

The Risk of Mortality in Patients With Psoriasis

Results From a Population-Based Study

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Objective: To determine the risk of mortality in patients with psoriasis.

Design: Cohort study.

Setting: General practitioners participating in the General Practice Research Database in the United Kingdom, 1987-2002.

Patients: Mild psoriasis, defined as any patient with a diagnostic code of psoriasis but no history of systemic therapy; severe psoriasis, any patient with a diagnostic code of psoriasis and a history of systemic therapy consistent with severe psoriasis. The unexposed (control) population was composed of patients with no history of a psoriasis diagnostic code. Control patients were selected in a 5:1 ratio from the same practice and date in practice as the patients with psoriasis.

Main Outcome Measure: Hazard ratio (HR) of time to death using Cox proportional hazards models adjusted for age and sex.

Results: There was no overall effect of mild psoriasis on mortality (HR, 1.0; 95% confidence interval [CI], 0.97-1.02), whereas patients with severe psoriasis demonstrated an increased overall mortality risk (HR, 1.5; 95% CI, 1.3-1.7). The association of severe psoriasis with mortality persisted after adjustment for risk factors for mortality (HR, 1.4; 95% CI, 1.3-1.6) and after exclusion of patients with inflammatory arthropathy (HR, 1.5; 95% CI, 1.3-1.8). Male and female patients with severe psoriasis died 3.5 (95% CI, 1.2-5.8) and 4.4 (95% CI, 2.2-6.6) years younger, respectively, than patients without psoriasis ($P < .001$).

Conclusion: Severe but not mild psoriasis is associated with an increased risk of death.

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PSORIASIS IS A COMMON, chronic inflammatory disease of the skin and joints that is heterogeneous in presentation. Approximately 80% to 85% of patients have limited skin involvement, whereas 15% to 20% have more extensive skin involvement that may require systemic therapy.^{1,2} Psoriasis has been associated with multiple comorbidities, including obesity, cardiovascular disease, and certain internal malignant neoplasms such as lymphoma, and with smoking and alcohol use, all of which could increase the risk of mortality in patients with psoriasis.³⁻⁵ In addition, certain systemic therapies for psoriasis may rarely be associated with mortality due to chronic cumulative drug toxicity or idiosyncratic reactions, and the disease itself may lead to death in rare instances.⁶⁻⁹

Few studies have assessed the risk of mortality in patients with psoriasis, and most have focused on patients hospital-

ized for treatment.¹⁰⁻¹³ Previous studies from Sweden and Finland¹⁰⁻¹² have demonstrated an increased risk in all-cause and/or cause-specific mortality among patients hospitalized for psoriasis compared with the general population. However, in 1 Swedish study, hospitalized patients with psoriasis had an increased risk of cardiovascular mortality, whereas

See also page 1567

patients with mild psoriasis who were treated exclusively as outpatients did not.¹¹ In contrast to studies of patients hospitalized for severe psoriasis, a study of US patients with severe psoriasis derived from a clinical trial of psoralen-UV-A (PUVA) therapy did not identify an increased risk of mortality.¹³ The studies that focused on patients hospitalized for psoriasis may not be generalizable to the broader population of patients with psoriasis because only a

few patients with the most severe disease require hospitalization. Furthermore, patients hospitalized for any condition generally have higher rates of comorbidities, smoking, and alcohol use, which can increase the risk of death compared with individuals who are not hospitalized.¹⁴ Presently, there are mixed data regarding the risk of mortality among patients with severe psoriasis, and the available data suggest a hypothesis that the risk of mortality may be related to disease severity.

To further investigate the relationship of psoriasis and mortality, we performed a population-based cohort study in the United Kingdom to determine the risk of mortality in patients with psoriasis.

