

# Deaths Associated with Ankylosing Spondylitis in France from 1969 to 2009

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**ABSTRACT. Objective.** To describe deaths for which ankylosing spondylitis (AS) was on death certificates in France.

**Methods.** Death certificates in which AS was indicated were evaluated. Standard mortality ratio (SMR) was assessed.

**Results.** AS appeared in 2940 death certificates. The mortality rate of AS seemed stable. The most frequent initial causes were diseases of the circulatory system [28.3% in the International Classification of Diseases, 10th ed (ICD-10)]. SMR adjusted for age and sex were 2.1 (95% CI 1.45–2.91) for infections and 0.43 (0.36–0.5) for cancers (ICD-10 period).

**Conclusion.** This study found an increase in mortality from infectious and external causes of death; conversely, patients with AS appear to die less frequently from cancer. (J Rheumatol First Release March 15 2017; doi:10.3899/jrheum.160942)

*Key Indexing Terms:*

ANKYLOSING SPONDYLITIS

MORTALITY

DEATH CERTIFICATE

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that can cause extraarticular manifestations. These comorbidities added to direct consequences of AS could explain increased mortality among patients with AS. In a review<sup>1</sup>, we wrote that in cohorts not given radiation therapy, standard mortality ratio (SMR) was 1.6–0.2. SMR were lower in studies with latest inclusions<sup>2</sup>. Reported causes of death responsible for increased mortality among patients with AS include traumatic spine injuries and cardiovascular (CV), renal, pulmonary, and gastrointestinal diseases. Surprisingly, in patients with AS not exposed to therapeutic irradiation, increased cancer mortality was not noticed. Using only the underlying cause of death (UCD) for chronic diseases such as AS underestimates the overall disease burden. A multiple-cause analysis that estimates disease-related mortality

by taking into account all the conditions listed on the death certificate is particularly warranted in these cases. In France, the reported prevalence of AS is 0.08%<sup>3</sup>, but there are no data on mortality in this population.

Our retrospective study of French mortality rates from 1969 to the end of 2009 aimed to describe the characteristics of deaths for which AS was mentioned on the death certificates and to analyze trends in AS-related mortality ratio.

## MATERIALS AND METHODS

**Data collection.** The data were collected in the French Epidemiological Center for the Medical Causes of Death (CépiDc, Inserm) database. CépiDc collects and codes all death certificates in France. The 2-part death certificates comply with the World Health Organization's standard international format. Part I asks for the UCD that is the disease that initiated the chain of events resulting in death. Part II allows the physician to list other conditions that contributed to the death. From 1969 to 1978, CépiDc used the International Classification of Diseases, 8th ed (ICD-8) to code causes of death and recorded a maximum of 3 causes. Data from this period were not available for the general population (www.cepidc.inserm.fr from 1979 to 2009). From 1979 to 1999, CépiDc used the ICD-9 and recorded a maximum of 2 associated causes. Since 2000 (ICD-10), all causes reported by physicians have been recorded. Multiple cause-of-death analysis takes into account not only the number of death certificates that listed AS as the UCD, but also those that listed AS anywhere on the death certificate [nonunderlying cause of death (NUCD)]<sup>4</sup>. The code for AS in ICD-8 is 712.4 (spondylitis ankylopoietica), the ICD-9 code is 7200 (AS), and the ICD-10 code is M45 (AS). Ethics board approval was not required in accordance with the policy of our institution because of the completely anonymous data.

**Statistical analysis.** Discrete variables were expressed as numbers with percentage, and continuous variables as mean and SD. Age- and sex-standardized mortality rates (SMR) were calculated by year, and for the period between 2000 and 2009 by a direct method using the 2008 general French population as reference. The SMR and their CI were calculated overall by sex, age, and period. A p value < 0.05 was considered significant. Statistical analyses were performed with SAS software, version 9.3 (SAS Institute Inc.).

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## RESULTS

**Characteristics of dead patients with AS.** In the global period (1969–2009), AS appeared in 2940 death certificates [2292 men (mean age at death 68.7 yrs) and 648 women (mean age at death 75.8 yrs)]. The number of deaths with AS on the death certificate (UCD and NUCD) could be explained by the modification of the ICD (no limitation of associate diagnosis from ICD-10). The mean of death certificates with AS was 60.1 a year (range 53–72) for ICD-8, 70.2 (range 56–85) for ICD-9, and 86.7 (range 72–96) for ICD-10. Death was more common after age 75 (35.9% among men and 61.4% in women; Table 1).

