







# The Risk and Consequences of Vertebral Fracture in Patients with Ankylosing Spondylitis: A Population-based Data Linkage Study

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**ABSTRACT. Objective.** To compare the long-term prevalence, incidence, and outcomes of vertebral fracture (VF) between ankylosing spondylitis (AS) patients and matched controls, including the role of extraarticular manifestations (EAM) and osteoporosis.

**Methods.** This was a statewide observational study using linked health data for 2321 patients with AS and 22,976 controls presenting to hospital from 1980 to 2015. Data were analyzed using incidence rates (per 1000 person-yrs) and ratios (IRR), multivariable Cox proportional hazards regression, and Kaplan-Meier survival curves.

**Results.** Over a median 13.92 (interquartile range 7.58–21.67) years of follow-up, patients with AS had a greater VF prevalence and greater incidence of developing a new VF compared to controls (9.3% vs 2.5%, 6.8% vs 1.9%, respectively, all  $P < 0.001$ ). Patients with AS had an increased risk of developing a VF after adjustments for age, sex, and osteoporosis (HR 2.55, 95% CI 2.11–3.09) compared to controls; this risk remained throughout the study period. Patients with AS were 5 years younger at time of first VF ( $P = 0.008$ ) and had a greater likelihood of a recurrent VF (IRR 4.64; 95% CI 4.54–4.75) compared to respective controls. Mortality overall was comparable between patients with AS and controls after adjustment for age, sex, osteoporosis, and VF status (HR 0.90; 95% CI 0.80–1.01).

**Conclusion.** The significantly increased risk of VF in patients with AS has not altered following the introduction of tumor necrosis factor inhibitor treatment. Although patients with AS experience a first VF at a younger age than controls, this does not lead to an increased risk of death.

*Key Indexing Terms:* ankylosing spondylitis, mortality, vertebral fractures

In ankylosing spondylitis (AS), chronic spinal inflammation contributes to bone loss and paravertebral calcification with syndesmophyte formation<sup>1</sup>. This can lead to a combination of spinal rigidity and reduced bone density, which increases the susceptibility of patients with AS to vertebral fracture (VF)<sup>1</sup>. The global prevalence of VF in patients with AS varies considerably (0.4–32%), mainly due to methodological differences<sup>2–11</sup>. Regardless of these varied prevalences of VF, an average 4-fold increased risk of VF in patients with AS compared to controls has been reported<sup>10</sup>.

Osteoporosis is an important and independent risk factor for the development of VF, with a reported prevalence between 19% and 61% in patients with AS<sup>12</sup>. Other extraarticular manifestations (EAM) in AS, including acute anterior uveitis (20–30%), psoriasis (10–25%), and inflammatory bowel disease (IBD; 5–10%)<sup>13</sup>, are increasingly important in the understanding of AS and can complicate disease management, including frequent use of corticosteroids. Yet there is limited information on the possible role of EAM in relation to VF risk.

The consequences of VF in cases of AS are highly unpredictable, with some patients incurring a spinal cord injury, some developing isolated functional neurological deficits, and others experiencing chronic pain, while VF itself can also be found incidentally or even go undiagnosed, as spinal pain is ascribed to AS flares<sup>14,15</sup>. Currently, there is limited longitudinal population-level data about VF in cases of AS.

The aim of our study was to estimate the prevalence, incidence, and risk factors for VF in patients with AS, including the roles of EAM and osteoporosis, and to determine the effect of VF on survival in a large population-based cohort in Western Australia, during the pre- and post-tumor necrosis factor inhibitor (TNFi) treatment eras.

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## MATERIALS AND METHODS

Our population-based observational study used routinely collected administrative health data linked through the Western Australian Data Linkage System<sup>16</sup> and stored in the Western Australian Rheumatic Disease Epidemiological Registry (WARDER). The WARDER database contains all private and public hospital separations in the state (emergency department presentation and inpatient episodes) for all individuals with a rheumatic disease ( $n \geq 200,000$ ) and a matched group of individuals free of rheumatic diseases ( $n \geq 200,000$ ) from January 1, 1980, to December 31, 2015, or date of death. Probabilistic matching achieved 99.7% accuracy<sup>16</sup> in identifying individuals across 4 linked datasets [Hospital Morbidity Data System (HMDS), WA Cancer Registry, WA Mortality Registry, and the Emergency Department Data Collection]. Date of death was extracted from WA Mortality and Cancer Registries. Approval for use of deidentified data was obtained from the Human Research Ethics Committee at the WA Department of Health (WADOH HREC#: 2016.24). Patient informed consent was not required in accordance with the policy of our institution because of completely anonymous data.

