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ORIGINAL PAPER

Multimorbidity and mortality risk in hospitalized adults with chronic inflammatory skin disease in the United States

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Abstract

Chronic inflammatory skin diseases (CISD) represent a significant burden of skin disease in the United States, and a growing number of studies demonstrate that CISD are associated with multiple comorbidities. However, few studies examined multimorbidity in adults with CISD. We sought to determine whether hospitalized US adults with chronic inflammatory skin disorders have increased multi-morbidity and mortality risk. Data from the 2002–2012 Nationwide Inpatient Sample were analyzed, including a representative 20% sample of US hospitalizations. Charlson comorbidity index (CCI) and mean estimated 10-year survival were calculated. Multivariable linear regression models were constructed with CCI score and mean estimated 10-year survival as the dependent variables and chronic inflammatory skin diagnosis, age and sex as the independent variables. CCI scores were significantly higher in bullous pemphigoid ($P=0.0005$) and dermatomyositis ($P<0.0001$), lower in hidradenitis suppurativa ($P<0.0001$), pemphigus ($P<0.0001$), rosacea ($P<0.0001$), and not significantly different in atopic dermatitis, alopecia areata, and lichen planus compared to psoriasis. Conversely, the mean estimated 10-year survival was higher in pemphigus ($P=0.0451$), lichen planus ($P=0.0352$), rosacea ($P<0.0001$), lower in bullous pemphigoid and dermatomyositis ($P<0.0001$), and similar in atopic dermatitis, alopecia areata, and hidradenitis suppurativa compared to psoriasis. Each CISD had a distinct profile of comorbidities when compared to psoriasis. Hospitalized adults with multiple CISD have increased multimorbidity and decreased 10-year survival. Further studies are needed to develop multidisciplinary strategies aimed at preventing and treating multimorbidity, especially modifiable cardiovascular factors in adults with CISD.

Keywords Psoriasis · Bullous pemphigoid · Pemphigus · Atopic dermatitis · Hidradenitis suppurativa · Dermatomyositis · Rosacea · Lichen planus · Alopecia areata · Chronic inflammatory skin disease · Comorbidity · Multimorbidity

Abbreviations

ICD-9-CM	International Classification of Disease 9th edition Clinical Modification
AD	Atopic dermatitis
COPD	Chronic obstructive pulmonary disease
CTD	Connective tissue disease
AIDS	Acquired immunodeficiency syndrome
MI	Myocardial infarction
CKD	Chronic kidney disease
CVA	Cerebrovascular accident
TIA	Transient ischemic attack
CHF	Congestive heart failure
PUD	Peptic ulcer disease
DM	Diabetes mellitus
BP	Bullous pemphigoid
HS	Hidradenitis suppurativa
AA	Alopecia areata
LP	Lichen planus
NIS	Nationwide inpatient sample
CI	Confidence interval
CCI	Charlson Comorbidity Index
HCUP	Healthcare cost and utilization project
AHRQ	Agency for healthcare research and quality
CISD	Chronic inflammatory skin disease

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Introduction

Chronic disease management is a key health system concern in developed countries owing to the rising prevalence and burden of chronic illness [1]. In 2014, the World Health Organization identified chronic diseases as having reached epidemic proportions and constituting the leading cause of death worldwide [2]. Multimorbidity is defined as the co-existence of two or more chronic conditions. Previous studies found that multimorbidity is common in the general population, but particularly so in the elderly population [3, 4]. Multimorbidity results in increased use of both inpatient and ambulatory care services [5], poor coordination and integration of care [5], increased disability, quality of life impact [6], and mortality [7].

Chronic inflammatory skin diseases (CISD), such as atopic dermatitis (AD), psoriasis, and hidradenitis suppurativa (HS), pose a significant health-burden in the United States. CISD were found to be associated with multiple comorbid health disorders. AD was found to be associated with multiple medical and mental health comorbidities, including cutaneous and systemic autoimmune disorders, cardiovascular disease, stroke, and depression [8–16]. In addition, psoriasis was found to be associated with chronic obstructive pulmonary disease, lymphoma, and osteoporosis, etc. [17–20]. Multiple chronic inflammatory skin disorders, including psoriasis, AD, pemphigus, bullous pemphigoid (BP), and HS were found to be associated with cardiovascular risk factors, including obesity, hypertension, diabetes, congestive heart failure (CHF), peripheral vascular disease, transient ischemic attacks (TIA), and cerebrovascular disease [21–23]. Yet, little is known about the role of multimorbidity, i.e. the co-occurrence of these morbidities, in CISD. A recent Danish study demonstrated that adult patients with AD had increased multimorbidity as indicated by elevated Charlson Comorbidity Index (CCI) scores compared to controls [24]. We hypothesized that different CISD are associated with multimorbidity. In this study, we sought to determine the patterns of multimorbidity in CISD among hospitalized adults and the impact of multimorbidity on hospitalization outcomes.

