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ORIGINAL RESEARCH

Association Between Diagnostic Delay and Economic and Clinical Burden in Axial Spondyloarthritis: A Multicentre Retrospective Observational Study

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ABSTRACT

Introduction: Axial spondyloarthritis (axSpA) is a chronic inflammatory condition associated with considerable pain and impaired health-related quality of life (HRQoL) for affected patients. Despite the documented increase in healthcare resource utilization (HRU) related to axSpA, few studies have explored the impact of diagnostic delays on these outcomes. This study sought to determine the association between diagnostic delay of axial spondyloarthritis (axSpA) and costs in the 3 years after diagnosis.

Methods: This is a retrospective, observational study based on routine follow-up data from adult patients with confirmed axSpA diagnosis in three tertiary Spanish hospitals. Sociodemographic and clinical variables were collected at diagnosis. Direct and indirect healthcare costs were estimated from healthcare resource use (HRU) and productivity losses. The correlation between diagnostic delay and total healthcare costs was analyzed.

Results: Eighty-two patients (62.2% men; mean age: 39.3 years at diagnosis) were included, mostly with radiographic axSpA (r-axSpA) (67.1%). The mean (standard deviation, SD) diagnostic delay was 10.1 (9.3) years, with a median (interquartile range, IQR) of 5.4 (2.3, 17.2) years. The mean total healthcare cost per patient accumulated over 3 years was €25,812.6 (direct: €16,384.7; indirect: €9427.9). Patients with longer diagnostic delay (>5.4 years) had 57% higher total healthcare cost (€31,717.7 vs. €20,188.7, $p=0.029$) and higher disease activity at diagnosis (BASDAI score 4.7 vs. 3.4, $p=0.007$) and after 3 years (3.9 vs. 2.9, $p=0.042$) compared to those with shorter delay (≤5.4 years).

Conclusions: The diagnostic delay in axSpA remains high and is associated with an increase in healthcare costs post-diagnosis. Actions to reduce diagnostic delay should be prioritized by

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healthcare systems to potentially improve outcomes and reduce long-term costs.

Keywords: Axial spondyloarthritis; Costs; Diagnostic delay; Disease activity; Healthcare resource utilization

Key Summary Points

Why carry out this study?

Axial spondyloarthritis (axSpA) is a chronic condition characterized by symptoms that substantially impair functional capacity, adversely affecting work productivity and social context.

The literature evaluating the relationship between diagnostic delay and the economic burden remains limited, often overlooking the economic impact of axSpA on patients and possibly hindering improvements in patient care and quality of life.

This study comprehensively assessed this relationship to enhance the understanding of disease management and improve care for patients with axSpA.

What was learned from the study?

The diagnostic delay in axSpA significantly increases healthcare costs within the first 3 years post-diagnosis.

The timing of diagnosis is critical, and the data presented here provide valuable insights into patient circumstances.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that affects the spine and sacroiliac joints, leading to chronic pain, structural damage, loss of mobility, and disability [1]. Globally, axSpA prevalence ranges from 0.13 to 1.4% [2]. In Spain, axSpA is estimated to affect approximately 1.9% of the general population, with an incidence of seven new cases per 100,000 inhabitants per year [3].

AxSpA is a spectrum of disease that includes both radiographic axSpA (r-axSpA), also known as ankylosing spondylitis, and non-radiographic axSpA (nr-axSpA) [4], with the distinction based on the presence or absence of significant radiographic damage at the sacroiliac joints and spine. The first symptoms of the disease are experienced at a mean age of 28 years [5]. Patients with axSpA report chronic back pain, stiffness, and physical function impairment [1, 6] and often present with extra-musculoskeletal manifestations and comorbidities [7, 8]. In addition, they may experience decreased functional capacity and a decline in their work productivity [4, 9]. Consequently, axSpA is associated with a high degree of disease burden, significantly impacting health-related quality of life (HRQoL) [4, 9] and increasing healthcare resource utilization (HRU) and associated costs [10].

