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Mortality Rates in Patients With Ankylosing Spondylitis With and Without Extraarticular Manifestations and Comorbidities: A Retrospective Cohort Study

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ABSTRACT. ***Objective.*** To examine mortality rates in hospitalized patients with ankylosing spondylitis (AS) and the association of extraarticular manifestations (EAMs) and comorbidities with mortality rates.

Methods. This study was a retrospective, population-based cohort study using linked administrative data from patients with AS who were hospitalized (n = 1791) and patients in a matched comparison group (n = 8955). Mortality data for patients were obtained from the Western Australia Death Register. The presence of EAMs and comorbidities was identified from hospital records. Mortality rates were compared between the 2 groups using Cox proportional hazard models overall and stratified by a history of EAMs, comorbidities, and smoking status.

Results. Crude mortality rates were significantly higher among patients with AS than among patients in the comparison group (hazard ratio [HR] 1.85, 95% CI 1.62–2.12), with excess mortality in the AS group associated with cardiovascular disease (CVD; HR 5.32, 95% CI 3.84–7.35), cancer (HR 1.68, 95% CI 1.27–2.23), external causes (HR 3.92, 95% CI 2.28–6.77), and infectious diseases (HR 25.92, 95% CI 7.50–89.56). When patients were stratified by history of EAMs, CVD, and smoking, the risk of mortality was elevated in patients both with and without each risk factor. Among patients with AS, histories of CVD (HR 6.33, 95% CI 4.79–8.38), diabetes (HR 2.81, 95% CI 1.99–3.95), smoking (HR 1.49, 95% CI 1.18–1.89), and EAMs (HR 1.62, 95% CI 1.24–2.11) were associated with an increased risk of mortality.

Conclusion. The presence of comorbidities, EAMs, and smoking contributes to an increased risk of all-cause mortality among patients with AS who are hospitalized compared to patients in the comparison group. These results support the need to prevent or reduce the occurrence of comorbidities and smoking in patients with AS.

Key Indexing Terms: all-cause mortality, axial spondyloarthritis, comorbidity, survival

Ankylosing spondylitis (AS) is a common form of arthritis, predominantly affecting the axial skeleton. AS can lead to spinal calcification and peripheral arthritis, but it is also associated with a number of extraarticular manifestations (EAMs), including inflammatory bowel disease, uveitis, and psoriasis, while an increased risk has been described for a range of comorbidities, including cardiovascular disease (CVD), liver disease, and mental health disorders.[1,2] The relationship between AS and the presence of EAMs and comorbidities is complex and multifaceted.

The heritability of AS is estimated to be approximately 77%, with HLA-B27 believed to contribute substantially to the high heritability.[3] While 80% to 95% of patients with AS have HLA-B27, only 1% to 2% of patients who have HLA-B27 develop AS,[4,5,6] suggesting a role for environmental factors, such as bacterial antigens, in the initiation of AS.[7] The presence of genetic variations commonly associated with AS has also been associated with the risk of EAMs. For example, the presence of acute anterior uveitis is more common in patients with AS who have HLA-B27 than in those without the antigen.[8] Systemic inflammation may also contribute to the occurrence of EAMs in patients with AS, with the incidence of EAMs reported to be higher in patients with AS who have uncontrolled systemic inflammation.[9] Systemic inflammation may also contribute to an elevated risk of comorbidities, such as CVD, particularly ischemic heart disease and valvular defects.[10]

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Lifestyle factors also contribute to the high prevalence of comorbidities in patients with AS. While exercise is recommended for patients with AS and is a protective factor for a range of comorbidities, including CVD, the pain, fatigue, and stiffness often experienced by patients can limit their desire to engage in regular exercise.[11] In fitting with this, high rates of obesity have also been observed in patients with AS.[12] Additionally, smoking has been associated with both an increased risk of AS and worse disease characteristics, such as lower spinal mobility, higher disease activity, and poorer quality of life.[13,14]

Finally, medication used to treat AS can also have adverse health effects. Nonsteroidal antiinflammatory drugs can cause a range of adverse effects, including gastrointestinal bleeding, liver and renal toxicity, and cardiovascular events,[15] while the use of anti–tumor necrosis factor (TNF-α) has been associated with an increased risk of serious infection.[16,17]

Given the wide-ranging effects of AS and its associated comorbidities, it is not surprising that AS is associated with elevated mortality rates.[18,19] However, it is unclear which aspects of AS that are associated EAMs, common comorbidities, and health behaviors, such as smoking, contribute to excess mortality risk. The aim of this study was to compare mortality rates and causes of death between patients with AS and those without AS, examining the extent to which EAMs, common comorbidities, and smoking contribute to overall and cause-specific mortality.