**Study population.** Patients with a diagnosis of AS were identified in the HMDS by the presence of at least one of the following International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) or ICD, 10th revision, Australian Modification (ICD-10-AM) codes: 720.0 (ICD-9-CM), M45.00-M45.09, or M08.10-M08.19 (ICD-10-AM). The ICD-10-AM (from coding implementation July 1, 1999, to December 31, 2015) provided coding for specific locations (cervical: C1–C7; thoracic: T1–T12; lumbar: L1–L5; and postmenopausal osteoporotic VF) of fractures along the vertebrae. The single ICD-9-CM code has been shown to have high sensitivity (91%) and specificity (99%) for AS in administrative data<sup>17</sup>. All ICD codes for AS, VF<sup>18</sup>, and EAM<sup>19,20,21</sup> were verified by the clinical coding department at WA Health and are available in Appendix 1. Patients with AS were matched up to 10 controls with no record of rheumatic disease using the WA Electoral Roll data throughout the entire observation period, according to year of birth per 5-year blocks, sex, Indigenous status, and year of the first hospital contact for AS. The first hospital contact for AS was defined as the baseline.

As controls were sourced from the WA Electoral Roll (introduced in 1988), we included only individuals alive at January 1, 1995, in mortality analyses to ensure sufficient lead time for stabilization of mortality across study groups. Patients with a date of diagnosis on or prior to January 1, 1995, entered the study on January 1, 1995, while patients with a date of diagnosis after January 1, 1995, were included from that date. All patients and controls were followed until December 31, 2014, or date of death.

**Statistical analyses.** Continuous variables were described with a median and IQR and compared with Mann-Whitney U tests. Categorical variables were described as a frequency (proportions) and compared by chi-square test or Fisher exact test ( $n < 5$ ). Developed characteristics were defined as presented at or after the baseline date and not present before baseline.

Incidence rates were expressed as number of patients with VF or (re) fractures per 1000 person-years (PY) at risk, presented as incidence rate ratio (IRR). The 95% CI from the IRR were derived from the Poisson regression models. PY was calculated from baseline to date of first VF, December 31, 2015, or date of death. Overall IRR is presented as number of patients developing a VF, while for refractures it is presented as total VF events (after excluding first VF event) out of the VF (developed) cohort in AS compared to controls.

Time-dependent risk for developing a VF in patients with AS compared to controls was determined by multivariable Cox proportional hazards regression models and presented as hazard ratios (HR) with corresponding confidence intervals (95% CI). Cox regression modeling included unadjusted (age-sex matched) and adjusted for sex, osteoporosis, and age at

cohort entry as the time-dependent predictor. We describe the median (IQR) time to a VF within the fractured cohort. Additionally, we compared specific levels of VF between patients with AS and controls who developed a VF between July 1, 1999, and December 31, 2015.

Kaplan-Meier survival curves for patients with AS and controls with VF were calculated from date of first developed VF (“time zero”) and analyzed by the log-rank test. We also used multivariable Cox proportional hazards regression models to calculate time-dependent mortality risk for the entire cohort, presented as HR (95% CI) and additionally adjusted (after sex, osteoporosis, and age as a time-dependent predictor) VF status as time of exposure after first VF event between January 1, 1995, and December 31, 2014 (or 0 for patients who did not sustain a VF), as a time-dependent predictor.

All regression models were stratified in 5-, 10-, or 15-year blocks to observe associations across the pre- (1980–1999) and post- (2000–2015) TNFi treatment era. We refined the year of cohort entry for analyses for the stratified year blocks. For example, in the 1990–1999 year block, time of entry was January 1, 1990, or first hospital contact (if date was between 1990–1999) to December 31, 1999, or date of death (if between 1990–1999). EAM were included as potential predictors for VF and mortality by applying backward regression models, retaining variables with a  $P < 0.100$  for each outcome. We tested for multiple interactions where independent variables had  $P < 0.05$  in the regression models. All analyses were performed using IBM SPSS 24.0 (IBM Corp.), except for the calculation of IRR using Stata v15 (StataCorp.)  $P$  values  $< 0.05$  were considered statistically significant (2-tailed).

