vitiligo, RA, autoimmune hemolytic anemia, and unspecified autoimmune disease. Pemphigus was also associated with EOE and connective tissue disease, and pemphigoid was also associated with MS, giant cell arteritis, UC, celiac disease, chronic urticaria, and ITP. These results are consistent with case series and smaller studies showing higher rates of comorbid cutaneous, extracutaneous, and systemic autoimmune disorders in these bullous diseases.¹ Pemphigoid was associated with increased autoimmune disorders in female patients, specifically MG, giant cell arteritis, RA, SLE, and TTP. Many of these disorders were associated with excess costs and numerically increased rates of mortality.

Comorbid autoimmune disorders in pemphigoid and pemphigus might be related to cross-reactivity of autoantibodies toward skin antigens with antigens in the nervous, musculoskeletal, and other organ systems.^{3,4,28} Immune dysregulation in pemphigus and pemphigoid might lead to epitope spreading and the development of additional autoantibodies leading to other autoimmune disorders.

Other studies have shown that certain autoimmune disorders occur in clusters, eg, pemphigus vulgaris with autoimmune thyroid disease, RA, and diabetes mellitus type I.¹¹ A potential mechanism studied for this linkage of autoimmune diseases relates to human leukocyte antigen alleles.^{29,30} It was proposed that human leukocyte antigen DQB1*3:01 binding to the immunogenic portion of bullous pemphigoid 180 (BP180) autoantigen might be a potential mechanism by which neuronal collagen BP180 leads to cutaneous disease.²⁴ Future research is needed to determine the mechanisms of pemphigus and pemphigoid with systemic autoimmune disorders.

Positive correlations among total serum IgE levels, disease severity, and basal membrane zone antibody levels were observed in pemphigoid.³¹ The presence of self-reactive IgE is well recognized in SLE³² and chronic idiopathic urticaria.³³ One open-label, uncontrolled study showed that 5 of 6 patients with pemphigoid treated with the anti-IgE monoclonal antibody omalizumab resulted in decreased itching,

blister count, urticarial plaques, and eosinophilic inflammation. These preliminary studies suggest that IgE might play a role in pathogenesis and severity of pemphigoid.

A multicenter, prospective case–control study found that aldosterone antagonists and neuroleptics might be risk factors for pemphigoid.³⁴ Pemphigoid was also found to be associated with numerous psychiatric disorders, including schizophrenia.²⁶ Cases of pemphigoid were reported with dipeptidyl peptidase 4 inhibitors.^{35,36} Dipeptidyl peptidase 4 inhibitors can change the proper cleavage of BP180, thereby affecting its antigenicity and function³⁴ and enhance the activity of proinflammatory cytokines leading to eosinophil activation in skin, tissue damage, and blister formation.³⁴

Strengths of this study include a nationally representative sample of >72 million hospitalizations spanning 11 years. Because manual chart review was not possible, prior patient history was unavailable. We could not determine the severity and phenotype of pemphigus or pemphigoid, outpatient treatment approaches (eg, oral immunosuppressive medications), or whether patients were previously hospitalized. Time of diagnosis of autoimmune conditions was not included in NIS, precluding study of temporal relationships of pemphigus and pemphigoid with autoimmune disorders. Moreover, we were unable to determine how many of the hospitalizations were readmissions or transfers between hospitals. Some patients could have been admitted repeatedly for infections. Some autoimmune comorbidities might have been misclassified. For example, urticarial pemphigoid could have been classified as CU. We do not believe misclassification was a major problem for other autoimmune comorbidities. Although the overall cohort was large, some of the comorbidities were rare in pemphigus and pemphigoid, resulting in smaller sample sizes. Thus, we were unable to examine differences in comorbidities among those with primary hospitalization for pemphigus or pemphigoid versus controls. Finally, there is potential for selection bias for more severe pemphigus and pemphigoid patients with an inpatient cohort. Patients admitted primarily for pemphigus or pemphigoid were likely to have more severe disease and do not represent the entire spectrum of pemphigus or pemphigoid patients. Thus, the results might not be generalizable to all pemphigus and pemphigoid patients. Alternatively, comorbidities might predispose patients to increased hospitalization. The prevalences of comorbid disorders in this study might be more reflective of moderate-severe pemphigus or pemphigoid and be overestimated for mild disease.

In conclusion, hospitalized adults with pemphigus or pemphigoid had higher odds of autoimmune disorders affecting the skin, gastrointestinal, hematologic, and neurologic systems. Further studies are needed to confirm these associations and develop interventions for their prevention, screening, and treatment.

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