METHODS

STUDY POPULATION AND DATA SOURCE

We conducted a retrospective cohort study using the General Practice Research Database (GPRD), which is a medical records database in the United Kingdom that was established for epidemiologic research in 1987.¹⁵ Data through 2002 were included in this study. The GPRD is representative of the UK population in terms of age, sex, and geographic distribution. Approximately 5% of the UK population is represented in the GPRD, and cumulative data are available for more than 9 million patients with more than 40 million person-years of follow-up. In the United Kingdom, greater than 99% of patients are registered with a general practitioner (GP) through the National Health Service; the GP coordinates all of the patient's medical care. Data on diagnoses and prescriptions are recorded by the GPs as part of the patient's electronic medical record. Patients with complex medical conditions are seen by specialists (at the request of the GP), who may initiate a new treatment; however, patients are then referred back to the GP for long-term monitoring as necessary. Certain treatments, such as PUVA and oral retinoids, are restricted to dermatologists in the United Kingdom; however, GPs capture these treatments through their electronic medical record. The GPRD has been shown to capture information on diagnoses and treatments from specialists through the GP's electronic medical record.^{16,17} General practitioners receive specific training and are subject to inducements and penalties to ensure high-quality data. The data are also audited for completeness, and a practice receives an up-to-standard (UTS) designation when at least 95% of relevant prescriptions and diagnoses are captured electronically. More than 250 peer-reviewed scientific articles have been published using GPRD data.¹⁵ The GPRD has also been assessed in numerous validation studies, including those on psoriasis and mortality, to demonstrate whether it captures these diseases and outcomes accurately.^{2,5,15,18} We used data from 1987-2002 for patients who were 18 years or older when their person-time recording began.

DEFINITION OF EXPOSURE

We defined *mild psoriasis* as a diagnostic code of psoriasis in patients with no history of systemic therapy. *Severe psoriasis* was defined as a diagnostic code of psoriasis in patients with a history of systemic therapy consistent with severe psoriasis. Systemic therapy included phototherapy, PUVA, methotrexate sodium, azathioprine, cyclosporine, oral retinoids (etretinate and acitretin), hydroxyurea, and mycophenolate mofetil. The unexposed (control) population comprised patients with no history of a psoriasis diagnostic code.

SAMPLING OF EXPOSED AND UNEXPOSED COHORTS

We included all patients defined as having mild or severe psoriasis (according to our definitions) who were 18 years or older at the study start date and who had at least 1 day of observation time. Up to 5 control subjects who were 18 years or older at the start date were selected for each patient with psoriasis, matched on practice and start date in the practice (defined as the later of either the date when the patient registered with the practice or the date the practice was deemed UTS).

PERSON-TIME CALCULATION

For patients with mild psoriasis, follow-up started at the latest date of when the patient first received a psoriasis code, when the patient registered with the practice, or when the practice was deemed UTS. For patients with severe psoriasis, follow-up started at the latest date of when the patient could first be defined as having severe psoriasis (eg, received a treatment code consistent with severe disease), when the patient registered with the practice, or when the practice was deemed UTS. For unexposed subjects (controls), follow-up started at the latest date of when the patient registered with the practice or when the practice was deemed UTS. For all groups, follow-up ended at the earliest date of one of the following: death, transfer out of the practice, or the end of UTS for the practice.

OUTCOME OF INTEREST

The outcome of interest was death. Deaths were identified via registration codes indicating that a patient was removed from a practice because of that person's death. Patients who had a medical diagnosis or prescription recorded 100 or more days after having received a death registration status code were reclassified as living and were censored at the date they received the change in registration status. This reclassification occurred in approximately 1% of all death records.

COVARIABLES OF INTEREST

Risk factors for death were identified by adapting a comorbidity index for use in a medical record database.¹⁹ The following covariables were assessed: smoking (classified as current smoker, former smoker, or nonsmoker), body mass index, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, moderate or severe liver disease, diabetes mellitus, diabetes with chronic complications, hemiplegia or paraplegia, renal disease, malignant neoplasm, metastatic solid tumor, and AIDS. These covariates were classified as present if they occurred at any time during the study.

