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Cervical Spinal Fracture and Other Diagnoses Associated With Mortality in Hospitalized Ankylosing Spondylitis Patients

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Objective. Little data exist regarding mortality in ankylosing spondylitis (AS). We assessed diagnoses associated with in-hospital mortality in AS using a population-based inpatient data set.

Methods. Data were abstracted from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample between 2007 and 2011. We identified AS admissions using International Classification of Diseases, Ninth Revision, Clinical Modification code 720.0. In-hospital mortality was the primary outcome. Logistic regression was used to evaluate the association between top diagnoses and in-hospital mortality. We performed a secondary analysis from the same years in all patients (with and without AS) with cervical spine (C-spine) fracture to determine whether AS was an independent risk factor for mortality.

Results. Between 2007 and 2011, we identified 12,484 admissions and 267 deaths in AS patients. C-spine fracture with spinal cord injury and sepsis had the highest odds of death, with odds ratios (ORs) of 13.43 (95% confidence interval [95% CI] 8.00–22.55, $P < 0.0001$) and 7.63 (95% CI 5.62–10.36, $P < 0.0001$), respectively. In the same time period, there were 53,606 C-spine fracture admissions, of which 408 were coded with AS. Among all C-spine fracture hospitalizations, an AS diagnosis was associated with inpatient death (OR 1.61 [95% CI 1.16–2.22], $P = 0.004$).

Conclusion. In AS patients admitted to the hospital, C-spine fracture is a leading cause of in-hospital mortality. Other diagnoses associated with mortality include sepsis, pneumonia, cardiovascular disease, and comorbid illnesses. Among all hospitalizations with C-spine fracture, AS was associated with increased odds of death. C-spine fracture–associated mortality warrants further study to elucidate risk factors in order to prevent such devastating fractures in AS patients.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the sacroiliac joints and spine. Extraarticular manifestations and comorbidities are common and include uveitis, inflammatory bowel disease, and psoriasis. Other complications include cardiovascular disease (CVD), osteoporosis,

and fracture. Studying mortality in AS is difficult because of the low disease prevalence and because the disease is not usually the primary cause of death.

During the era of radiation treatment for AS, Weiss et al demonstrated that radiation-treated patients had an increased risk of death attributed to cancer, notably leukemia. Patients who did not receive radiation therapy, however, had mortality rates similar to those of the general population (1). The majority of studies in the postradiation-treatment era have shown increased mortality rates in AS when compared to the general population, with standardized mortality ratios between 1.32 and 3.07 (2–7). Using hazard ratios (HRs), a study of Swedish AS patients found increased mortality compared to controls (HR 1.60 [95% confidence interval (95% CI) 1.44–1.77]) (8). The etiologies of this excess mortality are not uniform, although there are commonalities, including cardiovascular and cerebrovascular disease, pulmonary disease, infections, and malignancy (2–5,8,9). There are few contemporaneous studies on mortality in AS and no population-based data in the US. In addition, most studies have been small and were published in the pre-tumor necrosis factor inhibitor era.

Vertebral fracture is a known complication of AS, carrying an estimated lifetime risk of 14%, based on a study

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Significance & Innovations

- Top causes of death for hospitalized ankylosing spondylitis (AS) patients were sepsis, spinal fracture, spinal cord injury, and pneumonia.
- Cervical spinal (C-spine) fracture with spinal cord injury had the strongest association with inpatient mortality in all AS admissions.
- A diagnosis of AS was associated with higher odds of death in all patients admitted with a C-spine fracture.
- The most common mechanism of C-spine fracture in AS was falling, compared to higher-impact trauma in non-AS patients.

surveying patients with AS (10). A review in the spinal trauma literature found a mortality rate of 6.4–11.3% in AS patients admitted to the hospital with spinal fracture (11). In a study of cervical spine (C-spine) fractures in the general inpatient population, mortality was found to be 5.3% using the same Healthcare Cost and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) data set over the years 2002–2010 (12).

Because AS flares rarely require hospital admission, and the disease is managed almost entirely in the ambulatory setting, little focus has been placed on studying hospitalized AS patients, and there are limited data on outcomes in this population. Hospitalization data, and specifically diagnoses associated with mortality, may elucidate disease-associated outcomes in AS. Identifying conditions that are unique to the AS population may provide the foundation for further studies and an improved focus on risk factor modification to prevent adverse outcomes.

