

ORIGINAL RESEARCH

Trends in amyloidosis in
spondyloarthritis: results from the
Spanish National Inpatient Registry
over a 17-year period (1999–2015) –
TREND-EspA study

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ABSTRACT

Objective To assess the incidence of amyloidosis and trends therein in patients with spondyloarthritis (SpA) over a long period (17 years).

Methods An observational retrospective population-based matched cohort study was conducted. All the admissions of patients with SpA, including ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (SpA-IBD) and reactive arthritis (ReA), reported between 1999 and 2015, were analysed and a control group matched by age, sex and year of admission was selected. Incidence rates for amyloidosis were calculated. Generalised linear models were used for trend analysis and unconditional logistic regression for calculating crude and adjusted ORs (AOR) to assess the association between amyloidosis and SpA.

Results The study database contained data on 107 140 admissions in each group. Between 1999 and 2015, 792 patients in the SpA cohort (0.7% of all admissions) had a diagnosis of amyloidosis versus 68 in the non-SpA cohort (0.1%) ($p < 0.001$). From 1999 to 2015, incidence rates of amyloidosis tended to decrease in the SpA cohort (−4.63%/year overall), while they increased in the Non-SpA cohort (+10.25%/year overall). We found strong associations of amyloidosis with all SpAs (AOR 10.4; 95% CI 8.2 to 13.3) and with each type studied (AORs 10.05 (7.84 to 12.88) for AS, 9.5 (7.3 to 12.4) for PsA, 22.9 (16.6 to 31.7) for SpA-IBD and 10.1 (6.1 to 16.7) for ReA).

Conclusions Incidence of amyloidosis among patients with SpA has strongly decreased in Spain. Amyloidosis is most strongly associated with SpA-IBD while the strength of association with PsA and ReA is similar to that with AS.

INTRODUCTION

The term spondyloarthritis (SpA) refers to a heterogeneous group of chronic inflammatory diseases that includes psoriatic arthritis (PsA), arthritis associated with inflammatory

Key messages

What is already known about this subject?

- The incidence of amyloidosis is decreasing in Western countries.
- The median age at diagnosis of Amyloid A amyloidosis has increased in recent decades.
- No recent studies have focused on amyloidosis in patients with spondyloarthritis.

What does this study add?

- We confirm a downward trend in the number of cases of amyloidosis in patients with spondyloarthritis (SpA) hospitalised in Spain.
- The mean age of patients with SpA and amyloidosis has increased by nearly 10 years over recent decades.
- Among patients with SpA, the incidence of amyloidosis is higher in men than women.
- Amyloidosis is strongly associated with all types of SpA, in particular, inflammatory bowel disease-associated SpA.

How might this impact on clinical practice?

- Although the incidence of amyloidosis in SpA is decreasing, the amyloidosis is strongly associated with all types of SpA and close monitoring to check for disease activity is needed.

bowel disease (SpA-IBD), reactive arthritis (ReA) and ankylosing spondylitis (AS).^{1 2} Amyloid A (AA) amyloidosis (formerly known as secondary amyloidosis) is a disorder characterised by the deposition of fibrils composed of the liver acute phase reactant serum AA or the intact protein.³ AA amyloidosis can complicate any chronic inflammatory disease, including rheumatoid arthritis, juvenile idiopathic arthritis, AS, IBD, familial

periodic fever syndromes, chronic infections and certain types of cancer.⁴ This type of amyloidosis most commonly affects the kidney, although it may also have an impact on other organ systems.³ Since 1990, a marked change has been observed, with an increase in the proportion of patients with inflammation of unknown origin. In a study analysing changes in its aetiology over 25 years, the percentage of new cases corresponding to AA amyloidosis of unknown origin rose from 10% to 27%.⁵ In part, this could be explained by the epidemic of obesity, this condition having been identified as an emerging cause of AA amyloidosis, and subsequent kidney disease, in combination with findings suggestive of low-grade but chronic inflammation, likely caused by the release of cytokines by adipocytes.^{6,7}

The overall incidence of AA amyloidosis in autopsies in Western countries has been reported between 0.5% and 0.86%.^{8,9} While both the incidence and the prevalence of AA amyloidosis are falling in Western countries, presumably reflecting advances in the treatment of underlying disorders,^{5,10–14} few studies have exclusively focused on this condition in patients with SpA,^{15–17} and few have compared the incidence of AA amyloidosis in patients with different types of SpA.¹⁸

The treatment of SpA has significantly improved over the last 20 years, due to early diagnosis and the introduction of biological therapies. Given all these, it seems reasonable to venture to suggest that the new treatment paradigm for SpA may have a positive impact on trends in the incidence rate ratios (IRRs) of amyloidosis in patients with SpA.