Methods

Data source

The 2002–2012 Nationwide Inpatient Sample (NIS) provided by the Healthcare Cost and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality (AHRQ) was analyzed. Each year of NIS contains an approximately 20% stratified representative cross-sectional sample of US hospitalizations. Sample weights were created by the NIS that factored the sampling design of US hospitals. These sample weights allow for representative estimates of hospital discharges across the entire country. All data were de-identified. No attempts were made to identify any of the individuals in the database. All parties with access to NIS were compliant to HCUP's formal data use agreement. The study was approved by the institutional review board at Northwestern University (Chicago, Illinois, USA).

CISD and comorbidities

The databases were searched for a primary and/or secondary diagnosis of AD, psoriasis, pemphigus, BP, HS, dermatomyositis, alopecia areata (AA), rosacea, and lichen planus (LP) using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Previous studies validated the use of the discharge diagnosis codes 691.8 (AD), 696.1, 705.83 (HS), 694.4 (pemphigus), 694.5 (BP), and 710.3 (dermatomyositis) in the inpatient setting for identifying these disorders [25–30].

Multimorbidity was defined using the CCI. CCI was calculated based on discharge diagnosis codes from that hospitalization. CCI was developed in 1987 as a measure of multimorbidity that consists of a weighted score including age and 19 conditions (16 diseases; 3 are stratified according to severity). CCI has been shown to predict 1-year mortality, inpatient mortality, length of hospital stay (LOS), readmission rate, functional decline, and healthcare utilization [31–33]. The ICD-9-CM codes for CCI comorbidities were previously validated [34]. Predicted 10-year survival was estimated by $0.983^{(e^{CCI \times 0.9})}$.

Statistical analysis

Data processing and statistical analyses were performed using survey-weighted procedures in SAS version 9.4 (SAS Institute, Cary, NC, USA). The unit of analysis was an individual hospitalization. All statistical models included discharge trend weights, sample strata that accounted for a hospital's census region or division, ownership and control, location and teaching status, number of beds that were provided by the NIS, and clustering by individual hospital. Least squares means (LSM) CCI scores and 10-year survival were estimated for each CISD.

Weighted frequency and prevalence ([95% confidence intervals [CI]) of either a primary or secondary diagnosis of individual CCI comorbidities were determined for patients with CISD. Survey weighted logistic regression models were constructed with the comorbidity (yes/no) as the dependent variable and CISD, age, and sex as the independent

variables. Psoriasis was selected as the reference disease since multimorbidity was previously established in psoriasis [35].

The relationship between CCI scores and inpatient LOS was examined using survey-weighted linear regression models. Multivariable models included sex (female/male), race (white/non-white), and insurance status (insured/uninsured). A two-sided P value < 0.05 was considered statistically significant.

Results

Population characteristics

There were 72,108,077 adult discharges captured in the NIS between 2002 and 2012. There were 9290 hospitalizations with AD (weighted frequency = 44,605), 185,609 (890,295) with psoriasis, 23,369 (111,731) with HS, 6315 (30,091) with pemphigus, 13,174 (63,092) with pemphigoid, 12,213 (58,201) with dermatomyositis, 3934 (18,839) with LP, 34,454 (165,061) with rosacea, and 945 (4551) with alopecia areata.

CCI scores

In multivariable linear regression models that adjusted for age and sex, CCI scores were found to be significantly higher in dermatomyositis (LSM; adjusted beta [95% CI]) (3.89; 1.00 [0.95, 1.05]), and BP (2.97; 0.08 [0.03, 0.12]) compared to psoriasis (LSM: 2.89), lower in HS (2.81; − 0.08 [− 0.11, − 0.05]), pemphigus (2.66; − 0.23 [− 0.29, − 0.18]), rosacea (2.50; − 0.40 [− 0.43, − 0.36]), but not significantly different in LP (2.91; 0.01 [− 0.06, 0.08]), AD (2.87; − 0.02 [− 0.06, 0.03]), or AA (2.85; − 0.04 [− 0.16, 0.08]) (Table 1).

