Archives of Dermatological Research (2019) 311:377–387
https://doi.org/10.1007/s00403-019-01913-0

ORIGINAL PAPER

Association of dermatomyositis with systemic and opportunistic infections in the United States

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Received: 15 October 2018 / Revised: 18 March 2019 / Accepted: 21 March 2019 / Published online: 6 April 2019

Abstract

Patients with dermatomyositis have multiple risk factors for serious and opportunistic infections, including immune dysregulation, long-term systemic corticosteroid treatment and comorbid health conditions. We sought to determine whether dermatomyositis is associated with increased odds and burden of systemic, opportunistic and antibiotic-resistant infections. We analyzed data from the Nationwide Inpatient Sample from 2002 to 2012, containing a cross-sectional representative 20% sample of all hospitalizations in the US. Overall, dermatomyositis was associated with serious infections in adults (multivariable logistic regression; adjusted odds ratio [95% confidence interval]: 2.19 [2.08–2.30]) and children (1.45 [1.20–1.76]). In particular, dermatomyositis was significantly associated with 32 of 48 and 15 of 48 infections examined in adults and children, respectively, including infections of skin, bone, joints, brain, heart, lungs, and gastrointestinal system, as well sepsis, antibiotic-resistant and opportunistic infections. Predictors of infections included non-white race/ethnicity, insurance status, history of long-term systemic corticosteroid usage, Cushing's syndrome (likely secondary to corticosteroid usage), diabetes, and cancer. Serious infections were associated with significantly increased inpatient cost and death in dermatomyositis patients. In conclusion, dermatomyositis is associated with higher odds, costs and inpatient mortality from serious and opportunistic infections.

Keywords Dermatomyositis · Hospitalization · Inpatient · Epidemiology · Infection · Opportunistic · Cryptococcus · Cytomegalovirus · Hepatitis A virus · Pneumocystis · Long-term steroid use

Abbreviations

ICD-9-CM	International Classification of Disease 9th edition Clinical Modification
NIS	National Inpatient Sample

Introduction

Dermatomyositis is a rare autoimmune microangiopathy of skin and muscle. Patients with dermatomyositis harbor multiple risk factors for serious infections, including epidermal barrier disruption and dysregulation secondary to cutaneous and/or systemic inflammation, and comorbid health conditions that are independently associated with infections, e.g., cancer [4]. Treatment often involves immunosuppressive agents, which may predispose toward serious infections, e.g., pneumonitis [6]. Several case series or retrospective studies highlighted the risk for infections in dermatomyositis patients [3, 8, 12]; however, the results were limited due to small sample sizes, certain subtypes of infections [8], and combining dermatomyositis with polymyositis [12]. Few large-scale and controlled studies investigated the impact of serious infections in children with dermatomyositis. In the present study, we sought to determine whether there are distinct associations of dermatomyositis with serious infections in adults and children. We hypothesized that both adults and children with dermatomyositis have significantly

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00403-019-01913-0) contains supplementary material, which is available to authorized users.

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higher risks for multi-organ, systemic and opportunistic infections. Serious infections are associated with morbidity, prolonged hospitalization, substantial excess costs, and increased risk of mortality. We hypothesized that infections are major contributors to excess costs and mortality in dermatomyositis patients.

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 all US hospitalizations. Sample weights were created by NIS that factored the sampling design of hospitals in the US. These sample weights allow for representative estimates of hospital discharges across the whole country. All data were de-identified and 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.

Identification of dermatomyositis and serious infections

The databases were searched for a primary and/or secondary diagnosis of dermatomyositis using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 710.3. A previous study validated the use of this discharge diagnosis code in the inpatient setting for the study of dermatomyositis [9]. The control group included all hospitalizations without any diagnosis of dermatomyositis, yielding a representative cohort of US hospitalizations. Serious infections were defined as infections which led to hospitalization, were life threatening, or required treatment in an inpatient setting. Serious infections were identified using ICD-9-CM or NIS Clinical Classification Software (CCS) codes provided in NIS (Supplement Table 1). Seborrheic keratosis (ICD-9 code: 702.1) was also examined as a negative control, as it was expected to not be associated with dermatomyositis.

Statistical analysis

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Analyses were performed using SURVEY procedures. The unit of analysis was an individual hospitalization. Adults were age ≥ 18 years, whereas children were age < 18 years. All statistical models included discharge trend weights, sample strata that account for hospital's census region or division, ownership/control, location/teaching and number of beds that were provided by NIS and clustering by individual hospital. Weighted frequency, prevalence, 95% confidence intervals [CI] of either a primary or secondary diagnosis of a serious infection were determined among inpatients with a primary, secondary or no diagnosis of dermatomyositis. The cost for inpatient care was estimated based on the total charge of the hospitalization and the cost-to-charge ratio estimated by HCUP. All costs were adjusted for inflation to the year 2014 according to the Consumer Price Index from the US Bureau of Labor Statistics [1]. Summary statistics were generated for each infection, including frequency, prevalence, geometric mean, 95% CI and total length of stay (LOS) and inflation-adjusted cost-of-care for hospitalizations with a diagnosis of a serious infection.

Survey logistic regression models were used to determine the association of dermatomyositis with serious infections. The dependent variable was a diagnosis of serious infection (yes/no). The independent variable was a diagnosis of dermatomyositis (yes/no). Crude odds ratios (OR) and 95% CI were estimated. Multivariable models included age (continuous), sex (male/female), race (white/non-white) and insurance status (yes/no).

To determine the associations of serious infections and mortality thereof in adults and pediatric inpatients with dermatomyositis, two different multivariable logistic regression models were constructed by invoking the stepwise selection approach to decide whether to include specific independent variables in the stepwise logistic model ($\alpha = 0.1$). In model 1, analysis was limited to adults or pediatric inpatients with a diagnosis of dermatomyositis, and serious infection was the dependent variable. In model 2, analysis was limited to adults or pediatric inpatients with a diagnosis of dermatomyositis and a serious infection, and inpatient mortality was the dependent variable. Covariables analyzed were age ($\leq$ 39/40–59/60–79/$\geq$ 80 years), sex (female/male), race (white/non-white), median annual income of the hospital ZIP code ($<$ \$64,000/$\geq$ \$64,000), number of chronic conditions (0–1/2–6/$\geq$ 6), season of admission (winter/spring/summer/autumn), hospital location (metropolitan ≥ 1 million, fringe/metropolitan < 1 million, micropolitan, not metropolitan or micropolitan), health insurance coverage (Medicare/Medicaid/private/self-pay, no charge or other). Metropolitan counties were defined as an urban cluster population between 10,000 and 49,999 residents. A chronic condition was defined as a condition lasting at least 12 months and meeting at least 1 of the following criteria: limitation on self-care and requirement of continuous treatment/therapy. Two-way interaction models were also constructed with predictors such as any serious infection, any skin infection,

pneumocystis carinii pneumonia, cytomegalovirus, Cryptococcus, hepatitis A and some well-known confounders' such as human immunodeficiency virus (HIV), long-term corticosteroid usage, Cushing's disease/syndrome (which was significantly with long-term corticosteroid usage; Rao–Scott Chi square, $P < 0.0001$), cancer, or diabetes to predict the risk of dermatomyositis in both pediatric and adult patients. Interactions of DM and interstitial lung disease and skin ulcers were also tested. Interactions were included in the final models if the interaction P value was < 0.01 and modification of estimation by > 20%.