The objectives of this study were to determine the incidence of amyloidosis and trends therein and its clinical characteristics and explore its relationship with different types of SpA (AS, PsA, SpA-IBD and ReA).

PATIENTS AND METHODS

Study design

We conducted a retrospective observational population-based matched cohort study.

Source of data

For this study, we used the Spanish minimum basic data set (MBDS) of hospital discharges during the period between 1999 and 2015. This database is created through the coding of hospital discharge reports, the data must be provided by all Spanish hospitals, both public and private, and it is estimated to cover 98% of the Spanish population.¹⁹ For the study period (1999–2015), it contains data on approximately 60 million hospital discharges.²⁰ In addition to demographic data (age, sex and place of residence), the MBDS includes the diagnosis, leading to hospital admission (primary diagnosis) and also data on patients' risk factors, comorbidities and complications of during their hospital stay (secondary diagnoses) as well as any diagnostic and surgical procedures performed.¹⁹ The diagnoses and data collected are coded in accordance

with the International Classification of Diseases, Ninth Revision (ICD-9-CM). Data were provided by the Spanish Ministry of Health and included 107 140 hospital admissions of men and women with a diagnosis of SpA cohort. The following ICD-9-CM codes were used to identify patients with SpA: (1) –720.* (*represents a wildcard character), AS and other inflammatory spondylopathies (AS); (2) –696.0, PsA; (3) –099.3, ReA and (4) –720 or 696.0, SpA-IBD +555.*, regional enteritis or 556.*, ulcerative colitis. Only data from records of patients aged 18 years or older were included in the study. The Spanish Ministry of Health manages the MBDS and allows researchers to access the data for research purposes once personal data have been anonymised.

For this research, we also asked the Ministry of Health for a random sample of records of patients without a diagnosis of SpA. The corresponding 3 million records were used to build a control group representative of the population from which the cases arose. Specifically, we selected a comparison cohort matched to cases (SpA cohort) by age, sex, region of residence and year of hospital discharge (no-SpA cohort).

Figure 1 is a flowchart outlining the selection process for the records included in this study.

Selection of records mentioning a diagnosis of amyloidosis

We identified all the records that used codes between 277.30 and 277.39, as the primary or secondary diagnosis, covering all types of amyloidosis. For each case, we collected specific data that included demographic characteristics (age, sex and place of residence), patients' risk factors, comorbidities and complications during their hospital stay (secondary diagnoses) as well the main diagnostic procedures and surgical interventions performed. Patients were classified into the following age groups: 20–39, 40–59, 60–79 and over 80 years.

Potential confounding factors

As well as demographic data such as age and sex, hospital stay and mortality, based on the ICD-9-CM codes, we collected data on the following comorbidities as potential confounding factors: the variables that are involved in the calculation of Charlson's index (severe and mild liver disease, kidney disease, chronic obstructive pulmonary disease, pressure ulcers, connective tissue disease, peripheral vascular disease, haemiplegia, dementia, congestive heart failure, ischaemic heart disease, metastatic tumours, leukaemia and lymphoma), also calculating Charlson's index itself²¹; cardiovascular diseases (ischaemic heart disease, heart failure, stroke, aortic aneurysm, valvular heart disease and pulmonary vein thrombosis and pulmonary embolism), cancer (colon, stomach, pancreas, lung, pleura, melanoma, breast, cervical, uterine, brain, ovary, prostate, bladder and kidney) and infectious diseases (parasitic (including toxoplasmosis), respiratory, neurological and skin diseases, bacterial meningitis, endocarditis, septic arthritis, osteomyelitis, prosthetic joint infection, postoperative infections, pulmonary

