

Overall and Sex-specific Mortality in Psoriatic Arthritis and Ankylosing Spondylitis: A Meta-analysis

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Objective. This study examined the all-cause and sex-specific standardized mortality ratios (SMRs) in patients with spondyloarthritis. **Methods.** Studies examining the all-cause and/or cause-specific SMRs in patients with psoriatic arthritis (PsA) and ankylosing spondylitis (AS) compared to the general population were surveyed using MEDLINE, EMBASE, and Cochrane databases and manual searches. A meta-analysis of the all-cause and sex-specific SMRs in patients with rheumatic diseases was then performed. **Results.** In total, 7 comparisons (5 PsA and 2 AS) from 6 reports met the inclusion criteria. Disease-specific meta-analysis showed that the pooled SMR was 1.299 (95% confidence interval [CI] 1.092 ~ 1.605, $p=0.015$) for PsA and 1.784 (95% CI 1.576 ~ 2.020, $p<0.001$) for AS. Meta-analysis showed that the SMRs of PsA and AS were significantly higher (1.299 to 1.784 times) than those in the general population. The age- and sex-adjusted SMR was highest for AS (1.784), followed by PsA (1.299). Moreover, sex-specific meta-analysis showed that the all-cause SMRs were increased in female and male patients with PsA. On the other hand, mortality increased in male patients with AS (SMR 1.834), whereas there was no significant increase in female patients with AS. **Conclusion.** All-cause mortality is higher in patients with PsA and AS compared to the general population. On the other hand, the mortality was higher in males with AS but not in females. (*J Rheum Dis* 2018;25:197-202)

Key Words. Psoriatic arthritis, Ankylosing spondylitis, Mortality, Meta-analysis

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis that can affect peripheral and axial joints, entheses, and the skin [1]. Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by inflammation in the spinal and sacroiliac joints that initially causes bone and joint erosion and eventually leads to new bone formation, syndesmophytes, and ankylosis [2].

These rheumatic diseases are chronic multisystemic illnesses that may be associated with significant mortality and morbidity [3]. In addition to disease-related complications, adverse events related to treatment may aggravate the risk of mortality [4]. However, mortality data for patients with PsA and AS are limited, and the few

studies that have investigated mortality in rheumatic diseases yielded conflicting results, mainly owing to the small number of studies conducted, small sample sizes, and clinical heterogeneity [5-11]. The inconsistent results from different studies prompted us to conduct a meta-analysis of mortality in PsA and AS.

The standardized mortality ratio (SMR) is calculated as the ratio of deaths observed in a cohort to those expected in a group of the same size from the general population and standardized for age and sex [12]. Thus, the SMR is considered the optimal method of assessing mortality. Current studies reporting on mortality in rheumatic diseases vary widely; therefore, an accurate and weighted analysis of the SMR is critical. The present study aimed to assess the data on all-cause and sex-specific SMRs in patients with PsA and AS using a meta-analysis approach.

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MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies that examined mortality in patients with PsA and AS. The MEDLINE, EMBASE, and Cochrane databases were searched to identify relevant articles (from 1990 to December 2017). The following key words and subject terms were used: “psoriatic arthritis,” “ankylosing spondylitis,” “mortality,” and “SMR.” All references in the studies were reviewed to identify additional studies not included in the electronic databases. Studies were included if they met the following criteria: 1) cohorts or longitudinal observational studies with patients with PsA or AS, and 2) all-cause and/or cause-specific SMR data available with 95% confidence interval (CI). We excluded studies (1) containing overlapping or insufficient data, or (2) if they were reviews or case reports. The following information was extracted from each study: first author, year of publication, country, ethnicity, enrollment period, follow-up period, midpoint year of the study period, number of participants, number of deaths, and all-cause and/or cause-specific SMR with 95% CI. We scored the quality of each study included in the meta-analysis based on the Newcastle-Ottawa Scale [13]. Scores ranging from 6–9, with 9 being the highest score possible, indicated high methodological quality.