Excess LOS and cost of care for an infection indirectly related to dermatomyositis were estimated by: ((prevalence of that infection in dermatomyositis inpatients)/(prevalence of that infection in non-dermatomyositis inpatients)) × (total hospitalization annual days or costs for that infection in dermatomyositis inpatients). Complete case analysis was performed. Two-sided P values < 0.05 were considered significant.

Correction for multiple dependent tests was performed by minimizing the false discovery rate with the approach of Benjamini and Hochberg [2]. Adjusted P values are presented and were considered statistically significant if < 0.05.

Results

There were a total number of 72,108,032 adult and 14,991,546 pediatric discharges captured in NIS between 2002 and 2012. There were 10,228 and 48,359 weighted admissions with a primary or secondary diagnosis of dermatomyositis in adults, and 4601 and 2755 weighted admissions in pediatric patients, respectively. There were 37,171,610 and 50,171,191 weighted admissions with a primary or secondary diagnosis of any serious infection in adults, and 5768,829 and 3692,624 weighted admissions in pediatric patients with dermatomyositis, respectively. Adult and pediatric patients with dermatomyositis were more likely to be female and older than those without dermatomyositis (Table 1).

Serious infections in dermatomyositis

Overall, the prevalences [95% CI] of serious infections were higher in adult (41.9% [95% CI 40.9–43.0%] vs. 25.4% [25.3–25.6%]) and pediatric (23.2% [19.9–26.4%] vs. 13.3% [12.8–13.8%]) inpatients with vs. without dermatomyositis, respectively. Of these, 38.4% [38.1–38.8%] and 61.6% [61.2–62.9%] were primary and secondary infections in adults, and 46.8% [45.5–47.4%] and 53.2% [52.6–54.5%] were primary and secondary infections in children.

The absolute risk difference was 16.5% in adults and 9.8% in pediatric patients. Similarly, in sensitivity analyses, the prevalence of more severe extracutaneous infections was higher in adult (24.6% [23.6–25.5%] vs. 18.4% [18.2–18.5%]) but not in pediatric (9.1% [7.2–11.0%] vs. 9.2% [8.8–9.5%]) inpatients with vs. without dermatomyositis. Serious infections were most common in hospitalizations occurring in the northeast, Midwest, Texas and California (Fig. 1). In both adult and pediatric inpatients with dermatomyositis, there was no cases of seborrheic keratosis.

In multivariable logistic regression models controlling for sex, age, race/ethnicity and insurance status, dermatomyositis was associated with any serious infection (aOR [95% CI] 2.19 [2.08–2.30]) and more severe extracutaneous infections (1.47 [1.38–1.55]) in adult but in pediatric inpatients only with serious infection (1.45 [1.20–1.76]) and not more severe extracutaneous infections (0.77 [0.59–1.01]). In particular, dermatomyositis was significantly associated with 32 of 48 infections examined in adult inpatients (Fig. 2a) and 12

Table 1 Subject characteristics

Variable	Adults			Pediatric		
	Dermatomyositis			Dermatomyositis		
	No	Yes	P value	No	Yes	P value
Age (year) (SEM)	57.0 (0.1)	57.4 (0.3)	0.12[a]	2.9 (0.04)	9.9 (0.2)	< 0.0001[a]
Female—freq (%)	207,255,789 (60.5%)	43,149 (73.7%)	< 0.0001[b]	35,045,348 (49.8%)	4817 (66.2%)	< 0.0001[b]
Race/ethnicity—freq (%)			< 0.0001			0.08
White	1895,788,383 (69.3%)	30,218 (63.6%)		28,341,651 (51.4%)	2711 (47.2%)	
Black	38,438,321 (14.0%)	8628 (18.2%)		8193,597 (14.9%)	1146 (19.9%)	
Asian	6335,150 (2.3%)	1143(2.4%)		2251,934 (4.1%)	102 (1.8%)	
Hispanic	29,529,187 (10.8%)	5790 (12.2%)		12,822,083 (23.3%)	1414 (24.6%)	
Multiracial/other	9772,396 (3.6%)	1709 (3.6%)		3489,598 (6.3%)	377 (6.5%)	