## RESULTS

A total of 2321 patients with AS and 22,976 matched non-AS controls presenting to WA hospitals throughout 1980–2015 were included and accounted for a total median 13.92 (IQR 7.58–21.67) years followed up (range 0–35 yrs).

Patients with AS were 50 (IQR 37–65) years of age at baseline, mostly male (59%), and presented with significantly more EAM than controls (1.7–7.0% vs 0.1–1.6%,  $P < 0.001$ , Table 1). We observed a 9.3% ( $n = 215$ ) overall prevalence of VF in patients with AS compared to 2.5% ( $n = 573$ ) in controls ( $P < 0.001$ ), observing in the fractured cohort a median of 8 (IQR 2.92–15.00) years of follow-up (range 0–33.92 yrs) until the first VF, and 3.17 (IQR 0.92–7.58) years of follow-up (range 0–35 yrs) after the first VF. Patients with AS accrued more VF at baseline ( $n = 58$ , 2.5% vs  $n = 135$ , 0.6%,  $P < 0.001$ ) and developed more VF ( $n = 157$ , 6.8% vs  $n = 438$ , 1.9%;  $P < 0.001$ ) across all spinal regions (Table 1) compared to controls. Patients with AS developed their first VF at 71 (IQR 58–82) years of age, 5 years earlier than controls ( $P = 0.008$ ), and had significantly more traumatic spinal cord injuries (16% vs 2%,  $P < 0.001$ ).

Patients with AS had a greater prevalence of osteoporosis than controls ( $n = 262$ , 11.3% vs  $n = 512$ , 2.3%;  $P < 0.001$ ). AS patients with osteoporosis were 10 years younger at their first hospital contact (52 yrs, IQR 39–62) than controls (62 yrs IQR 53–69;  $P < 0.001$ ). Among those who accrued a VF at baseline, osteoporosis was more frequent in patients with AS than in controls (55% vs 16%,  $P < 0.001$ ).

Patients with AS had an increased risk of developing VF in the unadjusted (HR = 3.88; 95% CI: 3.24, 4.67) and age-sex adjusted models (HR 4.46, 95% CI 3.71–5.36), and remained

Table 1. Characteristics at baseline visit and during follow-up for patients with AS and controls.

| AS Patients,                          | Baseline Characteristics |             |                   | Developed Characteristics at Follow-up |                    |         |
|---------------------------------------|--------------------------|-------------|-------------------|--|--------------------|---------|
|                                       | Controls,<br>N = 2321    | N = 22,976  | AS Patients,<br>P | Controls,<br>N = 2321                  | N = 22,976         | P       |
| Age, yrs                              | 50 (37–65)               | 52 (39–66)  | < 0.001           |  |                    |         |
| Yrs observed                          |                          |             |                   | 11.83 (6.25–21.17)                     | 14.08 (7.75–21.75) | < 0.001 |
| Sex                                   |                          |             | 0.823             |  |                    |         |
| Male                                  | 1377 (59)                | 13,686 (60) |                   |  |                    |         |
| Female                                | 944 (41)                 | 9290 (40)   |                   |  |                    |         |
| Indigenous status                     | 16 (0.7)                 | 104 (0.5)   | 0.114             |  |                    |         |
| Osteoporosis                          | 93 (4)                   | 83 (0.4)    | < 0.001           | 169 (7.3)                              | 429 (1.9)          | < 0.001 |
| Single VF                             | 34 (1.5)                 | 108 (0.5)   | < 0.001           | 88 (3.8)                               | 313 (1.4)          | < 0.001 |
| Multiple VF                           | 24 (1)                   | 27 (0.1)    | < 0.001           | 69 (3)                                 | 125 (0.5)          | < 0.001 |
| Total with VF                         | 58 (2.5)                 | 135 (0.6)   | < 0.001           | 157 (6.8)                              | 438 (1.9)          | < 0.001 |
| Total patients by VF location         |                          |             |                   |  |                    |         |
| Cervical                              | 5 (0.2)                  | 21 (0.1)    | 0.076             | 41 (1.8)                               | 47 (0.2)           | < 0.001 |
| Thoracic                              | 15 (0.6)                 | 43 (0.2)    | < 0.001           | 38 (1.6)                               | 113 (0.5)          | < 0.001 |
| Lumbar                                | 12 (0.5)                 | 48 (0.2)    | 0.004             | 33 (1.4)                               | 135 (0.6)          | < 0.001 |
| Sacral and coccyx                     | 7 (0.3)                  | 14 (0.1)    | < 0.001           | 14 (0.6)                               | 30 (0.1)           | < 0.001 |
| Unspecified                           | 3 (0.1)                  | 5 (0.02)    | 0.006 *           | 13 (0.6)                               | 25 (0.1)           | < 0.001 |
| Osteoporotic pathological             | 28 (1.2)                 | 21 (0.1)    | < 0.001           | 50 (2.2)                               | 153 (0.7)          | < 0.001 |
| Extraarticular disease manifestations |                          |             |                   |  |                    |         |
| Synovitis                             | 93 (4)                   | 54 (0.2)    | < 0.001           | 107 (4.6)                              | 97 (0.4)           | < 0.001 |
| Psoriasis                             | 162 (7)                  | 368 (1.6)   | < 0.001           | 140 (6)                                | 350 (1.5)          | < 0.001 |
| Inflammatory bowel disease            | 132 (5.7)                | 229 (1)     | < 0.001           | 227 (9.8)                              | 738 (3.2)          | < 0.001 |
| Anterior uveitis                      | 40 (1.7)                 | 14 (0.1)    | < 0.001           | 72 (3.1)                               | 26 (0.1)           | < 0.001 |