METHODS

Study population. The study cohort consisted of patients admitted to hospital with a diagnosis of AS between 1990 and 2014 in Western Australia (WA); patients were identified from the Hospital Morbidity Data Collection (HMDC) within the WA Rheumatic Disease Epidemiological Register. Within the HMDC, primary diagnoses and up to 20 codiagnoses are listed for each separation using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM), or 10th revision, Australian Modification (ICD-10-AM).

Codes used to identify AS were ICD-9-CM 720.0 and ICD-10-AM M45.0. The cohort was limited to patients aged between 18 and 80 years at their index AS hospital admission, with the index AS event being the patient's first AS hospitalization within the study period. A non-AS comparison cohort, matched (1:5) based on age at the index admission within 1 year, sex, and Aboriginal status, was also selected from the HMDC.

Study data. For each patient, mortality data from January 1990 to December 2015 were obtained from the WA Death Register. The WA Death Register is a statutory data collection, encompassing all deaths within WA. EAMs and comorbidities were identified from inpatient hospital records prior to and including the index AS event (minimum 10 years prior). History of smoking was taken from all available hospital data using the ICD-9-CM codes 305.1, V15.82, and V15.83, and the ICD-10-AM codes F17, Z72.0, and Z86.43. Smoking codes from hospital data have been shown to have good specificities (93–97%) but lower sensitivities (45–74%) for ever-smoked status.[20] Despite these limitations, it was deemed an important variable to include in the study. EAMs and comorbidities were identified within the HMDC dataset from diagnosis variables using International Classification of Diseases codes (Supplementary Table 1, available from the authors upon request). The Charlson Comorbidity Index was calculated for each patient using hospital data for the 10 years prior to their index event.[21] Data linkage and extraction was performed by the WA Data Linkage Branch using best-practice probabilistic matching with clerical review.[22]

Statistical analyses. The characteristics of patients in the 2 groups at their index admission were summarized and compared using univariable logistic regression and linear regression. Cox proportional hazard models were used to compare mortality rates between the 2 groups. For the comparison of mortality rates by smoking status and comorbidities, age groups and sex were included as covariates in the model to account for discrepancies between the 2 groups. For the mortality analysis, patient follow-up was censored at death; on December 31, 2015; or at 10-year follow-up, whichever occurred first. The choice was made to censor data at a maximum of 10 years, since beyond this point the assumption of proportionality did not hold, as assessed using Schoenfeld residuals. Crude mortality rates were calculated and were expressed as the number of deaths per 1000 patient-years (PY). Additionally, mortality rates stratified by age at index event (18–39, 40–59, and 60–79 yrs), sex, smoking status, comorbidities, and year of index event (1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2014) were also calculated. Cumulative incidence adjusted for competing risk of death was calculated for cause-specific mortality. All analyses were carried out in Stata/IC (version 15; StataCorp LLC). P values < 0.05 were considered statistically significant (2-tailed).

Ethics. The study received ethics approval from the Western Australian Department of Health Human Research Ethics Committee (WADOH HREC No. 2016.24). A waiver of consent was granted for this study, as it met the requirements set out under the National Statement on Ethical Conduct in Human Research.

RESULTS

The study included 1791 patients with AS (14,257 PY) and 8955 patients in the comparison group (73,742 PY). The average (SD) period of follow-up was 8.0 (2.9) years for patients in the AS group and 8.2 (3.0) years for patients in the comparison group. At their index event, patients were typically middle-aged and male (57.0%). Patients with AS were more likely to have a history of smoking and comorbidities, including diabetes and CVD, prior to their index event compared with patients in the comparison group (Table 1).

Mortality rates. Crude mortality rates among patients in the AS group were significantly higher than those among patients in the comparison group (Table 2). This was reflected across sex- and age-specific mortality hazard ratios (HRs). However, the year of the index event affected the difference between the 2 groups, with significant HRs occurring in patients prior to 2005, but there was no difference between the 2 groups when the index event was in 2005 or later.

