ORIGINAL ARTICLE

Association of herpes zoster and chronic inflammatory skin disease in US inpatients

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Background: Patients with chronic inflammatory skin disease (CISD) have potential risk factors for herpes zoster (HZ). However, little is known about HZ risk in CISD.

Objective: To determine whether CISD is associated with HZ.

Methods: Data were analyzed from the 2002 to 2012 Nationwide Inpatient Sample, a representative cohort of US hospitalizations (N = 68,088,221 children and adults).

Results: In multivariable logistic regression models including age, sex, race/ethnicity, insurance, household income, and long-term systemic corticosteroid use, hospitalization for HZ was associated with atopic dermatitis (adjusted odds ratio [95% confidence interval], 1.38 [1.14-1.68]), psoriasis (4.78 [2.83-8.08]), pemphigus (1.77 [1.01-3.12]), bullous pemphigoid (1.77 [1.01-3.12]), mycosis fungoides (3.79 [2.55-5.65]), dermatomyositis (7.31 [5.27-10.12]), systemic sclerosis (1.92 [1.47-2.53]), cutaneous lupus erythematosus (1.94 [1.10-3.44]), vitiligo (2.00 [1.04-3.85]), and sarcoidosis (1.52 [1.22-1.90]). Only lichen planus (crude odds ratio [95% confidence interval], 3.01 [1.36-6.67]), Sézary syndrome (12.14 [5.20-28.31]), morphea (2.74 [1.36-5.51]), and pyoderma gangrenosum (2.44 [1.16-5.13]) showed increased odds in bivariable models. Sensitivity analyses among those younger than 60 and younger than 50 years showed similar results. Predictors of HZ in CISD included female sex, fewer chronic conditions, and long-term systemic corticosteroid use.

Limitations: Cross-sectional study.

Conclusions: Many CISDs are associated with increased hospitalization for HZ, even below the ages recommended for HZ vaccination. Additional studies are needed to establish CISD-specific vaccination guidelines. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2019.12.073.)

Key words: autoimmune; burden; chronic; cost of care; dermatitis; herpes zoster; hospitalization; inflammation; inflammatory skin disease; length of stay; shingles.

Herpes zoster (HZ) is a painful, vesicular eruption caused by reactivation of latent varicella zoster virus (VZV) in sensory ganglion. Despite childhood varicella vaccination and effective antiviral therapy, HZ incidence has steadily increased over several decades.[1-3] Nearly 1 in 3 people in the United States will develop HZ in their lifetime, with approximately 1 million cases annually and a 3% hospitalization rate.[4] HZ can present with dissemination and complications requiring hospitalization, especially in immunosuppressed individuals.[5] Despite 2 HZ vaccines

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approved for adults 50 years and older,[6] evidence-based guidelines, and public health advocacy, many individuals at high risk remain unvaccinated and at risk for significant morbidity from HZ.[7]

Chronic inflammatory and autoimmune diseases, including rheumatoid arthritis,[8] inflammatory bowel disease,[9] and systemic lupus erythematosus (SLE),[10] were found to be associated with increased HZ risk.[11] This risk is augmented by immunosuppression medications, such as systemic corticosteroids, immunosuppressants, and biologic agents.[8,11-13] Patients with other chronic inflammatory skin diseases (CISDs), including atopic dermatitis (AD), psoriasis, pemphigus, bullous pemphigoid (BP), hidradenitis suppurativa (HS), chronic idiopathic/spontaneous urticaria (CIU), lichen planus (LP), mycosis fungoides (MF), Sézary syndrome (SS), dermatomyositis, morphea, systemic sclerosis (SSc), cutaneous lupus erythematosus (CLE), vitiligo, sarcoidosis, alopecia areata (AA), and pyoderma gangrenosum (PG) have potential risk factors for HZ, including long-term use of systemic immunosuppressants and immune dysregulation in the skin and periphery. We hypothesized that multiple CISDs are associated with HZ, and we examined whether these CISDs are associated with HZ in hospitalized US patients.

CAPSULE SUMMARY

- Patients with a variety of chronic inflammatory skin disease had higher odds of hospitalization for herpes zoster, even at ages below current vaccination guidelines, as well as prolonged inpatient length of stay and increased cost of hospital care.
- Dermatologists should consider disease-specific risk factors in these patients and encourage enhanced vaccination coverage.