Evaluation of statistical associations

We performed meta-analyses to evaluate the SMRs for all-cause- and sex-specific mortality. The effect sizes of outcomes were expressed as SMRs and corresponding 95% CIs. We assessed within- and between-study variation and heterogeneities using Cochran’s Q-statistics [14]. The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When a significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis; otherwise, the fixed effects model was used. The fixed effects model assumes that all studies estimate the same underlying effect and considers only within-study variation. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance. We quantified the effect of heterogeneity using $I^2 = 100\% \times (Q - df) / Q$ [15], where I^2 measures the degree of inconsistency between studies and determines whether the percentage of total variation across studies is due to heterogeneity rather than chance. I^2 ranges between 0% and 100%; I^2 values of 25%, 50%, and 75% are referred to as low, moderate, and high estimates, respectively. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA).

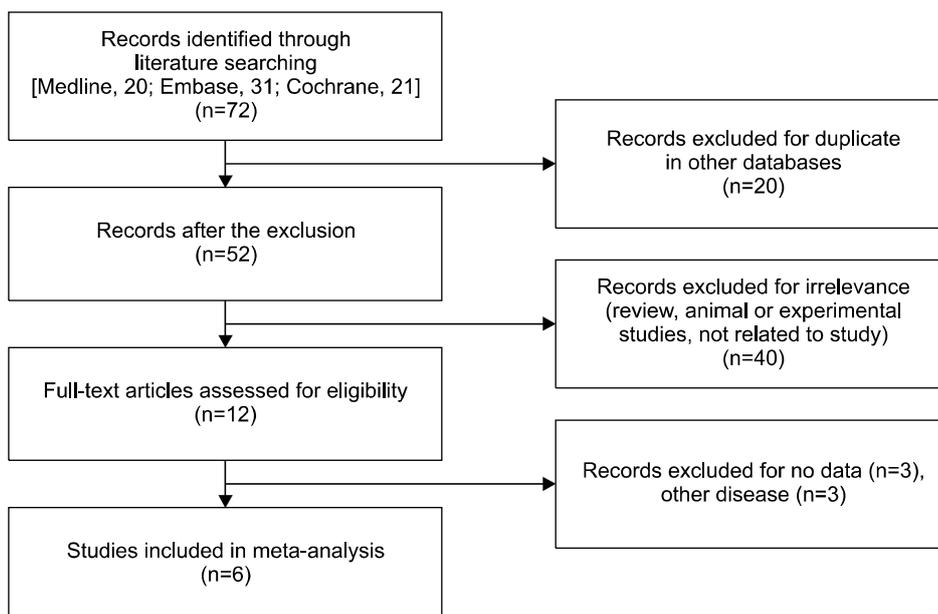


Figure 1. Study flow chart of the article selection process.

Evaluation of heterogeneity, sensitivity, and publication bias

To examine the potential sources of heterogeneity observed in the meta-analysis, a meta-regression analysis was performed using the following variables: ethnicity, disease, publication year, midpoint year of the study period, and sample size. Sensitivity analysis was performed to assess the influence of each study on the pooled SMR by omitting each study. Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgment. Therefore, we assessed publication bias using Egger's linear regression test [16], which measures funnel plot asymmetry using a natural

logarithm scale of odds ratios.

RESULTS

Studies included in the meta-analysis

In total, 72 studies were identified by electronic and manual searches, 60 of which were excluded owing to repeated publication or irrelevance. The remaining 12 studies were selected for a full-text review based on titles and abstracts. Three of these were excluded owing to the absence of SMR data. Thus, 6 articles met the inclusion criteria (Figure 1) [5,7-11]. One of these studies contained data on 2 different groups [10], which were treated independently. Thus, 7 comparisons were considered in

Table 1. Characteristics of the individual studies included in the meta-analysis

Study	Country	Disease	Enrollment period	Follow-up period	Patient number	Number of deaths	Overall mortality		Mortality studied	Quality
							SMR	95% CI		
Juneblad, 2016 [11]	Sweden	PsA	1995~2011	Retrospective study	464	44	1.22	0.89~1.63	All-cause (male, female)	6
Mok, 2011 [10]	China	PsA	1999~2008	Retrospective study	778	50	1.59	1.16~2.03	All-cause (male, female)	6
Buckley, 2010 [9]	UK	PsA	1985~2007	Retrospective study	453	37	0.82	0.58~1.13	All-cause (male, female)	6
Ali, 2007 [8]	UK	PsA	1978~2004	NA	680	106	1.36	1.12~1.64	All-cause (male, female)	7
Wong, 1997 [7]	UK	PsA	1978~1993	Median 11.4 years	428	53	1.62	1.21~2.12	All-cause (male, female)	8
Bakland, 2011 [5]	Norway	AS	1969~2009	Mean 31.9 years	677	98	1.61	1.29~1.93	All-cause (male, female)	8
Mok-1, 2011 [10]	China	AS	1999~2008	Retrospective study	2,154	199	1.87	1.61~2.13	All-cause (male, female)	6

SMR: standardized mortality ratio, CI: confidence interval, PsA: psoriatic arthritis, AS: ankylosing spondylitis, NA: not available.