ANALYSIS

The sample size was determined by including the maximum number of eligible patients with severe psoriasis based on age criteria. We randomly selected 5 control subjects per patient with psoriasis because additional matching yields minimal increases in statistical power. Data were summarized descriptively. Dichotomous variables were tested with the Fisher exact test and continuous variables were tested with an unpaired, 2-tailed *t* test. We fit age- and sex-adjusted Cox proportional hazards regression models to determine the overall hazard ratio (HR) of death in patients with psoriasis.²⁰ When indicated by an association of psoriasis with mortality based on the Cox

Table 1. Characteristics of Study Groups

Characteristic	Study Group			
	Mild Psoriasis		Severe Psoriasis	
	Controls (n=560 358)	Patients (n=133 568)	Controls (n=15 075)	Patients (n=3951)
Sex, No. (%)				
Male	261 710 (46.7)	64 004 (47.9)	7023 (46.6)	1921 (48.6)
Female	298 648 (53.3)	69 564 (52.1) ^a	8052 (53.4)	2030 (51.4) ^b
Age, mean (median; IQR), y	45.3 (42.0; 29.2-59.5)	46.9 (44.8; 31.4-61.3) ^a	45.9 (42.8; 29.8-60.3)	52.4 (52.3; 38.7-65.8) ^c
Systemic therapies, No. (%)	NA	NA	NA	
Methotrexate				2302 (58.3)
Psoralen or phototherapy				662 (16.8)
Azathioprine				651 (16.5)
Cyclosporine				408 (10.3)
Etretinate or acitretin				350 (8.9)
Hydroxyurea				224 (5.7)
Mycophenolate mofetil				11 (0.3)
Follow-up, mean (median; IQR), y	5.6 (5.2; 2.2-9.2)	4.5 (3.8; 1.6-7.1)	5.9 (5.6; 2.4-9.5)	3.6 (2.8; 1.3-5.3)
Cumulative person-years	3 147 693	600 902	88 391	14 203
Deaths, No.	38 258	7198	1064	303
Incidence rate of mortality per 1000 person-years (95% CI)	12.2 (12.0-12.3)	12.0 (11.7-12.3)	12.0 (11.3-12.8)	21.3 (19.0-23.9)

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable.

^a *P* < .001 (mild psoriasis group vs mild control group).

^b *P* = .02 (severe psoriasis group vs severe control group).

^c *P* < .001 (severe psoriasis group vs severe control group).

models, we fit models with covariates for death included (as already described) and models with age and sex interaction terms to determine whether the relative risk of mortality in patients with psoriasis differed by sex or age characteristics. Each dichotomous variable in the model was checked for proportionality while adjusting for the other covariates in the model by examining diagnostic log-log plots. Multiple sensitivity analyses were performed to test the underlying assumptions of our primary analysis. All analyses were performed using Stata statistical software, version 9.2 (StataCorp, College Station, Texas).

PROTECTION OF HUMAN SUBJECTS

This study was approved by the University of Pennsylvania institutional review board and by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency of the UK Department of Health. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

We identified 133 568 patients with mild psoriasis, 3951 patients with severe psoriasis, and 560 358 and 15 075 matched controls, respectively (**Table 1**). Patients with psoriasis were older and more likely to be male compared with controls, and the psoriasis groups had less observation time than the control groups. Most patients identified as having severe psoriasis were treated with methotrexate (Table 1). The overall use of oral systemic therapy for psoriasis in the GPRD is similar to other population-based estimates in the United Kingdom²¹; however, phototherapy and PUVA are likely to be underreported in the GPRD owing to difficulties in capturing these therapies in the electronic medical record and re-

strictions on the prescription of these modalities to the specialist.

The absolute incidence of death in controls and patients with psoriasis is shown in Table 1. The overall incidence was similar in the 2 control groups and similar to rates of death reported using national statistics from England and Wales.²² The unadjusted overall risk of death per 1000 person-years was similar in patients with mild psoriasis (12.0; 95% CI, 11.7-12.3) and their controls (12.2; 95% CI, 12.0-12.3). The unadjusted overall risk of death per 1000 person-years was higher in the patients with severe psoriasis (21.3; 95% CI, 19.0-23.9) than in their controls (12.0; 95% CI, 11.3-12.8).