METHODS

The 2002 through 2012 Nationwide Inpatient Sample (NIS) was analyzed. The NIS is sponsored by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. Each year of the NIS contains an approximately 20% stratified representative sample of hospitalizations in the United States. Sample weights were created by the NIS that factor in the complex sampling design and allow for representative estimates of hospital discharges across the United States. Data were deidentified, and no attempts were made to identify individuals in the database. Patient consent was not obtained because the data were received deidentified. All parties were compliant with the HCUP's formal data use agreement. This study was approved by the institutional review board at Northwestern University.

The NIS lists 1 primary diagnosis, that is, the primary reason for hospitalization, and up to 24 secondary diagnoses. The databases were searched for a primary diagnosis of HZ and secondary diagnosis of various CISDs or history of long-term systemic corticosteroid use based on International Classification of Disease, Ninth Revision, Clinical Modification codes (Supplemental Table I; available via Mendeley at https://data.mendeley.com/datasets/7z9656xvgy/1).[14-27] CISDs were selected based on skin conditions associated with chronic, systemic inflammation.

Statistical analysis

Statistical analysis was performed by using survey procedures adjusting for sample weighting, clustering, and strata in SAS, version 9.4 (SAS Institute, Cary, NC). Incidences of hospitalization for HZ in the general population were estimated. Baseline characteristics of inpatients with and without an HZ diagnosis were determined. The cost for inpatient care was estimated based on the total charge of the hospitalization and the cost-to-charge ratio estimated by HCUP. Costs were adjusted for inflation to the year 2018 according to the Consumer Price Index from the US Bureau of Labor Statistics. Weighted *t* tests and Rao-Scott chi-square tests were used to compare the characteristics of mean and categorical variables, respectively.

Associations of HZ hospitalization were examine, including age (0-19, 20-39, 40-59, ≥60 years), race/ethnicity (white, black, Hispanic, multiracial/other), number of chronic conditions (HCUP chronic condition indicator included in NIS: 0-1, 2-5, >5), and history of long-term systemic corticosteroid use (no, yes).

Binary logistic regression models were constructed with secondary diagnosis of CISD as the independent variable (yes/no) and primary HZ hospitalization (yes/no) as the dependent variable. Multivariable models included age, race/ethnicity, sex, and history of long-term systemic corticosteroid use covariables. Cost and length of stay (LOS) were log-transformed because model residuals were not normally distributed. Complete case-analysis was performed. Post hoc correction for multiple dependent tests was performed by minimizing the false discovery rate.[28] Two-sided, corrected *P* values of .05 or less were considered statistically significant.

Abbreviations used:

AA:	alopecia areata
AD:	atopic dermatitis
BP:	bullous pemphigoid
CISD:	chronic inflammatory skin diseases
CIU:	chronic idiopathic/spontaneous urticaria
CLE:	cutaneous lupus erythematosus
HCUP:	Healthcare Cost and Utilization Project
HS:	hidradenitis suppurativa
HZ:	herpes zoster
LOS:	length of stay
LP:	lichen planus
MF:	mycosis fungoides
NIS:	Nationwide Inpatient Sample
PG:	pyoderma gangrenosum
Poh:	per 100,000 hospitalizations
RZV:	recombinant herpes zoster virus vaccine
SLE:	systemic lupus erythematosus
SS:	Sézary syndrome
SSc:	systemic sclerosis
VZV:	varicella zoster virus

RESULTS

Population characteristics

There were 68,088,221 discharges (weighted frequency, 324,310,797) included in the NIS between 2002 and 2012, including 166,453 weighted cases of primary hospitalization for HZ. The estimated annual incidence of hospitalization for HZ in the US population was 5.0 per 100,000 persons and remained relatively stable between 2002 and 2012 (Fig 1, *A*). Across all years, patients with versus without HZ were older (mean ± standard error of the mean, 65.7 ± 0.2 vs 57.2 ± 0.2 years) and were more likely to be female (61.9% vs 54.3%), have Medicare insurance (61.8% vs 47.4%), have a history of long-term systemic corticosteroid use (1.9% vs 0.7%), be of white race/ethnicity, have fewer chronic conditions, and be evenly distributed across discharge quarters and income quartiles (Table I).