Currently, axSpA diagnosis remains a challenge, which might be due to the difficulty in distinguishing the inflammatory back pain caused by axSpA from other causes of back pain prevalent in the general population. Also, the lack of clear and well-established diagnostic criteria or specific biomarkers may contribute to the delay [11, 12]. Given these circumstances, patients with axSpA may experience delays from the onset of the first symptoms to proper diagnosis, estimated to average 8.5 years for Spain and 7.2 years for other European countries [13]. Diagnostic delay in axSpA has been documented and identified as a major problem on numerous occasions [4, 14–16], but despite improvements in recent decades, patients with axSpA often suffer significant delays in diagnosis, which remains a serious problem worldwide [11]. In this context, a recent systematic review highlighted the patient's journey to diagnosis, revealing greater functional impairment, worse HRQoL, and increasing HRU in patients with higher diagnostic delay. Similar results were observed in a cross-sectional study highlighting that patients with delayed diagnosis exhibit worse clinical outcomes in terms of disease activity and treatment response [17]. Thus, diagnostic delay has been linked to a higher disease progression; however, the studies in this area are

limited and involve small patient populations [18]. At present, there is no evidence on how the diagnostic delay could impact HRU and its associated costs after the patient has been properly diagnosed and treated. In this context, understanding the clinical and economic impact of diagnostic delay on disease management post-diagnosis can raise awareness about the need to reduce the time from initial symptoms to diagnosis and optimize the care of patients with axSpA.

Considering the above, we aimed to determine the correlation between the diagnostic delay in patients with axSpA and costs related to HRU, as well as the impact on work productivity in up to 3 years following diagnosis. Additionally, we aimed to assess the correlation between diagnostic delay and clinical outcomes during patient follow-up, and clinical and economic outcome variables based on patients' sex and type of axSpA.

METHODS

Study Design

This was a retrospective, observational study of adult patients with a confirmed axSpA diagnosis from three Spanish tertiary centers between January 2014 and December 2016, with 3-year follow-up data and at least one visit per year (Supplementary Figure S1).

The study was approved by the Ethics Committee for Research on medicinal products (ECRm) of Parc Taulí of Sabadell (Barcelona) (reference 2022/5001) and conducted in accordance with the Declaration of Helsinki, following the standards of Good Clinical Practice. All ethics committees of the participating centers provided their approval for this study.

Sociodemographic and clinical variables (including age, sex, diagnosis date, symptoms onset, axSpA type, HLA-B27 status, disease activity, spinal mobility, radiographic progression, extra-musculoskeletal manifestations, and comorbidities) were collected at diagnosis and follow-up visits.

Diagnostic delay was defined as the time (in years) from symptom onset to axSpA diagnosis (as well as years of observation). Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [19], Axial Spondyloarthritis Disease Activity Score (ASDAS) [20], C-reactive protein (CRP; mg/l) and erythrocyte sedimentation rate (ESR; mm/h). Bath Ankylosing Spondylitis Function Index (BASFI) [19] and musculoskeletal signs/symptoms were also recorded. Radiographic progression was defined as an increase of at least one grade in the degree of sacroiliac involvement and/or an increase of at least one syndesmophyte.

HRU (number of primary care visits, specialist and emergency department, hospitalization data, procedures performed, and pharmacological treatment), and work productivity loss data (number of periods of sick leave, days of absence, permanent work impairment) were collected from the patients' electronic medical records. Direct costs (including healthcare visits, hospitalizations, procedures, and medications) and indirect costs (temporary and permanent work impairment) were estimated.

Costs were calculated from the Spanish National Health System perspective, using official local sources and 2023 prices. The number of visits or hospitalization days and the number of diagnostic and laboratory procedures performed were multiplied by the associated costs or fees obtained from the Spanish eHealth cost database [21]. Pharmacological costs corresponded to the official selling price [22] and the deductions set out in Royal Decree-Law 8/2010 [23]. Indirect costs were calculated as the sum of days of sick leave due to a patient's temporary work impairment and days elapsed from the date of permanent impairment until the end of the follow-up period of the study or until the patient reached the age of 65 years. The number of days with temporary or permanent work impairment was multiplied by the cost of one working day according to the Spanish labor cost per worker [24].