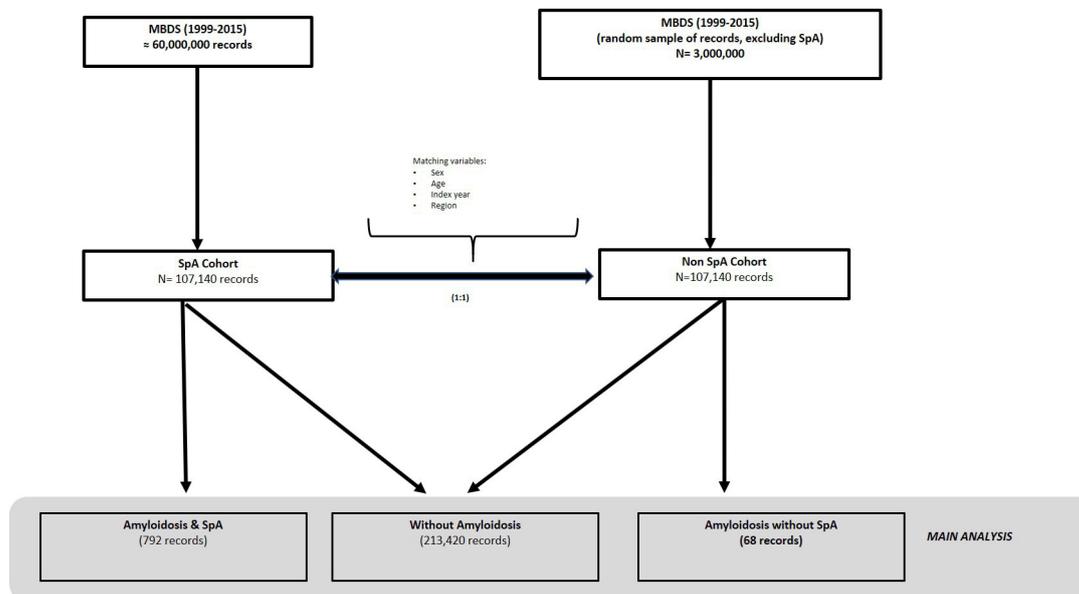


Figure 1 Process of record selection. MBDS, minimum basic data set; SpA, spondyloarthritis.

and extrapulmonary tuberculosis, other mycobacterial infections, cytomegalovirus infection, Epstein-Barr virus, Herpes Zoster, candidiasis, pneumocystosis, listeriosis, nocardiosis, aspergillosis, blastomycosis, strongyloidiasis, leishmaniasis, cryptosporidiosis, hepatitis C and B, HIV chlamydiosis). Data were also gathered on patients' history of hypertension, smoking, obesity, erythema nodosum, cauda equina syndrome, uveitis, depression and orthopaedic surgery (hip and knee replacement, upper limb surgery, arthrodesis, surgery of the axial skeleton) or fractures.

Statistical analysis

Exact matching 1:1 was performed with Matching R package to balance the SpA cohort and a non-SpA cohort by age, gender, region of residence and year of discharge, with a calliper of 5 years in age. We compared the clinical characteristics of the two cohorts using univariate analysis, expressing categorical data as absolute and relative frequencies and quantitative data as mean and SD. To analyse sex differences, the χ^2 test was used for qualitative variables and Student's t-test or the Mann-Whitney U test for quantitative variables, depending on the data distribution. Because of the large sample size, to facilitate the interpretation of results from the univariate analysis, the MSD was calculated and ≥ 0.1 was used as the cut-off to consider that there were differences between cohorts.

Annual crude rates of amyloidosis (cases per 100 000 per year) were calculated for both cohorts (SpA and non-SpA) by sex and age group. The number of cases in the MBDS was used as the numerator and the population at risk as the denominator. Age-adjusted rates, with 95% CIs were also calculated, using the 2015 population as a reference. The at-risk population was estimated based on national census data provided by the Spanish Statistics Institute, and the prevalence rates of SpA were taken as 0.84% overall, 1.13% in men and 0.54% in women, these

prevalence rates are corresponding to the sum of the rates for AS and PsA estimated in the Spanish epidemiological study EPISER.²²

Changes in annual rates (linear trends) were analysed using generalised linear models with a Poisson or a negative binomial distribution if data were overdispersed. We report the estimated rates provided by the models with their corresponding 95% CIs expressed as percentages per year and as IRRs. The analysis was performed for the entire sample and separately for each sex.

The association of amyloidosis with SpA (all types and each type separately) was assessed by calculating ORs and the corresponding 95% CIs using unconditional logistic regression models. First, we estimated the crude ORs that included only the exposure and the variables used in the matching (age, sex, region of residence and calendar year); and then we calculated adjusted ORs (AORs) adding those variables with statistical significance (sex, age, year of admission, Charlson index, infectious diseases, cardiovascular disease, hypertension, smoking, diabetes mellitus, HBV, depression, obesity, axial surgery and uveitis) or those with clinical relevance (Readmission, HCV, tuberculosis and osteoporosis). For the statistical assessment of interactions, adjusted models were run for different categories of the interaction variables and the AORs associated with the different subtypes of SpA were calculated. The AORs of the different strata were compared using the method described by Altman and Bland.²³ This analysis was not carried out if fewer than five cases were identified in the corresponding group.

All the tests were considered two tailed and the level of significance was set at $p < 0.05$. The statistical analysis was carried out using IBM SPSS V.24.0, Epidat V.4.2 and Stata V.14 statistical software.