Among inpatients with versus without HZ, the prevalence of CISD, reported as frequency per 100,000 hospitalizations (poh) was significantly higher for AD (55 vs 26 poh), psoriasis (383 vs 270 poh), pemphigus (47 vs 8 poh), BP (46 vs 17 poh), LP (18 vs 6 poh), MF (94 vs 21 poh), SS (14 vs 1 poh), dermatomyositis (129 vs 16 poh), morphea (23 vs 8 poh), SSc (202 vs 87 poh), CLE (54 vs 22 poh), sarcoidosis (337 vs 199 poh) and PG (21 vs 9 poh) and was numerically higher in those with CIU (42 vs 40 poh), vitiligo (29 vs 17 poh), and AA (3 vs 2 poh) (Fig 1, *B*).

In multivariable survey logistic regression models including age, race/ethnicity, sex, and history of long-term systemic corticosteroid use as covariables, hospitalization for HZ was associated with AD, psoriasis, pemphigus, BP, MF, dermatomyositis, SSc, CLE, vitiligo, and sarcoidosis (Table II). LP, SS, morphea, and PG showed increased odds in bivariable models but not in multivariable models; there were no associations of HZ with HS, CIU, and AA.

In sensitivity analyses among patients younger than 60 years, AD, pemphigus, LP, MF, DM, SSc, CLE, vitiligo, and sarcoidosis showed increased odds of hospitalization for HZ in multivariable models, whereas psoriasis and SS showed increased odds only in bivariable models (Supplemental Table II; available via Mendeley at https://data.mendeley.com/datasets/7z9656xvgy/1).

Associations with hospitalization for HZ

Among hospitalizations for HZ, there were significant differences of patient characteristics between those with versus without a CISD in bivariable analyses. Those with pemphigus (mean ± standard error of the mean, 74.6 ± 3.9 years) and BP (78.2 ± 2.9 years) were significantly older, whereas those with AD (41.5 ± 7.1 years), HS (39.5 ± 5.6 years), MF (53.3 ± 4.1 years), dermatomyositis (49.9 ± 3.0 years), SSc (58.6 ± 1.9 years), CLE (57.1 ± 2.8 years), and sarcoidosis (57.9 ± 1.3 years) were significantly younger ($P < .01$ for all) (Fig 1, *C*). Those with HS (26.3%) and MF (37.1%) were less likely to be female, whereas those with dermatomyositis (79.1%), SSc (94.6%), sarcoidosis (72.3%) were more likely to be female ($P < .05$ for all) (Fig 1, *D*). Those with psoriasis (94.7%), pemphigus (94.1%), MF (88.7%), SSc (98.6%), and sarcoidosis (96.5%) were more likely to have 2 or more chronic conditions ($P < .005$ for all) (Fig 1, *E*). Those with pemphigus (12.4%), BP (19.9%), dermatomyositis (9.3%), and sarcoidosis (12.5%) were more likely to have a history of long-term systemic corticosteroid use ($P < .005$ for all) (Fig 1, *F*).

In multivariable survey logistic regression models, hospitalization for HZ was associated with older age (adjusted odds ratio [95% confidence interval] for 40-59 years: 1.71 [1.61-1.82]; ≥60 years: 3.28 [3.09-3.49] compared with 0-19 years), female sex (1.31 [1.28-1.35]), race/ethnicity (Hispanic: 1.16 [1.12-1.21]; Asian/Pacific Islander/Native American/other: 1.22 [1.16-1.28] compared with white), and long-term systemic corticosteroid use (3.05 [2.80-3.31]) but was inversely associated with a higher number of chronic conditions (2-5: 0.75 [0.72-0.78]; ≥6: 0.42 [0.40-0.44] compared with 0-1) and black race/ethnicity (0.94 [0.91-0.98] compared with white) ($P < .0001$ for all).