[a]Two sample t test

[b]Chi square test

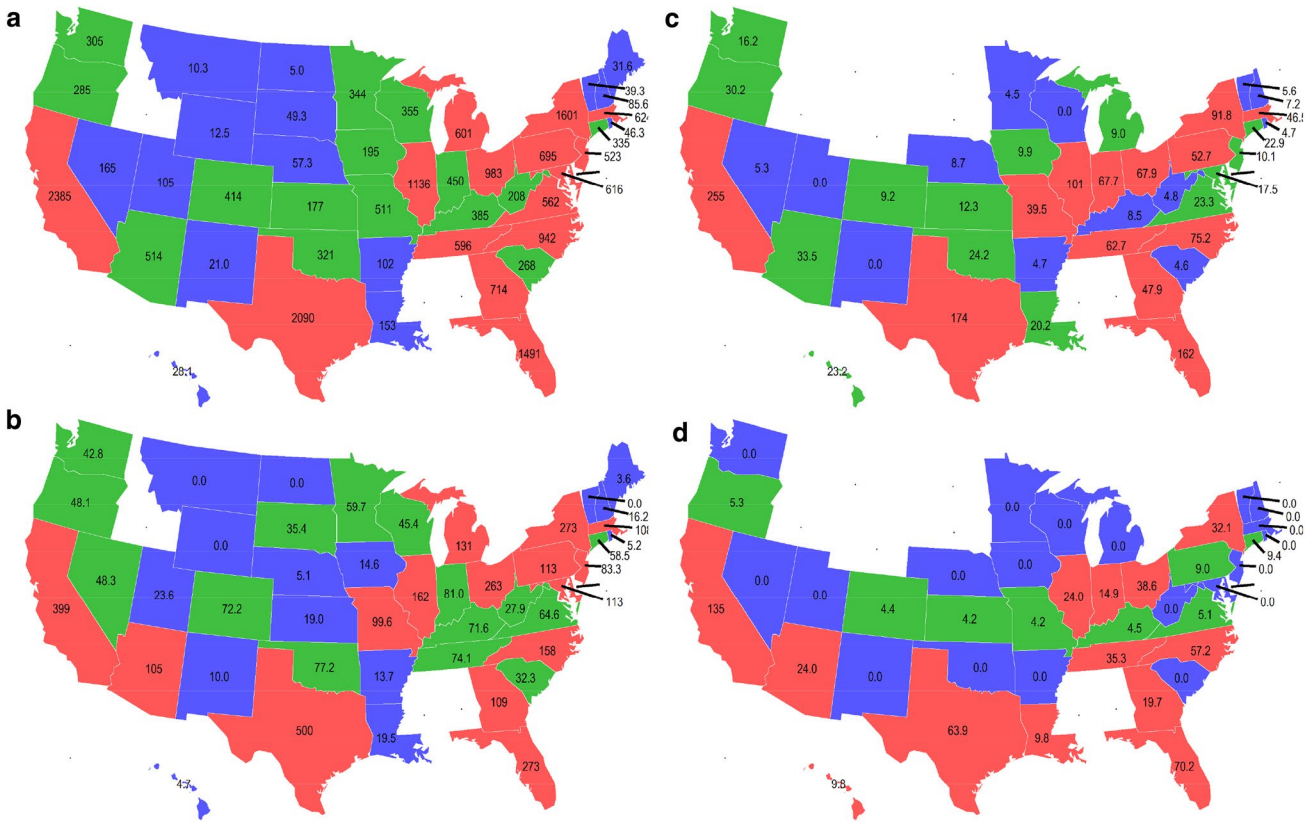

Fig. 1 State prevalence of serious infection and skin infection in adults and pediatric patients with dermatomyositis. **a** State prevalence of any serious infection in adult patients. **b** State prevalence of skin infection in adult patients. **c** State prevalence of any serious infection in pediatric patients. **d** State prevalence of skin infection in pediatric patients

of 48 infections examined in pediatric inpatients (Fig. 2b), respectively. Dermatomyositis was associated with higher odds of skin infections, including cellulitis and infections with herpes simplex virus and herpes zoster virus, as well as extracutaneous and systemic infections, including septicemia, meningitis, encephalitis, infectious arthritis, bone infections, endocarditis, enterocolitis, peritonitis or peritoneal abscess, pneumonia and empyema. Dermatomyositis was also associated with higher odds of antibiotic-resistant and opportunistic infections, including pneumocystis carinii pneumonia in children and adults, cytomegalovirus and cryptococcus in adults, and hepatitis A in children. Similarly, DM was associated with higher odds of primary admission for serious infections (Supplement Tables 2, 3). In a sensitivity analysis that excluded patients with any diagnosis of diabetes mellitus, there was still significant association of DM with serious infections (aOR [95% CI] for adults: 2.17 [1.99–2.25]; pediatric: 1.44 [1.18–1.76]).

Long-term steroid usage (adult: 11.28% vs. 0.62%, $P<0.0001$; pediatric: 8.77% vs. 0.08%, $P<0.0001$), a diagnosis of Cushing's syndrome (adult: 1.56% vs. 0.20%, $P<0.0001$; pediatric: 1.81% vs. 0.06%, $P<0.0001$) and diabetes (adult: 27.48% vs. 22.31%, $P<0.0001$; pediatric: 3.08% vs. 0.89%, $P<0.0001$) were diagnosed more commonly in both adult and pediatric hospitalizations, whereas cancer (adult: 17.29% vs. 13.37%, $P<0.0001$; pediatric: 0.93% vs. 1.46%, $P=0.16$) was diagnosed more commonly in adults with vs. without dermatomyositis. There were significant interactions of dermatomyositis with long-term systemic corticosteroid usage ($P<0.0001$), a diagnosis of Cushing's syndrome ($P<0.0001$), cancer ($P<0.0001$), diabetes ($P<0.0001$), and HIV ($P<0.0001$) as predictors of any serious infections, the opportunistic infections pneumocystis carinii pneumonia, cytomegalovirus, Cryptococcus, and/or hepatitis A in both pediatric and adult inpatients (Supplemental Table 4). Further, there were significant interactions of dermatomyositis with interstitial lung disease as predictors of any serious infection, particularly pneumocystis carinii pneumonia, cytomegalovirus, and Cryptococcus in adults, as well as any serious infection and cytomegalovirus in children. There were also significant interactions of dermatomyositis with skin ulcers as predictors of any serious infection, any skin infection, pneumocystis carinii pneumonia, and Cryptococcus in adults, as well as any serious infection, any skin infection, pneumocystis carinii pneumonia, cytomegalovirus and hepatitis A in children.