Table 1 Distribution and clinical characteristics of patients with and without amyloidosis in the SpA and non-SpA cohorts

	SpA without amyloidosis	SpA and amyloidosis	P value	SpA and amyloidosis	Non-SpA and amyloidosis	P value
N (%)	106348 (100)	792 (100)		792 (100)	68 (100)	
Mean age (SD)	58.9 (15.4)	55.8 (13.1)	<0.001	55.8 (13.1)	65.4 (13.2)	<0.001
Mean Charlson index (SD)	1.14 (1.81)	1.80 (1.34)	<0.001	1.80 (1.34)	1.69 (1.18)	0.477
Average length of stay in days (SD)	10.5 (15.3)	12.7 (15.1)	<0.001	12.7 (15.1)	10.3 (8.9)	0.038
Male n (%)	70792 (66.5)	596 (75.2)	<0.001	596 (75.2)	43 (58.1)	0.002
Death during admission, n (%)	3537 (3.3)	82 (10.3)	<0.001	82 (10.3)	5 (6.8)	0.329
Ankylosing spondylitis (%)	67207 (63.1)	538 (67.9)	<0.001	538 (67.9)	NA	
Psoriatic arthritis (%)	37673 (35.4)	243 (30.6)	0.005	243 (30.6)	NA	
Spondyloarthritis-associated inflammatory bowel disease (%)	5238 (4.9)	81 (10.2)	<0.001	81 (10.2)	NA	
Reactive arthritis (%)	2178 (2.0)	20 (2.5)	0.318	20 (2.5)	NA	
Uveitis (%)	542 (0.5)	12 (1.5)	<0.001	12 (1.5)	0 (0)	
Diabetes mellitus (%)	14822 (13.9)	34 (4.3)	<0.001	34 (4.3)	5 (6.8)	0.378
Dementia (%)	626 (0.6)	3 (0.4)	0.638	3 (0.4)	3 (4.1)	0.01
Hypertension (%)	31395 (29.5)	185 (23.3)	<0.001	185 (23.3)	16 (21.6)	0.886
Smoking (%)	13283 (12.4)	56 (7.1)	<0.001	56 (7.1)	3 (4.1)	0.469
Hyperlipidaemia (%)	17748 (16.6)	99 (12.5)	<0.001	99 (12.5)	15 (20.3)	0.071
Obesity (%)	1323 (1.2)	3 (0.4)	0.023	3 (0.4)	0 (0)	0.1
Deep vein thrombosis (%)	648 (0.6)	7 (0.9)	0.351	7 (0.9)	1 (1.4)	0.512
Depression (%)	5939 (5.6)	23 (2.9)	<0.001	23 (2.9)	6 (8.1)	0.031
Tuberculosis (%)	544 (0.5)	3 (0.4)	0.803	3 (0.4)	1 (1.4)	0.416

bold, $p < 0.05$; SpA, spondyloarthritis.

RESULTS

In total, we identified 107140 hospital admissions of patients with SpA (from 76224 patients) during the 17 years of the study. Among these, 62291 (58.1%) (from 45920 patients) were coded as AS, 37369 (34.9%) (from 24786 patients) as PsA, 5283 (4.9%) (from 3845 patients) as SpA-IBD and 2198 (2.1%) (from 1673 patients) as ReA.

Online supplemental table 1 shows the clinical characteristics of the SpA and non-SpA cohorts.

Description of amyloidosis in the SpA and non-SpA cohorts

Overall, 860 records mentioned amyloidosis (0.4% of all admissions), 792 (0.73%) in the SpA cohort and 68 (0.06%) in the non-SpA cohort ($p < 0.001$). In the SpA cohort, the mean age of patients with amyloidosis overall (based on 792 cases) was 55.8 (SD 13.1) years old, the mean age rising from 49.3 years (SD 12.1) in 1999 to 58.9 years (SD 13.1) in 2015. Three-quarters (75.2%) of these patients were men (online supplemental table 2 shows the distribution of admissions by sex and SpA subtype). Their mean length of hospital stay was 12.7 (SD 15.1) days and mean Charlson comorbidity index score was 1.80 (SD 1.3); 82 patients (10.3%) died during admission. [Table 1](#) shows the data regarding other clinical characteristics, compared with the SpA cohort without amyloidosis and the cases of amyloidosis in the Non-SpA cohort. In contrast, in the non-SpA cohort, the mean age of patients

with amyloidosis (based on 68 cases) was 65.5 (SD 13.2) years old ($p < 0.001$), and the mean age remained stable during the study period: 70.5 years (SD 6.3) in 1999 and 70.4 years (SD 13.2) in 2015. In this cohort, 58.1% of patients were men, the mean stay was 10.3 days (SD 8.98) ($p < 0.001$), the mean Charlson comorbidity index score was 1.69 (SD 1.18) ($p = 0.477$) and five (6.8%) patients died during hospitalisation ($p = 0.329$) ([table 1](#)).

