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ORIGINAL RESEARCH

Seventeen-year reassessment of diagnostic transitions, biologic therapy initiation and mortality in spondyloarthritis: results from the REGISPON-3 study

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ABSTRACT

Objectives To evaluate disease evolution, diagnostic transitions, time to biologic treatment initiation and mortality in patients with spondyloarthritis (SpA) after 17 years from the original Spanish Registry of Spondyloarthritis (REGISPONSER).

Methods Spondyloarthritis Registry 3 (REGISPON-3) is a two-timepoint longitudinal study with patients fulfilling the European Spondyloarthropathy Study Group criteria participating in the REGISPONSER study and re-evaluated after 17 years. Clinical, laboratory, radiological and treatment data were collected and compared with baseline. Diagnostic changes according to the rheumatologist's judgement and their associated factors were analysed using multivariable logistic regression. Time to initiation of biologic therapy was evaluated using Kaplan-Meier survival analysis.

Results A total of 536 patients from the REGISPONSER study conducted in 2004 were contacted in 2021 for the REGISPON-3 visit. Of these, 411 were physically re-evaluated, while 125 were confirmed deceased. Among the 411 patients, 31.6% experienced a change in diagnosis in the REGISPON-3 visit, mainly from undifferentiated SpA to axial SpA or psoriatic arthritis. In multivariable analysis, dactylitis, younger age and lower Bath Ankylosing Spondylitis Radiology Index scores were associated with diagnostic change. The use of biologic disease-modifying antirheumatic drugs (bDMARDs) increased from 13.1% to 52.1%. However, the median time to first bDMARD from symptom onset was 32 years (95% CI 30 to 35) and 28 years from diagnosis (95% CI 26 to 32). Among the 125 patients who died, the leading causes were infections (21.6%), cardiovascular (CV) events (20.0%) and cancer (19.2%).

Conclusions This long-term reassessment reveals significant diagnostic changes in SpA and a mortality burden mainly attributed to infections and CV diseases.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long-term data on the natural history and diagnostic trajectories of spondyloarthritis (SpA) are scarce, with most cohorts reporting shorter follow-up.

WHAT THIS STUDY ADDS

⇒ Nearly one in four patients experienced a diagnostic transition over 17 years, particularly those initially classified as undifferentiated SpA, underlining the dynamic nature of the disease.

⇒ Almost half of the cohort received biologic therapy during follow-up, and we provide novel data on long-term mortality, with infections, cardiovascular disease and malignancy as the leading causes of death.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings provide a comprehensive picture of the long-term clinical trajectories of SpA in routine care, highlighting diagnostic variability, therapeutic evolution and key outcomes over time.

⇒ Future efforts should aim to minimise diagnostic delay and promote individualised therapeutic approaches to reduce long-term morbidity and mortality.

INTRODUCTION

Spondyloarthritis (SpA) represents a group of chronic inflammatory diseases with heterogeneous clinical manifestations, affecting both axial and peripheral joints and often associated with extra-musculoskeletal manifestations such as psoriasis, uveitis and inflammatory bowel disease (IBD).[1] Patients with SpA have traditionally been classified into subtypes including ankylosing spondylitis (AS), psoriatic arthritis (PsA), IBD-associated SpA (IBD-SpA), reactive arthritis (ReA), juvenile SpA (juv-SpA) and undifferentiated SpA (u-SpA).

The classification of SpA has evolved over time, particularly with the introduction of MRI in 2009, which allowed for earlier detection of sacroiliac inflammation and reduced diagnostic delay. As a result, the Assessment of Spondyloarthritis International Society (ASAS) introduced new criteria, differentiating between two main phenotypes based on the predominant symptom: axial SpA (axSpA), which can be classified as non-radiographic (nr-axSpA) and radiographic axSpA (r-axSpA) depending on the presence of sacroiliitis on pelvic radiographs, and peripheral SpA (pSpA).[2] Patients may transition between diagnostic categories or remain within the same diagnostic category as the disease progresses. For example, individuals with nr-axSpA may progress to r-axSpA,[3] and some patients previously diagnosed as u-SpA may have later progressed to PsA or axSpA. Identifying the clinical and biological factors associated with these transitions could help refine current classification systems and determine predictors of disease progression or poor outcomes.

In parallel with advancements in classification, treatment strategies for SpA have also evolved significantly over the past two decades. The increasing use of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) has transformed disease management. However, no data on long-term follow-up regarding bDMARD initiation have been published yet.

Beyond disease progression and treatment optimisation, understanding the long-term outcomes of SpA, including mortality, is equally important. However, mortality rates in patients with SpA remain a subject of debate, with conflicting findings in the literature. While some studies suggest an increased risk of mortality compared with the general population, others report similar survival rates.[4 5] The main causes of death in these patients reported in the literature include cardiovascular disease (CVD), infections, malignancies and complications related to chronic inflammation.[4 6–8] Among these, CV mortality has been described as particularly relevant in SpA, potentially due to systemic inflammation, endothelial dysfunction, accelerated atherosclerosis, increased carotid intima-media thickness and a higher risk of myocardial infarction and stroke.[9 10] Similarly, infection-related mortality has been observed to be increased in patients with SpA, possibly influenced by immunosuppressive therapy and reduced mobility.[7 9]

Given the complexity of SpA and its long-term consequences, longitudinal studies are necessary for a more comprehensive understanding of disease progression, treatment responses and survival outcomes. The cross-sectional REGISPONSER study, conducted in 2004, included patients across the full spectrum of SpA.[10] Between 2021 and 2023, these patients were re-evaluated in the REGISPON-3 study, resulting in two assessments approximately 17 years apart. In this REGISPON-3 study, we aim to: (a) evaluate diagnostic changes over time and identify factors associated with these changes, (b) analyse the timing of bDMARD initiation and (c) evaluate the proportion of deaths and their causes.

PATIENTS AND METHODS

Study design and population

This was a multicentre, cross-sectional observational study involving patients previously included in the REGISPONSER registry, a Spanish nationwide registry of patients with SpA who fulfilled the European Spondyloarthropathy Study Group (ESSG) classification[11] criteria from March 2004 to March 2007. Data from both the baseline (REGISPONSER) and the follow-up (REGISPON-3) visit were merged into a single comprehensive database to enable direct longitudinal comparisons.