**Causes of death among patients with AS.** AS was listed as the UCD in 731 death certificates (24.8%) and as an NUCD in 2209 death certificates (75%). AS is mentioned as a UCD in 38.3% in 1969–1978, 32.2% in 1979–1999, and 3.1% in 2000–2009. Except AS as an UCD, the other UCD reported in death certificates were CV disease (46% ICD-8, 32%

ICD-9, 28.3% ICD-10), neoplasm (12.7% ICD-8, 15.6% ICD-9, 15.7% ICD-10), respiratory diseases (12.1% ICD-8, 16.7% ICD-9, 9.4% ICD-10), external causes of death (5.9% ICD-8, 13.2% ICD-9, 13.4% ICD-10), and gastrointestinal diseases (8.4% ICD-8, 8.2% ICD-9, 6.4% ICD-10).

**Comparison of individuals with AS and the general population.** When AS is an NUCD, an age- and sex-adjusted SMR ratio of > 1 in patients with AS compared with the general population was observed among men and women whose UCD was infectious diseases (ICD-10: 2.1; Table 2), respiratory diseases [1979–1989: 1.9, 1990–1999: 1.8 (data not shown), and ICD-10: 1.66], and external [1990–1999: 1.36 (data not shown) and ICD-10: 1.9]. The SMR among patients with AS whose death certificates listed neoplasms as the UCD was < 1. Lung cancer and prostate cancer were the most frequent cancers reported as the UCD in the AS population, whereas lung cancer and colon cancer were the most frequent in the general population. Surprisingly, SMR for CV diseases was also < 1 in patients with AS who died

Table 1. Characteristics of AS-related deaths in France from 1969 to 2009 stratified by the ICD. Values are n (%) unless otherwise specified.

Characteristics	ICD-8, 1969–1978	ICD-9, 1979–1999	ICD-10, 2000–2009	Total, 1969–2009
All AS-related deaths, n	601	1473	866	2940
Men, n	401	1199	692	2292
Age, yrs, mean	65.4	68.6	70.7	68.7
25–54 yrs	77 (19.2)	176 (14.7)	81 (11.7)	334 (14.6)
55–64 yrs	93 (23.2)	241 (20.1)	117 (16.9)	451 (19.7)
65–74 yrs	139 (34.7)	358 (29.8)	186 (26.9)	683 (29.8)
≥ 75 yrs	92 (22.9)	424 (35.4)	308 (44.5)	824 (35.9)
Women, n	200	274	175	648
Age, yrs, mean	76.2	75.9	75.2	75.8
25–54 yrs	8 (4.0)	15 (5.5)	19 (10.9)	42 (6.5)
55–64 yrs	15 (7.5)	24 (8.8)	18 (10.3)	57 (8.8)
65–74 yrs	54 (27.0)	74 (27.0)	23 (13.2)	151 (23.3)
≥ 75 yrs	123 (61.5)	161 (58.7)	114 (65.5)	398 (61.4)
Ratio of men to women	2.01	4.38	3.95	3.53
AS listed as the UCD, n	230	474	27	731
%	38.3	32.2	3.1	24.8
Men, n	127	352	21	500
Women, n	103	122	6	231
Ratio of men to women	1.23	2.9	3.5	2.16
Age, yrs, mean	70.4	70.9	68.8	70.7
25–54 yrs	27 (11.7)	70 (14.8)	5 (18.5)	102 (14.0)
55–64 yrs	43 (18.7)	67 (14.1)	5 (18.5)	115 (15.7)
65–74 yrs	60 (26.1)	126 (26.6)	9 (33.3)	195 (26.7)
≥ 75 yrs	100 (43.5)	211 (44.5)	8 (29.7)	319 (43.6)
AS listed as an NUCD	371	999	839	2209
%	61.7	67.8	96.9	75.15
Men, n	274	848	671	1793
Women, n	97	152	169	418
Ratio of women to men	2.82	5.58	3.97	4.28
Age, yrs, mean	68.1	69.5	71.7	70.1
25–54 yrs	58 (15.6)	121 (12.1)	95 (11.3)	274 (12.4)
55–64 yrs	65 (17.5)	198 (19.8)	130 (15.5)	393 (17.8)
65–74 yrs	133 (35.9)	306 (30.6)	200 (23.8)	639 (28.9)
≥ 75 yrs	115 (31.0)	374 (37.5)	414 (49.4)	903 (40.9)

AS: ankylosing spondylitis; ICD: International Classification of Diseases; UCD: underlying cause of death; NUCD: nonunderlying cause of death.

Table 2A. Sex-adjusted SMR (CI) for the UCD when AS was an NUCD.

