

# Mortality and Causes of Death in Psoriatic Arthritis

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**ABSTRACT. Objective.** To evaluate the mortality associated with psoriatic arthritis (PsA) and causes of death.

**Methods.** Data were evaluated from several published studies identified by a literature search. A standardized mortality ratio was documented when available, as were causes of death derived from clinical databases, death certificates, and mortality databases. In some studies, mortality data was stratified by sex, age, and calendar year with time trend analysis.

**Results.** There were variable reports of increased mortality in PsA that may be explained by factors such as pattern of referral, the severity of arthritis and/or skin psoriasis, and treatment exposure. There appears to be a greater incidence of cardiovascular death in psoriatic disease, although further studies are needed to separate the effect of skin psoriasis from arthritis.

**Conclusion.** PsA is not a mild disease and mortality may be increased in more severe disease. Although cardiovascular risk is more substantiated in severe psoriasis than in arthritis, it would be remiss not to evaluate the cardiovascular risk profile in all patients with psoriatic disease. It is important to treat patients with PsA early and aggressively to prevent disease severity that may influence longevity. (J Rheumatol 2012;39 Suppl 89:32–35; doi:10.3899/jrheum.120239)

*Key Indexing Terms:*

PSORIATIC ARTHROPATHY

MORTALITY

CAUSES OF DEATH

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis, affecting 1% of the population. PsA is characterized by bony proliferation, osteolysis, and inflammation at tendon ligaments and capsular insertion (enthesitis). PsA was initially thought to be a benign arthropathy; however, it is now known to be associated with significant joint damage and disability. Gladman, *et al*<sup>1</sup> demonstrated that 67% of patients had joint erosion and 20% complete joint destruction at presentation. There was a significant degree of joint damage, with osteolysis and ankylosis seen both clinically and radiologically; on the 5-year followup there was an increased number of deformed joints, and 11% had severe functional limitation and American College of Rheumatology functional class 3 or 4 (Steinbrocker criteria) restriction of daily activity. Similarly, Torre Alonso, *et al*<sup>2</sup> demonstrated 57% erosive arthritis and 19% Steinbrocker functional class III to IV in a large Spanish cohort of PsA. Gladman<sup>3</sup> demonstrated that disease progression was common and that 10 years after diagnosis, 55% of patients had 5 or more deformed joints. The presence of 5 or more joints at presentation and actively inflamed joints at each visit predicted progression of clinical damage.

There have been several studies on mortality rate and

causes of death in PsA. In some studies, death and causes of deaths were identified from the clinical databases and confirmed by death certificates and mortality databases. In most studies, age- and sex-adjusted standardized mortality ratios (SMR) were calculated and are given in Table 1.

Wong, *et al*<sup>4</sup> reported the SMR to be 1.62 in 428 patients followed from 1978 to 1994. However, the patients who died were older at presentation and had longer disease duration, with higher joint damage at presentation. A subsequent study on an extended cohort of patients with PsA was reported by Ali, *et al*<sup>5</sup>, with 680 patients followed between 1978 and 2004, and this showed an overall SMR of 1.36. The SMR for periods 1978–1986, 1987–1995, and 1996–2004 were 1.89, 1.83, and 1.21, respectively, indicating improvement of mortality risk over time, which may be due to earlier diagnosis and more aggressive treatment in the more recent followup period.

However, Shbeeb, *et al*<sup>6</sup>, in epidemiological studies based on a linked medical record system in Olmsted County, Minnesota, USA, did not find a significant increase in mortality in patients with PsA. A later study by Wilson, *et al*<sup>7</sup> confirmed this when it demonstrated no difference in the mean followup survival of the same cohort of patients with PsA when compared to the general population. Over the period of 1977–2000, 147 patients were diagnosed with PsA. At presentation, 49% had oligoarthritis, 39% polyarticular involvement, 55% had inflammatory changes on plain radiographs, and 32% had joint erosions. The incidence of PsA diagnosed increased with time, but the SMR was 0.91 (CI 0.58–1.37) over 13.6 years mean followup, which was no different from the general population. However, patients with severe PsA were underrepresented in the Wilson study,

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Table 1. Mortality studies in psoriatic arthropathy.

