Mortality rates in patients with ankylosing spondylitis with and without extra-articular manifestations and co-morbidities: A retrospective cohort study

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Abstract

Objectives: To examine the mortality rates in hospitalised patients with ankylosing spondylitis (AS), and the association of extra-articular manifestations (EAM) and co-morbidities with mortality rates.

Methods: The study was a retrospective population-based cohort study using linked administrative data of hospitalised AS patients (n=1,791) and a matched comparison group (n=8,955). Mortality data for patients were obtained from the Western Australian Death Register. The presence of EAM and co-morbidities were identified from hospital records. Mortality rates were compared between the two groups using Cox proportional hazard models, overall and stratified by a history of EAM, comorbidities and smoking status.

Results: Crude mortality rates were significantly higher in AS patients than the comparison group (HR:1.85, 95%CI:1.62-2.12) with excess mortality in the AS group associated with cardiovascular disease (HR:5.32, 95%: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 infections (HR:25.92, 95%CI:7.50-89.56). When patients were stratified by a history of EAM, cardiovascular disease, and smoking the risk of mortality was elevated in both patients with and without each risk factor. Within patients with AS, a history of cardiovascular disease (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 EAM (HR:1.62, 95%CI: 1.24–2.11) were associated with an increased risk of mortality.

Conclusion: The presence of co-morbidities, EAMs, and smoking contribute to an increased risk of all-cause mortality in hospitalised AS patients compared to the comparison group. These results support the need to prevent or reduce the occurrence of co-morbidity and smoking in AS patients.

Keywords: all-cause mortality, axial spondyloarthritis, co-morbidity, survival.

Introduction

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

The heritability of AS is estimated to be approximately 77%, with human leukocyte antigen-B27 (HLA B27) believed to contribute substantially to the high heritability [3]. While 80-95% of patients with AS have HLA-B27, only 1-2% of HLA-B27 positive patients develop AS [4-6], 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 have also been associated with the risk of EAM. For example, the presence of acute anterior uveitis is more common in AS patients with HLA-B27 than without [8]. Systemic inflammation may also contribute to the occurrence of EAM in patients with AS, with the incidence of EAM reported to be higher in AS patients with uncontrolled systemic inflammation [9]. Systemic inflammation may also contribute to the elevated risk of co-morbidities such as cardiovascular disease, in particular ischemic heart disease and valvular defects [10].

Lifestyle factors also contribute to the high prevalence of co-morbidities in AS patients. While exercise is recommended for patients with AS and is a protective factor for a range of co-morbidities including cardiovascular disease, the pain, fatigue and stiffness often experiences 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 less spinal mobility, higher disease activity, and poorer quality of life [13,14].

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

Given the wide-ranging effects of AS and associated co-morbidities, it is not surprising that AS is associated with elevated mortality rates [18,19]. However, it is unclear which aspects of AS associated EAMs, common co-morbidities and health behaviours (such as smoking) contribute to excess

mortality risk. The aim of this study was to compare mortality rates and causes of death between AS and non-AS patients, examining the extent to which EAM, common co-morbidities 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), identified from the Hospital Morbidity Data Collection (HMDC) within the WA Rheumatic Disease Epidemiological Register (WARDER). Within the HMDC, primary and up to 20 co-diagnoses are listed for each separation using the International Statistical Classification of Diseases and Related Health Problems, 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 the patient's first AS hospitalisation within the study period. A non-AS comparison cohort, matched (1:5) on age at the index admission (within 1 year), sex and Aboriginal status were also selected from the HMDC.

Study data

For each patient, mortality data were obtained from the WA Death Register from January 1990 to December 2015. The WA Death Register is a statutory data collection, encompassing all deaths within WA. EAM and co-morbidities were identified from in-patient 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 ICD-9-CM codes: 305.1, V15.82, V15.83, and ICD-10-AM codes: F17, Z72.0, Z86.43. Smoking codes in hospital data have been shown to have good specificities (93-97%) but lower sensitivity (45-74%) for ever smoked [20]. Despite these limitations, it was deemed an important variable to include in the study. EAM and co-morbidities identified within the HMDC dataset from diagnosis variables using ICD codes (supplementary table 1). 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 two groups at their index admission were summarised and compared using univariable logistic and linear regression.

Cox proportional hazard models were used to compare mortality rates in the two groups. For the comparison of mortality rates by smoking status and co-morbidities, age groups and sex were included as covariates in the model to account for discrepancies between the two groups. For the mortality analysis, patient follow-up was censored at death, the 31st of December 2015, or at 10 years of follow-up (whichever occurred first). The choice was made to censor data at a maximum of ten years, as beyond this point the assumption of proportionality did not hold (assessed using Schoenfeld residuals). Crude mortality rates were calculated and were expressed as number of deaths per 1,000 patient years. Additionally, mortality rates stratified by age of index event (18 to 39, 40 to 59, and 60 to 79 years), sex, smoking status, co-morbidities and year of index event (1990-94, 1995-99, 2000-04, 2005-09, and 2010-14) were also calculated. Cumulative incidence adjusting for competing risk of death were calculated for cause specific mortality. All analysis was carried out in Stata/IC version 15. P-values less than 0.05 were considered statistically significant (two-tailed).