Our objective was to evaluate diagnoses associated with death in hospitalized AS patients using a large population-based data set. As C-spine fracture was found to have a strong association with inpatient mortality, we secondarily aimed to study whether a comorbid diagnosis of AS increased the risk of death in all patients hospitalized with C-spine fracture.

PATIENTS AND METHODS

Data were derived from the NIS, part of the HCUP, sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP-NIS is the largest publicly available inpatient health care database in the US. It contains data on approximately 8 million hospitalizations each year from nearly 1,000 hospitals, and is a 20% representative sample of all US hospital discharges (13). Each observation in the NIS represents a single de-identified hospital discharge record, with information including patient demographics, a primary discharge diagnosis and up to 24 secondary diagnoses, whether the hospitalization was elective or urgent, and whether the patient died during the hospitalization. Diagnoses are based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-

CM) codes. Clinical Classification Software (CCS) codes were developed by the AHRQ to group the >14,000 unique ICD-9-CM codes into 296 clinically meaningful diagnostic categories (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22934/abstract>) (14). CCS codes have been used in the study of other rheumatic disease states when analyzing the HCUP-NIS data set (15,16). The Committee on Human Research at the University of California, San Francisco, determined that this study was exempt from review, as the data set was de-identified.

Primary analysis: identification of AS hospitalizations.

We identified admissions with AS ICD-9-CM code 720.0 listed as a discharge diagnosis between the years 2007 and 2011. This ICD-9-CM code has been previously validated for use in administrative data using a Veterans Health Administration data set (17). It has also been used in the study of AS patients in several other administrative data sets (18,19). Patients under 18 years of age or those who were dual-coded for systemic lupus erythematosus (710.0) or rheumatoid arthritis (714.0) were excluded in order to improve specificity. We also excluded hospitalizations where data on age and the variable describing in-hospital death were not coded (Figure 1).

Variables. We used CCS codes to identify primary diagnostic categories associated with mortality in AS patients. The primary CCS code is based on the principal diagnosis, which is the first ICD-9-CM code listed on each discharge summary. We identified the top 5 primary diagnostic CCS codes associated with death and created corresponding variables based on validated ICD-9-CM codes (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22934/abstract>) (9,17,19–23). Statistical modeling was based on variables using all discharge ICD-9-CM codes rather than CCS codes, as ICD-9-CM codes have more specificity for each diagnosis.

Two of the top 5 CCS codes were “spinal cord injury” and “other fractures,” which were broad categories largely driven by spinal fracture. The CCS code “other fractures” contained ICD-9-CM codes for nonspinal fractures that were not associated with mortality in the univariate analysis and therefore were dropped from our analysis. To represent the CCS categories “spinal cord injury” and “other fractures,” we created variables based on previously validated definitions of spinal fractures by level (cervical, thoracic, and lumbar spinal fracture) with and without spinal cord injury (20).

We did not include respiratory failure in our multivariable model, as it only included ICD-9-CM codes for acute respiratory failure and ventilator dependence, a common final pathway to mortality. ICD-9-CM codes for restrictive lung disease and pulmonary fibrosis, diseases that have been associated with AS, were not represented as a top diagnosis in patients who died. CVD was included in the multivariable model even though it was not one of the top categories associated with inpatient mortality in AS

