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Cause-specific mortality in patients with severe psoriasis: A population-based cohort study in the United Kingdom

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Abstract

Background—Severe psoriasis is associated with excess mortality and increased risk of cardiovascular death. Population-based data evaluating cause-specific mortality in patients with psoriasis are limited.

Objective—To describe cause-specific mortality in patients with severe psoriasis.

Patients/Methods—We performed a cohort study from 1987–2002 of patients ≥ 18 years using the General Practice Research Database. We compared patients with a psoriasis code and a history of systemic therapy consistent with severe psoriasis (N=3,603) to patients with no history of psoriasis (N=14,330). Age- and sex-adjusted Cox models were created for each of the leading causes of death defined by the Centers for Disease Control.

Results—Patients with severe psoriasis were at increased risk of death from cardiovascular disease (HR 1.57; 95%CI 1.26–1.96), malignancies (HR 1.41; 95%CI 1.07–1.86), chronic lower respiratory disease (HR 2.08; 95%CI 1.24–3.48), diabetes (HR 2.86; 95%CI 1.08–7.59), dementia (HR 3.64; 95%CI 1.36–9.72), infection (HR 1.65; 95%CI 1.26–2.18), kidney disease (HR 4.37; 95%CI 2.24–8.53), and unknown/missing causes (HR 1.44; 95%CI 1.09–1.88). The absolute and excess risk of death was highest for cardiovascular disease (61.9 and 3.5 deaths per 1000 patient-years respectively).

Conclusions—Severe psoriasis is associated with an increased risk of death from a variety of causes with cardiovascular death being the most common etiology. These patients were also at increased risk of death from causes not previously reported such as infection, kidney disease, and dementia. Additional studies are necessary to determine the degree to which excess causes of death are due to psoriasis, its treatments, associated behaviors, or other factors.

Keywords

Psoriasis; mortality; infection; cardiovascular epidemiology

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Introduction

Psoriasis is a chronic inflammatory disease affecting 1–3% of the population. Approximately 15–20% of patients have extensive skin involvement or severe disease requiring systemic therapy.^{1–2} Psoriasis has been associated with multiple comorbidities including cardiovascular disease, the metabolic syndrome, cancer, gastrointestinal disease, and chronic obstructive pulmonary disease (COPD).^{3–6} It has also been associated with psychological comorbidities such as depression and suicidality, and is known to significantly impact patients' quality of life.^{7–11} Additionally, psoriasis patients tend to have higher rates of behavioral risk factors including smoking and alcohol use.^{12–14} The physical, psychological, and socio-behavioral aspects of psoriasis are likely interrelated and the associations complex.⁴⁷ Nonetheless, studies have found an independent relationship between psoriasis and diabetes, atherosclerosis, myocardial infarction, stroke, even after controlling for traditional risk factors.^{15–18}

Although psoriasis was not traditionally viewed as a disease associated with mortality, a large population-based study found that patients with severe disease requiring systemic or phototherapy had an increased risk of both cardiovascular mortality and overall mortality.^{19–20} Smaller, non population-based studies of patients with severe psoriasis (i.e., those hospitalized for their disease or derived from clinical trial populations from tertiary care medical centers) also found higher mortality rates among psoriasis patients than among the general population, particularly for cardiovascular disease,^{21–22} cancer,^{21, 23} and liver disease.^{23–24} Finally, a series of small cohort studies of psoriatic arthritis patients reviewed by Gladman, *et al*, also found an elevated risk of death from cardiovascular disease, respiratory diseases, cancer, injuries, and poisoning.²⁵

These studies suggest that multiple causes of mortality may be elevated among patients with severe psoriasis and highlight the need for additional population-based data. It is important to identify the leading causes of excess mortality among psoriasis patients in order to focus prevention efforts. Additionally, such data may help inform research on the relationships between the pathophysiology, treatment and social aspects of the disease. The objective of this study was to determine cause-specific mortality in patients with severe psoriasis.