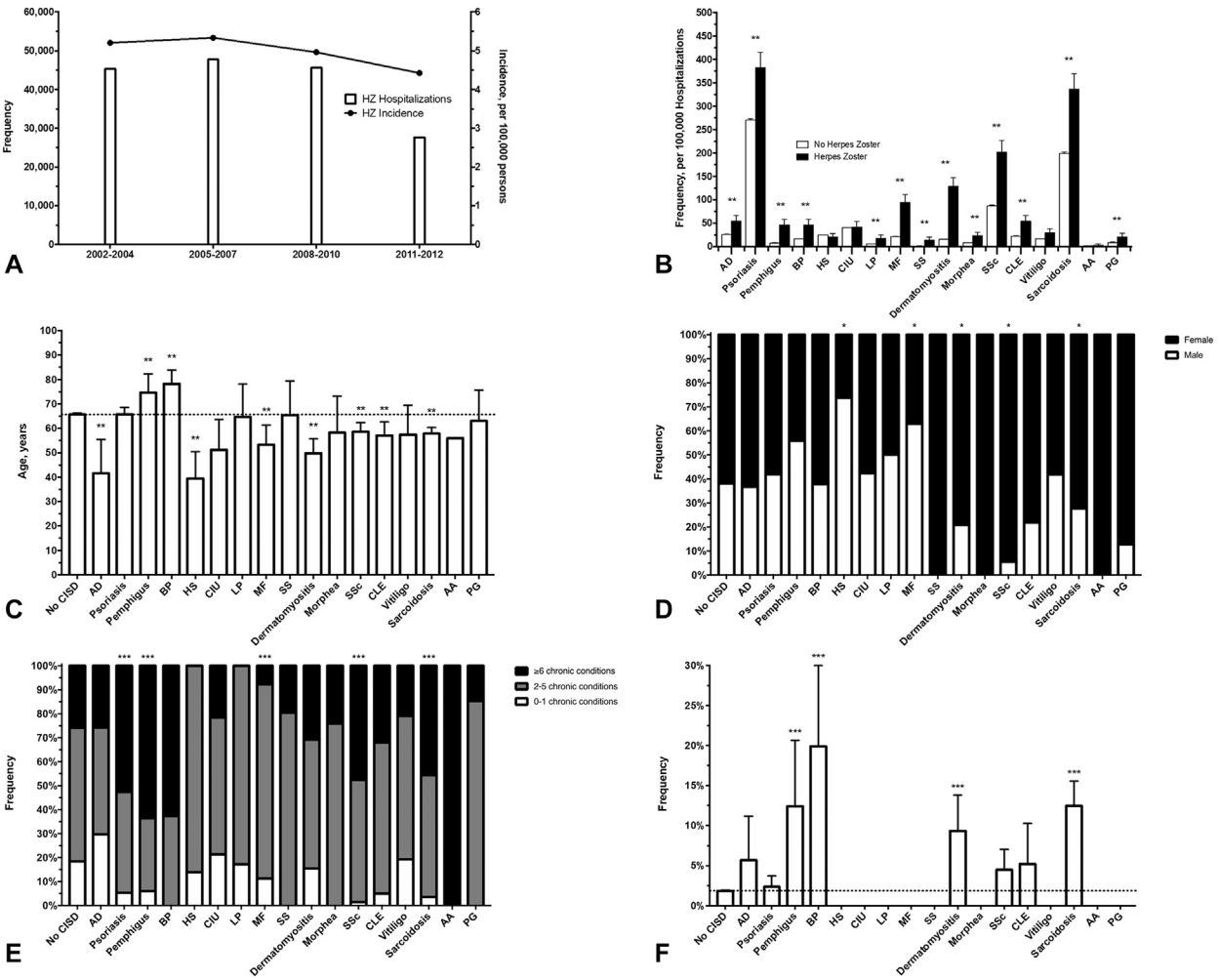

Fig 1. **A**, HZ hospitalizations and incidence by year. **B**, Frequency of CISD among patients with versus without HZ. **C**, Mean age of inpatients with HZ with versus without CISD. The dashed line represents the mean for inpatients with HZ without CISD. **D**, Frequency of sex in inpatients with HZ with versus without CISD. **E**, Frequency of number of chronic comorbid conditions in inpatients with HZ with versus without CISD. **F**, Frequency of history of long-term systemic corticosteroid use in inpatients with HZ with versus without CISD. The dashed line represents the frequency in inpatients with HZ without CISD. *$P < .05$; **$P < .01$; ***$P < .005$. *AA*, Alopecia areata; *AD*, atopic dermatitis; *BP*, bullous pemphigoid; *CISD*, chronic inflammatory skin disease; *CIU*, chronic idiopathic/spontaneous urticaria; *CLE*, cutaneous lupus erythematosus; *HS*, hidradenitis suppurativa; *HZ*, herpes zoster virus; *LP*, lichen planus; *MF*, mycosis fungoides; *PG*, pyoderma gangrenosum; *SS*, Sézary syndrome.