Values expressed as median (IQR) or n (%). \* Fisher exact test. AS: ankylosing spondylitis; VF: vertebral fractures; IQR: interquartile range.

elevated but attenuated after adjustment for osteoporosis (HR 2.55; 95% CI 2.11–3.09; Table 2). A greater risk of AS patients for developing a VF was strongly reduced after the 1980s (HR 6.11, 95% CI 3.44–10.86) to an HR of 1.75 (95% CI 1.13–2.70) during the 1990s, and an HR of 2.33 (95% CI 1.85–2.92) from 2000 to 2015. The EAM did not independently predict the risk of VF development in AS patients. There were no interactions observed for age, sex, and osteoporosis (all  $P > 0.10$ ).

The VF incidence rates were 4.49/1000 PY in the AS cohort and 1.14/1000 PY in controls over 34,938 PY and 381,010 PY of follow-up, respectively, resulting in an overall IRR of 3.94 (95% CI 3.69–4.21) for patients with AS developing a VF compared to controls. The incidence rates for refracture in patients with AS were 43.32/1000 PY and 9.33/1000 PY in controls (IRR 4.64, 95% CI 4.54–4.75).

Among the 157 patients with AS who developed a VF, 56% ( $n = 88$ ) had a single VF and 44% ( $n = 69$ ) had multiple VF. In AS patients with a single VF, thoracic fractures were the most

common ( $n = 17$ , 19%), followed by cervical ( $n = 15$ , 17%), lumbar ( $n = 13$ , 15%), and sacral and coccyx ( $n = 6$ , 7%). For AS patients with multiple VF, cervical fractures were the most common ( $n = 26$ ), followed by thoracic ( $n = 21$ ), lumbar ( $n = 20$ ), unspecified VF ( $n = 13$ ), and sacral and coccyx ( $n = 8$ ). Table 3 shows patients with AS developed significantly more cervical fractures located at C3–C7 compared to controls with a VF (1999–2015).

Among 130 AS patients with a first VF occurring from 1995, 68 deaths were observed (52% vs 57% in controls,  $P = 0.434$ ) and survival time from first developed VF was slightly higher for patients with AS than controls at 1, 5, 10, and 15 years (80% vs 75%, 57% vs 44%, 40% vs 29%, and 30% vs 27%, respectively;  $P = 0.048$ ; Figure 1). Overall mortality risk was comparable between patients with AS and controls after adjustment for age, sex, and osteoporosis (HR 0.90, 95% CI 0.80–1.01), and remained after further adjustment for VF status (HR 0.91, 95% CI 0.81–1.02; Table 4). Patients with AS were at greater risk of

Table 2. Cox regression model for vertebral fracture risk in AS patients compared to controls.

|              | Crude HR (95% CI) | P       | Adjusted HR (95% CI) * | P       |
|--------------|-------------------|---------|------------------------|---------|
| AS           | 3.88 (3.24–4.67)  | < 0.001 | 2.55 (2.11–3.09)       | < 0.001 |
| Time periods |                   |         |                        |         |
| 1980–1989    | 5.75 (3.29–10.03) | < 0.001 | 6.11 (3.44–10.86)      | < 0.001 |
| 1990–1999    | 3.14 (2.08–4.73)  | < 0.001 | 1.75 (1.13–2.70)       | 0.011   |
| 2000–2015    | 3.94 (3.18–4.88)  | < 0.001 | 2.33 (1.85–2.92)       | < 0.001 |

\* Adjusted for age, sex, and ever had osteoporosis. AS: ankylosing spondylitis.