As expected, age and male sex were associated with a higher risk of death (data not shown). Based on Cox proportional hazards regression models, there was no overall effect on mortality of psoriasis of any severity (1.00; 95% CI, 0.99-1.04) or mild psoriasis (HR, 1.00; 95% CI, 0.97-1.02) (**Table 2**). In contrast, Cox models in patients with severe psoriasis demonstrated an increased overall mortality risk (HR, 1.50; 95% CI, 1.32-1.71). Adjustment of the overall mortality risk in patients with severe psoriasis for major risk factors of death (described in the "Methods" section) did not result in a clinically significant reduction in the association between severe psoriasis and mortality (fully adjusted HR, 1.42; 95% CI, 1.25-1.62). The increased relative risk of mortality in patients with severe psoriasis was similar in men and women (sex interaction term, *P* = .86); the relative risk, however, did vary with age (Table 2). For example, the relative risk of mortality for a 45-year-old patient with severe psoriasis compared with controls was 2.2 (95% CI, 1.6-2.9), whereas the relative risk of mortality for a 75-

Table 2. Hazard Ratio of Mortality in Patients With Psoriasis

Age, y	Hazard Ratio (95% Confidence Interval) ^a		
	All Patients With Psoriasis	Patients With Mild Psoriasis	Patients With Severe Psoriasis
All ages (≥ 18)	1.0 (0.99-1.04)	1.0 (0.97-1.02)	1.5 (1.3-1.7)
35			2.5 (1.7-3.7)
45			2.2 (1.6-2.9)
55			1.9 (1.5-2.3)
65			1.6 (1.4-1.9)
75			1.4 (1.3-1.6)
85			1.3 (1.0-1.5)
95			1.1 (0.8-1.5)

^aData are adjusted for age and sex.

Table 3. Attributable Risk (AR) and Excess Risk of Death in Patients With Severe Psoriasis

Age Group, y	Mortality Rate per 1000 Patient-Years in Severe Psoriasis Control Group	AR, No. of Deaths per 1000 Patient-Years ^a	Excess Risk, No. of Excess Deaths ^b
All ages (≥ 18)	12.0	6.0	1/166 Patients per year
30-39	0.8	1.8	1/856 Patients per year
40-49	2.0	2.3	1/440 Patients per year
50-59	6.4	5.6	1/179 Patients per year
60-69	20.1	12.9	1/78 Patients per year
70-79	48.5	20.9	1/48 Patients per year
80-89	106.7	26.7	1/38 Patients per year

^aAR=risk of mortality for patients in the severe psoriasis group – risk of mortality for persons in the severe psoriasis control group.

^bExcess risk=1/AR.

year-old patient with severe psoriasis was 1.4 (95% CI, 1.3-1.6). Although the relative risk of mortality in patients with severe psoriasis decreased with age, the attributable risk of mortality associated with severe psoriasis (calculated by subtracting the risk of mortality for persons in the control group from the risk of mortality in patients with severe psoriasis) increased with age (as did the excess risk) because the baseline risk of mortality increases significantly with age (**Table 3**). Among patients who died, those with severe psoriasis died at a younger age than controls. For example, men with severe psoriasis died 3.5 years (95% CI, 1.2-5.8 years; $P < .001$) younger than men without psoriasis, and women with severe psoriasis died 4.4 years (95% CI, 2.2-6.6 years; $P < .001$) younger than women without psoriasis.

Several additional analyses were performed to further investigate the association of severe psoriasis with mortality (**Table 4**). Sensitivity analyses demonstrated that the increased relative risk of mortality in patients with severe psoriasis persisted when we excluded patients with concomitant psoriatic arthritis or rheumatologic disease and when we restricted the severe psoriasis group to those who received oral retinoids, therapies that are highly specific for psoriasis. The increased risk

Table 4. Sensitivity Analyses

Analysis	Mortality in Severe Psoriasis, HR (95% CI) ^a
Patients with psoriatic arthritis excluded from severe psoriasis group	1.5 (1.3-1.8)
Patients with rheumatologic diseases excluded from psoriasis group	1.5 (1.3-1.8)
Person-time starts with first diagnosis of psoriasis during UTS time	1.1 (1.0-1.3)
Start date for severe psoriasis control group matched to start date for severe psoriasis group	1.7 (1.5-2.0)
Severe psoriasis group restricted to patients who received methotrexate sodium	1.3 (1.1-1.5)
Severe psoriasis group excluding patients treated with methotrexate	1.9 (1.6-2.2)
Severe psoriasis group restricted to patients who had been prescribed an oral retinoid	1.8 (1.3-2.3)

Abbreviations: CI, confidence interval; HR, hazard ratio; UTS, up-to-standard designation.