Figure 2a. Associaton of serious infections with DM hospitalization in adults

Serious Infection	Primary and secondary diagnosis of Dermatomyositis								
	No		Yes						
	Weighted Frequency	% Prevalence [95% CI]	Weighted Frequency	% Prevalence [95% CI]	Absolute Risk (%Prevalence) Difference	Crude OR [95% CI]	Adj. P	Adjusted OR^ [95% CI]	Adj. P
Necrotizing fasciitis	145095	0.042 [0.041-0.044]	34	0.068 [0.015-0.10]	0.026	1.37 [0.65-2.88]	0.42	1.59 [0.71-3.53]	0.28
Meningitis	552412	0.164 [0.0157-0.165]	219	0.373 [0.254-0.492]	0.209	2.33 [1.69-3.21]	0.00016*	2.41 [1.70-3.44]	0.00016*
Septicemia	13834064	4.03 [3.97-4.09]	4646	7.93 [7.37-8.49]	3.9	2.05 [1.90-2.21]	0.00016*	1.35 [1.32-1.38]	0.00016*
Enterocolitis	4790655	1.40 [1.37-1.42]	1321	2.25 [1.94-2.56]	0.85	1.64 [1.43-1.89]	0.00016*	1.58 [1.36-1.85]	0.00016*
Bronchitis	2124903	0.62 [0.60-0.63]	436	0.74 [0.58-0.91]	0.12	1.20 [0.97-1.50]	0.11	1.22 [0.96-1.55]	0.12
Urinary tract infection	30699109	8.94 [8.85-9.04]	7006	11.96 [11.29-12.63]	3.02	1.38 [1.30-1.47]	0.00016*	1.36 [1.27-1.46]	0.00016*
Pneumonia	2479814	7.23 [7.14-7.31]	7223	12.33 [11.64-13.01]	5.1	1.82 [1.71-1.94]	0.00016*	1.98 [1.84-2.13]	0.00016*
Peritonitis or peritoneal abscess	1860217	0.54 [0.53-0.55]	488	0.089 [0.66-1.01]	-0.451	1.55 [1.26-1.91]	0.00016*	1.72 [1.37-2.16]	0.00016*
Appendicitis	2564444	0.75 [0.74-0.76]	129	0.22 [0.13-0.30]	-0.53	0.29 [0.20-0.43]	0.00016*	0.36 [0.23-0.56]	0.00016*
Encephalitis	231340	0.067 [0.065-0.069]	114	0.19 [0.11-0.28]	0.123	2.89 [1.90-4.40]	0.00016*	3.48 [2.26-5.34]	0.00016*
Tuberculosis	627560	0.18 [0.18-0.19]	154	0.26 [0.15-0.38]	0.08	1.44 [0.92-2.26]	0.13	1.52 [0.94-2.49]	0.12
Influenza	500617	0.15 [0.14-0.15]	121	0.21 [0.13-0.28]	0.06	1.42 [0.97-2.06]	0.1	1.40 [0.91-2.15]	0.15
Aspergilosis	143506	0.042 [0.040-0.044]	142	0.24 [0.13-0.36]	0.198	5.84 [3.65-9.34]	0.00016*	6.04 [3.48-10.48]	0.00016*
Lung or mediastinal abscess	182224	0.053 [0.052-0.054]	89	0.15 [0.07-0.23]	0.097	2.87 [1.71-4.82]	0.00016*	3.00 [1.59-5.64]	0.0011*
Empyema	376867	0.110 [0.108-0.112]	94	0.16 [0.09-0.24]	0.05	1.47 [0.92-2.35]	0.13	1.84 [1.10-3.09]	0.029*
Acute sinusitis	508794	0.15 [0.14-0.15]	105	0.18 [0.10-0.26]	0.03	1.21 [0.79-1.87]	0.42	1.21 [0.73-1.98]	0.48
Acute pharyngitis	510402	0.149 [0.146-0.152]	163	0.278 [0.186-0.371]	0.129	1.88 [1.34-2.62]	0.00031*	2.00 [1.39-2.88]	0.00031*
Acute tonsillitis	102319	0.0298 [0.0287-0.0309]	18	0.0315 [0.0005-0.0624]	0.0017	1.06 [0.40-2.83]	0.91	1.3 [0.42-4.07]	0.081
Mycobacterial infection	170979	0.0498 [0.0471-0.0525]	193	0.33 [0.19-0.46]	0.2802	6.62 [4.37-10.02]	0.00016*	8.59 [4.22-10.28]	0.00016*
Streo throat	131797	0.0384 [0.0375-0.0393]	33	0.057 [0.015-0.099]	0.0186	1.48 [0.71-3.11]	0.34	1.27 [0.47-3.40]	0.65
Strep pneumonia	674516	0.197 [0.192-0.201]	161	0.276 [0.180-0.371]	0.079	1.41 [0.99-1.99]	0.067	1.38 [0.92-2.08]	0.14
Chickenpox	23655	0.0069 [0.0066-0.0072]	18	0.0156 [0.0007-0.062]	0.0087	4.55 [1.72-12.07]	0.0035*	3.09 [0.77-12.32]	0.13
Herpes Zoster	495915	0.145 [0.143-0.147]	368	0.63 [0.49-0.77]	0.485	4.38 [3.51-5.46]	0.00016*	1.19 [1.17-1.21]	0.00016*
Cellulitis	12742551	3.71 [3.67-3.75]	4296	7.33 [6.80-7.86]	3.62	2.05 [1.90-2.22]	0.00016*	2.19 [2.01-2.38]	0.00016*
Herpes Simplex Virus infection	1151012	0.33 [0.32-0.35]	497	0.85 [0.68-1.02]	0.52	2.57 [2.11-3.13]	0.00016*	2.46 [1.97-3.08]	0.00016*
Infectious arthritis	598064	0.17 [0.17-0.18]	324	0.55 [0.40-0.70]	0.38	3.19 [2.43-4.18]	0.00016*	3.66 [2.71-4.94]	0.00016*
Methicillin resistant Staphylococcus aureus infection	2617580	0.76 [0.73-0.79]	901	1.54 [1.26-1.81]	0.78	2.03 [1,70-2.43]	0.00016*	2.24 [1.86-2.70]	0.00016*
Bone or joint infection	2268502	0.66 [0.65-0.67]	735	1.26 [1.03-01.48]	0.6	1.91 [1.60-2.29]	0.00016*	2.21 [1.81-2.68]	0.00016*
Methicillin sensitive Staphylococcus aureus infection	4486286	1.31 [1.28-1.33]	1794	3.06 [2.73-3.40]	1.75	2.40 [2.14-2.68]	0.00016*	2.56 [2.26-2.90]	0.00016*
Clostridium difficile	3119743	0.91 [0.89-0.93]	939	1.60 [1.34-1.87]	0.69	1.78 [1.51-2.09]	0.00016*	1.76 [1.47-2.12]	0.00016*
Pyelonephritis	2448965	0.71 [0.70-0.72]	405	0.69 [0.55-0.84]	-0.02	0.97 [0.78-1.20]	0.79	0.84 [0.66-1.08]	0.2
Endocarditis	720189	0.210 [0.206-0.214]	165	0.28 [0.18-0.38]	0.07	1.35 [0.95-1.91]	0.12	1.45 [1.00-2.09]	0.071
Diverticulitis	3322355	0.97 [0.95-0.98]	460	0.78 [0.62-0.95]	-0.19	0.81 [0.65-1.00]	0.067	0.82 [0.65-1.04]	0.12
Pneumocystis carinii pneumonia	161507	0.047 [0.043-0.051]	186	0.32 [0.22-0.42]	0.273	6.78 [4.85-9.49]	0.00016*	7.01 [4.72-10.40]	0.00016*
Any fungal infection	5867844	1.71 [1.68-1.74]	4295	7.33 [6.79-7.87]	5.62	4.55 [4.20-4.93]	0.00016*	4.67 [4.28-5.10]	0.00016*
Any viral infection	3322085	0.97 [0.95-0.99]	1501	2.56 [2.27-2.85]	1.59	2.69 [2.40-3.02]	0.00016*	2.60 [2.29-2.95]	0.00016*
Any skin infection	13185346	3.84 [3.80-3.88]	4510	7.70 [7.16-8.24]	3.86	2.09 [1,94-2.25]	0.00016*	2.23 [2.06-2.42]	0.00016*
Any strep infection	3659072	1.07 [1.05-1.08]	852	1.45 [1.23-1.68]	0.38	1.37 [1.17-1.60]	0.00016*	1.42 [1.20-1.69]	0.00016*
Pseudomonas	1982710	0.58 [0.57-0.59]	654	1.12 [0.91-1.32]	0.54	1.94 [1.62-2.34]	0.00016*	2.21 [1.83-2.67]	0.00016*
Cytomegalovirus	75751	0.022 [0.0214-0.0227]	32	0.054 [0.014-0.094]	0.032	2.47 [1.19-5.16]	0.028*	4.92 [2.35-10.27]	0.00016*
Cryptococcus	60158	0.0175 [0.0162-0.0188]	42	0.072 [0.025-0.12]	0.0545	4.09 [2.14-7.79]	0.00016*	4.86 [2.44-9.67]	0.00016*
HIV	2571169	0.75 [0.69-0.81]	127	0.22 [0.13-0.30]	-0.53	0.29 [0.20-0.43]	0.00016*	0.29 [0.18-0.45]	0.00016*
Hepatitis A	86428	0.025 [0.024-0.026]	38	0.065 [0.016-0.12]	0.04	2.63 [1.24-5.58]	0.015*	2.43 [0.98-6.02]	0.081
Hepatitis B	743650	0.22 [0.21-0.23]	156	0.27 [0.14-0.39]	0.05	1.23 [0.78-1.94]	0.4	1.33 [0.82-2.16]	0.27
Hepatitis C	5243023	1.53 [1.47-1.59]	771	1.32 [1.06-1.57]	-0.21	0.87 [0.71-1.06]	0.18	0.97 [0.78-1.21]	0.77
Antibiotic resistant infection	2193581	0.64 [0.62-0.66]	650	1.11 [0.90-1.31]	0.47	1.75 [1.45-2.10]	0.00016*	1.84 [1.50-2.26]	0.00016*
Any serious infection	87318227	25.44 [25.25-25.63]	24573	41.94 [40.87-43.02]	16.5	2.12 [2.03-2.21]	0.00016*	2.19 [2.08-2.30]	0.00016*