Variables	Age 25–54 Yrs		Age 55–64 Yrs		Age 65–74 Yrs		Age 75 and Over Yrs	
	SMR (CI)	p	SMR (CI)	p	SMR (CI)	p	SMR (CI)	p
Infectious diseases	1.52 (0.76–2.73)	0.28	2.46 (1.34–4.12)	0.001	2.19 (1.35–3.34)	<0.001	1.31 (0.83–1.99)	0.24
Neoplasm	0.27 (0.18–0.39)	<0.001	0.28 (0.21–0.36)	<0.001	0.33 (0.26–0.41)	<0.001	0.51 (0.42–0.61)	<0.001
Disease of circulatory system	1.31 (0.99–1.7)	0.054	1.21 (0.98–1.48)	0.07	0.82 (0.69–0.96)	0.016	0.66 (0.58–0.74)	<0.001
Disease of respiratory system	2.61 (1.55–4.12)	<0.001	2.26 (1.56–3.17)	<0.001	2.15 (1.7–2.69)	<0.001	1.47 (1.22–1.76)	<0.001
External cause	0.76 (0.55–1.03)	0.088	1.53 (1.13–2.03)	0.003	1.96 (1.52–2.5)	<0.001	1.72 (1.37–2.12)	<0.001

SMR: standard mortality ratio; UCD: underlying cause of death; AS: ankylosing spondylitis; NUCD: nonunderlying cause of death.

Table 2B. Age-adjusted SMR (CI) for the UCD when AS was an NUCD.

Variables	Men		Women		Total	
	SMR (CI)	p	SMR (CI)	p	SMR (CI)	p
Infectious diseases	1.6 (1.19–2.11)	<0.001	2.33 (1.36–3.73)	<0.001	1.74 (1.35–2.2)	<0.001
Neoplasm	0.38 (0.33–0.43)	<0.001	0.23 (0.15–0.33)	<0.001	0.36 (0.32–0.41)	<0.001
Disease of circulatory system	0.85 (0.77–0.93)	<0.001	0.69 (0.56–0.84)	<0.001	0.81 (0.74–0.88)	<0.001
Disease of respiratory system	1.69 (1.47–1.94)	<0.001	1.54 (1.1–2.1)	0.007	1.79 (1.57–2.02)	<0.001
External cause	1.42 (1.23–1.63)	<0.001	1.33 (0.93–1.83)	0.1	1.42 (1.25–1.61)	<0.001

SMR: standard mortality ratio; UCD: underlying cause of death; AS: ankylosing spondylitis; NUCD: nonunderlying cause of death.

Table 2C. Age- and sex-adjusted SMR (CI) for the UCD when AS was an NUCD.

Variables	2000–2009	
	SMR (CI)	p
Infectious diseases	2.1 (1.46–2.91)	<0.001
Neoplasm	0.43 (0.36–0.51)	<0.001
Disease of circulatory system	1.06 (0.93–1.21)	0.35
Disease of respiratory system	1.66 (1.31–2.06)	<0.001
External cause	1.91 (1.57–2.29)	<0.001

SMR: standard mortality ratio; UCD: underlying cause of death; AS: ankylosing spondylitis; NUCD: nonunderlying cause of death.

after 65 years of age. Increased mortality associated with infectious diseases was higher among patients with AS who died between the ages of 55–64 years (SMR 2.46) and women. Mortality associated with external causes increased with age (SMR 1.96 ages 65–74 yrs). Conversely, the SMR for respiratory diseases tended to decrease with age (2.61 at ages 25–54 yrs and 1.47 > 75 yrs).

*Age-SMR.* While the mortality rates decreased in the French population and AS since 1979, mortality rates of AS seem stable from the 1990s (Figure 1).

## DISCUSSION

In our study, we evaluated causes of death and mortality rates from 2940 French death certificates by exhaustive analysis of death certificates with AS mentioned from 1969 to 2009. We confirmed increased mortality associated with infectious diseases and external causes of death (suicides and falls) and lower mortality rates because of neoplasm.

We used the multiple-cause-of-death analysis because it provides information at a country level, with complete coverage of all deaths<sup>5,6</sup>. Indeed, most studies on mortality in AS involve cohorts followed up at a single medical center. Also, patients followed up in hospitals often have more severe disease and may not be representative. Another strength of our analysis is that it included assessment of death certificates that listed AS as one of the NUCD, not just those that listed AS as the UCD.

Our study has certain limitations. Our approach was based on declarative data, thus the mention of AS may be missing and diagnosis may be wrong. The lack of information about age at onset, treatments, and diseases activity makes accurate analysis difficult. These elements and the inertia of effect of treatment on death could be issues in analyzing the evolution of mortality rate in AS.