Among patients with AS, an increased risk of mortality was associated with having CVD (HR 6.33, 95% CI 4.79–8.38), having diabetes (HR 2.81, 95% CI 1.99–3.95), having chronic lower respiratory disease (HR 3.45, 95% CI 2.67–4.46), smoking (HR 1.49, 95% CI 1.18–1.89), and the presence of an EAM (HR 1.62, 95% CI 1.24–2.11).

When stratified by the presence of certain comorbidities, differences in mortality risk were observed between patients with and without CVD or chronic lower respiratory disease. Similar findings were observed for patients with and without a history of smoking (Table 3).

Primary causes of death. Of the 285 deaths in patients with AS, CVD (n = 74, 26.0%) and cancer (n = 64, 22.5%) were the 2 most common primary causes of death. The risk of death as a result of

Table 1. Demographics and disease characteristics of patients with AS compared with a matched comparison group.

	AS Group, n = 1791	Comparison Group, n = 8955	*P*
Age at baseline, yrs, mean (SD)	48.5 (15.8)	48.5 (15.8)	0.97
Sex (base: male), n (%)	1020 (57.0)	5100 (57.0)	> 0.99
Aboriginal, n (%)	14 (0.8)	70 (0.8)	> 0.99
History of smoking, n (%)	875 (48.9)	3122 (34.9)	**< 0.001**
Extraarticular manifestations, n (%)			
Anterior uveitis	34 (1.9)	< 5 (< 0.1)	**< 0.001**
Inflammatory bowel disease	99 (5.5)	58 (0.7)	**< 0.001**
Osteoporosis	94 (5.3)	20 (0.2)	**< 0.001**
Psoriasis	38 (2.1)	15 (0.2)	**< 0.001**
Synovitis	120 (6.7)	28 (0.3)	**< 0.001**
Charlson Comorbidity Index, n (%)			**< 0.001**
0	1193 (66.6)	7478 (83.5)	
1	346 (19.3)	653 (7.3)	
2+	252 (14.1)	824 (9.2)	
Comorbidities, n (%)[a]			
Cardiovascular disease	718 (40.1)	2203 (24.6)	**< 0.001**
Valvular heart disease	18 (1.0)	45 (0.5)	**0.01**
Diabetes	113 (6.3)	335 (3.7)	**< 0.001**
Chronic kidney disease	26 (1.5)	38 (0.4)	**< 0.001**
Chronic lower respiratory infection	222 (12.4)	409 (4.5)	**< 0.001**
Liver disease	54 (3.0)	78 (0.9)	**< 0.001**

[a] Comorbidities recorded at hospitalization prior to and during the index AS event and at study entry. Values in bold are statistically significant. AS: ankylosing spondylitis.

Table 2. Mortality rates (per 1000 PY) in patients hospitalized with AS compared to non-AS comparison group.

	AS Group, n = 1791			Comparison Group, n = 8955			HR (95% CI)[b]
	Deaths, n	PY, n	Mortality Rates[a] (95% CI)	Deaths, n	PY, n	Mortality Rates[a] (95% CI)	
All-cause mortality	285	14,257	20.0 (17.8–22.5)	795	73,742	10.8 (10.1–11.6)	1.85 (1.62–2.12)
Sex-specific mortality							
Male mortality	175	8258	21.2 (18.3–24.6)	539	40,526	13.3 (12.2–14.5)	1.60 (1.35–1.90)
Female mortality	110	5999	18.3 (15.2–22.1)	256	33,217	7.7 (6.8–8.7)	2.38 (1.91–2.89)
Age-specific mortality, yrs							
18–39	14	5211	2.7 (1.6–4.5)	19	27,248	0.7 (0.4–1.1)	3.81 (1.90–7.59)
40–59	57	5973	9.5 (7.4–12.4)	145	29,098	5.0 (4.2–5.9)	1.94 (1.42–2.63)
60–79	214	3074	69.6 (60.9–79.6)	631	17,396	36.3 (33.5–39.2)	1.91 (1.64–2.23)
Charlson Comorbidity Index							
0	74	10,245	7.2 (5.8–9.1)	293	64,256	4.6 (4.1–5.1)	2.03 (1.57–2.62)
1	75	2645	28.4 (22.6–35.6)	143	5079	28.2 (23.9–33.2)	1.57 (1.18–2.09)
2+	136	1368	99.4 (84.0– 117.6)	359	4408	81.4 (73.4–90.3)	1.17 (0.96–1.42)
Year of index event							
1990–1994	84	3417	24.6 (19.8–30.4)	160	11,557	13.8 (11.9–16.2)	1.76 (1.35–2.29)
1995–1999	81	4056	20.0 (16.1–24.8)	117	11,562	10.1 (8.4–12.1)	1.96 (1.48–2.60)
2000–2004	57	2398	23.8 (18.3–30.8)	126	12,501	10.1 (8.5–12.0)	2.31 (1.69–3.16)
2005–2009	53	3543	15.0 (11.4–19.6)	127	10,149	12.5 (10.5–14.9)	1.19 (0.86–1.64)
2010–2014	10	843	11.9 (6.4–22.1)	59	4451	13.3 (10.3–17.1)	0.95 (0.49–1.86)