^adjust for age (continuous), gender, race (other vs. white), insurance (yes vs. no)
*significant at p-value 0.05

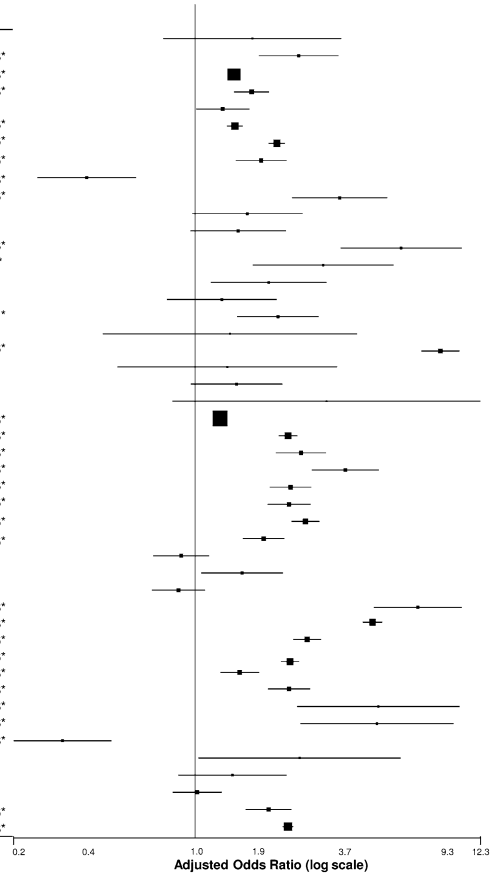

Fig. 2 Association between dermatomyositis and serious infections in adults (**a**) and pediatric patients (**b**). Survey logistic regression models were constructed with dermatomyositis as the independent variable and the respective serious infection as the dependent variable. Models included age, gender, race/ethnicity, and insurance status as covariates. Adjusted odds ratios and 95% confidence intervals were estimated. Forest plots of the adjusted odds ratios and 95% confidence intervals are presented

Table 2b. Associaton of serious infections with DM hospitalization in children age<=18

Serious Infection	Primary and secondary diagnosis of Dermatomyositis								
	No				Yes				
	Weighted Frequency	% Prevalence [95% CI]	Weighted Frequency	% Prevalence [95% CI]	Absolute Risk (%Prevalence) Difference	Crude OR [95% CI]	Adj. P	Adjusted OR^ [95% CI]	Adj. P
Meningitis	238992	0.34 [0.32-0.36]	62	0.85 [0.36-1.34]	0.51	2.56 [1.43-4.55]	0.0036*	2.17 [1.19-3.98]	0.033*
Septicemia	889067	1.25 [1.19-1.32]	162	2.20 [1.47-2.93]	0.95	1.81 [1.30-2.52]	0.0015*	1.66 [1.13-2.45]	0.033*
Enterocolitis	745496	1.05 [1.00-1.10]	112	1.52 [0.85-2.20]	0.47	1.46 [0.93-2.30]	0.14	1.20 [0.71-2.03]	0.58
Bronchitis	1785689	2.51 [2.40-2.63]	28	0.38 [0.07-0.69]	-2.13	0.15 [0.067-0.34]	0.00033*	0.47 [0.21-1.06]	0.15
Urinary tract infection	1058243	1.49 [1.44-1.55]	179	2.43 [1.63-3.23]	0.94	1.66 [1.19-2.32]	0.0062*	0.74 [0.50-1.10]	0.22
Pneumonia	2388269	3.36 [3.24-3.49]	258	3.51 [2.59-4.44]	0.15	1.05 [0.79-1.38]	0.76	0.92 [0.68-1.23]	0.62
Peritonitis or peritoneal abscess	61833	0.087 [0.080-0.094]	21	0.28 [0-0.57]	0.193	3.21 [1.14-9.07]	0.045*	1.54 [0.46-5.13]	0.58
Appendicitis	940612	1.32 [1.27-1.38]	20	0.27 [0-0.55]	-1.05	0.21 [0.078-0.56]	0.0043*	0.09 [0.028-0.29]	0.0006*
Tuberculosis	11215	0.016 [0.014-0.018]	10	0.14 [0-0.41]	0.124	9.02 [1.44-56.37]	0.033*	4.59 [0.78-26.83]	0.18
Influenza	239952	0.34 [0.32-0.36]	41	0.56 [0.16-0.95]	0.22	1.67 [0.82-3.38]	0.2	1.15 [0.52-2.52]	0.73
Empyema	36944	0.052 [0.046-0.058]	10	0.14 [0-0.33]	0.088	2.72 [0.72-10.24]	0.18	2.18 [0.57-8.31]	0.33
Acute sinusitis	76779	0.11 [0.096-0.12]	19	0.25 [0.0023-0.50]	0.14	2.36 [0.87-6.39]	0.13	1.92 [0.70-5.23]	0.3
Acute pharyngitis	181747	0.26 [0.24-0.27]	21	0.29 [0.011-0.57]	0.03	1.14 [0.44-2.98]	0.79	0.63 [0.21-1.90]	0.51
Acute tonsillitis	87767	0.124 [0.118-0.130]	5	0.07 [0-0.21]	-0.054	0.58 [.08-4.13]	0.64	0.42 [0.06-3.00]	0.5
Mycobacterial infection	5799	0.0082 [0.0066-0.0097]	5	0.068 [0-0.20]	0.0598	8,.33 [1.15-60.58]	0.057	4.87 [0.67-35.59]	0.22
Streo throat	154625	0.22 [0.21-0.23]	4	0.06 [0-0.18]	-0.16	0.28 [0.04-1.94]	0.24	0.22 [0.03-1.57]	0.22
Chickenpox	12303	0.017 [0.016-0.019]	19	0.26 [0.001-0.51]	0.243	14.86 [5.48-40.32]	0.00033*	3.48 [0.48-25.12]	0.32
Herpes Zoster	10010	0.014 [0.013-0.016]	37	0.50 [0.15-0.85]	0.486	35.96 [17.73-72.92]	0.00033*	20.85 [10.11-43.01]	0.0006*
Cellulitis	858782	1.21 [1.14-1.28]	583	7.92 [5.64-10.20]	6.71	7.03 [5.15-9.59]	0.00033*	4.14 [2.90-5.92]	0.0006*
Herpes Simplex Virus infection	98838	0.14 [0.13-0.15]	51	0.69 [0.19-1.19]	0.55	5.02 [2.42-10.45]	0.00033*	3.15 [1.50-6.61]	0.0096*
Infectious arthritis	49486	0.070 [0.065-0.075]	28	0.39 [0.044-0.73]	0.32	5.57 [2.32-13.37]	0.00033*	4.12 [1.68-10.10]	0.009*
Methicillin resistant Staphylococcus aureus infection	172683	0.24 [0.22-0.27]	40	0.54 [0.16-0.92]	0.3	2.25 [1.12-4.52]	0.04*	1.27 [0.57-2.81]	0.62
Bone or joint infection	80737	0.11 [0.10-0.12]	25	0.34 [0-0.79]	0.23	2.98 [0.77-11.60]	0.16	0.74 [0.18-3.02]	0.69
Methicillin sensitive Staphylococcus aureus infection	398655	0.56 [0.52-0.61]	258	3.51 [2.45-4.57]	2.95	6.49 [4.77-8.84]	0.00033*	3.96 [2.79-5.62]	0.0006*
Clostridium difficile	89736	0.13 [0.11-0.14]	24	0.33 [0.0046-0.65]	0.2	2.62 [0.99-6.91]	0.075	2.08 [0.79-5.48]	0.22
Pyelonephritis	386783	0.54 [0.52-0.57]	30	0.40 [0.08-0.72]	-0.14	0.74 [0.33-1.64]	0.52	0.30 [0.11-0.81]	0.051
Pneumocystis carinii pneumonia	2680	0.0038 [0.0032-0.0044]	5	0.065 [0-0.19]	0.0612	17.26 [2.49-119.50]	0.0074*	12.16 [1.71-86.25]	0.035
Any fungal infection	413127	0.58 [0.54-0.62]	288	3.92 [2.96-4.88]	3.34	6.98 [5.42-8.98]	0.00033*	5.15 [3.96-6.69]	0.0006*
Any viral infection	1172374	1.65 [1.65-1.74]	222	3.02 [2.00-4.05]	1.37	1.86 [1.30-2.65]	0.0017*	1.48 [1.01-2.18]	0.1
Any skin infection	1082416	1.52 [1.45-1.60]	620	8.43 [6.09-10.77]	6.91	5.95 [4.41-8.04]	0.00033*	3.85 [2.73-5.42]	0.0006*
Any strep infection	430536	0.61 [0.58-0.64]	39	0.53 [0.15-0.91]	-0.08	0.88 [0.44-1.79]	0.76	0.64 [0.30-1.37]	0.33
Pseudomonas	146239	0.21 [0.18-0.23]	42	0.57 [0.23-0.91]	0.36	2.78 [1.52-5.10]	0.0026*	1.75 [0.91-3.39]	0.19
Cytomegalovirus	88382	0.12 [0.12-0.13]	15	0.20 [0-0.42]	0.08	1.64 [0.55-4.89]	0.43	0.74 [0.19-2.85]	0.69
Hepatitis A	3514	0.0049 [0.0045-0.0054]	13	0.18 [0-0.0044]	0.1751	36.73 [8.52-158.43]	0.00033*	12.83 [1.77-93.23]	0.035*
Antibiotic resistant infection	182981	0.26 [0.23-0.28]	51	0.69 [0.25-1.13]	0.43	2.69 [1.43-5.04]	0.0044*	1.99 [1.02-3.88]	0.1
Any serious infection	9459750	13.32 [12.81-13.83]	1703	23.16 [19.88-26.43]	9.84	1.98 [1.64-2.38]	0.00033*	1.45 [1.20-1.76]	0.001*

