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ORIGINAL ARTICLE

Mortality and Ankylosing Spondylitis in the US population: leading causes and associated factors

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Abstract

Objective Ankylosing Spondylitis (AS) is a chronic inflammatory condition that affects the axial skeleton. Recent studies have shown that mortality risk is higher in AS patients and that it is possibly related to disease activity and duration. Our aim was to investigate the leading causes and factors associated with mortality in hospitalized AS patients in the USA.

Methods This is a case–control study using the Cerner Health Facts® database between 2015 and 2017. The search was done using ICD codes and administrative claims. Cases were hospitalized AS patients who died during that hospitalization, while controls were patients who survived. In addition to demographics, we collected data on the inpatient use of medications such as NSAIDs, as well as different comorbidities and systemic disease manifestations. The discharge diagnoses for deceased patients were collected to infer causes of mortality. Analysis of association was performed using chi-square tests, *t*-tests, Wilcoxon rank-sum tests, and logistic regression methods.

Results The leading causes of death were cardiovascular, infectious, respiratory, and traumatic. The Elixhauser comorbidity index was the factor most associated with mortality (p-value < 0.0001), with congestive heart failure and renal disease the most contributing. Drug use disorder was associated with mortality (adjusted OR = 10.9; $p = 0.001$). Inpatient NSAIDs use was not associated with increased odds for mortality (p-value 0.33).

Conclusion Cardiovascular and renal comorbidities are associated with mortality and need to be targeted early on to lower the odds of mortality as patients age. Strategies to prevent opioid and drug abuse should be strengthened in the AS population.

Key Points
- *Cardiovascular and renal comorbidities are associated with mortality and need to be screened for and targeted early on to lower the odds of mortality as patients age.*
- *Drug use disorder including opioid dependence is associated with mortality, and strategies to prevent opioid and drug abuse should be strengthened in the AS population.*

Keywords Ankylosing Spondylitis · Axial Spondyloarthritis · Epidemiology · Mortality · Outcomes

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Introduction

Axial spondyloarthritis (AxSpA) is a chronic inflammatory condition that affects the axial skeleton including the sacroiliac joints and the spine. It can also affect peripheral joints and other organs such as the skin, eyes, and gastrointestinal tract. AxSpA can be further characterized as either radiographic or non-radiographic; this distinction depends on the presence of advanced sacroiliitis findings on plain radiographs. Ankylosing Spondylitis (AS) is the radiographic form, where patients have evidence of either bilateral grade 2 or more sacroiliitis, or unilateral grade 3 or 4 sacroiliitis [1]. AS is associated with increased odds

of multiple comorbidities including but not limited to cardiac disease, depression, and osteoporosis [2, 3]. Recent studies have showed that mortality risk is higher in AS patients and possibly related to disease activity and duration [4–9]. Mortality in AS has not been well studied in the US population. The aim of this project was to investigate the leading causes and factors associated with mortality in hospitalized patients with established AS diagnosis.

Materials and methods

Study design

This is a case–control study using the Cerner Health Facts® (HF) database. HF is a database that stores de-identified, longitudinal electronic health record (EHR) patient data. It contains data on almost 50 million patients and almost 300 million encounters. Utilizing the HF database, we collected data on hospitalized AS patients from in-patient encounters. The study years were 2015–2017. The study population was adults with AS, which was defined by the presence of one or more International Classification of Diseases (ICD) codes for AS (ICD-9: 7200, ICD-10: M45.#, M45.A#, M45.AB) and administrative claims for a hospitalization. We defined mortality as those administratively listed as deceased during their hospitalization. The cases were hospitalized AS patients who died during that hospitalization, while the controls were hospitalized AS patients who survived. Control-to-case ratio was 8-to-1, based on the sample size and power calculations that were performed. Controls were selected randomly from the same years as the cases, 2015 through 2017. Duplicates were excluded. Patients 18 years of age or older were included.