Table 3. Level of developed vertebral fractures between AS and controls for period 1999–2015.

|                                      | AS Patients, N = 117 | Controls, N = 315 | P       |
|--------------------------------------|----------------------|-------------------|---------|
| Cervical fractures                   |                      |                   |         |
| C1                                   | 1 (0.9)              | 6 (1.9)           | 0.680 * |
| C2                                   | 5 (4.3)              | 12 (3.8)          | 0.826   |
| C3                                   | 5 (4.3)              | 3 (1)             | 0.037 * |
| C4                                   | 7 (6)                | 4 (1.3)           | 0.011 * |
| C5                                   | 8 (6.8)              | 4 (1.3)           | 0.004 * |
| C6                                   | 14 (12)              | 9 (2.9)           | < 0.001 |
| C7                                   | 9 (7.7)              | 8 (2.5)           | 0.014   |
| Thoracic fractures                   |                      |                   |         |
| T1–T2                                | 4 (3.4)              | 9 (2.9)           | 0.756 * |
| T3–T4                                | 1 (0.9)              | 3 (1)             | 1.000 * |
| T5–T6                                | 1 (0.9)              | 13 (4.1)          | 0.125 * |
| T7–T8                                | 4 (3.4)              | 17 (5.4)          | 0.462 * |
| T9–T10                               | 3 (2.6)              | 12 (3.8)          | 0.768 * |
| T11–T12                              | 10 (8.5)             | 32 (10.2)         | 0.615   |
| Lumbar fractures                     |                      |                   |         |
| L1                                   | 13 (11.1)            | 42 (13.3)         | 0.538   |
| L2                                   | 8 (6.8)              | 33 (10.5)         | 0.252   |
| L3                                   | 5 (4.3)              | 22 (7)            | 0.301   |
| L4                                   | 1 (0.9)              | 16 (5.1)          | 0.051 * |
| L5                                   | 1 (0.9)              | 6 (1.9)           | 0.680 * |
| Postmenopausal osteoporotic fracture | 0                    | 1 (0.3)           | 1.000 * |

\* Fisher exact test. Values expressed as n (%) unless otherwise specified. AS: ankylosing spondylitis; IQR: inter-quartile range.

mortality between 1995–1999 (HR 1.31, 95% CI 1.06–1.60) and 2000–2004 (HR 1.23, 95% CI 1.01–1.49) after adjustment for age, sex, osteoporosis, and VF status (Table 4). None of the EAM were independent risk factors of mortality.

## DISCUSSION

Our population-based study demonstrated that the increased risk of sustaining a VF in patients with AS has remained unchanged over the last 35 years. Patients with AS developed their first VF 5 years earlier, but this did not increase the risk of death compared to people without the condition.

Only 2 earlier studies, to our knowledge, have also compared long-term outcomes of VF in patients with AS and controls. A Swedish longitudinal cohort spanning 22 years, including pre- and post-TNFi era, found that 4% of 17,764 patients with AS have had a VF, and that the proportion admitted to hospital increased from 0.8% in 1987 to 11.3% in 2008<sup>22</sup>. While this confirms that long-term observations are important to accurately estimate VF prevalence and risk, the study did not adjust for predisposing factors such as age, sex, and diagnosis of osteoporosis as performed here, thereby complicating comparisons. A Danish case-control study<sup>8</sup> found patients with AS who have had the disease for over 10 years to be at increased odds (OR 4.21, 95% CI 1.78–9.96) of a VF after adjusting for fracture history, annual income, social status, working status, educational status, alcohol, medication, and number of consultations to general practitioners. We observed an unadjusted risk of nearly 4-fold of sustaining a VF in patients with AS, which is congruent with the

Danish study and a metaanalysis<sup>10</sup> that reported a pooled OR of 4.25 (95% CI 1.07–7.42) based on 6 case-control studies.