^adjust for age, gender, race (other vs. white), insurance (yes vs. no)
*significant at p-value 0.05

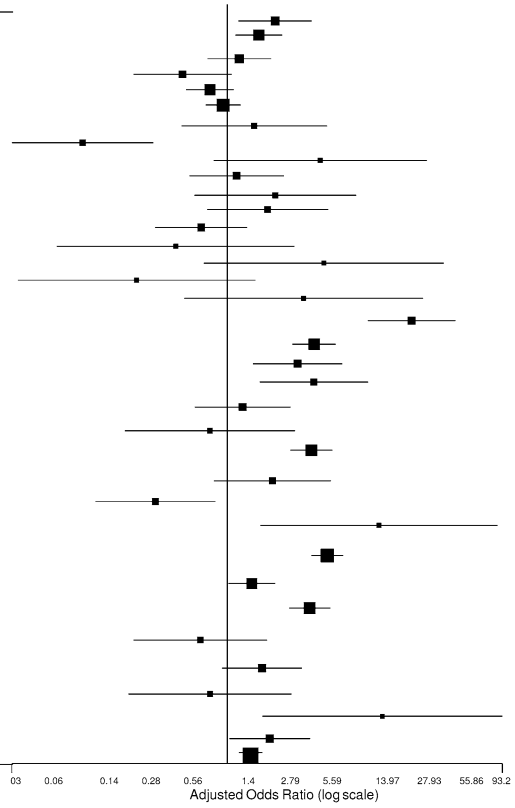

Fig. 2 (continued)

Admission primarily for serious infections occurred more frequently in non-teaching vs. teaching hospitals for both adult (56.6% vs. 48.8%, $P < 0.0001$) and pediatric (91.3% vs. 78.4%, $P = 0.002$) inpatients with dermatomyositis. The difference was not significant when combining the primary and secondary diagnosis of serious infections ($P > 0.05$).

In multivariable regression models with stepwise selection, the associations with a higher risk for any serious infection in adults were old age, female sex, non-white race/ethnicity, government insurance, number of chronic conditions, winter season, and non-metropolitan or micropolitan hospital location. In children, the associations of any serious infection with dermatomyositis were non-white race/ethnicity, number of chronic conditions, and non-metropolitan or micropolitan hospital location (Table 2).

Table 2 Associations of serious infections in adult and pediatric patients with dermatomyositis

Variable	Adult		Pediatric	
	Adjusted OR [95% CI]	*P* value	Adjusted OR [95% CI]	*P* value
Age (year)				
18–39	1.00 [ref]	–		
40–59	1.06 [1.00–1.12]	0.08		
60–79	1.13 [1.06–1.20]	0.0013		
≥ 80	1.34 [1.24–1.46]	< 0.0001		
Sex				
Female	1.06 [1.02–1.11]	0.012		
Male	1.00 [ref]	–		
Race/ethnicity				
White	1.00 [ref]	–	1.00 [ref]	–
Other	1.13 [1.08–1.17]	< 0.0001	1.73 [1.49–2.01]	< 0.0001
Household income				
≥ $64,000	1.00 [ref]	–		
< $64,000	0.92 [0.88–0.96]	0.0008		
Insurance				
Medicare	1.20 [1.12–1.27]	< 0.0001	NA	NA
Medicaid	1.18 [1.12–1.23]	< 0.0001	0.89 [0.77–1.04]	0.22
Private	1.00 [ref]	–	1.00 [ref]	–
Uninsured	1.03 [0.95–1.11]	0.59	0.31 [0.24–0.40]	< 0.0001
No. of chronic conditions				
0–1	1.00 [ref]	–	1.00 [ref]	–
2–5	1.49 [1.34–1.66]	< 0.0001	1.53 [1.84–2.89]	< 0.0001
≥ 6	1.86 [1.67–2.07]	< 0.0001	2.31 [1.84–2.09]	< 0.0001
Season				
Spring	1.00 [ref]	–		
Summer	0.95 [0.90–1.00]	0.07		
Fall	1.02 [0.97–1.07]	0.53		
Winter	1.08 [1.03–1.14]	0.0087		
Hospital Location				
Metropolitan > 1 million people	1.00 [ref]	–	1.00 [ref]	–
Fringe metropolitan < 1 million people	0.97 [0.93–1.01]	0.17	1.08 [0.93–1.24]	0.40
Micropolitan	0.99 [0.92–1.07]	0.87	4.24 [3.29–5.46]	< 0.0001
Not metropolitan or micropolitan	1.11 [1.02–1.22]	0.0426	3.75 [2.61–5.39]	< 0.0001