Ethics

The study received ethics approval from the WA Department of Health Human Research Ethics Committee (WADOH HREC#: 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 1,791 AS patients (14,257 patient years) and 8,955 comparison group patients (73,742 patient years). 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%). AS patients were more likely to have a history of smoking and co-morbidities including diabetes and cardiovascular disease prior to their index event, compared with the comparison group (Table 1).

Mortality rates

Crude mortality rates in patients in the AS group were significantly higher than for 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 two groups, with

significant HRs occurring in patients prior to 2005, but no difference between the two groups with an index event in 2005 or later.

Within patients with AS, an increased risk of mortality was associated with having cardiovascular disease (HR: 6.33, 95%CI: 4.79 – 8.38), diabetes (HR: 2.81, 95%CI: 1.99 – 3.95), CLRD (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 co-morbidities, differences in mortality risk were observed between patients with and without cardiovascular disease, chronic lower respiratory disease. Similar was observed for patients with and without a history of smoking (Table 3).

Primary causes of death

Cardiovascular disease (n=74, 26.0%) and cancer (n=64, 22.5%) were the two most common primary causes of death in AS patients. The risk of death due to cardiovascular disease (p<0.001), respiratory (p<0.001), disease, cancer (p<0.001), and infection (p<.0001) was significantly higher in patients with AS compared with the matched comparison group (Table 4). The risk of death as a result of mental health disorders was also more than two and half times higher in patients with AS. However, the increase was not statistically significant (p=0.097).

Discussion

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

The increased risk of mortality was observed in both male and female patients, and within all age groups. Although mortality rates were overall low in the youngest age category (18-39 years), the relative risk/hazard of death was highest (3-fold higher) in AS patients in this age bracket compared with comparison group. An increased rate of death due to external causes in younger AS patients has been reported before [23,24]. Interestingly, crude mortality rates in female patients with AS were slightly lower than for males (18.3 compared with 21.2 deaths ptpy) as was also reported by Exarchou et. al. 2016 [18]. However, the HR for death in female AS patients was higher than that for male patients. This suggests that while absolute risk is lower than in male AS patients, females with AS are at a much higher risk of death than female comparators. Furthermore, while there were clear

differences in mortality risk in patients first admitted to hospital prior to 2005, there was no significant difference between AS and non-AS patients from 2005 onwards. This may be in part attributable to reduced period of follow up in patients with an index event from 2005. 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 medications.

In AS patients the presence of EAMs, co-morbidities and a history of smoking was 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 between mortality rates between AS patients and non-AS patients with inflammatory bowel disease. However, the numbers were relatively small.

In fitting with the current literature, the main primary causes of death observed regarded cardiovascular disease, cancer, respiratory disease and external causes for which AS patients were at significantly higher risk than comparators [18,25-27]. Mortality associated with infection was the primary cause of death in approximately 5.3% of death in the AS group, which is substantially lower than the 23.2% observed by Bakland et. al. (2011)[28] but consistent with the 5.0% observed by Exarchou et. al. (2016)[18]. The risk of dying from infectious disease was much higher in for AS patients than comparators (HR 25.0), although this was based on small numbers with only three events in the comparison group. The high rates of mortality due to infection are consistent with the elevated rates of serious infection have been previously observed in patients with AS treated with anti-TNF [16,17].

Limitations

Limitations exist with this study. As the data linkage process does not capture patients seen outside of hospital (e.g. private practice) or outpatient visits, there is the potential for selection bias in our study. Capturing only patients hospitalised, we have likely included patients who had more severe disease. Additionally, it is likely that some EAM and comorbidities would have 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 low 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 HMDS in the identification of AS patients. However, one study found that 11.6% of AS patients will present to hospital in a given year [29]. While this would indicate that our state-wide data over a 20-year period will have captured a large proportion of existing AS patients, some patients may not have been included in this study. .

Additionally, the nature of our data set did not allow 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 socio-economic status, that may have differed between the two groups. A major strength is 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 allowing accurate estimation of causes of death.

Conclusion

There is a high presence of co-morbidities and smoking in hospitalised AS patients, which contributes to increased risk of all-cause mortality. To reduce this mortality risk will require prevention or reduction of these factors in AS patients.

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Table 1: Demographics and disease characteristics of patients with ankylosing spondylitis (AS) compared with a matched comparison group.

