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Objective Measures of Psoriasis Severity Predict Mortality: A Prospective Population-Based Cohort Study

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To The Editor:

A broad and growing body of literature suggests psoriasis is associated with higher rates of major comorbidities, including mortality (Gelfand et al., 2007, Lee et al., 2017, Lindegard, 1989, Ogdie et al., 2014, Poikolainen et al., 1999, Salahadeen et al., 2015, Springate et al., 2017, Stern and Huibregtse, 2011, Svedbom et al., 2015). Most current literature does not adjust for major mortality risk factors such as obesity, and critically, to our knowledge, there are no studies that evaluate how direct measures of psoriasis severity influence risk of death. Therefore, the objective of this study is to examine the risk of mortality in psoriasis patients compared to adults without psoriasis, stratified by simple physician-reported objective measures of disease severity while adjusting for major mortality risk factors routinely collected in clinical practice.

We conducted a prospective, population-based, cohort study using The Health Improvement Network (THIN), an electronic medical records database in the United Kingdom. Within THIN, we created a nested cohort of patients with psoriasis, who were followed prospectively as the “Incident Heath Outcomes and Psoriasis Events” (iHOPE) study, as previously described (Yeung et al., 2013). Physician survey was used to confirm the diagnosis of psoriasis and classify, *a priori,* the extent of disease based on standard categories used by the Centers for Disease Control and the National Psoriasis Foundation for epidemiological studies of psoriasis. The outcome of interest was death. Data was collected prospectively from the date of physician survey until the individual died, transferred out of the practice, or reached the end of the data collection period. Covariates of interest included age, sex, BMI, alcohol use, smoking and medical comorbidities from the Charlson comorbidity index (CCI)(Charlson et al., 1987). The CCI classifies comorbid health conditions that may affect the risk of mortality and has been previously validated to be a

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Conflict of Interest:

In the previous 12 months, Dr. Gelfand served as a consultant for Coherus (DSMB), Dermira, Janssen Biologics, Merck (DSMB), Novartis Corp, Regeneron, Dr Reddy’s labs, Sanofi and Pfizer Inc., receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp, Regeneron, Sanofi, Celgene, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Abbvie. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Drs. Noe, Shin and Wan state no conflict of interest.

strong predictor of 5-year mortality in UK medical records databases (Khan et al., 2010). Descriptive statistics were used to examine age, sex, and comorbidity distribution between psoriasis patients and controls. The mortality rate was calculated by dividing number of deaths over the total observation time, in 1000 person-years. Cox proportional hazard regression models, adjusted for age, sex, CCI were created to determine the adjusted risk of death in psoriasis. Sensitivity analyses controlling for BMI, alcohol and tobacco use and use of systemic therapy were performed. Statistical analysis was performed in STATA 14.2 (College Station, TX).

The analysis included 8760 adults with psoriasis and 87,600 adults without psoriasis (Table 1). Psoriasis patients were more likely to be male and had a slightly higher BMI, but the average age was similar in both groups. Psoriasis patients had higher rates of chronic kidney disease, chronic obstructive pulmonary disease, diabetes and history of myocardial infarction. Among the 8760 patients with psoriasis there were 125 deaths, which resulted in a mortality rate of 3.35 deaths per 1000 person-years (95% CI: 2.81 – 3.99). In 87,600 adults without psoriasis, there were 1188 total deaths or 3.24 deaths per 1000 person-years (95% CI: 3.06 – 3.43). (Table 2)

After stratification by physician-reported BSA, there were 58, 38 and 29 deaths in the < 3%, 3–10% and >10% psoriasis groups, respectively (Table 2). In age and sex- adjusted models only those with >10% BSA had a statistically significant increased risk of death (hazard ratio (HR): 2.12, 95% CI: 1.46 – 3.07). The risk of mortality in those with BSA >10% remained elevated when adjusting for CCI (HR: 1.79, 95% CI: 1.23 – 2.59). Results were robust to sensitivity analyses adjusting for BMI, alcohol and tobacco use, and use of systemic therapy (Table 2).

In this large, population based, prospective study from the United Kingdom, patients with psoriasis BSA >10% had 1.79 times increased risk of death, compared to age- and sex-matched adults without psoriasis after controlling for baseline predictors of mortality. Those with less than 10% BSA may be at a higher risk for clinically important comorbidities, but not with elevated mortality. Based on our results, we estimate there is 1 excess death in every 390 psoriasis patients with a BSA greater than 10% annually that cannot be explained by traditional risk factors identified in routine medical practice.

The findings are consistent with what can be inferred from the existing mortality literature. Previously published population-based studies found an increased risk of death in psoriasis patients compared to controls; however, this was using treatment received as a proxy for psoriasis severity (Gelfand et al., 2007, Ogdie et al., 2014, Salahadeen et al., 2015, Springate et al., 2017). In our psoriasis patients, only 21% of those with BSA > 10% had a history of treatment with systemic therapy (phototherapy, oral systemic medication or biologic), demonstrating the need to use objective measures of disease severity to more fully capture the patient experience. One previous study has examined mortality risk, using physician-reported objective measures of psoriasis severity. The PUVA Follow-Up Study, prospectively followed 1376 adults with severe psoriasis enrolled in a clinical trial for treatment with oral PUVA (Stern et al., 1984). Our results confirm what was demonstrated in the PUVA Follow-

Up Study: a one-time measurement of psoriasis severity is a powerful predictor of future mortality (Stern and Huibregtse, 2011).