Materials and Methods

Study population and data source

We performed a cohort study to determine the risk of the most common forms of death in patients with severe psoriasis, using the General Practice Research Database (GPRD) from the United Kingdom. The GPRD was developed as a tool for conducting public health research and is representative of the national population in terms of age, sex, and geographic distribution.¹ General Practitioners (GPs) are responsible for maintaining their patients' electronic medical record, including information on hospitalizations, referrals, and deaths. Data quality is monitored, and practices receive an “up to standard” designation when >95% of prescriptions and diagnoses are captured electronically. The GPRD has been well validated for psoriasis²⁶ in addition to many other diagnoses.^{27–28}

We included all patients defined as having severe psoriasis who were ages 18 or older at their index date and had at least one day of follow-up between 1987 and 2002. Patients were considered to have severe psoriasis and included in our exposed cohort if they had any diagnostic code for psoriasis and a prescription consistent with severe disease on or after the first diagnosis date for psoriasis. Prescriptions for the following medications were used to define severe disease: phototherapy, PUVA, methotrexate, azathioprine, cyclosporin, oral retinoids (etretinate, acitretin), hydroxyurea, and myophenolate. This approach has been

accepted in numerous previous studies.^{15–16, 29–31} Of note, biologic therapies for psoriasis were not approved in the UK during the observation period for this study.

For each severe psoriasis patient, we chose up to four unexposed patients that had no history of a psoriasis diagnostic code at any time. Unexposed patients were matched on practice, date of registration in the practice (within 90 days if registration occurred after 1980, or within 5 years if registration occurred before 1980), and index date. For psoriasis patients, the index date was the first date they received a prescription for a treatment consistent with severe disease on or after their psoriasis diagnosis date, if they were registered with a practice and the practice was considered up to standard. For unexposed patients, the index date was the date of any medical record entry within 60 days of the psoriasis index date.

Person-time calculation

For severe psoriasis patients, follow-up began at the latest of the following dates: when the patient received the first code for a prescription consistent with severe disease, was registered with a practice, and the practice was deemed up to standard. Unexposed patients' follow-up time began at the latest of their index date, the date when the patient was registered in the practice, and the up to standard date. Follow-up time for all subjects ended at the earliest of the following: date of death, date of transfer out of practice, or end of up to standard designation.

Outcome of interest

The outcome of interest was cause of death. We used the Centers for Disease Control's fifteen leading causes of death from 2003–2004 to create the categories for the data abstracted from the GPRD database. The categorizations were made based on the process described below, and did not come directly from ICD-10 codes as they are not used in the UK medical system; we present the codes here to clarify the categories as defined by the CDC.³² We used the categories for the following diseases as defined by the CDC: nephritis, nephrotic syndrome and nephrosis or non-hypertensive kidney disease (ICD-10 codes N00–N07, N17–N19, N25–N27); diabetes mellitus (ICD-10 codes E10–E14); accidents and unintentional injuries (ICD-10 codes V01–X59, Y85–Y86); chronic lower respiratory disease (ICD-10 codes J40–J47); malignant neoplasms (ICD-10 codes C00–C97); intentional self-harm or suicide (ICD-10 codes *U03, X60–X84, Y87.0); and chronic liver disease (ICD-10 codes K70, K73–K74). We made a few modifications *a priori* to the other categories to better accommodate our data. First, we collapsed cerebrovascular disease (ICD-10 codes I60–I69) and diseases of the heart (ICD-10 codes I00–I09, I11, I13, I20–I51) into one category termed cardiovascular disease. We also collapsed influenza and pneumonia (ICD-10 codes J10–J18), and septicemia (ICD-10 codes A40–A41) into one category termed infection, and Alzheimer's (ICD-10 code G30) and Parkinson's disease (ICD-10 codes G20–G21) into a category termed dementia. We did not include essential (primary) hypertension and hypertensive renal disease (ICD-10 codes I10, I12) because there were no deaths among psoriasis patients from this cause. Finally, we included separate categories for “other” causes of death that were identifiable yet did not belong to any of the predefined categories, for “unknown” cases in which clear causes of death were not identifiable or could not be deduced; and for “missing” cases in which no cause of death information was available whatsoever.

Each patient was assigned a cause of death based on data that was available in the medical record. If a patient had a code for a medical condition that could lead to death that was coded on the date of death, this condition was listed as the cause of death. If there was no medical condition listed on the death date that could lead to death, then the pattern of diagnostic codes from the two months prior to death were used to determine a cause of

death. If more than one diagnosis was listed that could potentially cause death, then each of these diagnoses was recorded as a contributing cause of death.

The investigators performing the cause of death coding were blinded to the study group. Each patient's cause of death was assigned individually and separately by two physicians (RSA and AN). If the primary coding physicians did not agree on the cause of death (N=198, 16.5%), discordant cases were then reviewed in a blinded fashion by a third physician (JMG), whose opinion was used to break any ties. Thus each deceased patient's cause or causes of death had to have been agreed upon by at least two out of three physicians. Overall agreement was achieved for 1,183 deaths (98.4%). Patients for whom agreement could not be reached among two out of three physicians were not included in the analysis (N=19, 1.6%).