Similarly, among inpatients with a diagnosis of CISD, hospitalization for HZ was associated female sex (adjusted odds ratio [95% confidence interval], 1.54 [1.25-1.90]) and was inversely associated with increasing number of chronic conditions (2-5: 0.58 [0.39-0.86]; ≥6: 0.29 [0.19-0.45] compared with 0-1). However, hospitalization for HZ among CISD patients was also associated with long-term systemic corticosteroid use (2.23 [1.55-3.23]) and inversely associated with early adulthood (20-39 years: 0.56 [0.32-0.97] compared with 0-19 years).

LOS and cost

LOS was significantly prolonged in inpatients with HZ with AD (geometric mean [95% confidence interval], 5.6 [4.7-6.7]), pemphigus (7.7 [5.6-10.6]), BP (7.1 [5.2-9.6]), MF (5.5 [4.7-6.5]), and SS (6.0 [4.9-7.2]) compared with no CISD (4.8 [4.7-4.8]) ($P < .01$ for all) (Fig 2).

The geometric mean (95% confidence interval) inflation-adjusted cost of inpatient care for patients admitted with a diagnosis of HZ was $6,279 ($6,159-$6,401). Cost was significantly higher in

Table I. Baseline characteristics of inpatients with herpes zoster

	Primary hospitalization for herpes zoster		
Variable	**No**	**Yes**	***P* value**
Age, y, mean (SEM)	57.2 (0.2)	65.7 (0.2)	<.0001
Age, y, weighted frequency (%)			
0-19	25,724,067 (7.9)	7,659 (4.6)	<.0001
20-39	43,244,161 (13.4)	11,312 (6.8)	
40-59	88,064,746 (27.2)	34,063 (20.5)	
≥60	166,757,759 (51.5)	113,327 (68.1)	
Sex, weighted frequency (%)			
Male	147,733,412 (45.7)	63,281 (38.1)	<.0001
Female	175,578,875 (54.3)	102,884 (61.9)	
Chronic conditions, n, weighted frequency (%)			
0-1	59,464,213 (18.4)	30,598 (18.4)	<.0001
2-5	155,858,820 (48.1)	92,765 (55.7)	
≥6	108,705,262 (33.5)	43,091 (25.9)	
Died, weighted frequency (%)			
No	315,703,014 (97.5)	165,044 (99.2)	<.0001
Yes	8,080,345 (2.5)	1326 (0.8)	
Discharge quarter, weighted frequency (%)			
January-March	83,206,882 (25.7)	39,975 (24.1)	<.0001
April-June	80,881,597 (25.0)	42,182 (25.5)	
July-September	79,515,042 (24.6)	42,930 (25.9)	
October-December	80,219,193 (24.8)	40,534 (24.5)	
Hospital location, weighted frequency (%)			
Metropolitan, ≥1 million	154,321,517 (53.1)	84,571 (57.1)	<.0001
Metropolitan, <1 million	79,338,435 (27.3)	36,455 (24.6)	
Micropolitan	33,529,682 (11.5)	15,583 (10.5)	
Not metropolitan or micropolitan	23,271,702 (8.0)	11,482 (7.8)	
Income quartile, weighted frequency (%)			
1st	84,888,498 (29.5)	40,463 (27.4)	<.0001
2nd	74,997,577 (26.0)	36,881 (24.9)	
3rd	67,912,744 (23.6)	35,904 (24.3)	
4th	60,270,995 (20.9)	34,581 (23.4)	
Long-term steroid use, weighted frequency (%)			
No	321,971,376 (99.3)	163,350 (98.1)	<.0001
Yes	2,172,968 (0.7)	3103 (1.9)	
Primary payer, weighted frequency (%)			
Medicare	153,373,060 (47.4)	102,752 (61.8)	<.0001
Medicaid	43,465,255 (13.4)	13,713 (8.2)	
Private insurance	96,691,650 (29.9)	39,871 (24.0)	
Self-pay/no charge	18,866,465 (5.8)	6600 (4.0)	
Other	11,094,035 (3.4)	3344 (2.0)	
Race/ethnicity, weighted frequency (%)			
White	181,035,015 (70.2)	96,024 (71.7)	<.0001
Black	37,052,033 (14.4)	15,683 (11.7)	
Hispanic	25,681,311 (10.0)	13,712 (10.2)	
Asian/Pacific Islander	5,092,051 (2.0)	3939 (2.9)	
Native American	1,509,086 (0.6)	698 (0.5)	
Other	7,499,301 (2.9)	3804 (2.8)	

inpatients with HZ who also had pemphigus ($10,890 [$6,844-$17,329]), BP ($9,325 [$6,811-$12,767]), SSc ($7,693 [$6,418-$9,220]), sarcoidosis ($7,846 [$6,725-$9,154]), and PG ($7,470 [$6,335-$8,807]) but was lower in those with HS ($3,775 [$2,550-$5,589]) and LP ($3,139 [$1,678-$5,874]) ($P < .01$ for all).