A total of eight Spanish rheumatology centres that had participated in REGISPONSER were actively involved in the REGISPON-3 study. These centres were selected based on their willingness and operational capacity to participate at the time of follow-up. Other centres did not participate due to investigator retirement (n=8), death (n=1), transfer to other hospitals (n=7), lack of research personnel, institutional restructuring or discontinuation of research activity. Eligible participants were contacted and invited to attend a single in-person follow-up visit between 2021 and 2024. Inclusion criteria were: (1) documented participation in REGISPONSER; (2) ability to complete clinical questionnaires and (3) signed informed consent. In cases where the patient had passed away before the REGISPON-3 visit, the family was contacted to request permission to review the clinical record.

Of the 2367 patients initially included in REGISPONSER, 1150 belonged to centres that accepted to participate in REGISPON-3. Among them, 536 patients were successfully contacted, 411 underwent in-person re-evaluation and 125 were confirmed deceased (online supplemental figure 1).

For the remaining 614 patients, re-evaluation was not possible due to several factors: outdated contact information, relocation to other regions, transition to private healthcare, refusal to participate or non-response despite multiple attempts. Patients who were not reassessed and not recorded as deceased are considered to have been unavailable for the second visit.

Data collection

During the re-evaluation visit, data were collected through a structured interview, clinical examination, laboratory testing and imaging studies. Additionally, a detailed retrospective review of the patients' clinical records was conducted to capture key disease-related events occurring between the baseline (2004–2007) and follow-up visit.

A standardised protocol was applied across all participating centres to ensure consistency with the original REGISPONSER methodology. Data collection was performed by rheumatologists with clinical expertise in SpA. A unified case report form, developed by the coordinating team, included predefined definitions, a checklist for retrospective data extraction and a structured interview guide. Historical information, such as prior diagnoses, treatment exposures, comorbidities and imaging findings, was retrieved from electronic health records and, when necessary, cross-checked with paper charts or hospital pharmacy records.

In all the centres, a single rheumatologist led the reassessments, ensuring consistency within that centre. The structured interview and clinical examination were conducted during the in-person follow-up visit, and a previous training with the investigators before the study initiation was conducted to homogenise procedures across centres.

To ensure comparability between both time points, the follow-up assessment closely replicated the original REGISPONSER methodology, using the same core variables and definitions.

The following procedures were performed, and the corresponding variables were collected:

1. Clinical interview and chart review
   a. Demographic data: age, sex, smoking status (ever), body mass index, work disability ever, educational level and job type.
   b. Articular and SpA-related features: inflammatory back pain (defined as chronic back pain fulfilling at least four of the following criteria: insidious onset, age at onset <45 years, duration >3 months, improvement with exercise and morning stiffness),[12] asymmetric arthritis, peripheral arthritis (upper and lower limbs), coxitis, cervical pain, dactylitis, alternating buttock pain, enthesitis, enthesopathy (as per ESSG criteria), tarsitis and a history of preceding gastrointestinal or genitourinary infection.
   c. Extra-musculoskeletal manifestations: uveitis, psoriasis and IBD.
   d. Disease chronology: diagnostic delay (years from symptom onset to formal diagnosis) and disease duration since symptom onset (years from first symptom to follow-up visit).
   e. Diagnosis: SpA diagnosis at baseline and follow-up was established according to the rheumatologist's assessment.
2. Physical examination: standard joint, enthesis and dactylitis assessment was conducted. Mobility measures included chest expansion, modified Schöber test, occiput-to-wall distance and lateral spinal flexion.
3. Radiological studies: conventional radiographs of the sacroiliac joints (anteroposterior view), spine (cervical, thoracic and lumbar lateral views) and hips were obtained if not performed in the previous year. MRI of the sacroiliac joints (Short Tau Inversion Recovery (STIR) and T1 sequences) was collected when available within 6 months of the visit, as per routine clinical care. Radiographic images of patients with sacroiliitis were also collected according to the modified New York criteria and evaluated by a local investigator.[13] Despite REGISPONSER, radiographs being evaluated using the Bath Ankylosing Spondylitis Radiology Index (BASRI; total and spine scores),[14] the new radiographs performed in the REGISPON-3 visit were assessed using the modified Stoke Ankylosing Spondylitis Spinal Score,[15] which provides a more detailed evaluation of structural changes in the anterior corners of cervical and lumbar vertebrae. All radiographs were interpreted by local readers at each participating centre.
4. Patient-reported outcomes: disease activity was evaluated using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[16] Ankylosing Spondylitis Disease Activity Score with C-reactive protein (CRP)[17] and Disease Activity index for Psoriatic Arthritis.[18] Functional status was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI).[19] Quality of life was assessed using the physical and mental component summaries of the Short Form-12 questionnaire.[20]
5. Laboratory tests: erythrocyte sedimentation rate (ESR), CRP and human leucocyte antigen (HLA)-B27 status were assessed using blood samples. Serum and plasma from peripheral blood samples were also stored.
6. Stool samples: collected from consenting participants and stored at −80°C for microbiome profiling.
7. Treatment data: previous and current treatments were recorded, including non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), bDMARDs, tsDMARDs, corticosteroids and opioids. The number and order of biologic or targeted therapies received were registered. Timing of bDMARD and tsDMARD initiation was calculated from both symptom onset and time of diagnosis.
8. Mortality and cause of death: the vital status of all patients was verified at the time of follow-up. In deceased cases, the cause of death was recorded and classified as: CV event, infection, cancer, respiratory disease, accident, other causes or unknown/not available.

Statistical analysis

Descriptive statistics were used to summarise demographic, clinical, treatment and mortality-related characteristics. Continuous variables were expressed as means and SDs or medians and IQRs, depending on distribution.

Categorical variables were described using absolute and relative frequencies.

Univariable and multivariable logistic regression models were used to identify factors independently associated with diagnostic change between baseline and follow-up (yes/no). The independent variables tested included: age, sex, HLA-B27 status, disease duration, smoking status, CRP levels, baseline diagnosis, clinical features (eg, dactylitis, enthesitis, sacroiliitis), presence of extra-musculoskeletal manifestations, physical activity, prior use of biologic therapy (yes/no) and radiographic damage scores (BASRI). These variables were selected based on clinical relevance and prior literature.

Variables with a p value <0.20 in univariable analysis were entered into the multivariable model using a backward elimination approach. Variables were retained in the final model if they reached statistical significance (p<0.05). Adjusted ORs and 95% CIs were reported.