Multivariable logistic regression models were constructed by invoking the stepwise selection approach ($\alpha = 0.1$) to determine the significant associations of any serious infection (dependent variable) in dermatomyositis (independent variables). The covariates analyzed were age (years) (≤ 39/40–59/60–79/≥ 80), sex (female/male), race/ethnicity (white/non-white), median annual income of the hospital zip code (< $64,000/≥ $64,000), number of chronic condition (0–1/2–6/≥ 6), season of admission (winter/spring/summer/autumn), hospital location (metropolitan ≥ 1 million, fringe metropolitan < 1 million, micropolitan, not metropolitan or micropolitan), health insurance coverage (Medicare/Medicaid/private/uninsured). Significant associations remaining in the final selection models are presented

Inpatient cost and LOS

Serious infections were associated with significantly increased geometric mean inpatient cost and LOS in pediatric (cost: $35,593 vs. $10,882, $P<0.0001$; LOS: 11.77 vs. 4.05 days, $P<0.0001$) and adult (cost: $23,425 vs. $12,516, $P<0.0001$; LOS: 10.20 vs. 5.24 days, $P<0.0001$) inpatients with dermatomyositis (Table 3). In multivariable selection models, specific serious infections and related complications, e.g., septicemia, pneumonia, and urinary tract infection, were associated with a considerable excess cost of hospitalization and LOS in both pediatric and adult inpatients with dermatomyositis (Supplement Table 5, 6).

Inpatient mortality

The diagnosis of any serious infection vs. no infection was associated with increased mortality in both adult (8.28% vs. 2.30%, $P<0.0001$) and pediatric (1.71% vs. 0.25%, $P=0.0029$) inpatients with dermatomyositis. There were no significant changes of inpatient mortality between 2002 and 2012 among adult or pediatric inpatients with dermatomyositis ($P>0.05$). Serious infections occurred in 72.3% and 67.2% of adult and pediatric dermatomyositis patients who died during hospitalization.

In multivariable models with stepwise selection, the significant associations of inpatient mortality in adults were fungal infection, tuberculosis, septicemia and pneumonia, older age, number of chronic conditions, and micropolitan hospital location (Table 4). The associations of inpatient mortality could not be determined in children due to inadequate sample size.

A diagnosis of Cushing's syndrome (adult: 2.38% vs. 1.52%, $P=0.09$; pediatric: 11.14% vs. 1.75%, $P=0.019$) was diagnosed more commonly in pediatric hospitalizations with dermatomyositis resulting in death vs. no death, whereas cancer (adult: 26.35% vs. 16.85%, $P<0.0001$; pediatric: 0% vs. 3.10%, $P=$NE) and diabetes (adult: 23.77% vs. 27.64%, $P=0.0429$; pediatric: 0% vs. 3.10%, $P=$NE) were diagnosed more commonly in adult hospitalizations with dermatomyositis resulting in death vs. no death. There were significant interactions of serious infections with cancer as predictors of inpatient mortality in adults with dermatomyositis ($P<0.0001$). Adults with dermatomyositis who had any serious infection had significantly higher odds of death when they also had cancer (aOR [95% CI] 12.02 [7.49–19.29]) than those without cancer (4.53 [3.63–5.67]).

Discussion

This study demonstrates that both adult and pediatric inpatients with dermatomyositis have significantly higher prevalences of multiple serious and opportunistic infections compared to those without dermatomyositis. These infections affect the skin, lungs, heart, brain, gastrointestinal tract, and bones. Serious infections were increased in adult and pediatric inpatients with dermatomyositis who were non-white, had more chronic conditions, including long-term steroid use, and a diagnosis of Cushing's syndrome, which were also associated with each other, cancer, diabetes, as well as dermatomyositis patients who had interstitial lung disease and skin ulcers. There were significant interactions of dermatomyositis with long-term steroid use as predictors of serious infections. Dermatomyositis alone was associated with increased odds of infection. However, dermatomyositis patients with long-term steroid use had even higher odds of infection. Serious infections were also associated with prolonged and very costly hospital admissions in both adult and pediatric inpatients with dermatomyositis. Indirect costs of serious infections should be considered in the financial burden of dermatomyositis and cost-effectiveness studies of their treatments. Finally, serious infections occurred in the majority of admissions resulting in death. The infections with greatest mortality in adults were fungal infection, tuberculosis, septicemia and pneumonia.

These results are consistent with previous studies that found high rates of pyogenic and non-pyogenic/opportunistic infections in dermatomyositis [3, 8, 10–12, 14]. A case series of 279 adults with polymyositis or dermatomyositis

Table 3 Inpatient cost of care and length of stay in adult and pediatric inpatients with dermatomyositis and serious infections

Any serious infection	Geometric mean length of stay (days) [95% CI]	Geometric mean cost of hospitalization [95% CI]	Excess annual LOS secondary to DM	Excess annual cost secondary to DM
Adult inpatients				
No	5.24 [5.10–5.40]	$12,516 [$12,104–$12,928]	–	–
Yes	10.20 [9.74–10.65]	$23,425 [$22,129–$24,721]	13,815.82	$28,938,249
Pediatric inpatients				
No	4.05 [3.31–4.80]	$10,882 [$9291–$12,473]	–	–
Yes	11.77 [8.89–14.66]	$35,593 [$26,253–$44,933]	1045.53	$2945,469

Table 4 Associations of serious infections with mortality in adult inpatients with DM

Variable	Adjusted OR [95% CI]	*P* value
Age (year)		
18–39	1.00 [ref]	–
40–59	1.56 [1.31–1.85]	< 0.0001
60–79	2.19 [1.83–2.62]	< 0.0001
≥ 80	3.92 [3.17–4.84]	< 0.0001
Hospital location		
Metropolitan > 1 million people	1.00 [ref]	–
Fringe metropolitan < 1 million people	0.69 [0.63–0.76]	< 0.0001
Micropolitan	1.38 [1.19–1.60]	0.0004
Not metro or micropolitan	0.86 [0.70–1.07]	0.25
Insurance		
Medicare	0.71 [0.60–0.83]	0.0005
Medicaid	0.65 [0.58–0.73]	< 0.0001
Private	1.00 [ref]	–
Uninsured	1.06 [0.87–1.28]	0.63
No. of chronic conditions		
0–1	1.00 [ref]	–
2–5	6.90 [3.28–14.50]	< 0.0001
≥ 6	9.53 [4.54–20.01]	< 0.0001
Infection		
Streptococcal infection	0.06 [0.03–0.13]	< 0.0001
Methicillin resistant *Staphylococcus Aureus*	0.31 [0.22–0.44]	< 0.0001
Any fungal infection	1.78 [1.57–2.03]	< 0.0001
Tuberculosis	3.77 [2.26–6.28]	< 0.0001
Septicemia	7.65 [6.94–8.44]	< 0.0001
Pneumonia	3.70 [3.37–4.07]	< 0.0001