	AS (n=1,791)	Comparison (n=8,955)	P-value
Age at baseline, mean (SD)	48.5 ± 15.8	48.5 ± 15.8	0.973
Sex (base: male), n (%)	1,020 (57.0%)	5,100 (57.0%)	> 0.999
Aboriginal, n (%)	14 (0.8%)	70 (0.8)	> 0.999
History of smoking, n (%)	875 (48.9%)	3,122 (34.9%)	**< 0.001**
Extra-articular 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			
0	1,193 (66.6%)	7,478 (83.5%)	**<0.001**
1	346 (19.3%)	653 (7.3%)	
2+	252 (14.1%)	824 (9.2%)	
Co-morbidities, n (%)[1]			
Cardiovascular disease	718 (40.1%)	2,203 (24.6%)	**< 0.001**
- Valvular heart disease	18 (1.0%)	45 (0.5%)	**0.013**
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**

1. Co-morbidities recorded at hospitalisation prior to and at/including the index AS event/study entry.

Table 2: Mortality rates (per 1000 patient years) in patients hospitalised with AS compared to non-AS comparison group.

	AS (n=1,791)			Comparison (n=8,955)			HR (95%CI)[2]
	No of deaths	Patient years	Mortality rates[1] (95%CI)	No of deaths	Patient years	Mortality rates[1] (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	8,258	21.2 (18.3, 24.6)	539	40,526	13.3 (12.2, 14.5)	1.60 (1.35, 1.90)
- Female mortality	110	5,999	18.3 (15.2, 22.1)	256	33,217	7.7 (6.8, 8.7)	2.38 (1.91, 2.89)
Age specific mortality							
- 18 to 39	14	5,211	2.7 (1.6, 4.5)	19	27,248	0.7 (0.4, 1.1)	3.81 (1.90, 7.59)
- 40 to 59	57	5,973	9.5 (7.4, 12.4)	145	29,098	5.0 (4.2, 5.9)	1.94 (1.42, 2.63)
- 60 to 79	214	3,074	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	2,645	28.4 (22.6, 35.6)	143	5,079	28.2 (23.9, 33.2)	1.57 (1.18, 2.09)
- 2+	136	1,368	99.4 (84.0, 117.6)	359	4,408	81.4 (73.4, 90.3)	1.17 (0.96, 1.42)
Year of index event							
- 1990 to 1994	84	3,417	24.6 (19.8, 30.4)	160	11,557	13.8 (11.9, 16.2)	1.76 (1.35, 2.29)
- 1995 to 1999	81	4,056	20.0 (16.1, 24.8)	117	11,562	10.1 (8.4, 12.1)	1.96 (1.48, 2.60)

- 2000 to 2004	57	2,398	23.8 (18.3, 30.8)	126	12,501	10.1 (8.5. 12.0)	2.31 (1.69, 3.16)
- 2005 to 2009	53	3,543	15.0 (11.4, 19.6)	127	10,149	12.5 (10.5, 14.9)	1.19 (0.86, 1.64)
- 2010 to 2014	10	843	11.9 (6.4, 22.1)	59	4,451	13.3 (10.3, 17.1)	0.95 (0.49, 1.86)

HR = hazard ratio,

1. per 1000 patient years
2. Hazard ratio adjusted for age and sex, unless stratified by age or sex.

Table 3: Mortality rates per 1,000 patient years (ptpy) in patients hospitalised with AS compared to non-AS comparison group, stratified by co-morbidities.

	AS (n=1,791)			Comparison (n=8,955)			HR (95%CI)[1]
	No of deaths	Patient years	Mortality ptpy (95%CI)	No of deaths	Patient years	Mortality ptpy (95%CI)	
Cardiovascular disease							
- Yes	222	5,014	44.3 (38.8, 50.5)	429	15,878	27.0 (24.6, 29.7)	1.80 (1.53, 2.12)
- No	63	9,244	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	2,000	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	1,480	56.1 (45.2, 69.5)	108	2,836	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	6,938	24.1 (20.7, 28.0)	338	24,825	13.6 (12.2, 15.1)	1.95 (1.62, 2.35)
- Never smoked	118	7,319	16.1 (13.5, 19.3)	457	48,918	9.3 (8.5, 10.2)	1.95 (1.59, 2.39)
Extra-articular manifestations							

- Yes	74	2,510	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)

1. Hazard ratio adjusted for age and sex.

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

	AS (n=1,791)		Comparison (n=8,955)		Hazard ratios
Cause of death	**No of deaths**	**Cumulative incidence[1]**	**No of deaths**	**Cumulative incidence[1]**	**(95%CI)**
Cardiovascular diseases	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)
Infection	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)

AS=ankylosing spondylitis.

1. Adjusted for the competing risk of deaths from other causes