Co-variables of interest

We collected information on age and sex from the medical record.

Analysis

The sample size was based on the maximum number of eligible patients with severe psoriasis. We randomly selected up to four unexposed subjects per exposed patient with severe psoriasis. Data were summarized using descriptive statistics. Dichotomous variables were tested with Fisher's exact test, and continuous variables were tested with a Student's t-test if normally distributed and the Wilcoxon rank-sum test if not normally distributed. Cox proportional hazards models were used to investigate the risk of death over time for each cause of death while controlling for age and sex. Each dichotomous variable in each model was checked for proportionality while adjusting for other covariates by examining log-log plots. Absolute risk of death was calculated as the number of deaths per 1000 patient-years. The adjusted excess risk of death was calculated as follows: we subtracted the baseline risk of death in the control group from the product of the risk of death in the unexposed group and the age- and sex-adjusted Hazard Ratio for psoriasis from the Cox Models. Multiple sensitivity analyses were performed to test the underlying assumptions from the primary analysis. All analyses were performed using Stata 10.1 (Stata Corp, College Station, TX). A p-value of <0.05 was considered statistically significant.

Results

There were 3,603 exposed patients who met our definition for severe psoriasis, and a corresponding 14,330 unexposed patients. As shown in Table 1, patients with severe psoriasis were on average older than unexposed patients when they entered the cohort (52 vs. 50 years, $p<0.001$), and more likely to be male (49% vs. 40%, respectively $p<0.001$). The overall death rate per 1000 patient-years was higher among psoriasis patients than among the unexposed patients (26, 95% CI:23–29 vs. 18, 95% CI:17–19).

The specific causes of death and relative risk of death by patient group are shown in Table 2. Cardiovascular disease was the most commonly identified cause of death among both psoriasis and unexposed patients, followed by infection and malignant neoplasms. There was a statistically significant increased risk of death from cardiovascular disease, malignant neoplasms, chronic lower respiratory disease, diabetes mellitus, dementia, infection, kidney disease, and unknown or missing causes of death. There was a statistically non-significant trend for an increased risk of death from intentional self-harm/suicide, accidents/unintentional injuries, and liver disease.

Table 3 shows the cause-specific absolute risk of death and the excess risk of death. Cardiovascular disease, infection, unknown or missing causes of death, and cancer conferred the top four highest absolute and excess risks of death.

We also calculated the mean age at death. Overall, psoriasis patients died at a younger age than unexposed patients (mean age of 73 vs 79 years respectively, $p < 0.001$), as shown graphically in Figure 1. This relationship was similar for all causes of death, even when the data were examined by sex. Table 4 shows the median age at death for all causes for which there were at least 5 deaths in each group. The largest differential in age at death was for kidney disease.

We performed sensitivity analyses and found similar results when we: excluded patients who had more than one cause of death listed, excluded patients with psoriatic arthritis, and included only patients receiving medications specific for severe skin psoriasis (i.e. oral retinoids or phototherapy).

Discussion

We performed a large, population-based study to examine cause-specific mortality, which is likely to be generalizable to patients receiving systemic or phototherapy treatment for psoriasis in the general population. Previously, we have shown in a large population-based cohort study that patients with severe psoriasis have an increased risk of all cause mortality and an increased risk of cardiovascular death that was independent of traditional cardiovascular risk factors.^{19–20} However, it was unknown whether other causes of death, in addition to cardiovascular causes, were contributing to the elevated overall risk of death in this population-based cohort. Smaller, non population-based studies of hospital- and clinic-based cohorts of psoriasis patients suggested that there may be an elevated risk of death with psoriasis due to a variety of causes.^{21–24} In this study, we also found that the most common causes of death were elevated in patients with severe psoriasis as compared to patients without psoriasis. Additionally, as in other studies, we found that the age at death was significantly younger among both male and female psoriasis patients with severe disease.^{19, 23} Additional studies are necessary to determine if patients with less severe psoriasis who do not receive systemic or phototherapy are particularly susceptible to the causes of death we found to be elevated in the current study. Based on our previous work, in which no increased risk of all cause mortality was found in psoriasis patients who did not receive systemic or phototherapy, we would not expect specific causes of death to be meaningfully increased in this group.¹⁹ Moreover, the process of defining cause specific mortality in our study was labor intensive (i.e. would have required the manual review of thousands of medical records) and therefore we did not undertake such an analysis in our mild group given our previous all-cause mortality results and lack of adequate resources to conduct such an analysis.