Incidence of amyloidosis

The age-adjusted and sex-adjusted incidence of amyloidosis was 16.72 per 100000 per year in the SpA cohort and 1.40 per 100000 per year in the non-SpA cohort. The incidence rates were 19.54 and 1.26 per 100000 per year in men, and 12.23 and 1.74 per 100000 per year in women, in the SpA and non-SpA cohorts, respectively ([tables 2–4](#) and online supplemental figure 1). In the SpA cohort, the incidence was higher in men than in women (19.54 vs 12.23 cases per 100000 per year), while in the non-SpA cohort, the incidence was lower in men than in women (1.26 vs 1.74 cases per 100000 per year) (online supplemental figure 1).

Trends in the incidence of amyloidosis

While the incidence of amyloidosis in the SpA cohort over the study period showed a downward trend of -4.63% per year (IRR 0.954; 95% CI 0.934 to 0.973), in the non-SpA

Table 2 Crude and age-adjusted and sex-adjusted incidence rates of amyloidosis, overall and in men and women

Year	Population*	SpA cohort				Non-SpA cohort			
		Cases	Crude rate (/100,000/year)	Adjusted rate† (/100,000/year)	95% CI	Cases	Crude rate (/100,000/year)	Adjusted rate† (/100,000/year)	95% CI
1999	265803	48	18.06	19.87	14.58 26.63	2	0.75	0.76	0.10 3.29
2000	268777	56	20.84	22.09	16.60 29.03	2	0.74	0.83	0.10 3.40
2001	271640	64	23.56	23.99	18.38 30.99	1	0.37	0.37	0.00 2.63
2002	277168	67	24.17	25.28	19.54 32.38	2	0.72	0.97	0.10 3.64
2003	283095	56	19.78	21.02	15.82 27.57	4	1.41	1.57	0.42 4.30
2004	288220	57	19.78	21.04	15.88 27.49	3	1.04	1.04	0.20 3.42
2005	294250	31	10.54	11.21	7.59 16.10	3	1.02	1.11	0.25 3.51
2006	299139	35	11.70	12.89	8.98 18.05	2	0.67	0.71	0.10 2.79
2007	305145	42	13.76	14.75	10.60 20.10	2	0.66	0.72	0.10 2.76
2008	310053	32	10.32	11.10	7.59 15.76	6	1.94	2.15	0.77 4.78
2009	312471	63	20.16	21.53	16.50 27.61	2	0.64	0.74	0.10 2.75
2010	313760	64	20.40	21.51	16.56 27.51	3	0.96	1.10	0.20 3.25
2011	314859	43	13.66	14.38	10.43 19.40	5	1.59	1.66	0.54 3.96
2012	315013	33	10.48	10.90	7.49 15.36	2	0.63	0.68	0.10 2.47
2013	313913	34	10.83	11.12	7.70 15.55	6	1.91	1.97	0.71 4.29
2014	312980	36	11.50	11.64	8.17 16.10	14	4.47	4.51	2.46 7.57
2015	312596	31	9.92	9.92	6.73 14.07	9	2.88	2.88	1.33 5.48
1999–2015	5058880	792	15.66	16.72		68	1.34	1.40	

*Estimated population of SpA.²²
 †Adjusted by sex and age.
 SpA, spondyloarthritis.

Table 3 Crude and age-adjusted and sex-adjusted incidence rates of amyloidosis, in men