A large primary care nested case-control study from the United Kingdom<sup>9</sup> also reported that patients with AS were at almost 3-fold higher odds of VF, and in contrast to our study, found IBD to be a significant risk factor. A population-based parallel cohort study from Spain<sup>7</sup> also found patients with AS with a median 5-year disease duration at almost doubled risk for VF after adjusting for smoking, alcohol, body mass index, and use of oral corticosteroids. The contribution of osteoporosis was not reported in these 2 studies.

While the VF prevalence of 9.3% in our study is comparable to that in the Swedish study and a number of previous reports<sup>5,6,10,23–25</sup>, it is much lower than in some studies that report a prevalence up to 40%<sup>2,26</sup>. While many of these other studies included patients with shorter disease duration, the differences can be explained by methodological variations due to patient selection, study design, and the lack of a universal gold standard in assessing the presence of a VF. Most studies reporting high VF prevalence assessed VF according to the Genant method<sup>27</sup>, which is sensitive and not widely used clinically in assessment by routine radiology<sup>28</sup>.

Our patients with AS also continue being at high risk for VF after point of introduction for TNFi treatment. Metaanalyses and systematic reviews demonstrate that TNFi medication improves disease activity (Bath Ankylosing Disease Activity Index), physical function (Bath AS Functional Index), vertebral mobility (Bath AS Metrology Index), and body mineral density

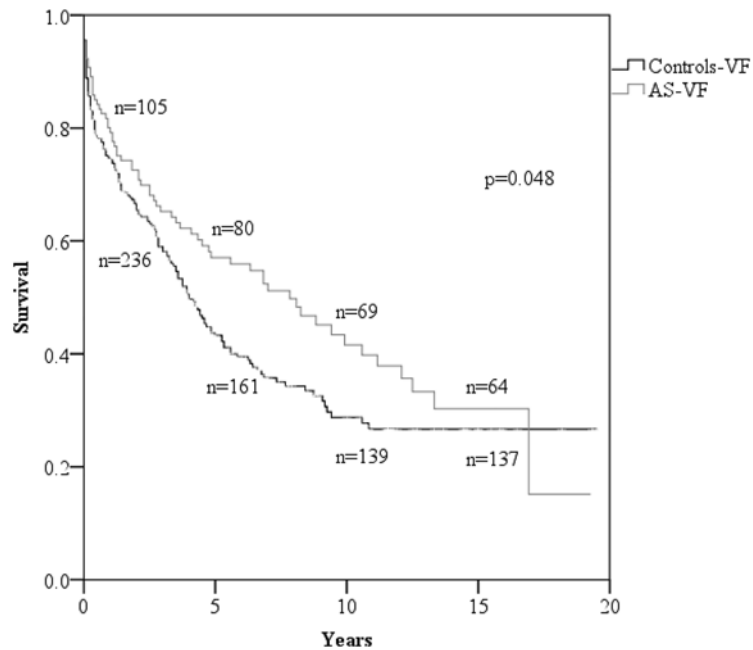


Figure 1. Kaplan-Meier survival curves between patients with ankylosing spondylitis (AS) and controls after developing their first vertebral fracture (VF) from 1995 to 2014.

Table 4. Cox regression model for risk of death in AS patients compared to controls for the period 1995 to 2014.

|              | Unadjusted HR<br>(95% CI) | P       | Multivariable Adjusted <sup>1</sup> HR<br>(95% CI) | P     | Multivariable Adjusted <sup>2</sup> HR<br>(95% CI) | P     |
|--------------|---------------------------|---------|--|-------|--|-------|
| AS           | 1.23 (1.12–1.34)          | < 0.001 | 0.90 (0.80–1.01)                                   | 0.066 | 0.91 (0.81–1.02)                                   | 0.099 |
| Time periods |                           |         |  |       |  |       |
| 1995–1999    | 1.13 (0.92–1.38)          | 0.251   | 1.31 (1.07–1.60)                                   | 0.010 | 1.31 (1.06–1.60)                                   | 0.010 |
| 2000–2004    | 1.20 (0.99–1.45)          | 0.057   | 1.22 (1.01–1.48)                                   | 0.040 | 1.23 (1.01–1.49)                                   | 0.033 |
| 2005–2009    | 1.19 (1.00–1.42)          | 0.052   | 1.04 (0.87–1.25)                                   | 0.663 | 1.05 (0.88–1.26)                                   | 0.603 |
| 2010–2014    | 1.37 (1.17–1.61)          | < 0.001 | 1.12 (0.95–1.32)                                   | 0.188 | 1.13 (0.96–1.33)                                   | 0.156 |

<sup>1</sup> Multivariable model adjusted for age, sex, and osteoporosis. <sup>2</sup> Multivariable model further adjusted for VF status (time exposed after first VF) as a time-dependent predictor. AS: ankylosing spondylitis; VF: vertebral fractures.