[a] HR per 1000 PY. [b] HR adjusted for age and sex, unless stratified by age or sex. AS: ankylosing spondylitis; HR: hazard ratio; PY: patient-years.

CVD ($P < 0.001$), respiratory disease ($P < 0.001$), cancer ($P < 0.001$), and infectious disease ($P < 0.0001$) was significantly higher in patients with AS compared to that of the matched comparison group (Table 4). The risk of death as a result of mental health disorders was also more than 2.5 times higher in patients with AS; however, the increase was not statistically significant ($P = 0.10$).

Table 3. Mortality rates per 1000 PY in patients hospitalized with AS compared to non-AS comparison group, stratified by comorbidities.

	AS Group, n = 1791			Comparison Group, n = 8955			HR (95% CI)[a]
	Deaths, n	PY, n	Mortality Rates[b] (95% CI)	Deaths, n	PY, n	Mortality Rates[b] (95% CI)	
Cardiovascular disease							
Yes	222	5014	44.3 (38.8–50.5)	429	15,878	27.0 (24.6–29.7)	1.80 (1.53–2.12)
No	63	9244	6.8 (5.3–8.7)	366	57,864	6.3 (5.7–7.0)	1.62 (1.24–2.12)
Diabetes							
Yes	38	712	53.4 (38.9–73.4)	86	2000	43.0 (34.8–53.1)	1.45 (0.99–2.13)
No	247	13,546	18.2 (16.1–20.7)	709	71,743	9.9 (9.2–10.6)	2.05 (1.77–2.37)
Chronic lower respiratory disease							
Yes	83	1480	56.1 (45.2–69.5)	108	2836	38.1 (31.5–46.0)	1.66 (1.25–2.21)
No	202	12,777	15.8 (13.8–18.1)	687	70,906	9.7 (9.0–10.4)	1.84 (1.57–2.15)
Smoking status							
History of smoking	167	6938	24.1 (20.7–28.0)	338	24,825	13.6 (12.2–15.1)	1.95 (1.62–2.35)
Never smoked	118	7319	16.1 (13.5–19.3)	457	48,918	9.3 (8.5–10.2)	1.95 (1.59–2.39)
Extraarticular manifestations							
Yes	74	2510	29.5 (23.5–37.0)	18	901	20.0 (12.6–31.70)	1.31 (0.78–2.20)
No	211	11,748	18.0 (15.7–20.6)	777	72,841	10.7 (9.9–11.4)	1.89 (1.63–2.20)

[a] HR adjusted for age and sex. [b] HR per 1000 PY. AS: ankylosing spondylitis; HR: hazard ratio; PY: patient-years.

Table 4. Cause-specific mortality (primary diagnosis) in patients with AS compared with non-AS matched comparison group.

Cause of Death	AS Group, n = 1791		Comparison Group, n = 8955		HR (95% CI)
	Deaths, n	Cumulative Incidence[a], %	Deaths, n	Cumulative Incidence[a], %	
Cardiovascular disease	74	4.6	72	0.9	5.32 (3.84–7.35)
Cancer	64	3.9	195	2.4	1.68 (1.27–2.23)
Respiratory disease	20	1.3	30	0.4	3.49 (1.98– 6.14)
Infectious disease	15	0.9	< 5	< 0.1	25.92 (7.50–89.56)
External causes	23	1.4	30	0.4	3.92 (2.28–6.77)
Mental health disorder	5	0.3	10	0.1	2.64 (0.90–7.74)

[a] Adjusted for the competing risk of deaths from other causes. AS: ankylosing spondylitis; HR: hazard ratio.