Year	Population*	SpA cohort				Non-SpA cohort			
		Cases	Crude rate (/100,000/year)	Adjusted rate† (/100,000/year)	95% CI	Cases	Crude rate (/100,000/year)	Adjusted rate† (/100,000/year)	95% CI
1999	172698	39	22.58	25.23	17.84 35.08	1	0.58	0.60	0.00 4.54
2000	174765	40	22.89	24.94	17.75 34.59		0.00	0.00	– –
2001	176763	56	31.68	32.47	24.39 42.85	1	0.57	0.59	0.00 4.37
2002	180809	45	24.89	26.46	19.23 35.94	1	0.55	0.66	0.00 4.41
2003	185045	48	25.94	27.52	20.23 36.94	4	2.16	2.44	0.68 6.77
2004	188736	47	24.90	27.03	19.82 36.31	1	0.53	0.41	0.00 3.52
2005	193291	22	11.38	12.46	7.78 19.22	2	1.03	1.16	0.15 4.70
2006	196663	25	12.71	14.49	9.34 21.65	1	0.51	0.55	0.00 3.62
2007	200927	31	15.43	16.61	11.26 23.86		0.00	0.00	– –
2008	204416	28	13.70	14.89	9.90 21.73	4	1.96	2.28	0.64 6.05
2009	205835	48	23.32	25.26	18.58 33.68	1	0.49	0.63	0.00 3.54
2010	206415	43	20.83	22.37	16.20 30.27	2	0.97	1.12	0.15 4.15
2011	206880	28	13.53	14.55	9.69 21.13	3	1.45	1.51	0.29 4.58
2012	206612	29	14.04	14.71	9.85 21.21	2	0.97	1.06	0.15 3.88
2013	205475	22	10.71	11.03	6.90 16.75	1	0.49	0.50	0.00 2.88
2014	204569	18	8.80	8.92	5.30 14.12	9	4.40	4.44	2.05 8.43
2015	204119	27	13.23	13.23	8.72 19.27	7	3.43	3.43	1.36 7.06
1999–2015	3314018	596	17.98	19.54		40	1.21	1.26	

*Población estimada de SpA.²²
 †Adjusted by sex and age.
 SpA, spondyloarthritis.

Table 4 Crude and age-adjusted and sex-adjusted incidence rates of amyloidosis, in women

Year	Population*	SpA cohort					Non-SpA cohort				
		Cases	Crude rate (/100,000/year)	Adjusted rate† (/100,000/year)	95% CI		Cases	Crude rate (/100,000/year)	Adjusted rate† (/100,000/year)	95% CI	
1999	88345	9	10.19	10.83	4.88	21.50	1	1.13	1.11	0.05	7.84
2000	89269	16	17.92	17.96	10.17	30.15	2	2.24	2.45	0.27	9.97
2001	90155	8	8.87	9.00	3.86	18.73		0.00	0.00	–	–
2002	91775	22	23.97	24.56	15.33	38.01	1	1.09	1.57	0.05	8.75
2003	93561	8	8.55	9.79	4.19	19.84		0.00	0.00	–	–
2004	95092	10	10.52	10.78	5.13	20.49	2	2.10	2.28	0.28	9.02
2005	96792	9	9.30	9.44	4.31	18.59	1	1.03	1.06	0.05	6.88
2006	98323	10	10.17	10.66	5.07	20.11	1	1.02	1.05	0.05	6.66
2007	100146	11	10.98	11.89	5.91	21.61	2	2.00	2.15	0.27	8.29
2008	101634	4	3.94	4.35	1.16	11.44	2	1.97	2.05	0.26	7.93
2009	102511	15	14.63	15.39	8.61	25.68	1	0.98	1.01	0.05	6.11
2010	103062	21	20.38	21.07	13.01	32.44	1	0.97	1.13	0.05	6.32
2011	103546	15	14.49	14.86	8.31	24.67	2	1.93	2.05	0.26	7.55
2012	103773	4	3.85	3.98	1.06	10.33		0.00	0.00	–	–
2013	103610	12	11.58	11.85	6.10	20.74	5	4.83	4.94	1.59	11.59
2014	103443	18	17.40	17.57	10.39	27.77	5	4.83	4.86	1.56	11.36
2015	103411	4	3.87	3.87	1.03	9.89	2	1.93	1.93	0.26	6.99
1999–2015	1 668 447	196	11.75	12.23			28	1.68	1.74		

*Población estimada de SpA.²²

†Adjusted by sex and age.

SpA, spondyloarthritis.

cohort, it showed an upward linear trend of +10.25% per year (IRR 1.102; 95% CI 1.042 to 1.167). The trends were similar in men and women. online supplemental table 3 and figure 2 show the results concerning trends by sex. The Year × Group interaction effect was statistically significant.

Association between amyloidosis and SpA (overall and each type)

As expected, amyloidosis was positively associated with being in the SpA cohort (AOR 10.4; 95% CI 8.2 to 13.3), and the strongest association was found with SpA-IBD

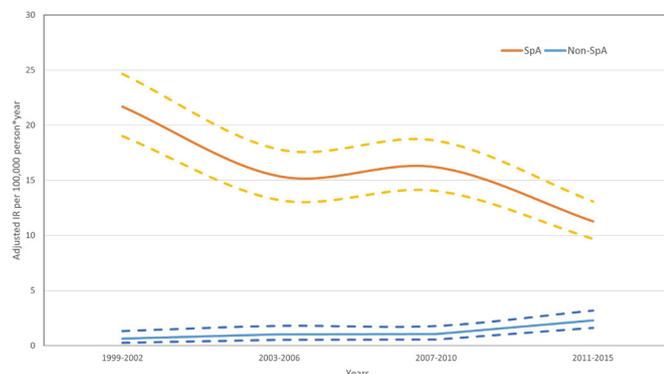


Figure 2 Trends in the incidence of amyloidosis in the SpA and non-SpA cohorts (overall, in both sexes). Adjusted incidence rate and 95% CI. SpA, spondyloarthritis.