Covariates

We collected administrative data on age, sex, race, smoking status, body mass index, c-reactive protein (CRP) levels, HLA-B27 positivity, the use of non-steroidal anti-inflammatory agents (NSAIDS) and biologics while hospitalized, and the presence of any of the following comorbidities (by ICD codes): congestive heart failure, arrhythmia, valvular disease, pulmonary disease, hypertension, renal disease, liver disease, neurodegenerative conditions, diabetes, thyroid disease, peptic ulcer disease, malignancy, HIV/AIDs, coagulopathy, obesity, abnormal weight loss, electrolyte and volume disorders, blood loss and deficiency anemias, alcohol use, drug or substance use disorder, depression, and psychosis. Using data from these comorbidities, we calculated the Elixhauser comorbidity index. The Elixhauser index categorizes comorbidities based on ICD codes and can be used to predict in-hospital mortality [10]. An assumption was made that patients had no comorbidities when no conditions other than AS were recorded. CRP levels were available on a small number of patients; it was not clear if CRP was checked on the rest. HLA-B27 positivity status was not available on any of the patients. We also abstracted data on the presence of extra-musculoskeletal disease manifestations such as uveitis, inflammatory bowel disease, and psoriasis. The top 5 discharge diagnoses for the cases were recorded in order to identify the leading causes of mortality in the hospitalized AS population. An attempt was made to link inpatient and outpatient records to collect data on intake of NSAIDs and biologics as outpatient; but this attempt was not successful.

Statistical analysis

To compare the prevalence of each potential predictor variable among cases and controls, 2×2 tables were constructed and comparisons were made using the usual chi-square tests or Fisher's exact tests, as appropriate. *T*-tests were used to compare the means of continuous variables between the cases and controls. Based on results from the Wilcoxon rank sum test, the *t*-test was robust to a violation of the normality assumption by the variable Elixhauser comorbidity index and those results are reported. Variables with p-value > 0.2 were no longer considered as potential predictors and excluded from the final regression models. Using logistic regression models, the association between the all-cause mortality and each potential predictor variable was tested after adjusting for possible confounders. Confounders included the following: age, sex, and Elixhauser comorbidity index. When a specific morbidity (for example congestive heart failure) was included in the model as an independent predictor, the component of this specific morbidity was omitted from the Elixhauser comorbidity index. The Elixhauser comorbidity index was dichotomized with zero cut-off (less than or equal zero vs more than zero) as there was an interaction between the continuous index and one of the independent variables (inpatient NSAID use). Sensitivity analysis was performed when missing data were present to assess the stability of the models. Statistical analysis was performed using SAS 9.4 software. *P*-values less than 0.05 were considered as statistically significant.

Results

Study sample characteristics

In the Cerner Health Facts Database, 9693 unique patients with a diagnosis code of AS were identified, out of which 2125 patients had an in-patient hospital encounter (Fig. 1). Forty-one (41) patients had a discharge administrative code consistent with death during their hospitalization between the years 2015 and 2017. Random controls (320 patients)

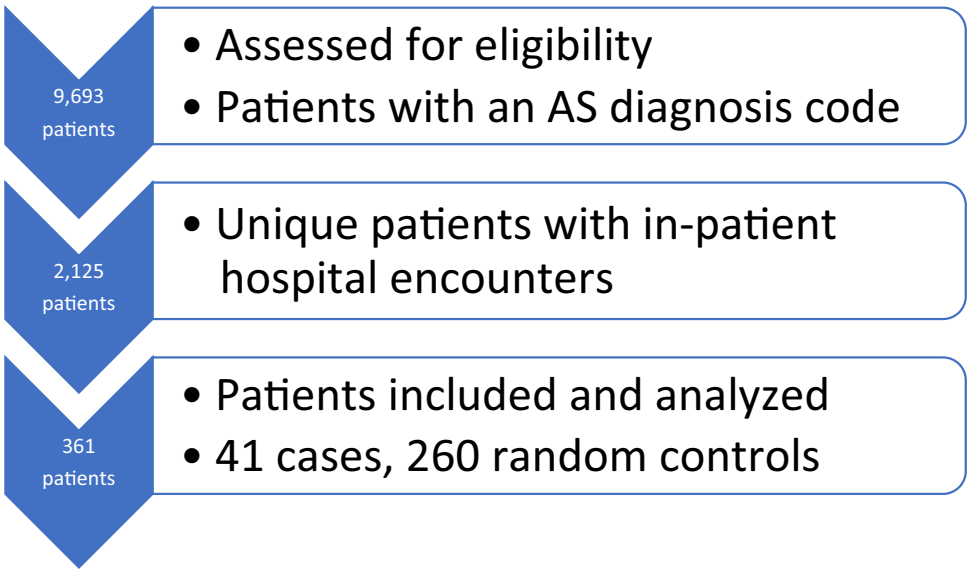

Fig. 1 STROBE flowchart describing how cases and controls were selected from the Cerner Health Facts Database. *STROBE: STrengthening the Reporting of OBservational studies in Epidemiology*

were selected from the in-patient encounters that occurred during the same years as the cases 2015–2017.