Table 2. Meta-analysis of the all-cause standardized mortality ratios in patients with PsA and AS

Group	Population	Number of studies	Test of association			Test of heterogeneity		
			SMR	95% CI	p-value	Model	p-value	I ²
All	Overall	7	1.432	1.137~1.728	<0.001	R	<0.001	84.8
	PsA	5	1.299	1.092~1.605	0.015	R	0.021	65.4
	AS	2	1.784	1.576~2.020	<0.001	F	0.273	16.9
Male	Overall	7	1.410	1.132~1.756	0.002	R	0.003	69.8
	PsA	5	1.245	1.043~1.485	0.015	F	0.155	39.8
	AS	2	1.834	1.605~2.095	<0.001	F	0.230	30.4
Female	Overall	7	1.473	1.245~1.743	<0.001	F	0.199	29.9
	PsA	5	1.457	1.134~1.976	0.004	R	0.075	72.9
	AS	2	1.380	0.807~2.360	0.240	F	1.000	0

PsA: psoriatic arthritis, AS: ankylosing spondylitis, SMR: standardized mortality ratio, CI: confidence interval, R: random effects model, F: fixed effects model.

the meta-analysis, and they consisted of 5 comparative studies of PsA and 2 of AS. The quality assessment score of each study ranged between 6 and 8, and all the studies had a quality score ≥ 6 (Table 1). Table 1 shows the characteristic features of each study, including the study population and quality score.

Meta-analysis of the all-cause standardized mortality ratios in PsA and AS

Compared with the general population, all-cause SMRs were increased in patients with PsA and AS (SMR 1.432, 95% CI 1.137~1.728, $p < 0.001$) (Table 2). Disease-specific meta-analysis revealed that the pooled SMR was 1.299 (95% CI 1.092~1.605, $p = 0.015$) for PsA and 1.784 (95% CI 1.576~2.020, $p < 0.001$) for AS (Table 2, Figure 2).

Meta-analysis of sex-specific standardized mortality ratio in PsA and AS

Sex-specific meta-analysis revealed that the pooled SMR was 1.245 (95% CI 1.043~1.485, $p = 0.015$) for PsA and 1.834 (95% CI 1.605~2.095, $p < 0.001$) for AS in males (Table 2, Figure 3). The pooled SMR was 1.457 (95% CI 1.134~1.976, $p = 0.004$) for PsA and 1.380 (95% CI 0.807~2.360, $p = 0.240$) for AS in females (Table 2, Figure 3). The risk of mortality was significantly increased in PsA and AS among males, while mortality was significantly increased in PsA but not in AS among females.

Heterogeneity, meta-regression, sensitivity test, and publication bias

Between-study heterogeneity was identified in the meta-analyses of overall SMRs (Table 2). Meta-regression analysis showed that ethnicity and disease ($p = 0.012$), but not sample size, midpoint year of the study period, or publication year ($p > 0.05$), had a significant impact on the heterogeneity in the meta-analysis of overall SMRs in patients with PsA and AS. Sensitivity analysis showed that no individual study significantly affected the pooled SMR, indicating that the results of this meta-analysis are robust. It was difficult to correlate the funnel plot, which is typically used to detect publication bias, owing to the small number of studies included. Egger’s test revealed no evidence of publication bias in the meta-analysis (Egger’s test p -values > 0.1).