(BMD) in patients with AS, and possibly reduces radiographic progression<sup>29,30,31</sup>. However, none of these studies observed VF as an outcome and our data cannot corroborate that the use of TNFi will be protective against developing a VF. In fact, some studies reported that despite improvements in BMD and disease activity following TNFi treatment over 4 years, the incidence of VF increased by 20%<sup>32</sup>, 8.6%<sup>33</sup>, and 18.4% after 2 years using etanercept treatment<sup>34</sup>. Given the variable case mix in our and other studies, long-term studies of patients with AS treated with TNFi for early disease with no structural damage will be required to delineate the effect of biological drugs on VF risk in patients with AS.

The extent to which osteoporosis develops and contributes to VF risk in AS is currently unclear. While the overall osteoporosis prevalence of 11% in our AS cohort was less than the 21% and 25% reported in prospective studies<sup>3,12,24,35</sup>, osteoporosis was mostly developed after first hospital contact for AS (baseline).

This suggests that restricted screening for osteoporosis occurs in AS, and may be related to the fact that BMD measurement is not fully reliable in AS due to the occurrence of calcifications. While active inflammation at spinal entheses may lead to release of cytokines, some of which are known to have negative local/systematic effects on bone turnover<sup>36</sup>, we found that even after accounting for osteoporosis, the risk of VF in patients with AS was over double than in controls and the risk of subsequent VF over 4 times higher. This suggests factors other than osteoporosis<sup>37,38,39,40,41</sup>, such as paraspinal calcification, syndesmophyte formation, and subsequent ankylosis, may contribute to increased VF risk in AS<sup>41</sup>.

The more than 4-fold risk of sustaining multiple VF events in patients with AS supports the widely accepted relationship between the number and severity of VF (silent or clinical) with an increased risk of new fractures in AS<sup>42</sup>. While the nature of ICD coding provides only for “one” or “2 or more” fractures

for each region, we found that in patients with AS, a single VF most commonly occurred in the thoracic spine, and multiple VF mostly in the cervical spine. A retrospective study from the National Inpatient Sample in the United States through 2005–2011 and a Danish self-administered questionnaire also found cervical fractures, followed by thoracic fractures, to be most common in individuals diagnosed with AS<sup>25,43</sup>. In contrast, other studies<sup>40,44</sup> found thoracic fractures to be most common for these patients. The differences in rates between thoracic and cervical fractures may also be partially explained by the cervicothoracic transition zone, which may be difficult to visualize on conventional radiography and lead to misclassification<sup>45</sup>.

Our long-term observations demonstrate comparable mortality in patients with AS and controls with VF. While there are no studies for direct comparison, a systematic review<sup>15</sup> also found mortality comparable to that of patients with diffuse idiopathic skeletal hyperostosis just below an average 12 months of follow-up. Four studies reported greater in-hospital mortality among AS patients with a VF; however, these studies may be underpowered as they only observed in-hospital mortality with shorter time periods, and 2 of the studies had a very low number of patients with different study designs<sup>14,25,46,47</sup>. Further studies are therefore warranted to conclude the role of VF in AS mortality.

These results need to be considered in light of the limitations in our study. Due to the nature of our data capture, we did not have accurate data on overall disease duration or severity at index visit. Despite the high specificity of ICD coding and a sizeable cohort, it is possible we have underestimated given that AS patients with VF may have been misdiagnosed with a disease flare and then not referred to hospital or the emergency department, as we did not capture patients not requiring hospital care. The nature of ICD coding limits our ability to extract complete data on serological biomarkers, AS disease activity, BMD scores, and the role of medication in explaining the risk and risk factors for VF and death. A major strength of our study is the population-based design with the use of a matched control grouping and the long-term observation with linkage to the death registry to study associations with VF and survival. Also, Australia funds its public hospitals under a prospective payments system using diagnostic-related groups as a strong incentive for accurate coding, and we ensured that the specific ICD codes for definition of the diseases were validated by other studies<sup>17,48</sup>, as well as the Western Australian Data Linkage Branch Coding Department.