Study and Location	Year Published	No. Patients	Controls	Findings
Coulton, UK	1989	40	N/A	No deaths
Wong, Canada	1997	428	General population	SMR 1.62
Shbeeb, USA	2000	66	General population	Similar survival
Alamanos, Greece	2003	221	N/A	4 deaths
Ali, Canada	2007	680	General population	SMR 1.36
Wilson, USA	2009	147	General population	SMR 0.91
Buckley, UK	2010	453	General population	SMR 0.82
Mok, Hong Kong	2011	778	General population/ other rheumatological diseases	SMR 1.59

N/A: not applicable; SMR: standardized mortality ratio.

undertaken in a community setting; the population cohort was 90% white. Nonetheless, our own studies from a hospital-based cohort of patients followed in Bath, UK, and reported by Buckley, *et al*<sup>8</sup> demonstrated no difference in the SMR when compared to the general population. The overall SMR for the PsA cohort of 453 patients between 1985 and 2007 was 0.82 (95% CI 0.57–1.5) with men at 0.67 and women at 0.97. The cohort was mainly referred from primary care and therefore may have included a larger number of patients with milder disease that was possibly treated more actively in an earlier stage. In addition, the cohort was virtually entirely white, which would not be representative of the general UK population.

Mok, *et al*<sup>9</sup> collected data from a total number of 778 patients with PsA in Hong Kong from 1999 to 2008. The age- and sex-adjusted SMR was 1.59 (95% CI 1.16–2.03), higher in women at 1.96 (95% CI 1.14–2.77) than in men (1.40; 95% CI 0.89–1.90). Of interest, the SMR was similar to that of rheumatoid arthritis (RA; 1.68) and ankylosing spondylitis (1.87) but much lower than systemic vasculitis (2.64), systemic sclerosis (3.94), and systemic lupus erythematosus (5.28), with all disease groups studied with the same methodology. However, the data were obtained from the hospital registry, where there may be an underestimation of PsA cases because of undercoding and unverified accuracy of clinical diagnosis by the attending physician.

The discrepancies between the reported SMR in PsA could be due to a number of reasons. Patients in the community have a less severe disease when compared to patients in the hospital. The control populations should be based on the regional data rather than the national data as used by Buckley, *et al*<sup>8</sup>. The method of ascertaining deaths is still not complete, because the diagnosis of PsA is not written in the death certificate. The more recent emphasis on early diagnosis and access to more effective treatments may reflect better survival compared to the earlier years.

From the psoriasis literature, Mallbris, *et al*<sup>10</sup> demonstrated no increased cardiovascular mortality in outpatients with psoriasis (n = 19,757), whereas risk increased by 50%

(SMR 1.54) in those hospitalized for psoriasis at least once (n = 8991). Similarly, in a study based on the UK general practice database, Gelfand, *et al*<sup>11</sup> demonstrated no increased mortality with mild psoriasis (defined as no systemic therapy for psoriasis; n = 133,568), whereas the mortality was increased for severe psoriasis (n = 3951). Therefore there is good evidence that enhanced mortality in psoriasis is associated with severe disease.

Psoriatic disease is well known to be associated with increased cardiovascular disease and the metabolic syndrome. Atherosclerosis is accelerated in many autoimmune diseases, and recent advances have recognized the inflammatory nature in the pathogenesis of atherosclerotic lesions. Both accelerated atherosclerosis and PsA are mainly mediated by Th1 cells and have a common pattern of T cell activation. The immunological factors in both diseases include C-reactive protein (CRP), tumor necrosis factor- $\alpha$  (TNF)- $\alpha$ , interferon  $\gamma$ , interleukin 1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-23, and Th17. TNF- $\alpha$  and IL-1 $\beta$  are proinflammatory to the vascular endothelium and synovial tissue in PsA.

PsA is also known to be associated with increased subclinical atherosclerosis<sup>12</sup>, and active PsA is associated with atherogenic lipid profile<sup>13</sup>. The low-density lipoprotein and high-density lipoprotein decrease during disease flare and increase in disease remission. This alteration in lipid metabolism may contribute to atherogenesis in chronic inflammatory disease<sup>14</sup>. Studies have also shown that there is an increase in arterial stiffness in patients with PsA, an important determinant in increased systolic and pulse blood pressure, and this increase is predictive of cardiovascular events<sup>15</sup>. There is an increase in carotid intima-media thickness in patients with PsA, which is associated with apolipoprotein A-I and A-B<sup>14</sup>. Patients with PsA tend to be more obese than the general population, and a higher body mass index (BMI) is associated with increased cardiovascular mortality<sup>14</sup>.