Assumptions for logistic regression were formally tested. Linearity of continuous variables with respect to the logit was assessed using the Box-Tidwell test, with non-significant interaction terms indicating linearity. Multicollinearity was evaluated using variance inflation factors, all of which were <2.0. Independence of observations was ensured by the study design (each patient contributed a single observation per time point). Sample size adequacy was verified based on the events-per-variable criterion, maintaining ≥10 events per predictor in the model.

Model performance was evaluated using the Hosmer-Lemeshow goodness-of-fit test, with non-significant p values indicating appropriate calibration. Additionally, Nagelkerke's R^2 was calculated to assess model explanatory power.

Time to initiation of biologic therapy (bDMARDs) was analysed using Kaplan-Meier survival curves. Two separate analyses were performed: (a) time to first bDMARD from first symptom onset and (b) time to first bDMARD from date of diagnosis. Kaplan-Meier curves were compared using the log-rank test, and subgroup analyses were conducted according to disease subtype (eg, PsA vs axSpA). Median time to event and 95% CIs were reported. Patients not initiating treatment were censored at the time of follow-up. All analyses were performed using IBM SPSS Statistics V.27.0 (IBM, Armonk, New York, USA) and Python V.3.10.4. A p value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the included population at baseline (REGISPONSER) and re-evaluation (REGISPON-3) visit

The description of clinical characteristics of the REGISPONSER and REGISPON-3 population is presented in table 1. A total of 536 patients from the REGISPONSER study were contacted for the REGIPON-3 follow-up visit. Of these, 411 patients were physically re-evaluated, while 125 were deceased. Among the 411 reassessed patients, 65.9% were male, with a mean age at follow-up of 60.7

Table 1 Demographic and clinical characteristics of the included population at baseline (REGISPONSER) and re-evaluation (REGISPON-3) visit

	REGISPONSER visit (2006) N=411, n (%) or mean (SD)	REGISPON-3 visit (2021–2023) N=411, n (%) or mean (SD)
Sex (men)	271 (65.9)	271 (65.9)
Age (years)	44.0 (10.3), n=410	60.7 (10.4), n=410
Disease duration (years)	17.7 (10.8), n=409	34.9 (10.9), n=409
Diagnosis of delay (years)	10.7 (8.4), n=402	10.7 (8.4), n=402
Inflammatory back pain	360 (87.6)	349/406 (86)
Asymmetric arthritis	177 (43.4)	200/406 (49.3)
Psoriasis (current or ever)*	89 (21.8)	66/406 (16.3)
IBD	20 (4.9)	34/406 (8.4)
Uveitis	72/409 (17.6)	102/405 (25.2)
Enthesitis	130 (31.8)	102/403 (25.3)
Dactylitis	53/409 (13)	59/405 (14.6)
Sacroiliitis	341 (83.2)	328/406 (80.8)
Smoker (ever)	25/58 (43.1)	238/410 (58)
HLA-B27+	282/347 (81.3)	302/405 (74.6)
NSAIDs (ever)	321 (78.1)	387 (94.2)
csDMARDs	146 (35.5)	205 (49.9)
bDMARDs	54 (13.1)	214 (52.1)
CRP (mg/L)	9.9 (12.7), n=395	6.1 (11.3), n=391
ASDAS	2.7 (1), n=390	2.1 (1), n=379
BASDAI	4.2 (2.2), n=407	3.6 (2.3), n=400
BASFI	3.3 (2.5), n=406	3.5 (2.4), n=400
Work disability ever	95/403 (23.5)	158/368 (42.9)
Physical exercise	167 (40.6)	260/408 (63.8)
Diagnosis		
Other diagnosis non-SpA	–	4/408 (0.9)
AS/r-axSpA	270 (65.6)	275/408 (67.4)
nr-axSpA	–	18/408 (4.4)
PsA	60 (14.5)	83/408 (20.3)
u-SpA	61 (14.8)	2/408 (0.4)
ReA	8 (1.9)	2/408 (0.4)
IBD-SpA	3 (0.7)	13/408 (3.1)
Juv-SpA	9 (2.1)	5/408 (1.2)
Peripheral SpA		6/408 (1.4)

Diagnostic categories: AS/r-axSpA, nr-axSpA, PsA, u-SpA, ReA, IBD-SpA, Juv-SpA, peripheral SpA. Other diagnosis non-SpA: patients reclassified into non-SpA conditions at follow-up.
Data are presented as mean (SD) or number (percentage).
*Psoriasis confirmed by a dermatologist.
AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HLA, human leucocyte antigen; IBD-SpA, inflammatory bowel disease-associated spondyloarthritis; Juv-SpA, juvenile-onset spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; r-axSpA, radiographic axial spondyloarthritis; ReA, reactive arthritis; u-SpA, undifferentiated spondyloarthritis.

years (SD 10.4) and a mean diagnostic delay of 10.7 years (SD 8.4). The prevalence of asymmetric arthritis (43.4% vs 49.3%), uveitis (17.6% vs 25.2%) and IBD (4.9% vs 8.4%) appeared slightly higher at re-evaluation in comparison with the baseline visit. In contrast, psoriasis and enthesitis were reported less frequently.

Disease activity scores showed numerically lower values at the re-evaluation compared with baseline, with a decrease in ASDAS from 2.7 (SD 1.0) to 2.1 (SD 1.0), and in BASDAI from 4.2 (SD 2.2) to 3.6 (SD 2.3). Functional status, assessed by BASFI, remained stable (3.3 (SD 2.4) at baseline vs 3.5 (SD 2.5) at re-evaluation).

Online supplemental table 1 presents a comparison of baseline characteristics between patients who were re-evaluated in REGISPON-3 and those who were not, using data from the original REGISPONSER registry, and online supplemental table 2 represents the comorbidities recorded at the REGISPON-3 visit.

Diagnostic changes

Diagnostic changes between REGISPONSER and REGISPON-3 visits are illustrated in figure 1. Over time, a total of 130 (31.6%) patients experienced a change in diagnosis.

Figure 1A shows the evolution of diagnostic categories from baseline to follow-up for the overall population, and figure 1B illustrates this specifically for patients initially diagnosed with u-SpA. Most patients originally diagnosed with AS (n=270) remained within the axial spectrum, now classified as r-axSpA under current nomenclature (n=223). In contrast, the most frequent transition was from AS to axPsA (n=15), IBD-SpA (n=12), PsA (n=9), nr-axSpA (n=5), Juv-SpA (n=2) and pSpA (n=1).