Of the 41 cases, 85% were males and 81% were Caucasians (Table 1). The mean age of deceased AS patients was 70 years. The majority of patients had hypertension (71%), while 32% and 22% had kidney disease and congestive heart failure, respectively. Twelve percent of the patients were coded as having drug abuse including opioid dependence, while 14% had a diagnosis code of obesity. Typical systemic manifestations of AS were not commonly documented including: uveitis (0/41), inflammatory bowel disease (0/41), and psoriasis (1/41). No information on the use of NSAIDs or

Table 1 Study sample characteristics of hospitalized AS patients with and without mortality outcome

	AS patients w/ mortality outcome Mean (± standard deviation) or count (percentage)	AS patients w/o mortality outcome Mean (± standard deviation) or count (percentage)	Missing data count (percentage)	*P*-value
Total number	41	320		
Age (Mean + / − SD)	70.49 (+/−13.02)	59.9 (+/−17.84)		< 0.0001
Females *N* (%)	6 (14.6)	120 (37.5)		0.006
Males *N* (%)	35 (85.4)	200 (62.5)		0.006
Caucasians *N* (%)	33 (80.5)	229 (71.6)		0.73
BMI (Mean + / − SD)	25.87 (+/−9.48)	23.01 (+/−9.1)	183 (51%)	0.19
Hx of smoking *N* (%)	1/22 (4.6)	5/156 (3.2)	183 (51%)	0.55
NSAIDs inpatient *N* (%)	2/17 (11.8)	66/260 (25.4)		0.26
CHF *N* (%)	9 (22.0)	16 (5.0)		0.0007
Hypertension *N* (%)	29 (70.7)	144 (45.0)		0.003
Diabetes *N* (%)	6 (14.6)	45 (14.1)		0.92
Kidney disease *N* (%)	13 (31.7)	36 (11.3)		0.0006
Obesity *N* (%)	6 (14.6)	29 (9.1)		0.26
Drug abuse *N* (%)	5 (12.2)	11 (3.4)		0.03
Depression *N* (%)	4 (9.8)	23 (7.2)		0.53
Uveitis *N* (%)	0 (0)	3 (1)		
Psoriasis *N* (%)	1 (2.4)	2 (0.6)		0.30
Elix. Index(Mean + / − SD)	10.29 (+/−7.88)	2.46 (+/−4.93)		< 0.0001

AS, Ankylosing Spondylitis; *BMI*, Body Mass Index; *NSAIDs*, Non-steroidal anti-inflammatory drugs; *CHF*, Congestive heart failure; *Elix. Index*, Elixhauser Comorbidity Index

NSAIDs inpatient was calculated after excluding patients who had contra-indications to NSAID use, i.e. patients with CHF, peptic ulcer disease, renal disease, and coagulopathy

biologics as outpatient was available. Regarding the causes of mortality, cardiovascular disease was the most reported (15 patients), followed by infection (14 patients), followed by respiratory failure (8 patients) and fracture/trauma (7 patients) (Table 2). Myocardial infarction and cardiac arrest were the most common cardiac causes, followed by heart failure and arrhythmia (Supplementary Table 1). Pneumonia and pulmonary embolism were the leading causes of acute respiratory failure in deceased AS patients. Among deceased patients who had a fracture or trauma listed as a diagnosis in their discharge summary, cervical fracture was the most common (5/7 patients).

Table 2 Causes of mortality based on the top 5 discharge diagnoses recorded for hospitalized AS patients with mortality outcome

Discharge diagnosis for cause of death	Number of patients
Cardiovascular	15
Infection	14
Respiratory	8
Fracture/trauma	7
Renal	5
Malignancy	3
Drug abuse	1
Intestinal obstruction	1
Unknown/Not recorded	7

Some patients had more than one cause of death recorded in the discharge summary. AS, Ankylosing Spondylitis

In the control group, 62% were males and 72% were Caucasians (Table. 1). The mean age was 60 years. NSAIDs were used by 23% of the patients while hospitalized. Hypertension was reported in 45% of the controls, congestive heart failure (CHF) in 5% and renal disease in 11%. Eleven patients (3.4%) were reported to have drug abuse including opioid dependence. Three patients were reported to have uveitis and 2 patients with psoriasis. No inflammatory bowel disease codes were detected. Smoking status and body mass index had approximately 51% missing data in the total sample.