DISCUSSION

This study found increased HZ hospitalization risk across multiple CISDs, including dermatomyositis, pemphigus, MF, AD, vitiligo, CLE, SSc, BP, sarcoidosis, and psoriasis in multivariable models and SS, LP, morphea, and PG in bivariable models. There were

Table II. Association of chronic inflammatory skin disease with herpes zoster hospitalization

	Primary hospitalization for herpes zoster					
	No	Yes				
Chronic inflammatory skin disease	Weighted frequency (%)	Weighted frequency (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Atopic dermatitis	84,126 (0.03)	91 (0.05)	2.11 (1.36-3.27)	.001	3.19 (1.93-5.28)	<.0001
Psoriasis	875,836 (0.27)	637 (0.38)	1.42 (1.20-1.68)	<.0001	1.38 (1.14-1.68)	.001
Pemphigus	24,724 (0.008)	77 (0.05)	6.10 (3.73-9.96)	<.0001	4.78 (2.83-8.08)	<.0001
Bullous pemphigoid	53,649 (0.02)	77 (0.05)	2.83 (1.74-4.61)	<.0001	1.77 (1.01-3.12)	.049
Hidradenitis suppurativa	79,690 (0.02)	34 (0.02)	0.84 (0.40-1.75)	.639	1.48 (0.70-3.13)	.321
Chronic idiopathic/ spontaneous urticaria	130,303 (0.04)	70 (0.04)	1.05 (0.62-1.77)	.886	0.89 (0.44-1.78)	.741
Lichen planus	18,929 (0.006)	29 (0.02)	3.01 (1.36-6.67)	.007	2.26 (0.85-6.00)	.104
Mycosis fungoides	69,223 (0.02)	157 (0.09)	4.43 (3.16-6.21)	<.0001	3.79 (2.55-5.65)	<.0001
Sézary syndrome	3,800 (0.001)	23 (0.01)	12.14 (5.20-28.31)	<.0001	2.23 (0.31-16.13)	.429
Dermatomyositis	50,184 (0.02)	214 (0.1)	8.32 (6.23-11.11)	<.0001	7.31 (5.27-10.12)	<.0001
Morphea	26,896 (0.008)	38 (0.02)	2.74 (1.36-5.51)	.005	1.48 (0.55-3.99)	.444
Systemic sclerosis	282,585 (0.09)	337 (0.2)	2.34 (1.85-2.95)	<.0001	1.92 (1.47-2.53)	<.0001
Cutaneous lupus erythematosus	72,320 (0.02)	90 (0.05)	2.46 (1.56-3.83)	<.0001	1.94 (1.10-3.44)	.023
Vitiligo	53,876 (0.02)	48 (0.03)	1.78 (0.96-3.28)	.065	2.00 (1.04-3.85)	.039
Sarcoidosis	645,943 (0.2)	560 (0.3)	1.68 (1.39-2.03)	<.0001	1.52 (1.22-1.90)	.0002
Alopecia areata	5,270 (0.002)	≤10 (0.003)	1.71 (0.25-11.87)	.588	2.74 (0.38-19.52)	.315
Pyoderma gangrenosum	27,417 (0.009)	34 (0.02)	2.44 (1.16-5.13)	.019	2.23 (0.91-5.40)	.079

CI, Confidence interval; *OR*, odds ratio.

no significant associations with HS, CIU, or AA. Previous studies in both outpatient and inpatient settings showed variable rates of HZ in AD,[29,30] psoriasis,[31,32] pemphigus,[33,34] BP,[33-35] HS,[36,37] MF,[38,39] SS,[38,39] dermatomyositis,[33,40,41] SSc,[42,43] CLE,[33] and sarcoidosis.[44] Associations of HZ with LP,[45] morphea,[46] vitiligo,[47] or PG[48] have not formally been studied, although case reports documented zosteriform eruptions of CISD in sites of prior HZ (ie, an isotopic response). Only AD, psoriasis, pemphigus, BP, and HS were shown to be associated with HZ in hospitalized patients.[30,32,34,37] Overall, interpretation of and interstudy comparison with previous studies is limited by small sample size, lack of detailed medical records, lack of controls, and/or confounding effects of medication use.