Patients initially diagnosed with u-SpA (n=61) were mostly reclassified as r-axSpA (n=36), nr-axSpA (n=10), pSpA (n=5), axPsA (n=2) and PsA (n=1). Only two

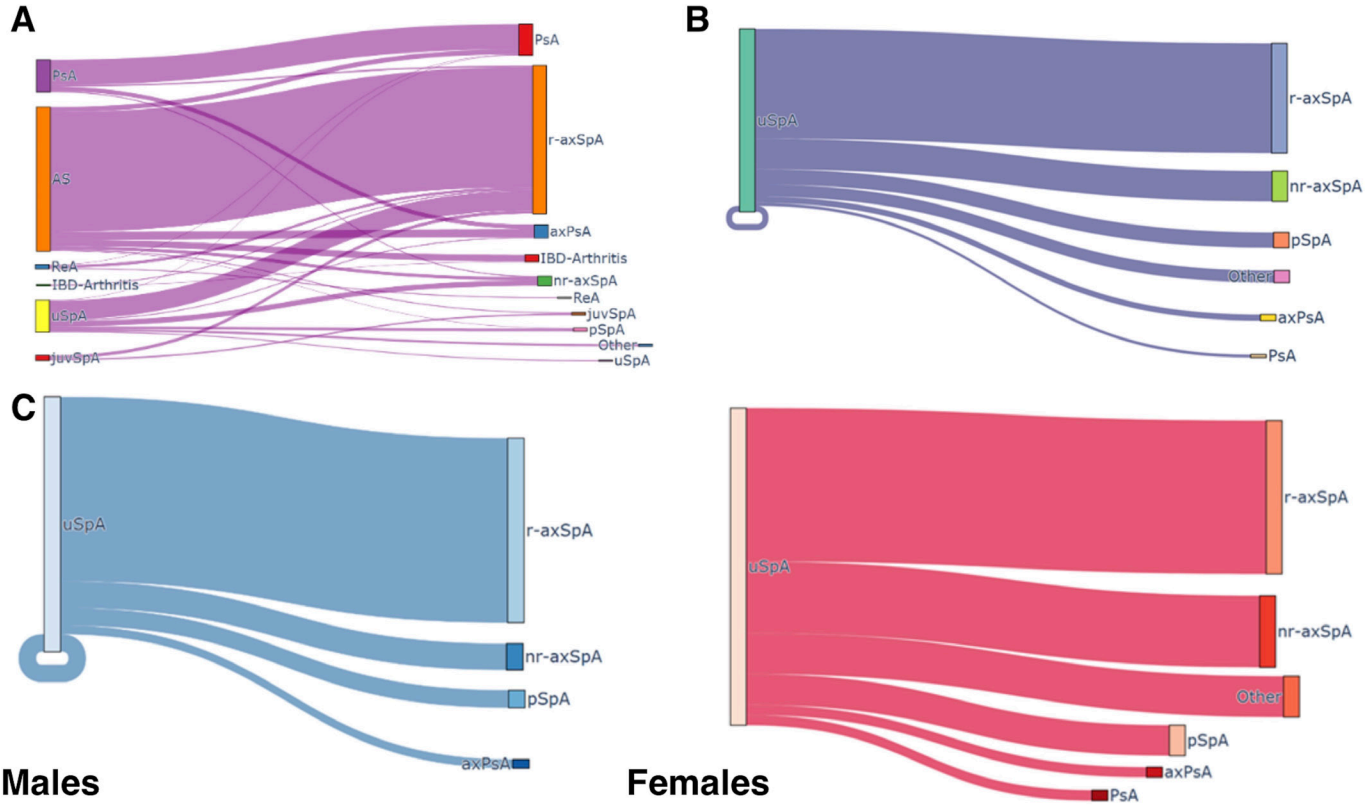

Figure 1 Sankey plot representing changes in the diagnosis in the overall population (A), among undifferentiated SpA (B) and among undifferentiated SpA stratified by sex (C). (A) Sankey plot illustrating diagnostic transitions of the overall cohort from baseline to follow-up; most patients with AS (n=270) evolved to r-axSpA (n=223, 82.6%). Other changes included AS to axPsA (n=15, 5.6%), IBD-SpA (n=12, 4.4%), PsA (n=9, 3.3%), nr-axSpA (n=5, 1.9%), Juv-SpA (n=2, 0.7%) and pSpA (n=1, 0.4%). (B) From the overall patients with u-SpA (n=61), 36 (60%) progressed towards r-axSpA, 10 (16.67%) towards nr-axSpA, five (8.33%) towards pSpA, four (6.67%) towards other diagnoses outside the SpA spectrum, two (3.33%) towards axPsA and one (1.67%) towatds PsA. Two patients (3.3%) retained the diagnosis of u-SpA, and for one patient (1.6%), diagnostic evolution could not be determined due to missing data. (C) Sankey diagrams illustrating sex-stratified diagnostic transitions for u-SpA: males (top, blue) mainly to r-axSpA (n=21, 72.4%), nr-axSpA (n=3, 10.3%), pSpA (n=2, 6.9%), axPsA (n=1, 3.4%), with two (6.9%) retaining u-SpA; females (bottom, red) to r-axSpA (n=15, 46.9%), nr-axSpA (n=7, 21.9%), pSpA (n=3, 9.4%), axPsA (n=1, 3.1%), PsA (n=1, 3.1%) and other diagnoses (n=4, 12.5%). AS, ankylosing spondylitis; axPsA, axial psoriatic arthritis; IBD-Arthritis, inflammatory bowel disease-associated arthritis; nr-axSpA, non-radiographic axial spondyloarthritis; p-SpA, peripheral spondyloarthritis; PsA, psoriatic arthritis; r-axSpA, radiographic axial spondyloarthritis; ReA, reactive arthritis; uSpA, undifferentiated spondyloarthritis.

patients retained the diagnosis of u-SpA after 17 years. In four cases, the initial suspicion of SpA was ruled out and patients were eventually diagnosed with other non-SpA conditions. For one patient, the final diagnosis could not be determined due to missing follow-up data. These transitions are detailed in figure 1B.