Specific morbidities

Each CISD had differential associations with the specific CCI elements when compared to psoriasis. Age was significantly increased in pemphigus, BP, LP and rosacea compared with psoriasis; AIDS was associated with AD, HS and LP; CHF was associated with HS, BP, and dermatomyositis; CKD was associated with HS and BP; COPD was associated with AD; CTD was associated with LP and dermatomyositis; CVA/TIA were associated with AA and BP; dementia was associated with AD, HS, pemphigus and BP; DM with end-organ damage was associated with HS; uncomplicated DM was associated with HS, pemphigus and BP; hemiplegia was associated with BP and rosacea; malignancy was associated with dermatomyositis, LP and rosacea; metastatic solid tumor was associated with dermatomyositis and rosacea; PUD was associated with BP and dermatomyositis (Table 2, Supplemental Table 1).

Table 1 Multimorbidity and mortality risk in hospitalized adults with chronic inflammatory skin disease

Skin disorder	Charlson Comorbidity Index				Mortality risk			
	Mean Score (SEM)	LSM	Adjusted β [95% CI]	P	Mean estimated 10-year survival % (SEM)	LSM	Adjusted β [95% CI]	P
Psoriasis	3.2 (0.01)	2.89	0 [REF]	–	63.1 (0.2)	67.3	0 [REF]	–
Dermatomyositis	3.9 (0.04)	3.89	1.00 [0.95 to 1.05]	< 0.0001	56.1 (0.6)	56.4	− 0.11 [− 0.12 to − 0.10]	< 0.0001
Bullous pemphigoid	4.9 (0.03)	2.97	0.08 [0.03 to 0.12]	0.0005	35.7 (0.4)	61.3	− 0.06 [− 0.07 to − 0.05]	< 0.0001
Lichen planus	3.5 (0.05)	2.91	0.01 [− 0.06 to 0.08]	0.7098	59.6 (0.7)	68.4	0.01 [0.00 to 0.02]	0.0352
Atopic dermatitis	2.7 (0.04)	2.87	− 0.02 [− 0.06 to 0.03]	0.4332	69.8 (0.6)	67.3	0.00 [− 0.01 to 0.01]	0.9969
Alopecia areata	2.0 (0.09)	2.85	− 0.04 [− 0.16 to 0.08]	0.4734	79.5 (1.1)	68.2	0.01 [− 0.01 to 0.03]	0.3041
Hidradenitis suppurativa	1.4 (0.02)	2.81	− 0.08 [− 0.11 to − 0.05]	< 0.0001	85.7 (0.2)	67.2	0.00 [− 0.01 to 0.00]	0.5782
Pemphigus	3.8 (0.05)	2.66	− 0.23 [− 0.29 to − 0.18]	< 0.0001	53.3 (0.7)	68.2	0.01 [0.00 to 0.02]	0.0451
Rosacea	3.1 (0.03)	2.50	− 0.40 [− 0.43 to − 0.36]	< 0.0001	65.5 (0.4)	74.3	0.07 [0.06 to 0.07]	< 0.0001

LSM least squares means, *SEM* standard error of mean, *REF* reference

Table 2 Comorbidities associated with chronic inflammatory skin disease in hospitalized US adults

Comorbidity	Psoriasis	Atopic dermatitis	Hidradenitis suppurativa	Pemphigus	Bullous Pemphigoid	Dermatomyositis	Lichen planus	Rosacea	Alopecia areata
Age	[REF]	↓	↓	↑	↑	↓	↑	↑	↓
DM without complications	[REF]	↓	↑	↑	↑	–	–	↓	–
DM with end-organ damage	[REF]	↓	↑	↓	–	↓	–	↓	–
Any malignancy, including lymphoma and leukemia	[REF]	↓	↓	↓	↓	↑	↑	↑	–
Metastatic solid tumor	[REF]	↓	↓	↓	↓	↑	–	↑	–
AIDS	[REF]	↑	↑	↓	↓	↓	↑	↓	–
Moderate to severe CKD	[REF]	↓	↑	–	↑	–	–	↓	–
MI	[REF]	↓	↓	↓	↓	↓	↓	↓	–
COPD	[REF]	↑	↓	↓	↓	↓	↓	↓	–
Peripheral vascular disease	[REF]	↓	↓	↓	↓	↓	↓	↓	↓
CVA or TIA	[REF]	–	↓	↓	↑	↓	↓	–	↑
Dementia	[REF]	↑	↑	↑	↑	↓	↓	↓	–
Hemiplegia	[REF]	–	↓	–	↑	–	↓	↑	–
Connective tissue disease	[REF]	↓	↓	↓	↓	↑	↑	↓	–
Peptic ulcer disease	[REF]	–	↓	–	↑	↑	–	–	–
Mild liver disease	[REF]	↓	↓	↓	↓	↓	–	↓	↓
Moderate to severe liver disease	[REF]	↓	↓	↓	↓	↓	–	↓	↓
Congestive heart failure	[REF]	–	↑	–	↑	↑	↓	↓	↓