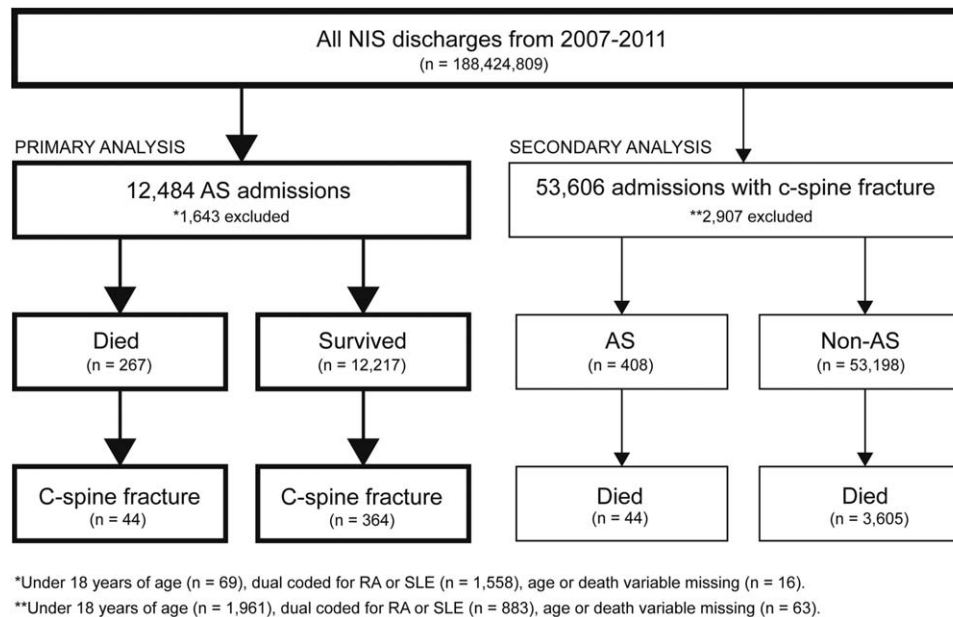


Figure 1. Flow chart depicting inclusion and exclusion criteria and characteristics of the primary and secondary analyses. NIS = National Inpatient Sample; AS = ankylosing spondylitis; C-spine = cervical spine.

patients, as it has been suggested to be a top cause of mortality in AS in the literature (8,9,18).

Measures. We assessed diagnoses associated with AS patients who died during their hospitalization. Demographic and hospitalization characteristics included age, sex, race (white, black, Hispanic, Asian, and other), and whether or not admission was elective. Diagnoses included spinal fracture by level (cervical, thoracic, lumbar) with and without spinal cord injury, sepsis, pneumonia, and CVD (ischemic heart disease, atherosclerosis, peripheral vascular disease, congestive heart failure, and cerebrovascular disease). To address the influence of comorbidity on mortality in AS, we used the Charlson Comorbidity Index (CCI). This is a validated measure that enables prediction of 1-year mortality based on composite comorbid conditions (24). We created a modified CCI for our multivariable analysis by removing CVD variables so that CVD could be analyzed as an independent variable (25). AS is not included in the CCI.

Statistical analysis. Because the HCUP-NIS does not provide information on readmissions, we were unable to perform analyses that would accommodate for this within-person variability. We therefore examined only characteristics that were unique to each hospitalization, such as age, hospital diagnoses, and whether the hospitalization was elective or not. Static characteristics such as race were only used to describe the cohort.

We examined the association of each variable with in-hospital mortality using univariate logistic regression. Variables significant at the P equals 0.05 level in univariate analyses were included in a multivariable logistic regression

model to identify independent associations with in-hospital mortality. Data were analyzed using Stata/SE, version 13.0.

Secondary analysis: C-spine fractures. Because C-spine fracture was associated with mortality in the primary analysis, we performed a secondary analysis over the same period, comparing C-spine fractures in patients with and without AS to determine if AS was an independent risk for inpatient mortality. We identified all admissions coded for C-spine fracture (ICD-9-CM 805.0, 805.1, 806.0, and 806.1) (20). We used the same exclusions as the primary analysis (Figure 1).

Identification of variables. To aid in describing our secondary data set, we sought to determine etiologies of C-spine fracture. External cause-of-injury codes (E-codes) were used to identify mechanisms of injury for each admission. E-codes are present in more than 90% of discharge records in the years 2008–2011 (26). E-codes describing different mechanisms of falls and motor vehicle accidents comprised the top 10 primary E-codes associated with C-spine fracture in this data set. Therefore, we classified E-codes into 3 categories: falls, motor vehicle accidents, and other. The “other” category also included mechanisms for which an E-code was not listed. The categories were based on the Centers for Disease Control and Prevention matrix of E-code groupings (21). These were used only to describe the data set and were not included in the multivariable model, as they were not direct causes of mortality.

