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 that 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 with 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, an electronic medical records database in the United Kingdom. Within The Health Improvement Network, we created a nested cohort of patients with psoriasis, who were followed prospectively as the Incident Heath Outcomes and Psoriasis Events (i.e., 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 Prevention and the National Psoriasis Foundation for epidemiological studies of psoriasis. The outcome of interest was death. Data were 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, body mass index (BMI), alcohol use, smoking, and medical comorbidities from the Charlson comorbidity index (CCI) (Charlson et al., 1987). The CCI classifies comorbidity health conditions that may affect the risk of mortality and has been previously validated to be a 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 control subjects. The mortality rate was calculated by dividing number of deaths over the total observation time, in 1,000 person-years. Cox proportional hazard regression models, adjusted for age, sex, and 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 (StataCorp, College Station, TX).

The analysis included 8,760 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 8,760 patients with psoriasis, there were 125 deaths, which resulted in a mortality rate of 3.35 deaths per 1,000 person-years (95% CI = 2.81–3.99). In 87,600 adults without psoriasis, there were 1,188 total deaths or 3.24 deaths per 1,000 person-years (95% CI = 3.06–3.43) (Table 2).

After stratification by physician-reported body surface area (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 more than 10% BSA had a statistically significant increased risk of death (hazard ratio = 2.12, 95% confidence interval = 1.46–3.07). The risk of mortality in those with BSA greater than 10% remained elevated when adjusting for CCI (hazard ratio = 1.79, 95% confidence interval = 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 of more than 10% had 1.79 times increased risk of death, compared with 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 with control subjects; however, this was using treatment received as a proxy for psoriasis severity (Gelfand et al., 2007; Ogdie et al., 2014; 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 with 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.

**Abbreviations:** BSA, body surface area; BMI, body mass index; CCI, Charlson Comorbidity Index

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Table 1. Baseline characteristics of psoriasis patients and controls

| Characteristics                              | Controls  | All Psoriasis | P-Value |
|---------------------------------------------|-----------|---------------|---------|
|                                             | N = 87,600| N = 8760      |         |
| Female, n (%)                               | 46,352 (52.9) | 4,330 (49.4)  | <0.001  |
| 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                                 |            |               |         |
| Never                                       | 8,659 (9.9)  | 733 (8.4)     |         |
| Current/former                             | 68,739 (78.5)| 7,076 (80.8)  |         |
| Missing                                     | 10,202 (11.7)| 951 (10.7)    |         |
| Smoking                                    |            |               | <0.001  |
| Never                                       | 42,609 (48.6)| 3,209 (36.6)  |         |
| Current/former                             | 43,616 (49.8)| 5,474 (62.5)  |         |
| Missing                                     | 1,375 (1.6)  | 77 (0.88)     |         |
| Medical comorbidities, n (%)                |            |               |         |
| Cerebrovascular disease                     | 969 (1.1)   | 108 (1.2)     | 0.282   |
| Chronic kidney disease                      | 1,889 (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)| 1,622 (18.5)  | 0.036   |
| Dementia                                    | 39 (0.04)   | 6 (0.07)      | 0.322   |
| Diabetes                                    | 3,831 (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          | 1–2         | 3–4        | >5         |
|---------------------------------------------|------------|------------|------------|------------|
|                                            | 63,201 (72.0)| 6,097 (69.6)|    |            |
|                                            | 21,728 (24.8)| 2,310 (26.4)|    |            |
|                                            | 2,316 (2.6) | 291 (3.3)  |    |            |
|                                            | 454 (0.5)  | 62 (0.7)   |    |            |

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2. Hazard ratio of mortality based on physician-reported psoriasis BSA

| Characteristics | Controls n = 87,600 | <3 % BSA n = 4,539 | 3–10% BSA n = 3,133 | >10% BSA n = 1,088 |
|----------------|---------------------|-------------------|---------------------|-------------------|
| Number of deaths | 1,188               | 58                | 38                  | 29                |
| Average follow-up time, years (SD)         | 4.17 (1.64)         | 4.25 (1.56)       | 4.31 (1.50)        | 4.16 (1.53)       |
| Mortality rate, per 1,000 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 and sex                    | REF                 | 0.89 (0.70–1.17)  | 0.87 (0.63–1.20)   | 2.12 (1.46–3.07)  |
| Adjusted for age, sex, and CCI              | REF                 | 0.87 (0.67–1.13)  | 0.79 (0.57–1.09)   | 1.79 (1.23–2.59)  |
| Attributable risk¹                           | N/A                 | N/A               | N/A                 | 2.56 per 1,000 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 and 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 factors²   | 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 = 4,478 | n = 2,944 | n = 856 |                       |
| Fully adjusted¹                             | 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 = 4,509 | n = 3,062 | n = 988 |                     |
| Fully adjusted¹                             | 0.88 (0.68–1.15)    | 0.78 (0.56–1.08)  | 1.87 (1.26–2.75)   |                     |

Abbreviations: BSA, body surface area; CI, confidence interval; CCI, Charlson Comorbidity Index; HR, hazard ratio; N/A, not applicable; REF, reference; SD, standard deviation.

¹Adjusted for age, sex, and CCI.
²Adjusted for age, sex, smoking, diabetes, history of myocardial infarction, and history of stroke.
A Missense Mutation within the Helix Termination Motif of KRT25 Causes Autosomal Dominant Woolly Hair/Hypotrichosis

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TO THE EDITOR

Woolly hair (WH)/hypotrichosis is an unusual condition characterized by sparse and tightly curled hair (Ramot and Zlotogorski, 2015a). WH may be isolated or be accompanied by additional complications including palmo-plantar keratoderma, hypotrichosis, epidermal naevus, and cardiomyopathy (Ramot et al., 2014; Veraitch et al., 2016). Isolated WH can manifest with autosomal dominant (AD) or autosomal recessive trait of inheritance (Shimomura, 2016).

Keratins are scaffolding proteins that form a network of intermediate filaments (IFs). Heterodimerization between type I and II keratin to form keratin IFs is the basic building block for hair structure (Ramot and Zlotogorski, 2015b). The phenotypic heterogeneity caused by different keratin genes also depends on their location within different hair structures, including the cortex of the hair shaft, the cuticle, and the inner root sheath (Naem et al., 2006).

Variants in keratins K71 and K74 were described in ADWH pedigrees, and polymorphisms in KRT75 were implicated in the pathogenesis of pseudofolliculitis barbae (Fujimoto et al., 2012; Wasi et al., 2011; Winter et al., 2004). Recently, biallelic variants within KRT25 were also related to autosomal recessive WH/hypotrichosis pedigrees (Ansar et al., 2015; Zernov et al., 2016).

Here, we describe a monoallelic pathogenic variant in a Chinese ADWH/hypotrichosis family, five-