Statistical analysis included descriptive statistics and correlation analysis (Spearman's coefficient) between diagnostic delay and total costs.

A sample size required to detect a correlation of 0.35 (moderate to low) with a confidence

level of 95% and a power of 90% was estimated [25]. On this basis, a minimum sample size of 82 patients was considered necessary.

Patients were categorized into two groups based on median diagnostic delay. One group consisted of patients with a diagnostic delay at or below the median, while the other group included patients with a diagnostic delay above the median. Mann–Whitney *U* test was used to assess differences in costs and disease activity between groups. Subgroups analyses by sex and axSpA type and were considered exploratory. The statistical package STATA version 14 was used to analyze the data. Significance was set at $p<0.05$.

RESULTS

Patient Characteristics

Eighty-two patients were included in the study. The majority were male ($n=51$, 62.2%), and the mean age (standard deviation, SD) at diagnosis was 39.3 (11.7) years.

Most patients had a diagnosis of r-axSpA (67.1%) and were positive for HLA-B27 (84.2%). Nineteen (23.2%) patients had a previous history of uveitis. Arterial hypertension and hypercholesterolemia were the most frequently recorded comorbidities (Table 1).

At diagnosis, 91.5% of patients presented musculoskeletal signs and symptoms, with inflammatory lower back pain (76.0%) and sacroiliac pain (52.0%) being the most frequent ones.

The majority of patients had active disease according to BASDAI and ASDAS indexes (50% and 86.5% of patients, respectively). The mean (SD) scores were 4.0 (2.4) and 2.8 (1.3), respectively (Table 1).

The mean (SD) diagnostic delay was 10.1 (9.3) years, with a median (interquartile range, IQR) of 5.4 (2.3, 17.2) years, and was significantly higher in patients with r-axSpA vs. nr-axSpA (12.6 vs. 4.8; $p<0.001$), with a median (IQR) of 14.6 (2.7, 18.5) and 2.7 (1.5, 5.4), respectively. No significant differences were found by sex: the mean diagnostic

Table 1 Clinical characteristics of the study population at symptom onset and diagnosis

Characteristics	
Sex, *n* (%)	
Men	51 (62.2)
Women	31 (37.8)
Age, mean (SD)	39.3 (11.7)
Type of axSpA, *n* (%)	
r-axSpA	55 (67.1)
nr-axSpA	27 (32.9)
HLA-B27, *n* (%)	
Positive	69 (84.2)
Negative	13 (15.9)
Symptoms at onset, *n* (%)	
Inflammatory lower back pain	67 (81.7)
Sacroiliac syndrome	55 (67.1)
Peripheral arthritis	15 (18.3)
Cervicalgia	16 (19.5)
Dactylitis	1 (1.2)
Enthesitis	12 (14.6)
Symptoms at diagnosis, *n* (%)	
Inflammatory lower back pain	57 (76.0)
Sacroiliac syndrome	39 (52.0)
Peripheral arthritis	15 (20.0)
Cervicalgia	18 (24.0)
Dactylitis	1 (1.3)
Enthesitis	10 (13.3)
Others[a]	6 (8.0)
History of uveitis, *n* (%)	19 (23.2)
BASDAI, mean (SD)	4.0 (2.4)
ASDAS, mean (SD)	2.8 (1.3)
BASFI, mean (SD)	3.3 (2.2)
CRP, mean (SD)	14.0 (28.9)

Table 1 continued

Characteristics	
ESR, mean (SD)	19.8 (19.7)
Radiographic involvement, *n* (%)	68 (82.9)
Bilateral sacroiliac involvement	58 (85.3)
Unilateral sacroiliac involvement	10 (14.7)
Syndesmophytes	15 (22.1)
Comorbidities, *n* (%)	26 (31.7)
Arterial hypertension	10 (38.5)
Hypercholesterolemia	7 (26.9)
Diabetes mellitus	3 (11.5)
Depression	3 (11.5)
Gastroduodenal ulcer	2 (7.7)
Neoplasia	2 (7.7)
Osteoporosis	2 (7.7)
Ischemic heart disease	1 (3.9)
Cardiovascular accident	1 (3.9)
Renal failure	1 (3.9)
Heart failure	1 (3.9)