Factors associated with death during hospitalization

Deceased AS patients were older in age (70 vs 60 years) and more frequently male when compared to hospitalized AS patients who survived. The effects of age and sex were not statistically significant after adjusting for the Elixhauser comorbidity index in separate analyses (Table 3). The Elixhauser comorbidity index was the predictor of mortality in hospitalized AS patients (mean index 10.3 vs 2.5, respectively ($p < 0.0001$)) (Table 1). Congestive heart failure and kidney disease were among the comorbidities that contributed the most to this index and these two comorbidities were alone strongly associated with mortality (Table 1). The presence of congestive heart failure was associated with 2.76-foldincreased odds of death in hospitalized AS patients, after controlling for age, sex, and other comorbidities (Elixhauser index minus CHF factor) ($p = 0.04$) (Table 3). The presence of kidney disease was similarly associated with 2.46-fold increased odds

Table 3 Association of different predictor variables with mortality outcome, in individual multivariable models, after adjusting for age, sex, and potential confounders specific to each model

	Unadj. OR	95% CI	Adj. OR	95% CI	*p* value
Female sex	0.29	[0.12, 0.70]	0.43	[0.17, 1.10]	0.08
Age	1.04	[1.02, 1.06]	1.02	[0.99, 1.05]	0.14
Elix. Index (dich.)	11.09	[4.24, 29.0]	7.70	[2.82, 21.01]	**< 0.0001**
Elix. Index (cont.)	1.20	[1.14, 1.27]	1.18	[1.12, 1.25]	**< 0.0001**
NSAID inpatient	0.39	[0.09, 1.76]	0.46	[0.10, 2.17]	0.33
CHF	5.34	[2.19, 13.1]	2.76	[1.04, 7.38]	**0.04**
HTN	2.95	[1.46, 5.99]	1.57	[0.71, 3.47]	0.2634
Kidney disease	3.66	[1.74, 7.70]	2.46	[1.07, 5.69]	**0.035**
Drug abuse	3.90	[1.28, 11.9]	10.9	[2.55, 46.6]	**0.001**
Obesity	1.72	[0.67, 4.43]	1.76	[0.61, 5.1]	0.29

Bold: statistically significant *p*-value; i.e. <0.05

Unadj., Unadjusted; Adj.: *Adjusted. Elix. Index*, Elixhauser comorbidity index; *Dich*., dichotomous *(≤0 vs > 0). Cont.,* Continuous; *NSAID*, non-steroidal anti-inflammatory drugs; *CHF*, congestive heart failure; *HTN*, Hypertension

NSAID inpatient: model excluded patients who had contra-indications to NSAID use, i.e. patients with CHF, peptic ulcer disease, renal disease, and coagulopathy. (After exclusion: NSAID intake was recorded in 2/17 cases and 66/260 controls)

CHF, kidney disease, drug abuse, obesity models adjusted for age, sex, and Elix. Index after excluding the respective comorbidity from the index

Drug abuse included opioid dependence

of death in hospitalized AS patients, after adjusting for age, sex, and other comorbidities (Elixhauser index minus renal factor) ($p=0.035$) (Table 3). Drug abuse including opioid dependence was strongly associated with death in hospitalized AS patients (adjusted OR = 10.9; $p=0.001$) (Table 3). It is important to mention that the 95% confidence interval is wide given the sparce number of patients with documented histories of drug abuse. While BMI had a large percentage of missing data (approximately 51%), we ran a regression model on the diagnosis code of obesity; even though the presence of obesity was slightly associated with increased likelihood of death; this association was not statistically significant ($p=0.29$) (Table 3). The use of NSAIDs as inpatient was not associated with mortality in hospitalized patients with AS (OR = 0.46, p-value 0.33), after adjusting for age, sex, and Elixhauser comorbidity index. It is important to note that when running this model, we excluded patients who had contra-indications to NSAIDs such as patients with CHF, renal disease, peptic ulcer disease, and coagulopathy, in order to avoid bias, thereby reducing the power to detect a significant association (Table 3). No statistically significant differences were detected between cases and controls when testing for the effects of race, hypertension, diabetes, or depression. No statistically significant difference was observed based on smoking status; however, this variable was not included in the regression model due to a large percentage of missing data (approximately 51%). Regression models were not fitted for uveitis and psoriasis due to the very small number of patients recorded with these disease manifestations.