There are several mortality studies looking at the causes of death in PsA and comparing it with the general population (Table 2). In all, the major cause of death is due to a car-

Table 2. Causes of death in psoriatic arthropathy. Data are percentages except where indicated.

Causes	Wong	Alamanos	Ali	Buckley	Mok
No. patients	428	221	680	453	778
No. deaths	53	4	106	37	51
Cardiovascular	28	50	25	38	20
Respiratory	21	25	10	27	2
Cancer	17	—	24	14	20
Injuries/poisoning	15	25	5	—	4
Infection	—	—	—	—	33
Other	8	—	5	—	18
Unknown	11	—	25	—	4

diovascular etiology, except in Mok, *et al*<sup>9</sup> (n = 778), where the highest cause of mortality was infection at 33%, followed by cardiovascular and cancer causes at 20% each, and respiratory at 2%. However, in the latter study some of the respiratory causes may have been attributed to infection. Infection was not distinguished as a separate cause in other studies.

In the other studies, Wong, *et al*<sup>4</sup> identified 53 deaths in 428 patients attending a PsA outpatient clinic, a primary, secondary, and tertiary referral center. The majority of deaths were cardiovascular in nature at 28%, followed by respiratory, cancer, and injuries/poisoning at 21%, 17%, and 15%, respectively. The prevalence of severe disease was similar to that of RA, with 67% having erosive disease, 30% complete joint destruction or ankylosis, and 11% having severe functional limitations. Similarly, Alamanos, *et al*<sup>16</sup> found a majority of deaths due to a cardiovascular etiology (n = 2, 50%) while the remaining 2 deaths were respiratory and due to injury. In the Bath study<sup>8</sup> (n = 453), cardiovascular, respiratory, and cancer accounted for 38%, 27%, and 14% of deaths, respectively, comparable to the findings of Ali, *et al*<sup>5</sup> (n = 680; 25%, 24%, and 10%).

Treatment with anti-TNF- $\alpha$  decreases cardiovascular events in patients with RA, as reported by the British (BRSBR)<sup>17</sup> and Swedish biological registries. Anti-TNF- $\alpha$  improves endothelial function and aortic stiffness in patients with RA and microvascular function in patients with AS. Angel, *et al*<sup>15</sup> demonstrated that aortic stiffness improved in RA, AS, and PsA. Insulin resistance contributes to the pathogenesis of metabolic syndrome, diabetes mellitus type 2, and endothelial dysfunction<sup>14</sup>. Anti-TNF- $\alpha$  has been shown to improve insulin resistance and sensitivity in patients with RA, thereby improving control of the diseases, leading to a decrease in cardiovascular mortality. However, prospective controlled studies are necessary in patients with PsA. There was an increase in BMI for patients with PsA who were taking anti-TNF- $\alpha$ , with no clear effect on lipids; however, there was a significant reduction in systemic inflammation with a decrease in CRP and TNF- $\alpha$ .

Patients on biologic registers for PsA (Table 3) were also explored for causes of death. The BRSBR showed no

Table 3. Biologic registers searched for deaths involving psoriatic arthritis.

Register	Region	Indication
BSRBR	UK	RA
DANBIO	Denmark	IA
NOR-DMARD	Norway	RA, PsA, AS
CORRONA	USA	RA, PsA
BIOBADASER	Spain	IA
RobFin	Finland	IA
SwePsA	Sweden	Early PsA
SSATG	South Sweden	IA

IA: inflammatory arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis.

increased risk of serious adverse events or serious infection when compared to seronegative RA. There were no cases of demyelination or tuberculosis. In the NOR-DMARD registry<sup>18</sup>, out of 146 patients, 21 stopped their anti-TNF- $\alpha$  because of serious adverse events, 5 of which were respiratory in nature. The South Swedish Arthritis Treatment registry<sup>19</sup> reported that of the 261 patients on anti-TNF- $\alpha$ , 2 developed malignancies: 1 chronic lymphocytic leukemia and 1 death from non-Hodgkin's lymphoma. Three patients had life-threatening serious adverse events including 1 case of septicemia.

Further prospective studies of longitudinal cohorts of patients with PsA are required to verify the increase in the SMR when compared to the population. There is an association of increased cardiovascular risk with more severe psoriasis and it would be remiss not to evaluate the cardiovascular risk profile in all patients with psoriatic disease.

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