Other relevant transitions included reclassification of patients with PsA (n=60) to axPsA (n=8), r-axSpA (n=3) and nr-axSpA (n=2); ReA (n=8) to r-axSpA (n=5) and PsA (n=2); IBD-SpA (n=3) to r-axSpA (n=2); and Juv-SpA (n=9) to r-axSpA (n=6).

Figure 1C displays these diagnostic changes among patients with u-SpA stratified by sex. Among u-SpA men (n=29), reclassification predominantly occurred towards r-axSpA (n=21), followed by nr-axSpA (n=3), pSpA (n=2), axPsA (n=1) and two retained the diagnosis of u-SpA. Among u-SpA women (n=32), although r-axSpA remained the most common destination (n=15), a relatively higher proportion was reclassified as nr-axSpA (n=7), pSpA (n=3), axPsA (n=1), PsA (n=1) or to 'other' categories outside SpA (n=4).

In univariable logistic regression (table 2), variables significantly associated with diagnostic change included male sex (OR 1.86, 95% CI 1.21 to 2.86), presence of cervical pain (OR 2.49, 95% CI 1.10 to 5.62), enthesitis in history (OR 2.31, 95% CI 1.09 to 4.88), psoriasis (OR 1.73, 95% CI 1.06 to 2.82), inflammatory spinal pain (OR 2.36, 95% CI 1.11 to 5.01) and dactylitis at follow-up visit (OR 2.78, 95% CI 1.55 to 5.01). Conversely, sacroiliitis (OR 0.49, 95% CI 0.29 to 0.83) and HLA-B27 positivity (OR 0.53, 95% CI 0.32 to 0.89) were associated with diagnostic stability. Full univariate and multivariable models are shown in table 2.

In the final multivariable logistic regression model (table 2), the presence of dactylitis (OR 2.72; 95% CI 1.28 to 5.76; p<0.01), younger age (OR per year 0.97; 95% CI 0.95 to 0.99; p=0.03) and lower BASRI-total scores (OR 0.83; 95% CI 0.76 to 0.91; p<0.01) were independently associated with diagnostic change between the REGISPONSER and REGISPON-3 assessments.

Use of bDMARDs

The use of bDMARDs increased substantially from 13.1% at baseline to 52.1% at follow-up. The use of csDMARDs also rose (35.5% to 49.9%).

Kaplan-Meier survival analysis revealed a median time from first symptom to initiation of bDMARD therapy of 32 years (95% CI 30 to 35) (figure 2A). When stratified by diagnosis, patients with axSpA initiated biologic therapy later (median 33 years; 95% CI 31 to 36) than those with PsA (median 24 years; 95% CI 18 to 30), with statistically significant differences (log-rank p<0.001) (figure 2B).

From the time of diagnosis, the median time to bDMARD initiation was 28 years (95% CI 26 to 32) (figure 3A). This interval was shorter for patients with PsA, with a median of 22 years (95% CI 17 to 27), compared with 29 years (95% CI 25 to 33) in those with axSpA, showing statistically significant differences (log-rank p=0.02) (figure 3B).

Mortality and causes of death

At the time of REGISPON-3, 125 patients had died. The main causes of death were infections (21.6%), CV events (20.0%) and cancer (19.2%) (table 3). Respiratory diseases accounted for 7.2%, and accidental deaths for 2.4%. In 14.4% of cases, the cause of death was not available.

DISCUSSION

In this nationwide longitudinal study of patients with SpA reassessed after 17 years, we found that nearly one in four individuals experienced a diagnostic transition, particularly those initially labelled as u-SpA. We also observed that nearly half of the re-evaluated patients had received biologic therapy during follow-up, reflecting increasing use of advanced treatments in real-life practice. Finally, we report mortality rates and causes of death in this long-term cohort, with infections, CVD and malignancy emerging as the most frequent categories. These findings provide a comprehensive picture of the long-term clinical trajectories of SpA in routine care, highlighting diagnostic variability, therapeutic evolution and key outcomes over time.

Diagnostic transitions: a reflection of evolving disease phenotype and diagnostic recognition

Nearly one in four patients in our study experienced a diagnostic change over the 17-year period. The majority of patients initially diagnosed with AS remained within the axSpA spectrum, now reclassified as r-axSpA under current ASAS nomenclature.[21] However, diagnostic instability was more common among patients initially labelled with u-SpA, juv-SpA or ReA. These transitions may reflect changes in disease phenotype over time and evolving clinical recognition patterns influenced by advances in imaging and classification systems. A subset of patients transitioned to diagnoses such as PsA or IBD-associated arthritis, likely reflecting the later development of extra-musculoskeletal manifestations (psoriasis or IBD) that were not present or not recognised at baseline. In parallel, reclassification to nr-axSpA may have been facilitated by the incorporation of MRI into diagnostic criteria,[2] allowing for the identification of sacroiliac inflammation in patients who would have remained unclassified using conventional radiography alone. Data from the SPondyloArthritis Caught Early (SPACE) cohort further support that diagnostic certainty in axSpA increases over time, emphasising the role of repeated clinical and imaging assessments in refining diagnosis in male HLA-B27-positive patients.[22]

Among all SpA subtypes, u-SpA stood out as the category with the highest frequency of diagnostic change, with a substantial proportion of these patients evolving towards more clearly defined phenotypes such as r-axSpA, nr-axSpA or PsA over time. These observations are

Table 2 Univariable and multivariable logistic regressions evaluating factors associated with a change in diagnosis over 17 years of follow-up in the overall population