Discussion

This case–control study shows that the leading causes of death in hospitalized patients with Ankylosing Spondylitis (AS) in the USA were cardiovascular disease, infection, respiratory failure, and fractures/trauma. This finding is consistent with previous studies from other countries that showed similar results. A study from France showed that infections and external causes were the most common causes of mortality in AS in France [11]. A population-based study from Ontario, Canada showed that there was increased risk of death due to vascular disease in AS patients [6]. A US-based study demonstrated that among hospitalized AS patients, cervical spine fracture was a leading cause of mortality [12]. A recent meta-analysis indicated that all-cause and cardiovascular mortality rates were increased in AS patients compared to the general population [5].

Our study shows that higher Elixhauser comorbidity index was associated with mortality in hospitalized AS patients. The main contributors to this increased mortality were the presence of congestive heart failure, kidney disease, and drug use disorder. Males and older patients had numerically higher odds of mortality, although these variables did not reach statistical significance after adjusting for comorbidities, thereby signaling that the presence of comorbidities had a stronger effect on the odds of death. Several previous studies have shown that the presence of comorbidities was strongly associated with mortality in AS, especially cardiovascular morbidities [6, 9]. Our study suggests that drug abuse including opioid dependence is associated with mortality. No studies evaluating drug abuse or opioid dependence and mortality have been published in the AS population. While we cannot make strong conclusions because of the small sample size in our study, future studies are needed to further validate this point. Our study showed that prescription of NSAIDs during hospitalization was not associated with an increased odds for mortality. A study by Haroon et al. revealed that the lack of exposure to NSAIDs could be a risk factor for vascular death among patients aged 65 or older [6]. A recent meta-analysis also concluded that the use of NSAIDs was not associated with an increased risk of cardiovascular events in AS patients [13].

There are very little data on mortality among patients with AS. While some studies have signaled that mortality risk is increased with disease duration and severity and by the presence of extra-articular manifestations [9, 14], these findings must be validated and replicated universally and in different populations. A strength of our study is that it is one of the very few studies of mortality in AS in the US population. These findings clearly show that underlying comorbidities (especially cardiac and renal ones) are associated with mortality, and suggests that these common comorbidities need to be screened for and targeted early on to lower the odds of mortality as patients age. This current study also signals that strategies to prevent opioid and drug abuse should be strengthened in the AS population.

Our study has several limitations, mainly related to the lack of availability of disease-specific data. AS-specific metrics such as disease activity scores are not available in the Cerner Health Facts database. It would be important to study the association of disease activity with mortality outcome. In addition, substantial amounts of data were missing on some variables (example smoking, BMI, CRP levels, HLA-B27 status); these variables have been linked to disease activity and possible mortality (smoking, CRP levels) [4, 14]. While we attempted to collect data on extra-articular manifestations (i.e., uveitis, psoriasis, and inflammatory bowel disease), we were able to detect only very small numbers of patients with these clinical characteristics. This apparent lack of extra-articular manifestations could be due to the lack of documentation or appropriate coding for these variables in inpatient encounters. Another limitation is that we were not able to capture outpatient use of biologics as the attempt to link inpatient with outpatient encounters was unsuccessful.

The small sample size (mainly for cases) is a limitation especially when trying to adjust for important confounding variables in the multiple logistic regression models. The cases and controls were selected based on ICD codes; it is worth mentioning that no studies were done previously to assess the positive predictive value of 1 AS diagnosis code in the inpatient setting; so the true positive predictive value of 1 inpatient AS diagnosis code is unknown. Lastly, Cerner health facts database does not have access to death certificates which makes it not possible to evaluate outpatient deaths. It would be very important to conduct future studies that can evaluate both inpatient and outpatient data.

Conclusion

Our study demonstrates that the leading causes of mortality in hospitalized AS patients in the USA were cardiovascular, infectious, respiratory, and traumatic/fracture. The presence of cardiovascular and renal comorbidities, as well as drug abuse including opioid dependence, are strong predictors of death during a hospitalization in the AS population. Additional studies are needed to assess AS-specific metrics and their association with mortality risk in the US population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-023-06776-5.

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Data Availability Data is available upon request.

Compliance with ethical standards

Ethics approval The University of Tennessee Health Science Center IRB has determined that this project qualifies for NHSR (Not Human Subjects Research) status in that it does not involve "human subjects" as defined in 45CFR46.102(e)(1).

Conflicts of interest MB, SN, ET: none.
MD: Advisory boards for UCB Inc and Amgen, Investigator initiated grant from Pfizer.
MM: Grants: Abbvie and UCB Pharma, Consulting fees: Novartis, Payment or honoraria: Novartis, UCB Pharma, Abbvie and Eli Lilly.

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