DISCUSSION

In this whole-population study, patients with AS had an increased risk of mortality compared to a matched comparison group of patients who were hospitalized, consistent with previously published research.[18] Compared to the matched comparison group, patients with AS were more likely to have EAMs and comorbidities. The presence of comorbidities and EAMs contributed to increased mortality in patients with AS.

The increased risk of mortality was observed in both male and female patients and within all age groups. Although mortality rates were low overall among patients in the youngest age category (18–39 yrs), the relative risk or hazard of death was highest (3-fold higher) among patients with AS in this age bracket compared to patients in the comparison group. An increased rate of death as a result of external causes in younger patients with AS has been reported before.[23,24] Interestingly, crude mortality rates in female patients with AS were slightly lower than those in males (18.3 compared with 21.2 deaths per 1000 PY), as was also reported by Exarchou et al.[18] However, the HR for death in female patients with AS was higher than that in male patients. This suggests that while absolute risk is lower in male patients with AS, female patients with AS are at a much higher risk of death than female comparators. Further, while there were clear differences in mortality risk between patients with AS and those in the comparator group who were first admitted to hospital prior to 2005, there was no significant difference between patients with AS and patients without AS from 2005 onward. This may be, in part, attributable to a reduced period of follow-up among patients with an index event in 2005 or later. Alternatively, it may be associated with changes in the treatment and management of AS resulting in better health outcomes, for example, with the introduction of TNF-α medications.

In patients with AS, the presence of EAMs, the presence of comorbidities, and a history of smoking were associated with an increased risk of mortality. However, the increased risk of death was commensurate with the risk for patients without AS. There was no significant difference in mortality rates between patients with AS and patients with inflammatory bowel disease who did not have AS. However, the numbers were relatively small.

In fitting with the current literature, the main primary causes of death observed were CVD, cancer, respiratory disease, and external causes, for which patients with AS were at significantly higher risk than their comparators.[18,25,26,27] Mortality associated with infectious disease was the primary cause of death in approximately 5.3% of deaths in the AS group, which is substantially lower than the 23.2% of deaths observed by Bakland et al,[28] but is consistent with the 5.0% of deaths observed by Exarchou et al.[18] In our present study, the risk of dying from infectious disease was much higher among patients with AS than among their comparators (HR 25.92), although this was based on small numbers with only 3 events in the comparison group. The high rates of mortality due to infectious disease are consistent with the elevated rates of serious infection that have been previously observed in patients with AS treated with TNF-α.[16,17]

Limitations exist with this study. As the data linkage process does not capture patients seen outside of hospital (eg, private practice) or during outpatient visits, there is the potential for selection bias in our study. By capturing only patients who were hospitalized, we have likely included patients who had more severe disease. Additionally, it is likely that some EAMs and comorbidities would not have been captured by the hospital data, particularly where the conditions were mild and/or well managed. Notably, the percentage of both uveitis and psoriasis appeared to be lower than what would typically be expected in an AS cohort. Unfortunately, there are currently no validation studies of the use of hospital data from the HMDC in the identification of patients with AS. However, one study found that 11.6% of patients with AS will present to hospital in a given year.[29] While this would indicate that our statewide data over a 20-year period will have captured a large proportion of existing patients with AS, some patients may not have been included in this study.

Additionally, the nature of our dataset did not allow for exact estimation of disease duration, clinical or laboratory measures of disease activity, or use of medication, which restricted our ability to adjust for these variables. The study also did not include a number of other patient characteristics, such as socioeconomic status, that may have differed between the 2 groups. Major strengths of this study include the large population-based cohort design with the use of a matched comparison group also requiring hospital care, the additional comparison with general population data, and the long-term follow-up, while linkage to the death register allowed for accurate estimation of causes of death.

In conclusion, there is a high presence of comorbidities and smoking among patients with AS who are hospitalized, which contributes to an increased risk of all-cause mortality. Reducing this mortality risk will require prevention or reduction of these factors in patients with AS.

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