	Univariable analysis			Multivariable analysis	
Predictor	**OR (95% CI)**	**P value**	**N**	**OR (95% CI)**	**P value**
Sex (men)	**1.86 (1.21 to 2.86)**	**<0.01**	411	n.s.	
Age (years)	**0.96 (0.94 to 0.98)**	**<0.01**	410	0.97 (0.95 to 0.99)	**0.03**
Time from diagnosis (years)	**0.95 (0.92 to 0.98)**	**<0.01**	403	n.s.	
Disease duration (years) from first sign/symptom	**0.97 (0.95 to 0.99)**	**<0.01**	403	n.s.	
Diagnostic delay (years)	0.99 (0.97 to 1.02)	0.86	402		
BMI at first visit	0.95 (0.90 to 1.01)	0.12	373	n.s.	
Low back pain	0.77 (0.50 to 1.17)	0.22	411		
Alternating buttock pain	0.93 (0.61 to 1.43)	0.76	409		
Inflammatory spinal pain	**2.36 (1.11 to 5.01)**	**0.02**	411	n.s.	
Cervicalgia	**2.49 (1.10 to 5.62)**	**0.02**	411	1.84 (0.64 to 5.35)	0.25
Asymmetric or predominant synovitis in LL (at the time of the visit)	1.12 (0.73 to 1.70)	0.59	411		
Coxitis	2.77 (0.73 to 10.49)	0.13	411	n.s.	
Enthesitis (history)	**2.31 (1.09 to 4.88)**	**0.02**	411	n.s.	
Enthesitis (current)	**1.99 (1.16 to 3.33)**	**0.01**	409	n.s.	
Dactylitis (history)	**0.19 (0.04 to 0.74)**	**<0.01**	411	n.s.	
Dactylitis (current)	**2.78 (1.55 to 5.01)**	**<0.01**	409	2.72 (1.28 to 5.76)	**<0.01**
Tarsitis	**3.62 (1.16 to 11.28)**	**0.02**	411	n.s.	
Psoriasis	**1.73 (1.06 to 2.82)**	**0.02**	409	n.s.	
Nail involvement	1.51 (0.70 to 3.25)	0.28	407		
IBD	1.82 (0.73 to 4.52)	0.19	411	n.s.	
Anterior iritis/uveitis	0.79 (0.45 to 1.39)	0.42	409		
Urethritis, cervicitis, acute diarrhoea in the month before arthritis	2.59 (0.85 to 7.89)	0.09	410	n.s.	
Sacroiliitis	**0.49 (0.29 to 0.83)**	**<0.01**	410	n.s.	
Pain improvement with previous NSAIDs	**0.31 (0.10 to 0.97)**	**0.04**	145	n.s.	
CRP (mg/L)	0.99 (0.97 to 1.009)	0.30	395		
HLA-B27 (positive)	**0.53 (0.32 to 0.89)**	**0.01**	379	1.05 (0.57 to 1.93)	0.86
VAS (cm) night pain in the last week	1.05 (0.98 to 1.12)	0.16	409	n.s.	
VAS (cm) pain last week	1.06 (0.98 to 1.15)	0.10	409	n.s.	
BASDAI	1.01 (0.92 to 1.10)	0.82	407		
BASFI	1.007 (0.92 to 1.09)	0.87	406		
ASDAS-CRP	0.94 (0.76 to 1.69)	0.61	390		
SF-12 Physical Component	0.99 (0.97 to 1.02)	0.88	411		
SF-12 Mental Component	1.01 (0.98 to 1.04)	0.41	411		
BASRI-total	**0.82 (0.77 to 0.89)**	**<0.01**	392	0.83 (0.76 to 0.91)	**<0.01**
BASRI-column	**0.81 (0.74 to 0.88)**	**<0.01**	395	n.s.	

Logistic regression assumptions met: linearity (Box-Tidwell, p>0.05), no multicollinearity (VIF<2), independence by design, adequate sample size (≥10 events/predictor). Model fit: Nagelkerke R^2=0.172; Hosmer-Lemeshow p=0.59.
N indicates the number of observations used in each univariable regression model, accounting for missing data. The multivariable model included 360 participants with complete data across all included predictors.
Bold typeface indicates significant results.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASRI, Bath Ankylosing Spondylitis Radiology Index; BMI, body mass index; CRP, C reactive protein; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; LL, lower limbs; n.s., non-significant; NSAIDs, non-steroidal anti-inflammatory drugs; SF-12, Short Form-12; VAS, visual analogue scale; VIF, variance inflation factor.

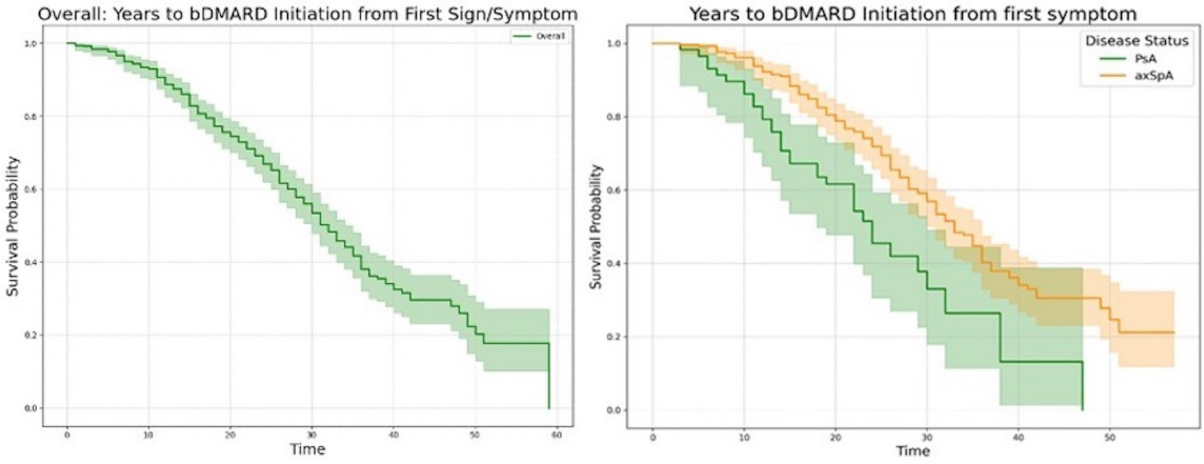

Figure 2 Time to bDMARD from first sign/symptom in the overall population (A) and stratified by disease (B). (A) Kaplan-Meier survival curve for the overall population (n=402; 208 events, 194 censored); median time: 32 years (95% CI 30 to 35). (B) Stratified by diagnosis: PsA (n=58; median 24 years, 95% CI 18 to 30) and axSpA (n=258; median 33 years, 95% CI 31 to 36); log-rank test p=0.00013. axSpA, axial spondyloarthritis; bDMARD, biologic disease-modifying antirheumatic drug; PsA, psoriatic arthritis.

consistent with findings from the DEvenir des Spondyloarthrites Indifférenciées Récentes (DESIR) and SPACE cohorts,[23] where latent class and transition analyses have shown that patients initially classified as u-SpA frequently evolve into axSpA or PsA as the disease progresses and new features emerge. Likewise, a systematic review and meta-analysis estimated that approximately one-third of patients with u-SpA progressed to AS during long-term follow-up, with longer disease duration associated with higher probabilities of reclassification.[24] These findings are consistent with the conceptual framework in which u-SpA may represent a forme fruste or incomplete stage of better-defined SpA entities (particularly AS or PsA) rather than a separate diagnostic category.[25 26]