Patients with AS remain at significantly increased risk of sustaining single and multiple VF despite the introduction of TNFi medication. Osteoporosis did not fully explain the increased VF risk in patients with AS. Although patients with AS sustained a first VF 5 years earlier than controls, they were not at increased risk for mortality. We recommend further population-based longitudinal studies on exposure to TNFi medication to confirm whether this reduces the risk of VF in patients with AS.

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APPENDIX 1. ICD-9 and ICD-10-AM coding.

|                                    | ICD-9<br>Jan 1, 1979–Dec 31, 1987                            | ICD-9-CM and *Australian versions<br>Jan 1, 1988–Jun 10, 1995                                      | ICD-10-AM<br>Jul 1, 1999–Current  |
|------------------------------------|--|--|---|
| Ankylosing spondylitis             | 720.0  | 720.0  | M45.00–M45.09, M08.10–M08.19  |
| Anterior uveitis                   | 360.1, 363.0, 363.1, 364.0, 364.10,<br>364.11, 364.21, 364.3 | 053.22, 054.44, 091.50, 091.52,<br>098.41, 360.11, 364.00–364.05, 364.10,<br>364.11, 364.21, 364.3 | H20.0, H20.1, H20.8, H44.1  |
| Psoriasis                          | 528.6, 696.1   | 528.6, 696.1   | L40.0–L40.4, L40.8  |
| Psoriatic arthritis                | 696.0  | 696.0  | L40.5   |
| Inflammatory bowel disease         | 555.0–555.2, 555.9, 556,<br>557.0, 557.1, 557.9, 558         | 555.0–555.2, 555.9, 556,<br>*556.0–556.9, 557.0, 557.1, 557.9, 558.9                               | K50.0, K50.1, K50.8, K50.9,<br>K51.0–K51.9, K52.3, K52.8, K52.9,<br>U84.1, U84.2  |
| Synovitis                          | 712.0–712.2, 712.9, 719.2,<br>727.0, 727.2                   | 095.7, 098.51, 712.10–712.29,<br>712.80–712.99, 719.20–712.29, 727.00,<br>727.01, 727.2            | M01.10–M01.19, M10.00–M10.09,<br>M12.20–M12.29, M49.00–M49.09,<br>M65.10–M65.19, M65.80–M65.99,<br>M67.30–M67.39, M68.00–M68.09,<br>M70.0, M70.8, M70.9 |
| Vertebral fractures                |  |  |   |
| Cervical fracture                  | 805.0, 805.1, 806.0, 806.1                                   | 805.00–805.18, 806.00–806.19,  | S12.0, S12.1, S12.21–12.25, S12.7–S12.9,<br>M48.41–M48.43, M49.51–M49.53  |
| Thoracic fracture                  | 805.2, 805.3, 806.2, 806.3                                   | 805.2, 805.3, 806.20–806.39  | S22.00–S22.06, S22.1, S22.2, M48.44, M48.45,<br>M48.54, M48.55, M49.54  |
| Lumbar fracture                    | 805.4, 805.5, 806.4, 806.5                                   | 805.4, 805.5, 806.4, 806.5   | S32.00–S32.05, S32.7, S32.82, M48.46, M48.47,<br>M49.56, M49.57   |
| Sacrum and coccyx fracture         | 805.6, 805.7, 806.6, 806.7                                   | 805.6, 805.7, 806.60–806.62, 806.69,<br>806.70–806.72, 806.79                                      | S32.1, S32.2, M48.48, M49.58  |
| Unspecified region fracture        | 805.8, 805.9, 806.8, 806.9                                   | 805.8, 805.9, 806.8, 806.9   | M48.49, M49.59, T08.0, T08.1  |
| Osteoporotic pathological fracture |  | 733.1, *733.13,  | M80.08, M80.18, M80.28, M80.38,<br>M80.48, M80.58, M80.88, M80.98   |

\* ICD-9-CM Australian version only codes. ICD-9-CM Australian version 1st and 2nd editions were implemented July 1, 1995, to June 30, 1999. ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; ICD-10-AM: ICD, 10th revision, Australian Modification.