We observed no increase in rate or risk of hospitalization for HZ in patients with CIU, HS, or AA. No prior studies showed a relationship between HZ and CIU. It may be that mast cell and immunoglobulin E–mediated inflammation does not affect T-cell responses to VZV. A retrospective US population-based cohort study of HS concluded that the incidence and risk of HZ irrespective of immunosuppression status was significant but only minimally higher than in control individuals.[36] A nationwide claims-based case-control study of Taiwanese adults suggested increased odds of HZ in patients with a diagnosis of AA in the preceding 3 years,[49] although psychological stress and the hypothalamus-pituitary-adrenal axis is an important confounder, as is possible isotopic response in the same skin areas affected by AA and HZ.[50,51]

HZ hospitalization among those without CISD was associated with older age, which is consistent with previous studies showing that HZ risk increased with age.[3,52,53] However, inpatients with HZ with DM or AD were significantly younger than those without CISDs, suggesting that these disorders may predispose younger patients to HZ. HZ hospitalization (with or without CISD) was inversely associated with a number of chronic conditions, which supports the idea that the majority of patients with HZ are generally healthy and do not have multimorbidity. In fact, the Centers for Disease Control and Prevention estimates that only 30% of patients hospitalized for HZ have weakened or suppressed immunity. Among inpatients with CISD, HZ was associated with history of long-term systemic steroid use. This is consistent with previous studies that found increased risk for HZ in patients with psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, SLE, and inflammatory bowel disease chronically taking systemic corticosteroids.[54]

HZ risk in patients with CISD is traditionally explained by a combination of age-related immune senescence, immune dysregulation, and immunosuppressive medication use. Systemic autoimmune conditions (especially SLE and DM) and hematopoietic malignancies may predispose toward HZ owing

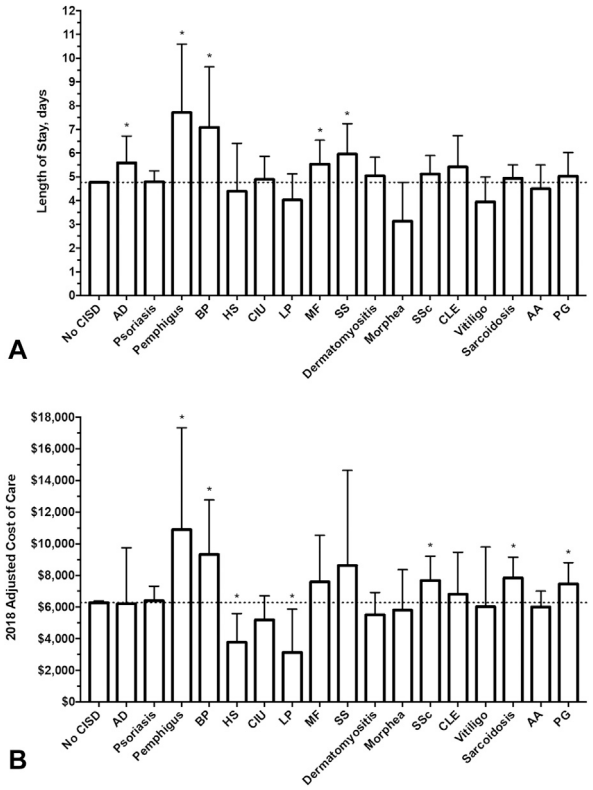

Fig 2. **A**, Mean length of stay of inpatients with HZ with versus without CISD. The dashed line represents the mean in inpatients with HZ without CISD. **B**, Mean cost of care in inpatients with HZ with versus without CISD. The dashed line represents the mean for inpatients with HZ without CISD. *$P < .01$. *AD*, Atopic dermatitis; *BP*, bullous pemphigoid; *CISD*, chronic inflammatory skin disease; *CIU*, chronic idiopathic/spontaneous urticaria; *CLE*, cutaneous lupus erythematosus; *HS*, hidradenitis suppurativa; *HZ*, herpes zoster virus; *LP*, lichen planus; *MF*, mycosis fungoides; *PG*, pyoderma gangrenosum; *SS*, Sézary syndrome.

to chronic inflammation and aberrant T-cell activity.[33,55] Other CISDs, including AD,[30] psoriasis,[56] pemphigus and BP,[34] and dermatomyositis,[57] were found to be associated with other viral, bacterial, fungal, and/or mycobacterial infections of the skin and other organ systems.