Survey weighted linear regression models were constructed with the Charlson comorbidity index as the dependent variable and chronic inflammatory skin diagnosis, age, and sex as the independent variables. Beta regression coefficients and 95% Cl were estimated

CHF congestive heart failure, *COPD* chronic obstructive pulmonary disorder, *CVA* cerebrovascular accident, *TIA* transient ischemic attack, *AIDS* acquired immunodeficiency syndrome, *DM* diabetes mellitus, *MI* myocardial infarction

CCI and LOS

CCI score ≥ 2 vs. 0–1 was associated with increased LOS in inpatients with all CISD. In patients with alopecia areata and lichen planus, CCI scores were lower in non-White ($P = 0.0212$, $P = 0.0040$, respectively), and uninsured patients ($P < 0.0001$ both). In patients with AD, HS, pemphigus, BP, dermatomyositis, rosacea, and psoriasis, CCI scores were lower in non-White, uninsured, and in female patients.

Estimated 10-year survival

Compared to psoriasis (67.3%), the estimated 10-year survival was significantly lower in dermatomyositis (56.4%; − 0.11 [− 0.12, − 0.10]) and BP (61.3%; − 0.06 [− 0.07, − 0.05]), higher in LP (68.4%; 0.01 [0.00, 0.02]), rosacea (74.3%; 0.07 [0.06, 0.07]), and pemphigus (68.2%; 0.01 [0.00, 0.02]) (Table 1), but not significantly different in AD (67.3%; 0.00 [− 0.01, 0.01]), AA (68.2%; 0.01 [− 0.01, 0.03]) or HS (67.2%; 0.00 [− 0.01, 0.00]) (Table 1).

Discussion

In the present study, we found that multiple CISD are associated with multimorbidity. Compared to psoriasis, BP and dermatomyositis were associated with significantly higher CCI scores and lower 10-year survival estimates. Whereas, HS, pemphigus, and rosacea had lower CCI scores and/or higher 10-year survival estimates. All CISD were associated with higher prevalence of at least one CCI comorbidity than psoriasis, though each CISD had a distinct constellation of comorbidities. Lower CCI scores were associated with non-white race and lack of insurance, which may reflect racial/ethnic and healthcare disparities leading to underdiagnosis of comorbidities and/or underrecognition of multimorbidity. Finally, inpatient LOS was prolonged across all CISD as the CCI scores increased. Together, these results highlight the burden of multimorbidity in CISD.

The issue of multimorbidity is often overlooked in clinical research and practice for CISD.

Most previous studies and clinical guidelines addressing the comorbidities of CISD focused on associations with individual comorbid diseases. The present study

indicates that there is a subset of CISD patients that have multimorbidity, which require special consideration.

Patients with multimorbidity are overall sicker, with greater disability and poorer quality of life impact [6], increased healthcare utilization [5] and increased mortality in the short- and long-term [7]. Yet, little is known about why some patients with CISD develop multimorbidity and others do not. Future studies examining comorbidities and burden of CISD should specifically examine multimorbidity. Further, the American Academy of Dermatology and the National Psoriasis Foundation developed clinical guidelines for the management of psoriasis. A significant portion of the guidelines was dedicated to the awareness of the individual comorbidities and what clinical guidelines and roles dermatologists can play in managing them [36]; however, the issue of multimorbidity was not addressed. Future guidelines should consider addressing the assessment and management of multimorbidity in CISD.

Strengths of this study include examination of a large, nationally representative sample hospitalizations. However, there are several weaknesses. We could not determine the duration and severity of the CISD and comorbidities, or outpatient treatment approaches used. Thus, we were unable to assess the temporal relationship between CISD and comorbidities. Future studies are needed to address these limitations.

In conclusion, multiple CISD are associated with multimorbidity, and consequently prolonged hospitalizations and increased mortality risk. Further research is needed to develop multidisciplinary strategies and clinical guidelines aimed at preventing and treating multimorbidity and reducing mortality risk in adults with CISD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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