ASDAS Axial Spondyloarthritis Disease Activity Score, *axSpA* axial spondyloarthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Function Index, *CRP* c-reactive protein, *DMARDs* Disease-modifying anti-rheumatic drugs, *ESR* erythrocyte sedimentation rate, *nr-axSpA* non-radiographic axial spondyloarthritis, *NSAIDs* Non-steroidal anti-inflammatory drugs, *r-axSpA* radiographic axial spondyloarthritis, *SD* standard deviation

[a]Others included hand arthralgia, arthralgia with mixed features, sternoclavicular arthritis, lumbosciatica, and non-specific polyarthralgia

delay was 10.5 years in women vs. 9.8 years in men ($p = 0.954$), with a median (IQR) of 5.3 (2.2, 18.3) years, and 5.4 (2.3, 17.2) years, respectively. The most common symptom at disease onset was inflammatory lower back pain (81.7%), followed by sacroiliac syndrome (67.1%) and cervicalgia (19.5%).

HRU, Loss of Work Productivity, and Associated Costs

HRU

During the follow-up period, almost all patients (92.7%) utilized primary care services with a mean (SD) number of annual visits per patient of 4.9 (5.2). All patients visited a specialist, rheumatologists being the most consulted specialists every year (100% of patients) with a mean (SD) number of annual visits per patient of 3.1 (1.7), followed by ophthalmologist and gastroenterologist (17.1% and 13.4% during the first year, respectively). Only 15.9% of patients visited rehabilitation and/or physiotherapy services during the first year, decreasing to 4.8% in the third year (Supplementary Table S1 and S2).

Over half of the patients (57.3%) visited the emergency department at least once during their follow-up, with a mean (SD) number of annual visits per patient of 0.9 (0.7). However, few patients required hospitalization throughout the study (11.0%). The mean (SD) hospital length of stay during the study period was 4.8 (6.6) days (Supplementary Table S3).

Almost all patients (97.2%) required some form of testing during the 3-year follow-up period. The most frequent test performed annually was blood analysis (98.7%), followed by X-ray (54.4%) and magnetic resonance imaging (22.2%).

Non-steroidal anti-inflammatory drugs (NSAIDs) were the most commonly prescribed medication class for axSpA in the first 3 years post-diagnosis, with etoricoxib being the most frequently used agent. The use of biological therapies increased during the study period, with up to 39.0% of patients receiving these drugs by the third year (Supplementary Figure S2). In addition, patients received medications for their comorbidities, the most frequent being antihypertensives, antidiabetics, and lipid-lowering agents (Supplementary Table S4).

Loss of Work Productivity

Among the four (4.9%) patients who presented permanent work impairment at the time of diagnosis, only one case was directly associated with the locomotor system (data not shown). Of these, three (75.0%) were completely unable to perform any kind of work, while one (25.0%) was totally impaired only for his usual occupation. Additionally, up to 42.7% of patients experienced temporary work impairment during the follow-up period. The mean (SD) annual number of days of sick leave days due to temporary impairment during the study was 33.8 (65.0) days and decreased over the study period (Supplementary Table S5).

Associated Costs

The mean (SD) annual total cost per patient was 8604.2€ (11,207.5) with a mean (SD) total cost during the study period of 25,812.6€ (33,622.5) (Table 2). Of the total costs, 63.5% and 36.5% corresponded to direct and indirect costs, respectively (Fig. 1).

Direct costs increased throughout the study period, while indirect costs were higher in the first-year vs. the second and third year, decreasing from 50.1% to 31.3%, and 28.9% of total cost, respectively (Supplementary Table S6 and Figure S3).

Cost analysis revealed higher total expenses for r-axSpA compared to nr-axSpA, primarily due to increased indirect costs (Supplementary Table S7). Similarly, men incurred higher total and indirect costs than women. However, these differences were not statistically significant.