(AOR 22.9; 95% CI 16.6 to 31.7). For the other types studied, the strength of observation observed was similar, with AORs of around 10 (table 5 and figure 3).

DISCUSSION

In this study, we have performed countrywide analysis over a long period of time (1999–2015), this enabling us to assess the trends in amyloidosis in patients with SpA admitted to hospital in Spain. Our main findings are: first, we confirmed a strong downwards trend in the incidence of amyloidosis in patients with SpA, in both men and women. The fact that steady increases have been seen in the overall number of diagnoses of amyloidosis in recent decades with decreases only in AA amyloidosis suggest that the majority of cases of amyloidosis in our patients were AA.²⁴ Second, the pattern in the incidence of amyloidosis differs between patients with SpA and controls: in patients with SpA, the incidence of amyloidosis was higher in men (respectively, in men and women: 19.54 vs 12.23 per 100 000 per year), while in the control group, the incidence was higher in women (respectively, in men and women: 1.26 vs 1.74 per 100 000 per year), and among patients with SpA, the mean age increased by 9.5 years over the 17 years of the study, a trend was not observed in the control group. Third, the type of SpA most strongly associated with amyloidosis was SpA-IBD (AOR 22.9; 95% CI 16.6 to 31.7). Fourth, while it is

Table 5 Risk of amyloidosis associated with SpA and subtypes of SpA

	Without amyloidosis	With amyloidosis	Crude OR	95% CI		AOR	95% CI	
N (%)	213 414 (99.6)	860 (0.4)						
Non-SpA (%)	107 066 (99.9)	68 (0.1)	ref			ref		
SpA (%)	106 348 (99.3)	792 (0.7)	10.7	8.4	13.6	10.4	8.2	13.3
AS (%)	61 837 (99.3)	454 (0.7)	10.6	8.3	13.5	10.0	7.8	12.8
PsA (%)	37 132 (99.4)	237 (0.6)	9.2	7.1	11.9	9.5	7.3	12.4
SpA-IBD (%)	5238 (98.5)	81 (1.5)	22.3	16.3	30.7	22.9	16.6	31.7
ReA (%)	2141 (99.1)	20 (0.9)	13.5	8.2	22.1	10.1	6.1	16.7

OR adjusted by: sex, age, year of admission, Charlson index, readmission, infectious diseases, cardiovascular disease, hypertension, smoking, diabetes mellitus, HCV, HBV, depression, obesity, tuberculosis, osteoporosis, axial surgery and uveitis.

AOR, adjusted OR; AS, ankylosing spondylitis; PsA, psoriatic arthritis; ReA, reactive arthritis; SpA, spondyloarthritis; SpA-IBD, SpA-associated inflammatory bowel disease.

generally perceived that the risk of amyloidosis is lower in patients with PsA than those with AS,¹⁸ in our study, the strength of association was similar for these two types.

As in previous studies, we observed a strong downward trend in the number of hospital admissions of patients with amyloidosis.^{5 10–14} In the last three decades, decreases have been seen in both the incidence and the prevalence of AA amyloidosis in Western countries, likely reflecting the effectiveness of newer treatments for the underlying disorders.^{5 10–14 25} In relation to this, we found that the mean age of patients admitted increased by 9.5 years over the 17-year study period. Such a trend has also been reported by other authors.⁹ This increase in the mean age is attributable to a change in the profile of AA amyloidosis, with percentage increases in primary (amyloid light chain) amyloidosis and transthyretin amyloidosis compared with AA amyloidosis, and a substantial change in the epidemiology of the diseases underlying AA amyloidosis (9,22) as well as to therapeutic advances in several chronic inflammatory diseases.^{5 10 13} In recent population-based studies, the incidence of amyloidosis was highest among 60-year to 80-year olds, while in previous series,

the mean age at diagnosis was substantially younger than this, at around 45–55 years of age.^{14 26–28}