As in our primary analysis, we found the top 5 primary diagnoses based on CCS codes for patients who died with C-spine fracture. These included intracranial injury, other fractures, spinal cord injury, and crushing or internal

Table 1. Characteristics and diagnoses in hospitalized ankylosing spondylitis patients, comparing those who survived and those who died 2007–2011*

| | Survived (n = 12,217) | Died (n = 267) |
|-----------------------------------|--------------------------|-------------------|
| Age, mean ± SD years | 58.9 ± 16.4 | 72.8 ± 12.9 |
| Male sex | 8,630 (71) | 208 (78) |
| Race† | | |
| White | 8,543 (70) | 192 (72) |
| Black | 579 (5) | 13 (5) |
| Hispanic | 516 (4) | 12 (4) |
| Other | 2,579 (21) | 50 (19) |
| Elective admission | 2,950 (24) | 26 (10) |
| Modified CCI score, mean ± SD‡ | 0.89 ± 1.3 | 1.78 ± 2.1 |
| Sepsis | 478 (4) | 81 (30) |
| Pneumonia | 995 (8) | 71 (27) |
| Cardiovascular disease | 3,851 (32) | 147 (55) |
| Cervical spinal fracture | 364 (3) | 44 (16) |
| Spinal cord injury | 84 (7) | 26 (10) |
| No spinal cord injury | 280 (2) | 18 (7) |
| Thoracic spinal fracture | 345 (3) | 18 (7) |
| Lumbar spinal fracture | 139 (1) | 3† |

* Values are the number (%) unless otherwise indicated. CCI = Charlson Comorbidity Index. Percentages may not equal 100%, as patients may have more than 1 diagnosis.
† Asian race and lumbar spine fractures resulting in death are not reportable by the Healthcare Cost and Utilization Project data use agreement (13).
‡ Modified CCI per 1-point scale (range 0–38), with cardiovascular disease variables removed.

injury. We created validated ICD-9-CM–based codes for intracranial injury (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22934/abstract>). The “crushing or internal injury” category was heavily weighted by patients coded for internal injury; we therefore created a validated variable, “internal injury,” to represent this category (20). We controlled for comorbid conditions using the CCI (24). We also evaluated elective admission, as it was likely to be protective in hospitalized patients with C-spine fracture.

We similarly performed univariate analyses followed by a multivariate logistic regression analysis to determine which variables were significantly associated with in-hospital mortality in C-spine fracture patients and whether AS was an independently associated diagnosis.

RESULTS

Primary analysis. There were 12,484 AS hospital admissions in 2007–2011, of which 267 died during the hospitalization. The characteristics of the sample are presented in Table 1. The mean ± SD age of AS patients admitted was 59.2 ± 16.4 years, and 71% were male. Elective admissions accounted for 24% of hospitalizations. The majority of the sample’s race was white or “other.” Other race was mostly comprised of admissions where race was not coded. Asian race was included in the “other race” category, as it represented only 1% of our population and was therefore not reportable as a discrete category by the

Healthcare Cost and Utilization Project data use agreement (13). Race did not differ significantly between patients who died and those who survived ($P = 0.485$). The mean ± SD age of those who died was 72.8 ± 12.9 years, 78% were males, and 10% were electively admitted. The mean ± SD CCI score of patients who survived was 0.89 ± 1.3, whereas for patients who died it was 1.78 ± 2.1 ($P < 0.0001$).

The leading CCS-based principal diagnoses associated with AS in-hospital mortality are presented in Table 2. Sepsis and spinal cord injury were the top 2 primary diagnostic categories in patients who died, followed by other fractures, respiratory failure, and pneumonia. Although the “other fractures” category was designed to represent fractures of the spine and other bones of the trunk, all patients who died with this primary CCS code had vertebral fractures.

ICD-9-CM–based diagnoses associated with mortality and their frequencies are presented in Table 1. Of those who died, 30% were coded as having sepsis, 27% with pneumonia, 55% with CVD, and 16% with C-spine fracture. Of patients with C-spine fracture, 11% died, and of those with concomitant spinal cord injury, 24% died. Although a diagnosis of CVD was coded in the majority of hospitalized patients in the cohort, only 4% of those coded with CVD died; thus it was a common comorbidity but rarely a cause of death in this population.