Sex-stratified analysis of patients with u-SpA revealed that, while reclassification towards r-axSpA was the most frequent outcome in both sexes, women were more frequently reclassified into nr-axSpA or into less specific diagnostic categories. This pattern is consistent with previous reports, where female sex has been associated with lower diagnostic stability and greater likelihood of remaining in unclassified states over time.[3 27 28]

Dactylitis, younger age, lower structural damage (as reflected by lower BASRI scores) and absence of HLA-B27 were identified as independent predictors of diagnostic change in our study. These associations suggest that milder or peripheral-onset SpA phenotypes are more susceptible to evolving classification as new disease features emerge. Supporting this, peripheral manifestations such as dactylitis have been identified as key determinants of phenotype and prognosis in early SpA and are associated with distinct disease trajectories compared with purely axial forms.[29] Moreover, HLA-B27-negative patients with AS tend to show

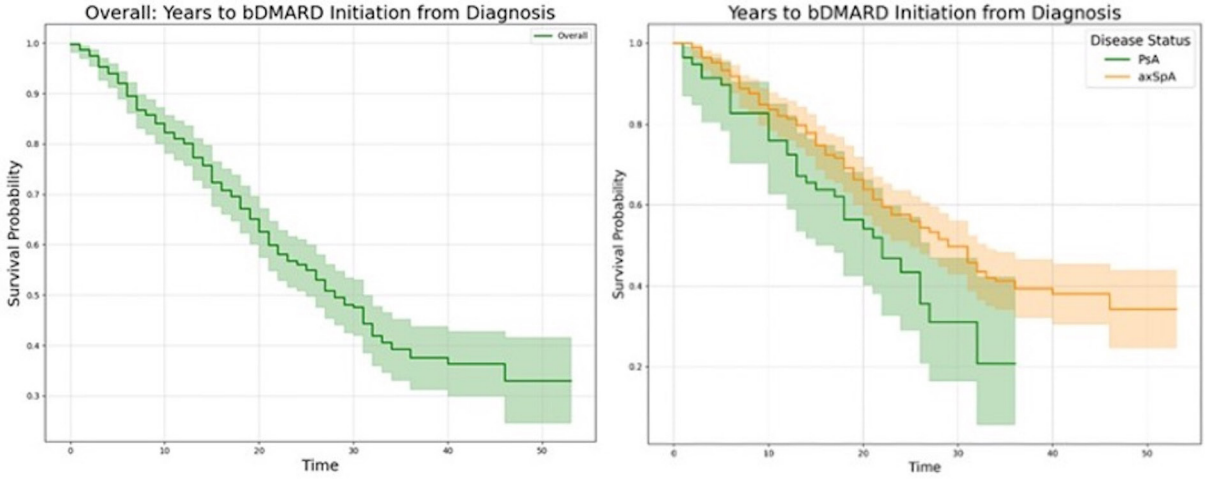

Figure 3 Time to bDMARD from diagnosis in the overall population (A) and stratified by disease (B). (A) Kaplan-Meier survival curve for the overall population (n=402; 208 events, 194 censored); median time: 28 years (95% CI 26 to 32). (B) Stratified by diagnosis: PsA (n=58; median 22 years, 95% CI 17 to 27) and axSpA (n=258; median 29 years, 95% CI 25 to 33); log-rank test p=0.02. axSpA, axial spondyloarthritis; bDMARD, biologic disease-modifying antirheumatic drug; PsA, psoriatic arthritis.

Table 3 Description of the causes of decease

	N=125 N (%)
Accident	3 (2.4)
Cardiovascular event	25 (20)
Cancer	24 (19.2)
Infection	27 (21.6)
Respiratory disease	9 (7.2)
Other causes	19 (15.2)
Not available	18 (14.4)

higher prevalence of peripheral arthritis, dactylitis and extra-musculoskeletal manifestations, suggesting a clinical pattern that may be more diagnostically unstable.[30] Structural progression in early SpA has also been shown to be more common in patients with HLA-B27, MRI-detected inflammation and persistently elevated inflammatory markers such as CRP and ESR, but overall remains modest and limited to a small subset of individuals.[31] Taken together, these findings reinforce the notion that patients presenting with less structural damage or a predominance of peripheral features (particularly in the absence of HLA-B27) may remain diagnostically unstable for longer periods.

Treatment initiation over time

Our results show a substantial evolution in treatment initiation over the 17-year period. The proportion of patients treated with bDMARDs increased from 13.1% at baseline to 52.1% at follow-up, reflecting the widespread adoption of advanced therapies in routine SpA care. Similarly, csDMARD use rose from 35.5% to 49.9%, suggesting a broadening of treatment approaches, particularly for peripheral manifestations.

However, despite this increased use, the timing of bDMARD initiation reveals critical insights into the historical management of SpA. The median time from symptom onset to the first bDMARD was 32 years, and 28 years from the time of diagnosis. These long intervals likely reflect a combination of factors specific to the historical context of this cohort, which spans from 2004 to 2024. In the early 2000s, diagnostic delays in SpA were common, often exceeding a decade. At that time, diagnostic tools such as MRI were not routinely used in clinical practice. During this period, the diagnosis of axSpA relied on radiographic evidence of sacroiliitis, which typically appears late in the disease course. The formal incorporation of MRI findings into the ASAS classification criteria did not occur until 2009–2011, which significantly improved the ability to detect early sacroiliac inflammation.[21] Moreover, the therapeutic landscape in 2004 was considerably more restricted. The early anti-tumour necrosis factor (TNF) agents, infliximab and etanercept, became available in the late 1990s (1998 and 1999, respectively), but access was limited, and indications were approved later on and were narrower than today.