^aAdjusted for age and sex.

of mortality was attenuated but remained elevated when we varied the start of follow-up time in the severe psoriasis group to the earliest date at which psoriasis could be identified. The risk of mortality in patients with severe psoriasis remained elevated when we adjusted the start of follow-up time in the severe psoriasis control group to coincide with the start of follow-up time in the severe psoriasis group, indicating that the increased risk of mortality in patients with severe psoriasis was not due to the shorter follow-up time in that group as was noted in our primary analysis. Finally, the risk of mortality in patients with severe psoriasis remained elevated in patients who did or did not receive methotrexate; however, the risk appeared most elevated for those who did not receive methotrexate therapy.

COMMENT

The results of this study demonstrate that patients with severe psoriasis have a 50% increased risk of mortality, whereas patients with milder psoriasis have no overall increased risk. Male and female patients with severe psoriasis died 3.5 and 4.4 years younger, respectively, than patients without psoriasis, which provides further insight into the effect of excess mortality risk associated with having severe psoriasis. The increased risk of death in patients with severe psoriasis persisted when we excluded patients with diagnoses of psoriatic arthritis and rheumatoid diseases. Likewise, the increased risk of death persisted when we restricted the severe psoriasis group to patients treated with oral retinoids, which are highly specific for severe psoriasis, suggesting that our observations do not result from misclassification of disease status.²³ The increased risk of death in patients with severe psoriasis was not significantly diminished when we controlled for major risk factors for mortality. This finding suggests that severe psoriasis is an important predictor of mortality risk. It is also possible that comorbid ill-

nesses that predict death are incompletely detected in medical practice.

The relative risk of mortality was greatest in younger patients with severe psoriasis; however, the excess risk of death attributable to having severe psoriasis increases with age, since the baseline risk of death increases sharply with age. The lower relative risk of death in older patients with severe psoriasis may be due to depletion in the number of patients with severe psoriasis who are susceptible to mortality (ie, through death) in the older groups available for this study because we did not study incident psoriasis exclusively (see the discussion of study limitations in a subsequent paragraph). Alternatively, as patients age, the competing risks of death in patients with severe psoriasis and those without psoriasis may become more similar. Our findings are consistent with those of our previous study,²⁴ which indicated that the relative risk of myocardial infarction is highest in younger patients with psoriasis, and with those of another study,¹¹ which indicated that the relative risk of cardiovascular mortality is highest in younger patients (those aged < 40 years) with severe psoriasis.

Our mortality findings in patients with severe psoriasis are in agreement with previous studies of patients hospitalized for severe psoriasis.¹⁰⁻¹² For example, a study¹⁰ of patients hospitalized for psoriasis in Gothenburg, Sweden, found an increased risk of death in men (standardized mortality ratio [SMR], 2.03) and women (SMR, 3.32) for those born between 1911 and 1940 compared with the general population. Excesses in cause-specific mortality were seen only in women for ischemic heart disease and lung cancer. A study¹² of Finnish patients with psoriasis who were hospitalized for their disease also observed excess mortality in men (SMR, 1.62; 95% CI, 1.52-1.71) and women (SMR, 1.54; 95% CI, 1.43-1.64), with alcohol-related deaths being the major cause for excess mortality. Finally, a Swedish study¹¹ demonstrated that patients hospitalized for psoriasis have an increase in cardiovascular mortality (SMR, 1.52; 95% CI, 1.44-1.60), whereas patients with milder psoriasis who are treated as outpatients have no increased alteration of cardiovascular mortality risk (SMR, 0.94; 95% CI, 0.89-0.99); this finding is consistent with the results of the present all-cause mortality study.