After adjustment for other covariates, C-spine fracture with spinal cord injury and sepsis were the diagnoses with the highest odds of death (odds ratio [OR] 13.43 [95% CI 8.00–22.55], $P < 0.0001$ and 7.63 [95% CI 5.62–10.36], $P < 0.0001$, respectively) (Table 3). C-spine fracture without spinal cord injury also remained significant (OR 2.88 [95% CI 1.67–4.95], $P < 0.0001$), as did pneumonia (OR 1.94 [95% CI 1.42–2.65], $P < 0.0001$). CVD, despite not being a top CCS diagnostic code, was independently associated with mortality in the adjusted model (OR 1.33 [95% CI 1.01–1.74], $P = 0.041$), but it was associated with a lower OR, as expected, compared to the diagnoses derived from the top CCS categories. Age by decade and modified CCI score were both independently associated with mortality (OR 1.61 [95% CI 1.46–1.79], $P < 0.0001$ and 1.23 [95% CI 1.15–1.32], $P < 0.0001$, respectively). As expected, elective admission was protective (OR 0.58 [95% CI 0.38–0.89], $P = 0.012$).

Secondary analysis. Between 2007 and 2011 there were 53,606 admissions whose discharge diagnoses included C-

Table 2. Principal diagnoses associated with ankylosing spondylitis in-hospital mortality*

| CCS definition | Died (n = 267) |
|---------------------|-------------------|
| Sepsis | 37 (14) |
| Spinal cord injury | 26 (9) |
| Other fractures† | 25 (9) |
| Respiratory failure | 17 (6) |
| Pneumonia | 16 (6) |

* Values are the number (%). Categories are based on Clinical Classification Software (CCS) codes.
† Includes International Classification of Diseases, Ninth Revision codes for vertebral fractures and fractures of other bones of the trunk.

| | Univariable analysis | | Multivariable analysis | |
|--------------------------|----------------------|-----------|------------------------|----------|
| | OR (95% CI) | P | OR (95% CI) | P |
| Age by decade | 1.83 (1.68–2.01) | < 0.0001 | 1.61 (1.46–1.79) | < 0.0001 |
| Male sex | 1.46 (1.09–1.96) | 0.010 | 0.95 (0.70–1.30) | 0.762 |
| Race | | | | |
| White | Reference | Reference | – | – |
| Black | 1.00 (0.57–1.76) | 0.997 | – | – |
| Hispanic | 1.03 (0.57–1.87) | 0.910 | – | – |
| Other | 0.86 (0.63–1.18) | 0.357 | – | – |
| Elective admission | 0.34 (0.23–0.51) | 0.024 | 0.58 (0.38–0.89) | 0.012 |
| Modified CCI† | 1.35 (1.27–1.43) | < 0.0001 | 1.23 (1.15–1.32) | < 0.0001 |
| Sepsis | 10.70 (8.11–14.10) | < 0.0001 | 7.63 (5.62–10.36) | < 0.0001 |
| Pneumonia | 4.09 (3.09–5.40) | < 0.0001 | 1.94 (1.42–2.65) | < 0.0001 |
| Cardiovascular disease‡ | 2.66 (2.08–3.40) | < 0.0001 | 1.33 (1.01–1.74) | 0.041 |
| Cervical spinal fracture | 2.68 (1.30–5.53) | < 0.0001 | – | – |
| Spinal cord injury | 15.58 (9.86–24.63) | < 0.0001 | 13.43 (8.00–22.55) | < 0.0001 |
| No spinal cord injury | 3.08 (1.88–5.04) | < 0.0001 | 2.88 (1.67–4.95) | < 0.0001 |
| Thoracic spinal fracture | 2.49 (1.52–4.06) | < 0.0001 | 0.95 (0.54–1.67) | 0.87 |
| Lumbar spinal fracture | 2.68 (1.30–5.53) | 0.007 | 1.98 (0.90–4.31) | 0.088 |

* Adjusted for age and other covariates. AS = ankylosing spondylitis; OR = odds ratio; 95% CI = 95% confidence interval; CCI = Charlson Comorbidity Index.
† Modified CCI per 1-point scale (range 0–38); cardiovascular disease variables were removed.
‡ Includes ischemic heart disease, atherosclerosis, peripheral vascular disease, congestive heart failure, and cerebrovascular disease.

spine fracture, and 408 of these were also coded for AS. Those with AS, compared to the control population, were older (mean \pm SD age 67.7 \pm 15.0 years versus 57.4 \pm 22.9 years), and 93% were male, compared to only 60% of those without AS. Falling was the predominant mechanism of injury for patients with AS and C-spine fracture (62%), whereas those without AS had nearly equal percentages of falls and motor vehicle accidents (35% and 37%, respectively). AS patients had a lower percentage of internal and intracranial injuries when compared to non-AS controls (7% versus 19%, respectively, for internal injury and 9% versus 30%, respectively, for intracranial injury) (Table 4).