Neoplasm SMR was < 1 among patients with AS. This finding is similar to other studies of patients with AS not given radiation therapy<sup>7,8</sup>. This result could be explained by premature mortality associated with infectious or respiratory causes in this population. Swedish cancer registries including 6621 patients with AS showed an overall standardized incidence ratio of 1.05 (0.94–1.17)<sup>9,10</sup>. No data in the literature indicate a beneficial involvement of nonsteroidal anti-inflammatory drugs (NSAID) on neoplasm. However, Bakland, *et al*<sup>11</sup> reported that not using any NSAID is associated with reduced survival.

In our study, increased mortality associated with external causes increased with age. Falls and traumatic accidents represented 47% of these causes of death. Spinal stiffness may increase the risk of falls. Several studies described an increased

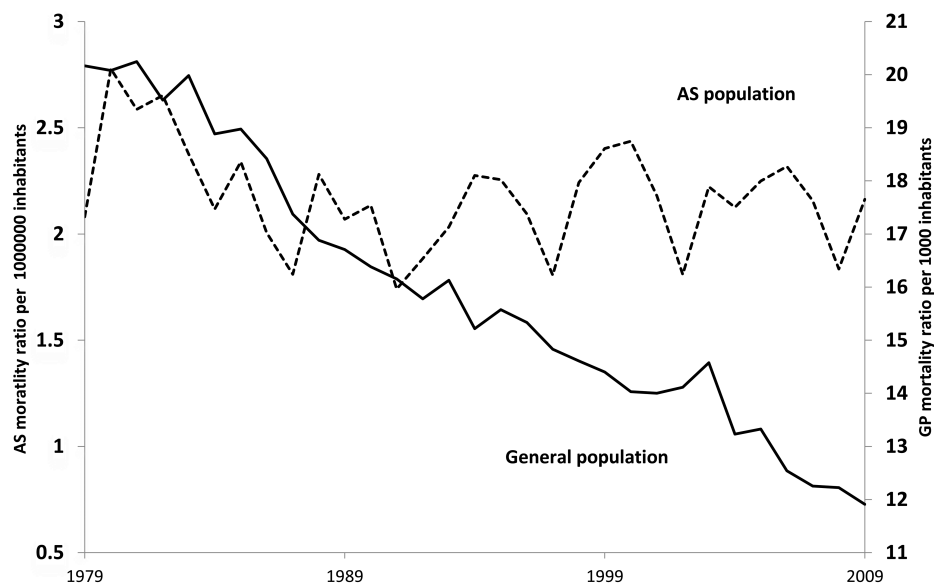


Figure 1. Evolution of mortality ratio in AS population in dotted line (rates per 1 million inhabitants) and GP in solid line (rates per 1000) from 1979 to 2009. AS: ankylosing spondylitis; GP: general population.

risk of death because of injury in patients with AS<sup>7,12,13</sup>.

Our study shows an increase in mortality associated with infectious and respiratory diseases. Strikingly, only 1 study published in 1977 showed increased respiratory mortality from tuberculosis<sup>12</sup>. In our study, chronic obstructive pulmonary diseases represent 44% and influenza/pneumonia 25% of overall pulmonary diseases responsible for deaths that is quite similar to the most common pulmonary abnormalities found in living patients with AS<sup>14,15</sup>. Two studies described SMR > 1 for infectious diseases (6.31 and 1.7)<sup>7,16</sup>.

CV disease (CVD) was identified as the leading cause of death. It is given on 33.6% of overall death certificates from 1969 to 2009, which is comparable to previously reported data<sup>12</sup>. Increased mortality ratio associated with CVD was described with SMR between 1.2 and 1.39<sup>7,8,13</sup>. In a study by Haroon, *et al*, increased risk for vascular mortality was found in men (adjusted HR 1.46, 95% CI 1.13–1.87)<sup>17</sup>. In our work, CVD represented a trend solely toward increased mortality in patients who died before 54 years. Deaths associated with CVD should be analyzed considering disease activity. A study by Lehtinen<sup>7</sup> indicated a linear relationship between mortality and disease severity. In the same way, Bakland, *et al* indicated that variables reflecting the duration and intensity of inflammation are associated with reduced survival in AS<sup>11</sup>. Exarchou, *et al*<sup>18</sup>, studying 496 deaths in an AS cohort, determined the following death predictors: lower level of education, association with general comorbidities, and previous hip replacement surgery.

CVD were the primary causes of death associated with AS, but significantly higher mortality rates were found in infectious and respiratory diseases and in external causes of death.

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