DISCUSSION

To date, information on mortality in PsA and AS is limited and conflicting. In the present meta-analysis, we combined the published data of all-cause and sex-specific SMRs in patients with PsA and AS. Patients with PsA and AS were found to have increased SMRs from all causes (1.299, 1.784, respectively). This meta-analysis showed that the SMRs of PsA and AS were significantly higher than those in the general population by 1.299 to 1.784 times. The age- and sex-adjusted SMR was highest for AS (1.784) followed by PsA (1.299). Mortality in PsA was not found to depend on sex. However, we found that mortality was increased in male patients with AS (SMR 1.834), while there was no significant increase in female patients

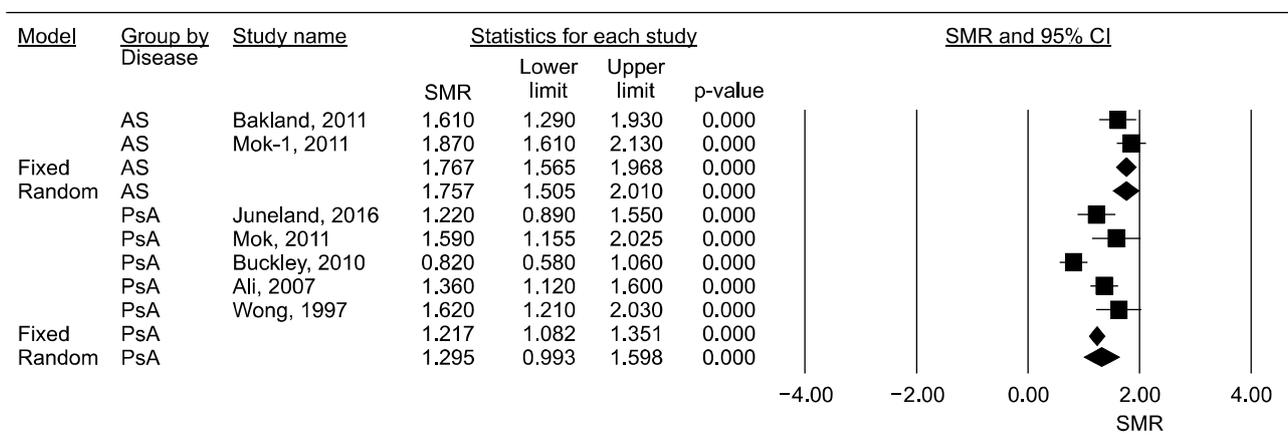
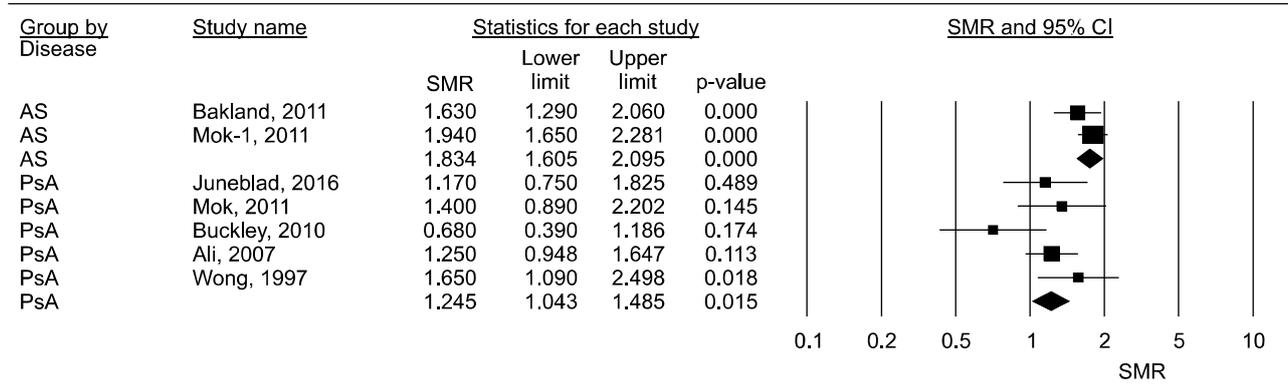


Figure 2. Meta-analysis of the all-cause standardized mortality ratios in patients with PsA and AS. PsA: psoriatic arthritis, AS: ankylosing spondylitis, SMR: standardized mortality ratio, CI: confidence interval.