Table 2 Mean annual and total costs (€) per patient

	Annual costs (€), mean (SD)	3-year total costs accumulated (€), mean (SD)
Direct costs	5461.6 (5487.8)	16,384.7 (16,463.5)
Indirect costs	3142.6 (8648.9)	9427.9 (25,946.7)
Total costs	8604.2 (11,207.5)	25,812.6 (33,622.5)

(direct + indirect cost)

SD standard deviation

Association Between Diagnostic Delay and Costs

The primary objective of the study was the analysis of the correlation between diagnostic delay and total costs in the 3 years following diagnosis, which showed a low positive correlation, although it was not statistically significant (Spearman's coefficient = 0.195, $p = 0.08$). Similarly, a low positive but not significant correlation was found between diagnostic delay and direct and indirect costs (Spearman's coefficient = 0.163, $p = 0.144$ and Spearman's coefficient = 0.79, $p = 0.108$, respectively), and total cost in each of the 3 years following diagnosis ($p = 0.052$; $p = 0.101$; $p = 0.063$, respectively) (Supplementary Figure S4).

At the time of data analysis, patients with a shorter diagnostic delay, based on the median, exhibited a significantly lower mean of total cost than those with a longer diagnostic delay (€20,188.7 vs. €31,717.7, $p = 0.029$). A

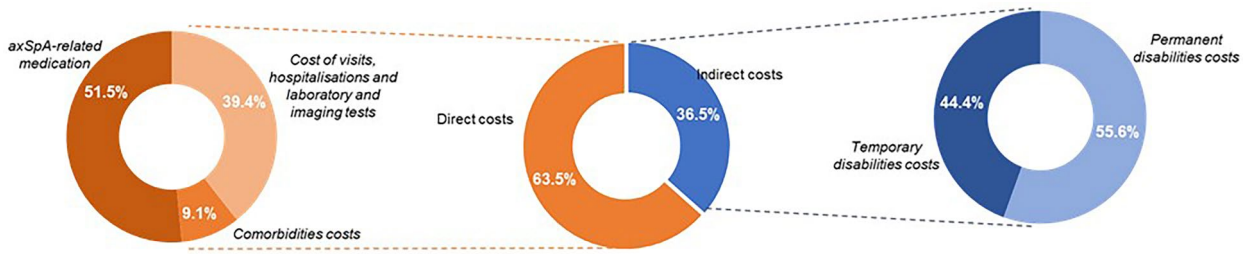

Fig. 1 Distribution of direct and indirect costs per patient. *axSpA* axial spondyloarthritis

Table 3 Mean and median annual cost (€) according to the median diagnostic delay (5.4 years)

Diagnostic delay	Direct costs (€)			Indirect costs (€)			Total costs (€)		
	Mean (SD)	Median (IQR)	*p* value	Mean (SD)	Median (IQR)	*p* value	Mean (SD)	Median (IQR)	*p* value
≤ Q2	13,656.74 (13,972.81)	7366.71 (3524.29–19,492.48)	0.069	6532.00 (23,296.52)	0.00 (0.00–772.80)	0.059	20,188.7 (27,621.3)	9247.8 (3941.8–26,321.9)	0.029
> Q2	19,249.03 (18,473.34)	12,954.94 (5688.35–25,111.55)		12,468.64 (28,445.89)	676.20 (0.00–6520.50)		31,717.7 (38,419.0)	17,298.3 (9640.0–38,074.5)	

IQR interquartile range, *Q2* median, *SD* standard deviation

statistically significant difference was found between groups ($p=0.029$) (Table 3). Patients with a diagnostic delay of > 5.4 years had 57.1% higher mean total expenditure and 87.1% higher median total expenditure, mostly due to differences in indirect costs. Differences in the cost of diagnostic delay in each of the follow-up years are shown in Supplementary Table S8.

The secondary goal was to assess the association between diagnostic delay and costs according to patients' sex and axSpA type. A statistically significant positive correlation between total cost and diagnostic delay was observed for men ($p=0.049$) but not for women ($p=0.933$). In addition, no significant correlation was observed between total, direct, and indirect costs according to axSpA type and diagnostic delay (all $p>0.05$).