Unlike in other studies,²⁸ which found similar incidence rates in men and women,²⁸ we observed markedly more cases in men than in women,²⁸ likely attributable to SpA severity (as measured by C reactive protein levels, radiological progression or the Bath Ankylosing Spondylitis Metrology Index) being greater in men than in women.²⁹ Most studies have revealed that men are more likely to show worse hip involvement and higher BASRI spine and modified Stoke Ankylosing Spondylitis Spine Score compared with women.²⁹

To our knowledge, no previous studies have explored the relationship between amyloidosis and different types of SpA. We found a very strong association of amyloidosis with SpA-IBD (AOR 22.954; 95% CI 16.608 to 31.725) and a somewhat weaker but still strong association with the other types (AS, PsA and ReA), with AORs around 10. The increased risk in SpA-IBD compared with other types of SpA is striking. Although unknown, due to the lack of studies that have analysed it, this is not unexpected. It is intriguing whether the specific pathogenic mechanism underlying the inflammatory process plays a role in amyloidogenesis. In this respect, it is notable that granulomatous inflammation is frequently present in diseases associated with AA amyloidosis (eg, Tuberculosis, leprosy, Whipple's disease, aspergillus infection, giant cell arteritis, Crohn's disease, sarcoidosis or Hodgkin's lymphoma).⁴ Serum amyloid A (SAA) production from macrophages might contribute to a local inflammatory microenvironment, especially when macrophages are compactly organised in granulomas.³⁰ Such a granulomatous disease process might somehow facilitate the development of the amyloid nidus as first hit. A second hit might be only increased SAA serum levels by another inflammatory process.

Our study has both strengths and limitations. Its main strength is the large sample size spanning a long time period and the standardised methodology used, which did not change over the study period and has been successfully used in numerous epidemiological studies

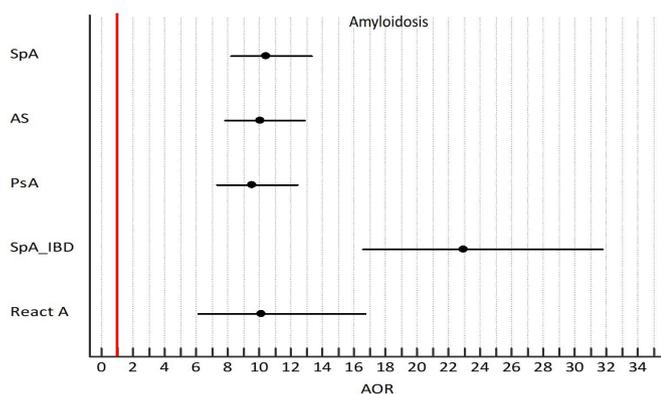


Figure 3 Risk of amyloidosis associated with SpA and subtypes of SpA (forest plot). AOR and 95% CI. AOR, adjusted OR; AS, ankylosing spondylitis; PsA, psoriatic arthritis; React A, reactive arthritis; SpA, spondyloarthritis; SpA_IBD, SpA associated with inflammatory bowel disease.

carried out in Spain.^{19 31} Specifically, our study includes 792 cases of amyloidosis associated with SpA, the largest series to date. We believe that the length of the study period and the comprehensiveness of the MBDS data provide sufficiently good internal validity, as seen in quantitative terms in the similar numbers of episodes detected each year, and in qualitative terms, in the identification of high-risk age groups. Another strength of our study is that it included a control group (non-SpA cohort) matched by age, sex, region of residence and date of hospital admission, which has enabled us to compare the results between the cohorts.

We should also recognise certain limitations of the study. As this was a retrospective observational study, we cannot determine whether the associations observed are causal. The main limitation is the lack of validation of the exposure (SpA) or the outcome of interest (amyloidosis), and we also do not know the distribution of the different types of amyloidosis. Furthermore, we do not have data on SpA severity or disease duration, which might help to understand the underlying mechanisms or on treatments received. Among these other considerations, we should also highlight that our study is based on patients admitted to hospital, and, hence, we will have missed cases in patients who did not require admission. Another limitation of our study is that the coding of diagnoses is based on ICD-9. This coding system predates the current nomenclature of SpA, which lump different diagnoses into axial SpA (and within these into radiological and non-radiological SpA) and peripheral SpA, so these entities are not included in ICD-9. Finally, although the MBDS provides information from a network of hospitals covering more than 98% of the Spanish population,²⁰ it is possible that some cases may have not been captured by the public registry of hospital discharges and that there may have been coding errors.

CONCLUSIONS

This matched cohort study in Spain shows a marked decrease in the incidence of amyloidosis in patients with SpAs in general, and strong associations with all types of SpA, the strongest association being observed with SpA-IBD.

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