Our study is among the first to show a significantly increased risk of death associated with kidney disease, infection, and dementia in addition to the causes listed above. Case reports in the literature suggest that patients with psoriasis may be more likely to have microalbuminuria and IgA nephropathy; this association warrants further study.^{33–34} Similarly, the finding of an increased risk of death associated with infection must be further investigated and is of special concern given that patients with severe psoriasis are increasingly treated with immunosuppressive therapies. Although there are few prior data that suggest a direct link between dementia and psoriasis, cerebrovascular comorbidities associated with psoriasis and lifestyle factors may relate to the observed increase in dementia-related deaths.^{35–39}

The objective of this study was to describe cause-specific death in patients with severe psoriasis; we did not determine why patients have an increased risk of death and tend to die at earlier ages. Our observations could be attributable to the disease itself, its treatments, psoriasis associated behaviors, or other factors. There are data of varying quality that suggest a plausible link between psoriasis or its treatments and cardiovascular disease,⁴⁰ malignancies,^{31, 41–44} liver disease,^{45–46} diabetes,^{47–49} suicide,^{11, 50–51} COPD,⁵² and kidney disease.^{33–34, 53} In addition, the psychosocial burden associated with psoriasis may relate to socioeconomic status and social supports and also play a role in the increased risk of death from any cause.^{10, 54–57} These data are important for directing future research efforts towards understanding the relationship between psoriasis, treatments for psoriasis, psychological and social factors, and patient outcomes.

We reported both the relative risk and the excess risk of death. It is important to emphasize that while the relative risk of death was highest for conditions such as kidney disease and dementia (HR of 4.37 and 3.64, respectively), the excess risk attributable to severe psoriasis for these conditions was relatively small given the lower incidence of death due to these causes (1.2 and 0.5 excess deaths per 1000 patient years). In contrast, although the relative risk of death for cardiovascular disease, infection, and malignant neoplasms was smaller (HR of 1.57, 1.65, 1.41 respectively), the excess risk was highest for these conditions (3.5, 2.6, and 1.6 excess deaths per 1000 patient years).

As with all studies, these results are subject to limitations. The use of a population-based study design helps minimize bias.⁵⁸ Nevertheless, the use of treatment patterns as a marker for psoriasis severity may introduce selection bias. It is possible that we missed some untreated patients with severe psoriasis or that some of the patients receiving systemic treatments may not have had severe skin disease. Nevertheless, sensitivity analyses restricting the psoriasis population to those receiving therapies specific for severe skin disease confirmed our primary analysis. Additionally, there could be a “healthy user” effect in that patients with severe psoriasis need to be healthy enough to be prescribed the therapies we studied (i.e. methotrexate) which would result in an underestimate of mortality risk. Alternatively, it is possible that only the sickest patients with psoriasis are actively seeking medical care and therefore are more likely to receive systemic treatment or phototherapy for their psoriasis than patients with severe skin disease who are otherwise healthy. In this scenario, the excess risk of specific causes of death in our study may overestimate the risk in those with severe skin disease who are not receiving treatment. Finally, there is the potential for information bias which occurs when the probability of detecting an outcome is different between the exposed and unexposed (i.e. control) populations.^{59–66} Since patients were followed by the same practices during the same time period and the endpoint was objective (i.e. death) it is unlikely that information bias affected our results.

Additional limitations of our study relate to the measurement of the cause of death. Our data were based on diagnoses from the electronic medical record entered by the patient’s physician on or near the date of death, and the cause of death was unknown or missing in 24% of patients who died. The GPRD has been widely validated, but we did not specifically validate our categorizations for death in this study.^{27–28} The gold standard of determining cause of death is autopsy, however, this procedure is rarely performed to confirm the cause of death in the UK.^{60–61} Ultimately, errors in determining the cause of death are likely to be random and therefore would bias our results towards null findings.

In summary, we found that patients treated for severe psoriasis are at an increased risk of death from cardiovascular disease, malignancies, chronic lower respiratory disease, diabetes, dementia, infection, and kidney disease. Additional studies are needed to examine potential causes for increased mortality and whether these differ by cause of death.

What's already known about this topic?