Disease Burden

The mean of BASDAI, ASDAS, and BASFI decreased at the 1-year follow-up visit and remained stable throughout the study. Levels of CRP and ESR showed a marked decrease during the first year and remained stable throughout the study. The proportion of patients with active disease decreased at the 1-year follow-up visit and remained stable throughout the study (Fig. 2 and Supplementary Figure S5).

During follow-up visits, the most common new peripheral signs and symptoms were peripheral arthritis (up to 25.0% of patients), and enthesitis (up to 50.0% of patients). Spinal mobility was similar at diagnosis and at the last follow-up visit (year 3): the mean (SD) scores in Schober's test were 4.2 (1.2) and 4.1 (1.3), respectively.

Of the 75 patients for whom radiographic progression data were available, 13 patients (17.3%) exhibited progression at the conclusion of the follow-up (year 3). Of these, six patients (46.2%) showed sacroiliac progression (an increase of at least one grade) and five patients (38.5%) experienced an increase in the number of syndesmophytes between diagnosis and year 3, while two patients (15.4%) progressed in both areas.

Association Between Diagnostic Delay and Clinical Variables

No statistically significant correlation was observed between diagnostic delay and the change from baseline of ASDAS, BASDAI, BASFI, CRP and ESR in the 3 years following diagnosis (all $p>0.05$). At year 3 of the follow-up period, a statistically significant positive correlation between diagnostic delay and BASDAI was observed (Spearman's coefficient = 0.2747, $p=0.0294$). A similar correlation was found for ASDAS at year 3, although it was not statistically significant (Spearman's coefficient = 0.211, $p=0.097$).

When analyzed based on the median diagnostic delay, a statistically significant higher BASDAI score was observed in patients with a longer vs.