The univariable and multivariable odds of death for patients admitted with a C-spine fracture are presented in

| | AS (n = 408) | Non-AS (n = 53,198) |
|---------------------------|-----------------|------------------------|
| Age, mean \pm SD years | 67.7 \pm 15.0 | 57.4 \pm 22.9 |
| Male | 378 (93) | 32,035 (60) |
| Died | 44 (11) | 3,605 (7) |
| CCI score, mean \pm SD | 0.9 \pm 1.4 | 0.7 \pm 1.2 |
| Elective admission | 44 (11) | 3,533 (7) |
| Motor vehicle accident | 62 (15) | 19,673 (37) |
| Fall | 252 (62) | 18,875 (35) |
| Other mechanism of injury | 94 (23) | 14,650 (28) |
| Internal injury | 28 (7) | 10,302 (19) |
| Intracranial injury | 38 (9) | 15,931 (30) |

* Values are the number (%) unless otherwise indicated. AS = ankylosing spondylitis; CCI = Charlson Comorbidity Index.

Table 5. A diagnosis of AS was associated with increased odds of death (OR 1.61 [95% CI 1.16–2.22], $P = 0.004$). Intracranial injury and internal injury were associated with increased odds of death (OR 2.56 [95% CI 2.38–2.76], $P < 0.0001$ and OR 2.82 [95% CI 2.59–3.07], $P < 0.0001$, respectively) as expected. Comorbid conditions, represented by the CCI, were also associated with increased odds of death (OR 1.17 [95% CI 1.14–1.20], $P < 0.0001$), whereas elective admission was protective (OR 0.70 [95% CI 0.59–0.83], $P < 0.0001$).

DISCUSSION

This is the first US population-based study describing in-hospital mortality in AS patients. C-spine fracture with spinal cord injury and sepsis were top causes of death in this data set and were most strongly associated with in-hospital mortality in AS patients. C-spine fracture without spinal cord injury, pneumonia, CVD, and comorbidities were also significantly associated with in-hospital death. In a secondary analysis of all patients admitted with C-spine fracture, we found that an AS diagnosis was an independent risk factor for death. Patients with AS fractured their C-spines with lower-velocity mechanisms of injury and sustained less polytrauma compared to patients without AS. Falling was listed as the primary mechanism of C-spine fractures in hospitalized AS patients.

Although C-spine fracture is a well-established complication of AS, it has not previously been reported to be a top cause of death in patients with AS. This may be due to the fact that C-spine fracture is a relatively rare complication in the nonhospitalized AS population, and previous cohort studies may not have been large enough to discern

| Table 5. Diagnoses associated with in-hospital mortality in all patients admitted with cervical spinal fracture 2007–2011* | | | |
|--|-------------------------------------|------------------------|----------|
| | Univariate analysis† OR (95% CI) | Multivariate analysis‡ | |
| | | OR (95% CI) | P |
| Male | 1.23 (1.14–1.31) | 1.52 (1.41–1.64) | < 0.0001 |
| Age by decade | 1.24 (1.22–1.26) | 1.39 (1.36–1.42) | < 0.0001 |
| Elective admission | 0.56 (0.47–0.66) | 0.70 (0.59–0.83) | < 0.0001 |
| AS | 1.66 (1.21–2.28) | 1.61 (1.16–2.22) | 0.004 |
| Intracranial injury | 2.22 (2.08–2.38) | 2.56 (2.38–2.76) | < 0.0001 |
| Internal injury | 2.06 (1.91–2.21) | 2.82 (2.59–3.07) | < 0.0001 |
| CCI | 1.23 (1.21–1.26) | 1.17 (1.14–1.20) | < 0.0001 |

* OR = odds ratio; 95% CI = 95% confidence interval; AS = ankylosing spondylitis; CCI = Charlson Comorbidity Index.
† P < 0.0001.
‡ Adjusted for elective admission, AS, intracranial injury, internal injury, and CCI score.