Multivariable logistic regression models were constructed by invoking the stepwise selection approach ($\alpha = 0.1$) to determine the significant associations of inpatient mortality (dependent variable) among patients with dermatomyositis and any serious infection. The covariates analyzed were age (≤ 39/40–59/60–79/≥ 80 years), sex (female/male), race/ethnicity (white/non-white), median annual income of the hospital zip code (< $64,000/≥ $64,000), number of chronic condition (0–1/2–6/≥ 6), season of admission (winter/spring/summer/autumn), hospital location (metropolitan ≥ 1 million, fringe/metropolitan < 1 million, micropolitan, not metropolitan or micropolitan), health insurance coverage (Medicare/Medicaid/private/uninsured). Significant variables remaining in the final selection models are presented

showed that 37.7% experienced serious infections, with a majority being pyogenic infections, e.g., aspiration pneumonia [3]. A study of hospitalized adults in the US similarly found high rates of bacterial infections and opportunistic infections from fungal infections in inpatients with polymyositis and/or dermatomyositis, and that infections were the largest cause of inpatient mortality among adults hospitalized for dermatomyositis [12]. A case–control study of Chinese patients hospitalized with polymyositis and dermatomyositis found that pulmonary infections were the most frequent cause of inpatient mortality [18]. In addition, the present study revealed significantly higher odds of multiple cutaneous, multi-organ and systemic infections, as well as opportunistic infections in adults and children, including pneumocystis carinii, cytomegalovirus, Cryptococcus and hepatitis A virus. Immunosuppression is a risk factor for increasing severity and mortality of hepatitis A and decreasing response to hepatitis A vaccination [5].

Increased risk of serious infections is not unique to dermatomyositis. Previous studies demonstrated increased odds of serious infections in other chronic inflammatory disorders, such as pemphigus, pemphigoid, atopic dermatitis and psoriasis [7, 13, 15–17]. However, a distinct profile of infections, especially opportunistic infections, was observed in dermatomyositis compared with other autoimmune disorders. In addition, dramatically higher inpatient mortality secondary to infections was observed in dermatomyositis. There may be common mechanisms for increased risk of infections across these disorders, including epidermal barrier dysfunction allowing transcutaneous penetration of pathogens; cutaneous and/or systemic immune dysregulation; use of long-term systemic corticosteroids and secondary

adrenal insufficiency; long-term use of immunosuppressive agents; association with comorbid health conditions that are independently associated with excess infectious risk, e.g., cancer and diabetes. In addition, there are distinct factors in dermatomyositis that contribute to increased serious infections, including interstitial lung disease and skin ulcers [3] as seen in the present study, as well as calcinosis, respiratory and other muscle weakness, dysphonia, and esophageal dysfunction [3]. These risk factors should be considered in risk stratification and prevention of infections and death. Interestingly, serious infections were more prevalent among dermatomyositis patients admitted to non-teaching vs. teaching hospitals. Yet, it is likely that severe and complicated cases of dermatomyositis were referred to teaching hospitals. It may be that teaching hospitals did a better job in managing dermatomyositis and/or employed specific approaches to prevent hospital acquired infections. If so, some serious infections may be preventable in dermatomyositis patients. Long-term use of systemic corticosteroids and other immunosuppressants are major drivers of serious and opportunistic infections in dermatomyositis. This highlights major unmet needs in the treatment of dermatomyositis, as there is a dearth of safe and effective systemic treatment options available. Finally, serious infections were associated with non-white race/ethnicity and hospitalization in a non-metropolitan or micropolitan area. Similar disparities were observed for serious infections in other autoimmune disorders [7, 13]. There may be racial/ethnic disparities and/or limited access to adequate specialty care in rural areas, resulting in increased infections in dermatomyositis and other autoimmune disorders. Future research is needed to identify optimal strategies to prevent serious infections in dermatomyositis.

Strengths of this study include analysis of a nationwide, representative cohort with a large number of cases and controls, and examination of children and adults. A previous study found the ICD-9-CM code 710.3 to be valid for identifying cases of dermatomyositis, particularly in the inpatient setting [9]. Thus, we believe the case definition used in this study is valid. We also found similar results in sensitivity analyses that excluded hospitalizations with a diagnosis of diabetes mellitus, which was previously found to be the main source of misclassification for DM [9]. Limitations include the cross-sectional design that precluded assessment of the directionality of association between dermatomyositis and serious infections. Thus, we can only conclude that there are associations between DM and serious infections, but are unable to make any inferences about causality. The absence of DM characteristics, severity, auto-antibodies and medications in NIS precluded analysis of risk from specific clinical features and/or systemic immunosuppressants. Long-term corticosteroid usage and Cushing's syndrome were identified by ICD code, which may underestimate their use. There may be a selection bias toward patients with more severe dermatomyositis in this hospital cohort. The date of onset of hospital acquired infections was not available in NIS, which precluded a specific assessment of hospital acquired infections. However, it is noteworthy that almost half of the infections occurring in dermatomyositis patients were present at the time of admission and were the primary reason for admission. The control group was not individually matched to dermatomyositis cases. However, dermatomyositis was not associated with seborrheic keratosis as a negative control, suggesting that the positive findings observed in this study are less likely to be attributable to surveillance bias.

In conclusion, dermatomyositis was associated with increased cutaneous, multi-organ, systemic and opportunistic infections in adults and children. Inpatients with dermatomyositis had prolonged hospitalizations, increased costs of care, and inpatient mortality due to serious infections. While infection risk in dermatomyositis is multifactorial, long-term corticosteroid use appears to be a major contributing factor. Future research is needed to develop safer and effective treatments for dermatomyositis, and interventions that can prevent and mitigate serious infections in dermatomyositis.

Funding This publication was made possible with support from the Agency for Healthcare Research and Quality (AHRQ), grant number K12 HS023011, and the Dermatology Foundation.

Compliance with Ethical Standards

J. I. Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: J. I. Silverberg. Acquisition of data: J. I. Silverberg, and Z. Ren. Analysis and interpretation of data: J. I. Silverberg, Z. Ren, A. Laumann. Drafting of the manuscript: J. I. Silverberg, Z. Ren, A. Laumann. Critical revision of the manuscript for important intellectual content: J. I. Silverberg, Z. Ren, A. Laumann. Statistical analysis: J. I. Silverberg, Z. Ren. Obtained funding: J. I. Silverberg. Administrative technical or material support: None. Study supervision: None.

Conflicts of interest J. I. Silverberg, A. Laumann and Ziyou Ren have no relevant conflicts of interest to declare.

Ethical approval The study was approved by the institutional review board at Northwestern University.

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