When stratifying by diagnosis, patients with PsA received bDMARDs significantly earlier than those with axSpA. This disparity may reflect earlier recognition of peripheral symptoms,[32] a clearer therapeutic indication in psoriatic phenotypes partly influenced by the ambitious treatment targets set in dermatology, such as achieving Psoriasis Area and Severity Index 90 or 100,[33] and the benefit of multidisciplinary care models involving dermatology and rheumatology.[34] Conversely, delays in axSpA may be attributed to its more insidious onset, a lack of specific biomarkers, historical under-recognition in women and HLA-B27-negative patients,[27] and a slower adoption of imaging techniques such as MRI in routine practice. In addition, the symptomatic improvement achieved with NSAIDs may have masked disease activity and contributed to delays in further evaluation or referral. Early hesitancy to initiate TNF inhibitors due to their relatively recent introduction at the time and concerns about their safety may also have played a role in therapeutic inertia during the early years of biologic therapy. Although current management strategies emphasise early intervention and treat-to-target approaches, our data suggest that a significant proportion of patients in earlier cohorts may have experienced prolonged periods of active disease before receiving bDMARD therapy.

Mortality: infections and cardiovascular disease as the leading causes of death

In our study, the leading causes of death were infections, CV events and malignancies. Other reported causes included respiratory diseases and accidental deaths. This distribution aligns with previously reported mortality patterns in SpA, where infections and CVD are consistently identified as prominent contributors.[7]

The predominance of infections among recorded causes of death is noteworthy. Although the present study does not include longitudinal data on treatment exposures, prior research has identified multiple potential contributors to infection-related mortality in SpA, including immune dysregulation, comorbidities, physical disability and, in some cases, exposure to immunosuppressive therapy.[35] Functional limitations associated with SpA (such as reduced mobility or impaired pulmonary capacity) may further predispose patients to respiratory complications. Moreover, infection-related outcomes may be worsened by diagnostic delays, particularly in older individuals or those with comorbidities, where atypical clinical presentations can lead to postponed recognition and management.[36]

CV disease emerged as a significant cause of death in our cohort, consistent with the known increased CV risk in SpA. This excess risk is believed to result from the interplay between chronic systemic inflammation, endothelial dysfunction and accelerated atherosclerosis. Inflammatory activity contributes to vascular damage by

impairing endothelial function, an early and reversible step in the atherogenic process and promoting the formation of atherosclerotic plaques.[8] Subclinical markers such as increased carotid intima-media thickness and plaque burden have been reported in SpA, supporting the presence of early vascular pathology.[37] This inflammatory component is further amplified by the presence of traditional CV risk factors, including hypertension, smoking, dyslipidaemia and diabetes mellitus, which are prevalent in this population.

Malignancy was a notable cause of death in our cohort, with 24 patients dying from cancer during follow-up, corresponding to a crude mortality rate of approximately 2.6 deaths per 1000 person-years. This estimate is consistent with rates reported in other long-standing SpA cohorts, where cancer is typically the second leading cause of death after CVD. Large population-based studies in Sweden, Israel and Norway have similarly identified malignancy as a major contributor to mortality in axSpA, with HRs for cancer-related death often in the range of 1.5–1.7 compared with the general population.[6 7 38 39]

This observation, in the context of long-standing disease and prolonged exposure to immunosuppressive therapies, warrants further consideration. The association between SpA and increased cancer risk has been described, particularly for malignancies of the digestive system, lymphoproliferative disorders and multiple myeloma.[40] The underlying mechanisms are likely multifactorial: chronic systemic inflammation may contribute to DNA damage and tumour promotion, while prolonged immunosuppressive therapy may further elevate oncological risk.[41]

Although accidental deaths represented a minority of the observed cases, this cause of mortality has been previously described in the context of axial SpA, particularly in relation to reduced cervical spine mobility. Even if infrequent, such events highlight the need to preserve physical function and to consider safety aspects in daily activities such as driving.[42 43]

Altogether, these findings illustrate the long-term burden of SpA beyond musculoskeletal symptoms, reinforcing the importance of comprehensive management strategies that include CV prevention, infection risk reduction, cancer surveillance and attention to physical function and safety.

Strengths and limitations

The main strength of our study lies in the long-term, real-world re-evaluation of a large multicentre cohort with standardised data collection at both baseline and follow-up. The integration of Spanish Registry of Spondyloarthritis (REGISPONSER) and Spondyloarthritis Registry 3 (REGISPON-3) allowed us to explore the natural history of SpA over nearly two decades, including diagnostic trajectories, treatment sequences and survival outcomes.

However, several limitations must be acknowledged. First, the study included only reachable patients who agreed to participate in the re-evaluation, potentially introducing survivor and selection bias. Comparative analyses showed that re-evaluated patients had predominantly axial phenotypes with radiographic sacroiliitis, whereas those not reassessed more frequently presented peripheral features, such as arthritis, and had a lower prevalence of HLA-B27 positivity. This pattern suggests that patients not re-evaluated may have had milder, more benign or self-limited disease courses. It is also possible that some non-reassessed patients had been misclassified at baseline, achieved remission or were eventually considered not to have SpA. Second, although diagnostic changes were based on rheumatologist assessment and modern criteria, misclassification cannot be entirely excluded. Third, the study design included retrospective data collection at the second time point, particularly regarding clinical course and treatment history over the previous 17 years. This introduces the possibility of recall bias. However, whenever feasible, the information provided by patients was cross-checked with their electronic medical records to improve accuracy and minimise potential misclassification. In addition, some apparent reductions in the prevalence of clinical features between baseline and follow-up—such as psoriasis—should be interpreted with caution, as they may reflect differences in reporting or recall, changes in patient awareness, intermittent disease courses or incomplete historical documentation, rather than true decreases in occurrence. The slightly lower proportion of patients with sacroiliitis at follow-up (83.2% vs 80.8%) is also more likely explained by intra-observer variability inherent to radiographic reading, rather than by true regression of structural changes. Fourth, the cause of death was unavailable in 14.4% of cases, which may underestimate the frequency of certain categories. Finally, the interpretation of diagnostic trajectories is limited by the availability of only two time points, 17 years apart. The directionality shown in the Sankey diagram is illustrative rather than temporal, and intermediate transitions, diagnostic instability or temporary misclassifications cannot be ruled out. This constraint limits the ability to fully assess the dynamics of diagnostic evolution over time.

Conclusions

In conclusion, our results illustrate the evolving nature of SpA diagnosis and treatment over time, as well as the persistent burden of delayed intervention and long-term complications. Dactylitis, young age and less structural damage may help identify patients at higher risk for diagnostic change. Treatment delays remain significant, especially in axSpA. Mortality rates remain substantial and are primarily attributed to infections and CV diseases. Future efforts should aim to minimise diagnostic delay and individualised therapeutic approaches in SpA to reduce long-term morbidity and mortality.

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Patient consent for publication Not applicable.

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