A



B

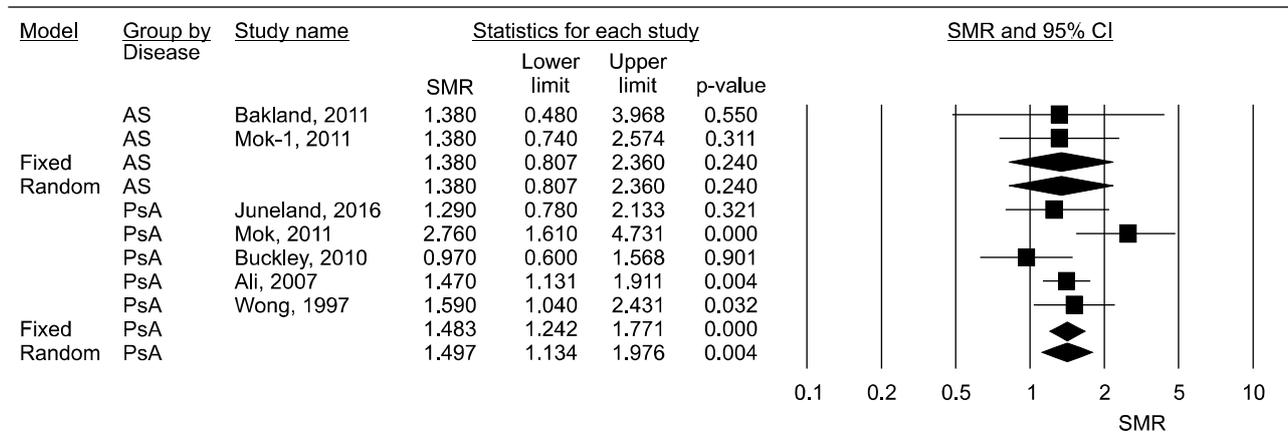


Figure 3. Meta-analysis of the all-cause standardized mortality ratios in male (A) and female (B) patients with PsA and AS. PsA: psoriatic arthritis, AS: ankylosing spondylitis, SMR: standardized mortality ratio, CI: confidence interval.

with AS. It is necessary to analyze what the main causes of death are in men and women and why the gender difference occurred. However, we could not investigate what the causes of death are in men and women, because there was no enough SMR data on the causes of death in men and women. The reason for this gender difference is unclear, but a similar increased mortality among male patients has also been reported in rheumatoid arthritis [17]. The longer life expectancy in women of any population would dilute an increased mortality. Considering the inclusion of only 2 AS studies in this review, further studies on mortality in female patients with AS are necessary. The common causes of death in rheumatic diseases are cardiovascular disease (CVD), infection, malignancies, uncontrolled disease activity, and adverse events related to treatment [18]. Immunosuppressive drugs for rheumatic diseases increase the incidence of infection and cancer [19]. In light of recent advances in the management of rheumatic diseases, such as therapeutic improvements, earlier diagnosis, increased physician awareness, and en-

hanced patient care, we expect to see an improved mortality risk in the future.

The present meta-analysis has several shortcomings. First, the heterogeneity of the clinical features, such as the study design and period, severity of organ impairment, and the proportion of patients with CVD, tended to confuse our findings and may have biased our analysis. Despite performing a meta-regression analysis using variables such as ethnicity, publication year, midpoint year of the study period, and sample size, we were unable to fully explain the source of the observed heterogeneity among the studies for all-cause mortality. Second, the SMR was adjusted only for age and sex, and we were unable to adjust for other confounding factors. Third, our findings regarding cause-specific SMR in PsA and AS are based on a small number of studies, and therefore may be affected by random errors and insufficient statistical power. Since only 2 studies were included in our analysis of the all-cause SMRs for AS, our findings should be interpreted with caution. Fourth, it is necessary to analyze the

cause-specific outcomes, as well as the overall and sex-specific mortality. However, we could not investigate them, because most of studies did not provide SMR on the cause-specific outcomes due to CVD, infection, and cancer, etc. Nonetheless, an important strength of this meta-analysis is its increased sample size leading to statistical power and precision. To the best of our knowledge, this is the first and most comprehensive meta-analysis evaluating all-cause and sex-specific mortality in PsA and AS to date.

In conclusion, our meta-analysis demonstrates that all-cause mortality is increased in patients with PsA and AS, compared with the general population, and that the all-cause SMRs in PsA do not depend on sex. However, mortality was significantly increased in male, but not female, patients with AS. Given the small number of studies, further investigations of sex-specific and cause-specific mortality in patients with rheumatic diseases are warranted.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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