- There is increasing evidence to suggest that psoriasis is a systemic inflammatory disease associated with multiple comorbidities.
- Severe psoriasis has been found to be an independent risk factor for cardiovascular mortality and overall mortality, but there are few studies looking at other causes of mortality in this population.

What does this study add?

- This is one of the first studies to evaluate cause-specific mortality in patients with psoriasis using broadly representative population-based methods.
- To our knowledge, an increased risk of death associated with infection, kidney disease, and dementia has not been previously reported in patients with severe psoriasis.
- The excess risk of death in patients with psoriasis is highest for cardiovascular disease followed by infection and cancer.

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Figure 1.
Age at death by study group

Table 1

Subject characteristics

	Control	Severe Psoriasis	P-value
N	14330	3603	
Age in years			
Mean (SD)	49.73 (19.33)	52.19 (16.71)	<0.001 [*]
Median (IQR)	480 (33, 65)	52 (39, 66)	
Sex			
Male	5783 (40.36%)	1750 (48.57%)	<0.001 [^]
Person time in years			
Mean (SD)	3.40 (2.76)	3.43 (2.73)	0.548 [^]
Median (IQR)	2.63 (1.18, 5.02)	2.69 (1.24, 5.05)	
Cumulative	48662	12346	
Mean number of causes of death listed (SD)	1.20 (0.47)	1.22 (0.47)	0.504 [*]
Number of deaths (%)	862 (6.02%)	321 (8.92%)	
Death Rate per 1000 patient-years	17.71	26.00	
(95% CI)	(16.55–18.94)	(23.23–29.01)	

^{*} Student's t-test;

[^] Chi-Square

Table 2

Cause and relative risk of death by treatment group

	Control			Psoriasis			Cox Model ^{***}		
	N	%	^	N	%	^	P- value [*]	HR	(95% CI)
Accidents	7	1%		2	1%		1.000	1.03	(0.21-4.96)
Cardiovascular Disease	301	35%		108	34%		0.002	1.57	(1.26-1.96)
Chronic lower respiratory disease	44	5%		22	7%		0.013	2.08	(1.24-3.48)
Dementia	10	1%		7	2%		0.060	3.64	(1.36-9.72)
Diabetes	10	1%		7	2%		0.060	2.86	(1.08-7.59)
Infection	195	23%		71	22%		0.009	1.65	(1.26-2.18)
Kidney disease	17	2%		18	6%		0.000	4.37	(2.24-8.53)
Liver disease	4	0%		2	1%		0.347	2.03	(0.37-11.12)
Malignant neoplasms	190	22%		67	21%		0.019	1.41	(1.07-1.86)
Other	33	4%		17	5%		0.020	2.12	(1.19-3.88)
Suicide	1	0%		1	0%		0.361	3.35	(0.21-53.77)
Unknown/ Missing	218	25%		70	22%		0.075	1.43	(1.09-1.89)
Total Deaths	862			321					

Notes:

[^] Percentages may not sum to 100 because each subject may have had more than one cause of death.

^{*} Two-sided fisher's exact test.

^{**} Adjusted for age and sex

Table 3

Absolute and excess risk of death

Cause of Death	Absolute Risk*	Excess Risk*
Cardiovascular Disease	61.9	3.5
Infection	40.1	2.6
Unknown/ Missing	44.8	1.9
Malignant neoplasms	39.0	1.6
Kidney disease	3.5	1.2
Chronic lower respiratory disease	9.0	1.0
Other	6.8	0.8
Dementia	2.1	0.5
Diabetes	2.1	0.4
Liver disease	0.8	0.1
Suicide	0.2	0.0
Accidents	1.4	0.0

Notes:

* Deaths per 1000 pt-years

Table 4

Median age at death by sex and cause

	Females			Males		
	Controls	Psoriasis	P-value*	Controls	Psoriasis	P-value*
Overall	82.85	75.49	<0.001	78.41	73.49	<0.001
Cardiovascular Disease	83.71	76.94	<0.001	77.98	73.80	0.018
Malignant neoplasms	76.15	71.52	0.518	74.13	69.21	0.034
Chronic lower respiratory disease	72.38	72.74	0.507	80.98	73.23	0.107
Infection	83.22	76.56	0.001	83.11	75.10	0.003
Kidney disease	83.65	65.59	0.003	79.10	66.09	0.026
Other	79.91	72.43	0.393	80.86	64.13	0.011
Unknown/ Missing	85.40	80.20	0.004	80.27	74.38	0.010

* Wilcoxon rank-sum test