In contrast to the excess mortality observed in patients hospitalized for severe psoriasis, there was no alteration in the risk of mortality in US patients with severe psoriasis exposed to PUVA on an outpatient basis at dermatology referral centers (SMR, 0.9; 95% CI, 0.8-1.1) compared with the general population.¹³ The death rates of patients with psoriasis in the PUVA cohort were compared with US national statistics, which may have introduced bias because it is unclear whether PUVA cohort patients who were initially part of an experimental clinical trial at selected tertiary care medical centers are representative of the general US population. Furthermore, use of external national data for calculating standardized mortality ratios (as opposed to use of an internal comparison group, as was done in the present study) may introduce additional bias toward underestimating the mortality risk.²⁵ Our study advances the literature of psoriasis and mortality because we used broadly repre-

sentative population-based methods to examine the risk of mortality in patients with mild and severe psoriasis, which minimizes selection bias and improves the generalizability of the results. Furthermore, mortality rates were determined by the same method in the exposed and unexposed populations (ie, the controls), which further substantiates the validity of our findings.

As with all studies, there are important limitations to consider. In database studies, there remains the possibility for misclassification of death due to coding errors, although this is believed to be uncommon. Although some may be present, there is little reason to believe that coding-related misclassification differed between the patients with psoriasis and the controls. If present, such nondifferential misclassification would be expected to bias our results toward the null.

Another potential limitation is that we did not examine patients with exclusively incident (new-onset) psoriasis because such cases are difficult to identify in a database setting. If patients with psoriasis died before entering the cohort, we may have underestimated the relative risk of death associated with psoriasis. Examining patients with severe psoriasis from the first time psoriasis was documented in the electronic medical record rather than from the first time they could be classified as having severe psoriasis based on treatment, as was done in our primary analysis, resulted in attenuation of the estimated relative risk of mortality. However, this analysis introduces a form of immortal time bias that would underestimate the association of psoriasis and mortality because the patients we classified as having severe psoriasis could not have developed the outcome (ie, death) prior to receiving a therapy that identifies them as having severe psoriasis.²⁶ Furthermore, we did not directly determine the severity of psoriasis based on the extent of skin disease, which may introduce misclassification of mild and severe psoriasis when using therapy as a marker of psoriasis phenotype. Our mild psoriasis group likely contains a small subset of patients with severe disease because systemic therapies are used infrequently for psoriasis in the general population. Our severe group likely contains a small subset of patients with mild skin disease despite the use of systemic therapy. This misclassification would result in an overestimation and underestimation of the risk of mortality in the patients with mild and severe psoriasis, respectively. Therefore, such misclassification is unlikely to have explained our results.

Finally, we did not determine why patients with severe psoriasis died at higher rates than patients without psoriasis. We have previously demonstrated that patients with severe psoriasis in the GPRD have higher prevalences of smoking, diabetes mellitus, obesity, hypertension, and hyperlipidemia and a higher incidence of myocardial infarction and lymphoma.^{5,24,27-29} In addition, psoriasis has been associated with excess alcohol intake, psychiatric disorders, and various types of internal malignant neoplasms such as lung, liver, pancreatic, breast, bladder, and kidney cancers, which could further explain the excess mortality observed in the severe psoriasis group.^{4,30} Severe psoriasis itself can lead to death in very rare instances, as could cumulative drug toxicity

and idiosyncratic reactions to systemic psoriasis therapies.^{6,7} Patients with severe psoriasis who were treated with methotrexate appeared to have a lower risk of mortality than such patients who were not treated with methotrexate, which could be owing to a protective effect of methotrexate on mortality or differences in health status among patients with severe psoriasis who are treated or not treated with methotrexate (ie, confounding by indication). Previous studies³¹⁻³³ have indicated that successful treatment of inflammatory diseases such as rheumatoid arthritis with methotrexate can lower the overall risk of mortality and that methotrexate may limit the occurrence of cardiovascular events in patients with psoriasis.

In summary, patients treated for severe psoriasis have an increased risk of death and die at a younger age than patients without psoriasis. Further studies are necessary to determine the cause of excess mortality in patients with severe psoriasis, how the extent of skin disease affects mortality risk, and whether the risk of mortality in patients with severe psoriasis is altered by various systemic therapies. Patients with severe psoriasis should receive comprehensive health assessments to enhance preventive health practices, improve overall health, and decrease the risk of mortality.

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