it. Additionally, as our data are gathered solely from hospitalized patients, death is driven by acute etiologies, such as infections or accidents, rather than sequelae of chronic diseases, which are more likely to lead to death outside the hospital setting. Similar to our findings, retrospective studies from the surgical literature have shown that patients with AS fracture their spine at lower velocities compared to controls (27). A small retrospective review of patients with spinal fracture admitted to a level I tertiary referral center found the most common location of fracture in AS patients to be located in the cervical region, a finding supported by our study (28). AS patients in that study also experienced a significant delay to spinal fracture diagnosis, as well as a 21% mortality rate. Their mortality rate is higher than that reported in this study, which is likely due to the high-risk trauma population studied at their center. Our study found similar C-spine fracture mortality rates in AS patients compared to those reported in a review of the spinal trauma literature, which is still nearly double that in patients without AS (11,12). The high rate of mortality in AS after C-spine fracture highlights the importance of prompt and specialized care for these patients.

Our study is the largest US in-hospital population-based study evaluating mortality in AS to date, permitting the study of rare outcomes such as C-spine fracture. Prior studies have shown that CVD is a leading cause of death in patients with AS, whereas in our study, although there was a high prevalence of CVD in the cohort, the diagnosis of CVD did not carry the strongest association with in-patient mortality (2–6,8,9,18). Prior studies have relied on death records (3–5) or infer cause of death based on clinic notes (4) that are weighted by deaths occurring outside the hospital setting. CVD in particular has been shown to be overrepresented in US death records (29). As a result, previous studies reliant on death records may have overestimated CVD as a primary cause of death in AS patients. The study by Mok et al was unique, showing infection to be the leading cause of death in AS patients (2). This may be explained by the inclusion of both inpatient deaths in addition to those that occurred in the outpatient setting. Increased all-cause mortality was found in AS patients in the Swedish nationwide

registry. CVD was found to be the primary cause of death in their cohort and contributed to a higher proportion of deaths than in the control group (8). Additionally, they found that death from spinal trauma was more frequent in the AS group but was not one of the top causes of death. Using a retrospective population-based Ontario cohort, Haroon et al found that vascular mortality was increased in AS patients. They did not, however, evaluate all-cause mortality, and therefore it could not be determined whether CVD was the leading cause of death in AS (9).

A limitation of our data set was that the HCUP-NIS does not assign unique identifiers to individual patients; therefore, we could not classify multiple hospitalizations belonging to a single patient. As a result, analyses could not be adjusted for within-patient correlations and were necessarily conducted under the assumption that each hospitalization represented an independent patient.

Although patients could accrue multiple hospital admissions, our primary outcome, in-hospital mortality, represents a unique event. Additionally, deaths that may have been related to the admission but occurred after discharge could not be included in our estimate of mortality. We also relied on coding data, which are inherently subject to specificity inaccuracies. We attempted to improve specificity by excluding those with dual classification for other rheumatic diseases. It is possible that mild AS may not be coded for in our data set, which would bias our results toward more severe disease. In order to improve the quality of our variables, we used diagnostic variables that had been previously validated or used in the published literature. Although the ICD-9-CM code for AS is validated, it is so only in a Veterans Health Administration data set; however, it has been used in many population-based studies of AS (2,8,9,18). Our data set was also limited by the fact that no medication data were available, nor were we able to ascertain AS disease severity, duration, or activity. Additionally, comorbid diagnoses such as osteoporosis are unlikely to be coded for inpatient data; therefore, we could not evaluate these potentially important factors.

In conclusion, we report for the first time in a population-based study that C-spine fracture is a leading cause of in-hospital mortality in AS patients. We found that C-spine fracture with and without spinal cord injury,

sepsis, pneumonia, CVD, and comorbid illnesses were independently associated with in-hospital mortality in AS. Additionally, we found that a diagnosis of AS independently increased the odds of death in patients admitted with C-spine fracture, and patients with AS sustained the majority of their fractures after falls. The high incidence of vertebral fractures and associated mortality in AS warrant further study to elucidate the mechanisms and associated risk factors in order to prevent these devastating fractures. Additional prospective studies evaluating risk factors such as disease duration, burden of radiographic damage, fall risk, osteoporosis, and medication use will be important to further understand the risk factors associated with the outcome of spinal fracture in AS.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Wysham had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Wysham, Yelin, Gensler.

Acquisition of data. Wysham, Gensler.

Analysis and interpretation of data. Wysham, Murray, Hills, Gensler.

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