Of the patients hospitalized with HZ, those with AD, pemphigus, BP, MF, or SS had prolonged hospitalization, and those with pemphigus, BP, SSc, sarcoidosis, and PG had higher cost of care versus control individuals. Together, these results suggest that CISD may indirectly confer additional patient and financial burden through excess risk of HZ.

Few have been able to accurately stratify HZ risk within CISD. As such, there are no CISD-specific guidelines for HZ vaccination. Currently, there are 2 vaccines available for HZ prevention: the live attenuated HZ vaccine and the recently approved nonlive recombinant HZ vaccine (RZV). Based on the superior performance of RZV in phase 3 randomized clinical trials,[58,59] the most recent Advisory Committee on Immunization Practice HZ vaccination guidelines recommend RZV for immunocompetent adults ages 50 years and older and continued use of the live attenuated HZ vaccine in immunocompetent adults aged 60 years and older.[6] Among immunocompromised adults, RZV is recommended for those taking low-dose immunosuppressive therapy (<20 mg/day of prednisone or equivalent). There are insufficient data to make an official recommendation for adults receiving high-dose immunosuppressive therapy because such patients were excluded from the RZV trials.

The National Psoriasis Foundation published consensus recommendations on vaccination for VZV in patients with psoriasis and psoriatic arthritis.[60] Despite heterogeneity and conflicting results in the literature, their systematic review found no increased HZ risk in patients with mild psoriasis receiving no systemic therapy and found strongly increased HZ risk in moderate to severe psoriasis and psoriatic arthritis for patients using systemic corticosteroids, tofacitinib, or combination therapy with biologic agents and nonbiologic immunomodulators. RZV was recommended for all patients with psoriasis older than 50 years and those younger 50 years taking systemic corticosteroids or tofacitinib. We did not observe increased odds of HZ hospitalization in patients with psoriasis younger than 60 and younger than 50 years, although other CISDs were associated with HZ hospitalization at younger ages. Among patients younger than 50 years, DM, MF, AD, and SSc showed increased odds of hospitalization for HZ. Vaccination for HZ is safe, is efficacious, and may reduce hospitalizations for HZ in patients with CISD. However, according to the 2016 National Health Interview Survey, only 33.4% of adults older than 60 years are vaccinated for HZ.[7] Patients with CISD may benefit from increased vaccination for HZ, especially those younger than 50 years old with appropriate risk factors. Dermatologists are often the primary physicians for patients with CISD and are at forefront of evaluation and vaccination for their patients.

Strengths of this study include analysis of a nationally representative sample of 11 years of all-payer data encompassing nearly 325 million hospitalizations with more than 160,000 admissions with a primary diagnosis of HZ. The International Classification of Diseases, Ninth Revision, Clinical

Modification code for HZ was previously validated for use with electronic health data in the United States and was found to have good reliability.[21,22] Limitations include potential misclassification and/or underreporting of CISD. Clinicians may report only diagnoses being addressed during a specific inpatient encounter, and diagnosis codes may not reflect chronic conditions treated mainly in the outpatient setting. As such, our findings may underestimate the effect size for the association of CISD on HZ. Additional limitations of this study include the absence of medical records with specific data regarding CISD severity, medication use, and vaccination, which are potential confounders. Despite the large overall sample size, some of the analyzed outcomes had low frequencies, resulting in wide confidence intervals. The NIS uses event-based records, and as such, individual patients with multiple inpatient hospitalizations in the same year may be present multiple times. However, this is unlikely to be a major issue, because most patients experience only 1 episode of HZ. Finally, patients hospitalized with CISD may have more severe disease, so the results may not be generalizable to those with milder CISD. Future studies are needed to address these points.

In conclusion, patients with CISD had higher odds of hospitalization for HZ with prolonged LOS and increased cost of care. Further studies are needed to confirm these findings, determine mechanisms of VZV reactivation, stratify patients based on medication- and disease-specific factors, and explore HZ vaccination guidelines to cover the spectrum of CISD.

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