In summary, patients with psoriasis affecting >10% BSA are at an increased risk of death compared to the general population, even after controlling for standard mortality risk factors. Our findings support the existing literature showing that patients with severe psoriasis have an increased risk of death and demonstrate that a one-time, simple clinical assessment can be predictive of future mortality. Based on these results, psoriasis patients identified in clinic with a BSA >10 % should be targeted for preventative health interventions. Additionally, future research is needed to better elucidate the specific causes of mortality in patients with extensive psoriasis and determine the effects of psoriasis treatment on mortality risk.

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Abbreviations:

BSA	body surface area
CCI	Charlson Comorbidity Index
GP	general practitioner
THIN	The Health Improvement Network

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Table 1:

Baseline Characteristics of Psoriasis Patients and Controls

	Controls N = 87,600	All Psoriasis N = 8760	p-value
Female, N (%)	46,352 (52.9)	4330 (49.4)	
Age in years, mean (SD)	45.3 (11.1)	45.4 (11.1)	0.596
BMI, mean (SD)	27.1 (5.7)	27.9 (6.1)	< 0.001
Alcohol Use			< 0.001
Never	8659 (9.9)	733 (8.4)	
Current/Former	68,739 (78.5)	7076 (80.8)	
Missing	10,202 (11.7)	951 (10.7)	
Smoking			< 0.001
Never	42,609 (48.6)	3209 (36.6)	
Current/Former	43,616 (49.8)	5,474 (62.5)	
Missing	1375 (1.6)	77 (0.88)	
Medical Comorbidities, N (%)			
Cerebrovascular Disease	969 (1.1)	108 (1.2)	0.282
Chronic Kidney Disease	1889 (2.1)	233 (2.66)	0.002
Congestive Heart Failure	251 (0.3)	32 (0.4)	0.194
Chronic Obstructive Pulmonary Disease	15,434 (17.6)	1622 (18.5)	0.036
Dementia	39 (0.04)	6 (0.07)	0.322
Diabetes	3831 (4.4)	461 (5.3)	<0.001
Hemiplegia	114 (0.2)	8 (0.1)	0.100
HIV	11 (0.01)	1 (0.01)	0.927
History of Myocardial Infarction	908 (1.0)	129 (1.5)	<0.001
Peripheral Vascular Disease	528 (0.6)	75 (0.9)	0.004
Liver Disease	695 (0.8)	93 (1.06)	0.008
Malignancy	2,188 (2.5)	185 (2.1)	0.026
Charlson Comorbidity Index, N (%)			< 0.001
0	63,201 (72.0)	6097 (69.6)	
1–2	21,728 (24.8)	2310 (26.4)	
3–4	2316 (2.6)	291 (3.3)	
>5	454 (0.5)	62 (0.7)	

Table 2:

Hazard Ratio of Morality Based on Physician-Reported Psoriasis BSA

	Controls N = 87,600	**< 3% BSA N = 4539**	**3–10% BSA N = 3133**	**> 10% BSA N = 1088**
Number of Deaths	1188	58	38	29
Average Follow-Up Time, yrs (SD)	4.17 (1.64)	4.25 (1.56)	4.31 (1.50)	4.16 (1.53)
Mortality Rate, per 1000 person-years (95% CI)	3.24 (3.06–3.43)	3.00 (2.32–3.88)	2.81 (2.04–3.86)	6.39 (4.45–9.21)
Unadjusted HR	REF	0.92 (0.71–1.20)	0.87 (0.63–1.20)	2.00 (1.38–2.89)
Adjusted for age & sex	REF	0.89 (0.70–1.17)	0.87 (0.63–1.20)	2.12 (1.46–3.07)
Adjusted for age, sex & CCI	REF	0.87 (0.67–1.13)	0.79 (0.57–1.09)	1.79 (1.23–2.59)
Attributable Risk[1]	N/A	N/A	N/A	2.56 per 1000 person-years
Sensitivity Analyses				
Adjusted for BMI	REF	0.90 (0.69 – 1.18)	0.77 (0.54 – 1.08)	1.81 (1.23 – 2.68)
Adjusted for smoking & alcohol use	REF	0.80 (0.61 – 1.06)	0.70 (0.49 – 0.99)	1.76 (1.21 – 2.57)
Adjusted for cardiovascular risk factors[2]	REF	0.82 (0.63 – 1.08)	0.76 (0.55 – 1.06)	1.87 (1.29 – 2.70)
Excluding those who received any systemic therapy (UV, oral systemic, or biologic)				
		N = 4478	N = 2944	N = 856
Fully Adjusted[1]		0.89 (0.68 – 1.15)	0.78 (0.55 – 1.09)	1.68 (1.08 – 2.61)
Excluding those who received oral systemic or biologic therapy				
		N = 4509	N = 3062	N = 988
Fully Adjusted[1]		0.88 (0.68 – 1.15)	0.78 (0.56 – 1.08)	1.87 (1.26 – 2.75)

Abbreviations: CI – confidence interval; CCI – Charlson Comorbidity Index; HR - hazard ratio; N/A – not applicable; REF - reference SD – standard deviation

[1]Adjusted for age, sex and CCI

[2]Adjusted for age, sex, smoking, diabetes, history of myocardial infarction, and history of stroke