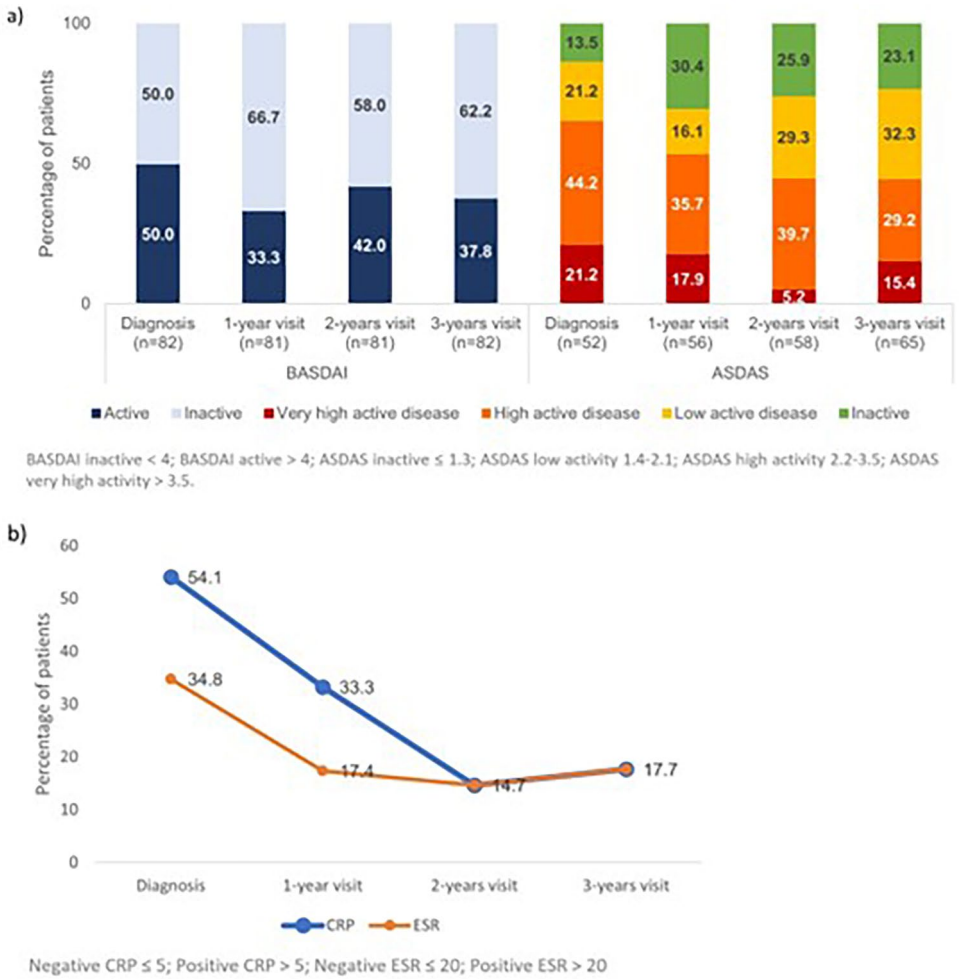

Fig. 2 Number of patients with active disease in each of the follow-up visit of the study. a) activity according to disease activity indices: BASDAI inactive < 4; BASDAI active > 4; ASDAS inactive ≤ 1.3; ASDAS low activity 1.4–2.1; ASDAS high activity 2.2–3.5; ASDAS very high activity > 3.5 and b) activity according to laboratory indices: Negative CRP ≤ 5; Positive CRP > 5; Negative ESR ≤ 20; Positive ESR > 20. *ASDAS* Axial Spondyloarthritis Disease Activity Score; *BASDAI* bath ankylosing spondylitis disease activity index; *CRP* C-reactive protein; *ESR* erythrocyte sedimentation rate

shorter diagnostic delay at baseline (4.7 vs. 3.4, $p=0.007$) and after 3 years (3.9 vs. 2.9, $p=0.042$). The differences in ASDAS did not reach statistical significance at baseline (3.1 vs. 2.5, $p=0.123$) nor at year 3 (2.5 vs. 2.1, $p=0.089$).

DISCUSSION

Our study confirms previous evidence of a high diagnostic delay in axSpA and suggests a possible association between diagnostic delay and post-diagnosis costs in a clinical practice setting during the 3 years after diagnosis.

Recent studies confirmed the persistence of a high diagnostic delay in patients with axSpA [11, 26–28]. In our study population, the mean diagnostic delay was 10.1 years, with a median of 5.4 years, consistent with previously reported findings in both Spanish and worldwide population [13, 27]. Notably, while no differences in diagnostic delay were observed by sex, a significantly longer diagnostic delay was found in

patients with r-axSpA compared to those with nr-axSpA. One possible explanation is that radiographic progression in axSpA is partially time-dependent. Therefore, the longer the delay in diagnosis, the higher the likelihood of developing radiographic damage.

In our study, the HRU and loss of work productivity were based on clinical records during the first 3 years after diagnosis. Most patients visited primary care facilities during this period, as well as specialty centers, with rheumatologists being the most consulted specialists followed by ophthalmologists and gastroenterologists. Notably, only 15.9% of patients attended rehabilitation and/or physiotherapy services, with this percentage decreasing over the study period. This result suggests that the regular use of these services could be insufficient considering that the Assessment of SpondyloArthritis international Society (ASAS)-EULAR recommendations encourage supervised exercise and physiotherapy for patients with axSpA [29]. Regarding employment status, four (4.9%) patients had permanent work impairment at diagnosis. The percentage of patients that experienced any temporary work impairment remained stable over the 3-year period, while the annual number of sick days decreased, likely reflecting a better control of the disease.

Overall, HRU and loss of work productivity in our study resulted in a mean annual cost of €8604.2 per patient, most of which were direct costs (63.5%). Most of direct costs were related to axSpA-specific medications, followed by costs of visits, hospitalization and tests, and comorbidities costs (detailed in the Methods section). Indirect costs were balanced between temporary and permanent work impairment costs (detailed in the Methods section). During follow-up, direct costs increased, which might be related to the prompt initiation of a long-term treatment, while indirect costs decreased, likely reflecting a better control of the disease. In this sense, it is important to recognize that while treatment itself represents a significant economic burden, delayed initiation of treatment can lead to disease progression, resulting in increased direct and indirect costs. These results are similar to those observed in a previous study conducted in Spain, whose authors reported a mean annual cost per patient of €11,462.3 of which 33.6% were attributed to indirect costs (vs. 36.5% in our study) [30]. Results in the literature reported for other populations are heterogeneous, ranging from €6122 in 2012 in France [31] and €5190 in 2013 in Germany [32] to $44,783 annual mean per patient in the USA [33].

Our primary objective was to analyze the correlation between diagnostic delay and total costs in the three years following diagnosis. An alternative approach was also used to estimate this association by categorizing the patient population into two groups based on the median of diagnostic delay. Although we did not find a significant statistical correlation between diagnostic delay and total, direct, and indirect costs during follow-up, our study results indicate statistically significant higher post-diagnosis total costs in the group of patients with a longer diagnostic delay based on the median: patients with a diagnostic delay of > 5.4 years had 57.1% higher mean total cost and 87.1% higher median total cost, mostly due to increases in indirect costs. This suggests that diagnostic delay could have a higher impact on costs related to work impairment compared to direct costs. We also observed that in men, a longer diagnostic delay was associated with a higher total cost after diagnosis, whereas this association was not observed in women. This can be expected as costs were slightly higher for men compared with women, mainly due to indirect costs after diagnosis. Although there are no data in our study to support this hypothesis, this can be expected, as costs (especially indirect costs) were possibly related to a higher degree of structural damage in men than in women, data that are in accordance with previous data in the literature [34]. On the other hand, we did not find any correlations between the diagnostic delay and the costs according to the type of axSpA, reinforcing a similar burden of the disease (35). However, these results should be interpreted with caution, as they are based on exploratory analysis. To our knowledge, this is the first study to assess the correlation between total, direct, and indirect costs after diagnosis and the diagnostic delay experienced by patients with axSpA.

When assessing the correlation between diagnostic delay and clinical outcomes, we found

a statistically significant positive correlation between diagnostic delay and disease activity (BASDAI) at the third year. Similarly, patients with a longer diagnostic delay (>5.4 years) had significantly higher disease activity at baseline and at the third year after diagnosis.

Our study has several strengths. The clinical characteristics and diagnostic delay of our study population are consistent with previous studies on axSpA, supporting the reliability of our results. We conducted a pragmatic study that included all patients, providing a clear picture of standard clinical practice. Additionally, we obtained clinical data, HRU, and work impairment information from clinical records of tertiary hospitals, instead of relying on patients' surveys. All interactions with the national health system, including sick leave, were collected. However, the study has several limitations. We did not find a strong linear association between HRU costs and diagnostic delay, possibly due to limited sample size. Moreover, considering the international variability among health systems, results obtained in this study should be cautiously extrapolated. The estimation of diagnostic delay is based on the data collected in the clinical history, and consequently calculated from the initial report of symptoms potentially associated with the disease, until the time of diagnosis. Thus, it is important to note that there might be patients with previous symptoms not identified in the patient's report. Therefore, we cannot exclude, although previous literature results seem to support this conclusion, that in some patients, diagnostic delay and disease progression do not occur in parallel. The associations between diagnostic delay and costs according to patients' sex and axSpA type should be considered exploratory. Finally, the cost of biological treatments was derived from reported prices. However, the actual price may be influenced by commercial discounts, potentially leading to an overestimation of the total cost.

CONCLUSIONS

In conclusion, our study population shows a high diagnostic delay in axSpA, which is in line with previous evidence. Moreover, patients with a longer diagnostic delay had significantly higher disease activity at diagnosis and after three years and incurred 57% higher total costs over the three years following diagnosis compared to those with a shorter delay.

This suggests the existence of a window of opportunity for earlier diagnosis and intervention, which will likely improve patient outcomes and lower management costs. Population measures such as educational projects and involvement of other specialties in the diagnostic journey of patients with axSpA could help reduce diagnostic delays in these patients.

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Declarations

Conflict of Interest. Laura Berbel-Arcobé, María Aparicio, Joan Calvet, Marta Arévalo, Annika Nack, Xavier Juanola and Jordi Gratacós declare that they have no conflicts of interest relevant to this article. Elide Toniolo and Stefano

Maratia are employees of UCB Pharma. Luis Lizán is an employee of Outcomes'10 and have received payments from the sponsor for support in design and methodology, study conduct and medical writing. methodology, conduct of the study, and medical writing.

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